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Tatlock H. Lauten

Tamara Natour

Adam J. Case

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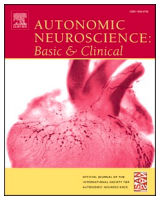

Review article

Innate and adaptive immune system consequences of post-traumatic stress disorder

Tatlock H. Lauten [1], Tamara Natour [1], Adam J. Case [*]

Department of Psychiatry and Behavioral Sciences, Texas A&M University, Bryan, TX, United States
Department of Medical Physiology, Texas A&M University, Bryan, TX, United States

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ABSTRACT

In the field of psychiatry, biological markers are rarely, if ever, used in the diagnosis of mental health disorders. Clinicians rely primarily on patient histories and behavioral symptoms to identify specific psychopathologies, which makes diagnosis highly subjective. Moreover, therapies for mental health disorders are aimed specifically at attenuating behavioral manifestations, which overlooks the pathophysiological indices of the disease. This is highly evident in posttraumatic stress disorder (PTSD) where inflammation and immune system perturbations are becoming increasingly described. Further, patients with PTSD possess significantly elevated risks of developing comorbid inflammatory diseases such as autoimmune and cardiovascular diseases, which are likely linked (though not fully proven) to the apparent dysregulation of the immune system after psychological trauma. To date, there is little to no evidence that demonstrates current PTSD therapies are able to reverse the increased risk for psychological trauma-induced inflammatory diseases, which suggests the behavioral and somatic consequences of PTSD may not be tightly coupled. This observation provides an opportunity to explore unique mechanisms outside of the brain that contribute to the long-term pathology of PTSD. Herein, we provide an overview of neuroimmune mechanisms, describe what is known regarding innate and adaptive immunity in PTSD, and suggest new directions that are needed to advance the understanding, diagnosis, and treatment of PTSD moving forward.

1. Introduction

The immune system protects the host from two primary insults: pathogens and damage. Whereas the immune mechanisms for neutralizing pathogens are diverse, those involved in physical tissue damage are more limited. With this, the immune system's primary method of repairing tissue damage is the orchestration of scar tissue deposition, regardless of the organ that is damaged. While this fibrotic repair mechanism likely served a strong evolutionary benefit towards physical damage to the skin, it falls short in the ability to fully repair intricate and diverse organs such as the heart, kidney, liver, or brain. As our species has extended our lifespan long beyond our mating years, this primitive damage repair mechanism has become implicated in more diseases associated with age. Moreover, as humans evolved to have more complex social and behavioral systems, the immune system was presented with a new challenge of experiencing psychological trauma and subsequent chronic mental health disorders like posttraumatic stress disorder (PTSD), which as we will discuss, has pushed this system to its functional capacity.

PTSD is a debilitating psychiatric condition characterized by heightened fear, arousal, and avoidance behavior, but is also highly associated with chronic inflammation and an elevated risk of various long-term autoimmune and cardiovascular outcomes (Pivac et al., 2023; Vaccarino et al., 2013). While the specific mechanisms of how psychological trauma impacts the immune system and body remain unclear today, the heightened sympathetic nervous system response associated with PTSD is believed to be a primary driver of both the behavioral and physiological pathological states, even more so than the hypothalamus-pituitary-adrenal (HPA) axis, which has demonstrated a paradoxical decrease in cortisol levels in patients with PTSD (Yehuda, 2005; Schneider and Schwerdtfeger, 2020; Yehuda et al., 1998; Yehuda et al., 1995; Halbreich et al., 1989). While short-term activation of the

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Department of Medical Physiology, 8447 Riverside Pkwy, MREB2 3414, Bryan, TX 77807, United States.
E-mail address: acase@tamu.edu (A.J. Case).
[1] Authors contributed equally to the manuscript. Each other has been authorized to list their name first on their respective CV's or comparable documents.

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sympathetic nervous system during a "fight or flight" response may provide acute survival benefits and positive effects on inflammation, it is possible that the pathological chronic activation of this system may cause long-term detriments to the immune system, which may underlie the predisposition to somatic pathology after PTSD. Moreover, it still remains unclear if current behavioral-targeted therapies are sufficient to attenuate the immune dysregulation, inflammation, and risk for inflammatory comorbidities associated with PTSD. While more studies are needed to support this notion, this could possibly suggest that the inflammatory and physiological sequelae of PTSD are not fully coupled with the behavioral manifestations. Therefore, understanding the exact etiology of the behavioral, autonomic, and inflammatory consequences is paramount for uncovering the cause of the disease for future intervention.

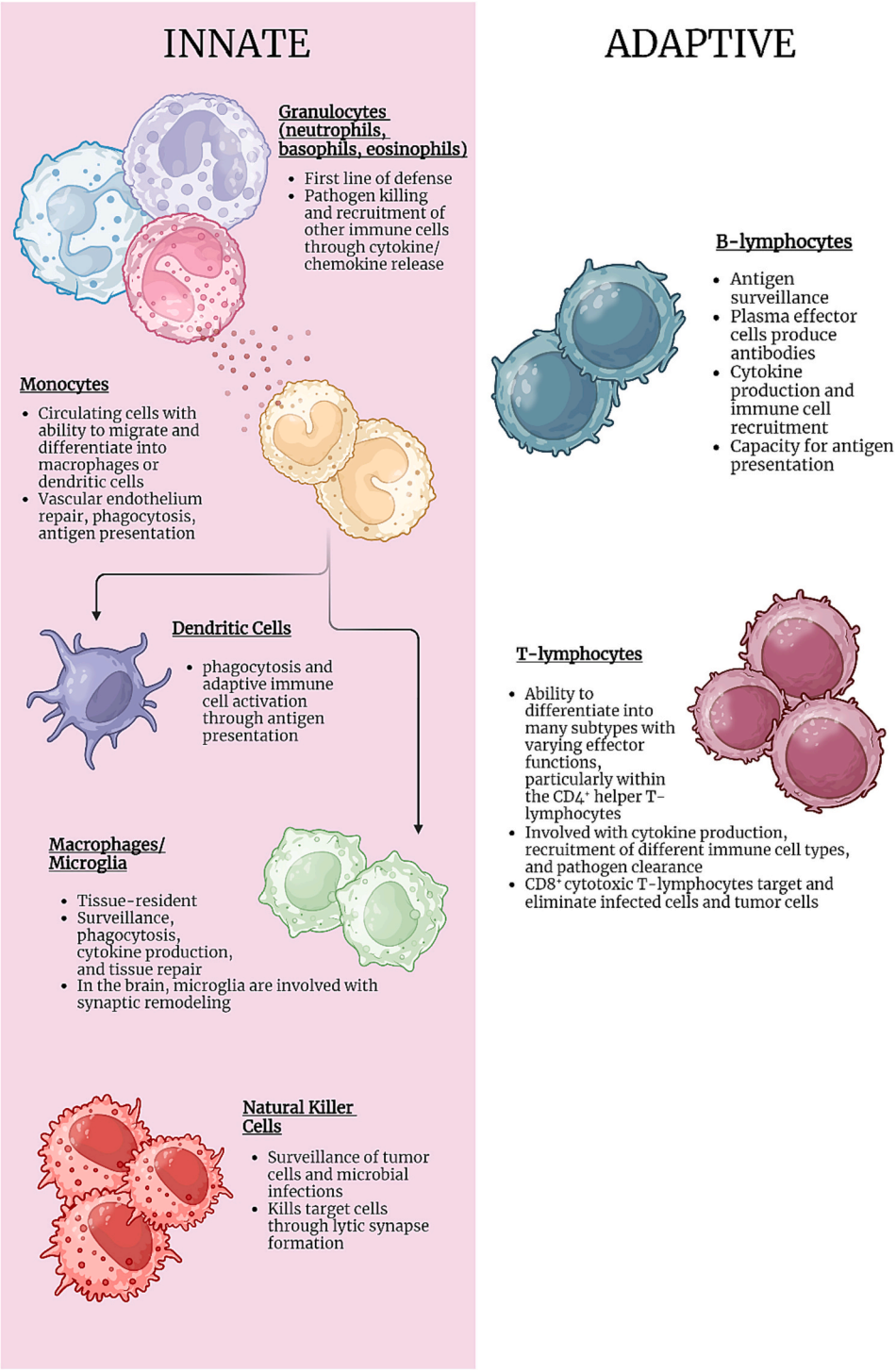

Fig. 1. Overview of the innate and adaptive immune systems. The classic delineation is to break the immune system into two major components: innate and adaptive. These two classes of immune cells differ in their ability to form long-term memory of previous immune challenges, however, this notion is also being challenged. While this classification is still the standard in the field, it is well known these two branches do not work independently, but in concert with one another to mount a complete immune response.

2. Immune system basics

Immune system development has been described extensively elsewhere (Weiskopf et al., 2009; Dorshkind et al., 2009; West, 2002). Therefore, the goal of this section is to provide the reader a generalized overview of the various types of immune cells, their primary function, and how they interact to set the premise for the following sections regarding neuro-immune communication and PTSD. A graphic overview of various immune cells and their general functions may be viewed in Fig. 1.

2.1. Innate versus adaptive immunity

Classically, the immune system is comprised of "white blood cells" (to contrast with red blood cells), or leukocytes, and is broken into two different branches: innate and adaptive. Innate immune cells include cell types such as granulocytes, monocytes, macrophages, dendritic cells, and innate lymphoid cells, and are primarily characterized by their lack of specificity towards antigens and their ability to respond in a non-specific or generalized fashion. This allows for a rapid response, and also permits immunity towards a diverse set of threats. Because of these characteristics, it has long been believed that the innate immune system does not possess any type of long-term "memory" of an immune challenge. In other words, this would imply that the innate immune system would not "remember" any specific antigen no matter how many times it had been encountered and would mount the same response each time. However, it has been recently observed that the innate immune system may indeed possess the ability to mount a heightened reaction to additional triggers of inflammation or infection, known as trained immunity (Netea et al., 2020; Netea et al., 2016; Netea et al., 2011). While still an emerging concept, this may provide a basis as to why 97 % of all earth's organisms thrive in the absence of a classical adaptive immune system. Moreover, while not yet investigated, trained innate immunity may play a role in PTSD given its chronic and recurring impacts on the immune system.

In contrast to the innate immune system which possesses an array of cell types, the adaptive immune system contains primarily T and B-lymphocytes, each of which have unique functions. First, antibody-mediated immunity, or humoral immunity, is a major component to long-term immune protection after an initial antigen encounter and is regulated by B-lymphocytes (Ansel et al., 2000; Gatto et al., 2011; Schuh et al., 2020). In contrast, T-lymphocytes provide cell-mediated adaptive immunity. While many subtypes of T-lymphocytes exist, there are two primary groups based upon unique surface markers on the respective cell types: CD4 and CD8. T-lymphocytes expressing CD4 are known as helper T-lymphocytes, and function primarily to augment immune responses from both B-lymphocytes and the innate immune system. In contrast, CD8 expressing T-lymphocytes are known as cytotoxic T-lymphocytes and given their namesake, possess the primary function of killing infected or potentially harmful cells (Cantor and Boyse, 1977; Shiku et al., 1975). In general, T-lymphocytes play a highly centralized role between all arms of the immune system, and may act as master orchestrators of a unified immune defense towards foreign pathogens or tissue damage.

Both T and B-lymphocytes possess a unique immunological characteristic: immunological memory. The fundamental concept of immunological memory is the ability for the immune system to respond to additional exposures of the same challenge more rapidly than when compared with the initial challenge. To achieve this feat, subsets of adaptive immune cells that have been activated by a primary antigen response will differentiate into memory forms of those lymphocytes. While these memory cells exist in large numbers scattered throughout secondary lymphoid organs such as the spleen and lymph nodes, their immunological functions are mostly dormant. However, upon repeat exposure to their specific antigen, these memory cells are able to respond faster than their naïve counterparts. These memory cells are highly reactive in their ability to proliferate and produce proinflammatory cytokines, which has been shown to contribute to the long-term inflammatory states of many chronic diseases.

2.2. Inflammation

The term inflammation is one of the most widely used descriptors of immune system function, but is also vague and possesses varying definitions. For example, inflammation is often used to describe a localized reaction in a tissue that consists of enhanced blood flow, swelling, redness, heat, and pain. In contrast, inflammation may also be used to describe activation of specific immune cells in an organ system, such as activated microglia in the brain referred to as neuroinflammation. Additionally, the simple observation of elevated immune-mediated proteins such as cytokines and chemokines either locally or systemically may be termed inflammation. These varying definitions often lead to confusion when utilizing the term inflammation, thus, the word has lost much meaning in the absence of specific context.

However, the unifying theme among all definitions of inflammation is the activation of a component of the immune system and the release of immune-mediated molecules (Borish and Steinke, 2003). The catalyst for inflammation often begins when a damage associated molecular pattern (DAMP) receptor or pathogen associated molecular pattern (PAMP) receptor are triggered on an innate immune cell by encountering a foreign or endogenous antigen (i.e., neoantigen). This initiates a cascade of intracellular signaling in the immune cell, which leads to the production and excretion of immune-mediated molecules such as cytokines and/or chemokines. Common examples of pro-inflammatory immune proteins are C-reactive protein (CRP), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), interleukin 17a (IL-17a), and tumor necrosis factor (TNF). In contrast, anti-inflammatory immune proteins are interleukin 4 (IL-4, context dependent), IL-6 (context dependent), and interleukin 10 (IL-10). The production of these immune-mediated molecules is imperative in mounting a rapid and appropriate immune response, thus, the assessment of these proteins (which has become a primary output of scientific investigations of inflammation) allows for a snapshot view into the general status of the immune system at a specific time. However, interpretation of immune function by assessment of immune-mediated proteins alone should be performed with extreme caution, as communication among immune and non-immune cells is highly complex and dynamic, and requires in depth temporal, spatial, cellular, and functional evaluation to fully appreciate the immune and inflammatory response in a specific context.

While the immune response is well known to occur in response to pathogens or cellular damage, there are additional signals that may also modulate immune cell activation. Over the last few decades, it has become highly appreciated that immune cells are in constant reciprocal communication with the nervous system and send/receive messages via neurotransmitters. The investigations into how immune cells utilize and respond to neurotransmitters are still in their infancy, but this neural communication appears to significantly affect immune system function and is likely imperative in the control of immunity and inflammation in mental health disorders such as PTSD.

3. Neural communication with immune system

3.1. Behavioral-immune connections

Since the 1920s, research into Pavlovian behavioral conditioning has yielded intriguing findings regarding its potential physiological impact on the immune system (Cohen et al., 1994). Early studies uncovered that pairing the taste of saccharin with an immunosuppressant led to a conditioned response, wherein the animal remained immunosuppressed even when exposed to saccharin treatment without the immunosuppressant during subsequent trials (Ader and Cohen, 1975). Additional studies have also demonstrated that immune challenges may also

associate with specific environments or foods due to the sickness behavior being linked with the initial pairing (Costa-Pinto et al., 2005). Conversely, the act of avoiding stimuli associated with a pathogen or its related illness has been found to trigger an adaptive immune response, preparing the body for immune interactions (Mirotti et al., 2010; Chen et al., 2004). This avoidant behavior elicits comprehensive physiological changes designed to bolster the body's natural defenses against pathogens, now referred to as the "learned placebo effect" in such cases (Schedlowski and Pacheco-López, 2010). Moreover, recent therapies have put this concept of behavior-influenced immunity to the test, with psychological treatments showing promising effects on leukemia prognosis in patients. These treatments have led to improved quality of life through enhanced immunity, shortened sickness behavior, and overall increased well-being of the patients (Chacin-Fernández et al., 2019). The culmination of this body of work, combined with newer evidence such as the innervation of the lymphoid organs (Felten et al., 1985) and the discovery of immune cells expressing neurotransmitter receptors (Hadden et al., 1970; Pert et al., 1985), underscores the mounting evidence suggesting a closer link between the neural and immune systems than previously believed.

Interestingly, the interactions between the nervous and immune systems appear to be bidirectional. The immune system is able to affect the central nervous system either directly (through physical migration of immune cells or cytokines into the brain) or indirectly (via immune interactions in the periphery affecting afferent sensory neurons). These interactions may affect major neural processes such as memory, behavior, and development (Boahen et al., 2023; Lotan and Schwartz, 1994; Matejuk et al., 2021). Additionally, upon receiving signals from immune cells, the central nervous system can respond and work through efferent pathways, towards the periphery, to signal to other immune cells as to how they should respond. However, the specific details underlying behavioral-immune interactions remain unknown, but continue to unravel fascinating insights into the complex relationship between the mind and the body's defenses.

3.2. Sympathetic regulation of immunity

Among the potential communication pathways between the nervous and immune systems, the autonomic nervous system, specifically the sympathetic arm of the autonomic system, has been implicated in playing regulatory roles and making significant contributions to numerous mental health disorders. The sympathetic nervous system (SNS), also known as the fight or flight response system, is a multifaceted mechanism that influences a wide range of physiological bodily functions, including cardiovascular, respiratory, gastro-intestinal, endocrine, metabolic, and importantly, immune system functions (Bottasso, 2019).

This sympathetic control is exerted through direct influence from key catecholaminergic signals, epinephrine (EP) and norepinephrine (NE), which are released into circulation or directly from sympathetic neurons (Leach and Suzuki, 2020). These catecholamines are released at the synapse at their target organ, where they bind to alpha and beta-adrenergic receptors (White et al., 2000; Elenkov et al., 2000; Molinoff, 1984). Notably, these adrenergic receptors are expressed on both innate and adaptive immune cell types, and they respond to the binding of NE and EP, resulting in the modulation of immune cell function (White et al., 2000; Elenkov et al., 2000). In addition to NE and EP, other neurotransmitters released by the sympathetic system bind to their own unique receptors as well as adrenergic receptors with less affinity, leading to the modulation of immune cells. Some of these neurotransmitters include dopamine, neuropeptide Y, and substance P (Levite and Chowers, 2001; Neve et al., 2004). The specific class of adrenergic receptor stimulated, whether alpha or beta, as well as whether the cell is of the innate or adaptive type, can result in different immune responses. For instance, stimulation of beta-adrenergic receptors on adaptive immune cells, such as T and B-lymphocytes, promotes immune cell trafficking, circulation, proliferation, and modulates their cytokine production (Elenkov et al., 2000; Ramer-Quinn et al., 2000). Notably, adaptive cells typically express a higher number of beta receptors than alpha receptors (Nance and Sanders, 2007). Conversely, stimulation of beta-adrenergic receptors on innate immune cells, such as macrophages and monocytes, has been observed to inhibit pro-inflammatory responses (Alaniz et al., 1999; Wohleb et al., 2014a; Wohleb et al., 2013), while stimulation of alpha-adrenergic receptors leads to augmented pro-inflammatory changes (Spengler et al., 1990). These examples highlight generalized responses of immune cells to various adrenergic receptor activation, however, extensive work has demonstrated that the responses are much more nuanced, context dependent, and the inflammatory response is not always binary when referring to a specific type of adrenergic receptor stimulation (Padro and Sanders, 2014).

In addition to receiving and responding to sympathetic signals, studies have found that immune cells are capable of synthesizing, storing, and releasing their own catecholamines to signal in a paracrine and autocrine fashion (Smith and Blalock, 1981; Flierl et al., 2007). This area of neuroimmunology is still developing, and many of the details regarding these immune-derived catecholamines are still being uncovered. Further, the discovery that immune cells produce neurotransmitters provides additional evidence of how intertwined the nervous and immune systems are within the body, and suggests they work in tandem more than previously appreciated.

3.3. Parasympathetic regulation of immunity

The parasympathetic system, also known as the "rest and digest" system, plays a regulatory role in response to the actions of the sympathetic system, particularly by inducing an anti-inflammatory response. Unlike the sympathetic system that utilizes several different neurotransmitters, the parasympathetic system communicates by releasing one primary neurotransmitter, acetylcholine (Goehler et al., 2000; Elkhatib and Case, 2019).

Immune cells express various receptors for acetylcholine, including both muscarinic and nicotinic receptors, which are crucial in ameliorating the pro-inflammatory response to prevent uncontrolled inflammatory consequences. Indeed, genetic knock-out of these types of parasympathetic receptors has been shown to be highly detrimental in experimental models of infection and sepsis (Elkhatib and Case, 2019; Maldifassi et al., 2018). Therefore, it is hypothesized that the parasympathetic system exerts a primary anti-inflammatory response that checks and balances the effects of the sympathetic system (though this is still highly debated (Elkhatib and Case, 2019)). One of the primary ways the parasympathetic system is believed to regulate immune function is by controlling inflammation and inducing anti-inflammatory signals, a process known as the anti-inflammatory reflex or cholinergic anti-inflammatory response (Goehler et al., 2000). The concept behind this reflex is that when peripheral tissues sense inflammation, sensory nerves transmit this information to the brain where it triggers the parasympathetic nervous system back in the periphery to attenuate inflammation, particularly in secondary lymphoid organs like the spleen (Goehler et al., 2000). These parasympathetic signals significantly inhibit cytokine production in the spleen and improve inflammatory complications by affecting both the innate and adaptive immune systems (Rosas-Ballina et al., 2011).

However, there is one major complication with this model: secondary lymphoid organs like the spleen do not possess any direct parasympathetic innervation (Padro and Sanders, 2014). In fact, most lymphoid organs possess exclusively catecholaminergic innervation, which is thought to be sympathetic in nature. So how is it that numerous studies have demonstrated parasympathetic actions and the presence of acetylcholine leading to anti-inflammatory effects in secondary lymphoid organs? The prevailing theory is that parasympathetic nerves communicate to secondary lymphoid organs through their synapses in upstream ganglia, which then induces specific immune cells (i.e., T-

lymphocytes) to generate/release acetylcholine to facilitate the anti-inflammatory effects (Rosas-Ballina et al., 2011; Rosas-Ballina et al., 2008). There are some significant caveats to this theory including the unknown mechanism by which immune cells can decipher sympathetic versus parasympathetic signals coming from one singular nerve and set of neurotransmitters, as well as conflicting evidence from researchers demonstrating the parasympathetic system plays less of a role than currently accepted (Gautron et al., 2013; Bratton et al., 2012). Whatever the mechanism may be, it is difficult to overlook the breadth of data demonstrating that the parasympathetic branch regulates peripheral immune function.

For example, studies have shown that parasympathetic signals, upon reaching adaptive cells, reduce the proliferation of multiple subtypes of T-lymphocytes and suppress the production of pro-inflammatory cytokines IL-17, IL-22, and TNFα (Nizri et al., 2009). Additionally, follow-up studies on anti-inflammatory regulatory T-lymphocytes (Tregs) have concluded that there is an increase in Treg-mediated immune suppression of pro-inflammatory lymphocytes in response to these parasympathetic signals (Wang et al., 2010). Further, acetylcholine has been observed to produce a similar anti-inflammatory effect in the innate immune system as well. The parasympathetic system has been shown to be responsible for lowering levels of various pro-inflammatory cytokines such as TNF-α, IL-6, and IFN-γ, which primarily originate from innate immune cell populations (St-Pierre et al., 2016). Additionally, the close contact observed between certain cholinergic neurons and innate cells, such as monocytes and macrophages in the gastrointestinal system, provides evidence that parasympathetic signaling impacts inflammation via cholinergic signals in these populations (Wang et al., 2003; Matteoli et al., 2014). Together, these anti-inflammatory effects of the parasympathetic nervous system have provided the basis for novel therapeutic approaches, such as vagal nerve stimulation (VNS), that attempt to stimulate this arm of the autonomic system and limit inflammation in an array of diseases.

4. Immunity and PTSD

Aforementioned, PTSD is a debilitating psychiatric condition characterized by heightened fear, social withdrawal, chronic stress, inflammation, and an increased risk of various long-term autoimmune and cardiovascular outcomes compared to unaffected individuals (Pivac et al., 2023; Vaccarino et al., 2013). The heightened sympathetic response associated with PTSD is believed to be a primary driver of both the behavioral and physiological pathological states, even more so than the HPA axis, which has demonstrated a paradoxical decrease in cortisol levels in patients with PTSD (Yehuda, 2005; Schneider and Schwerdtfeger, 2020; Yehuda et al., 1998; Yehuda et al., 1995; Halbreich et al., 1989). This long-term dysregulation of the stress-response systems is also associated with an increased systemic level of pro-inflammatory cytokines, chronic inflammation, and a reduction in anti-inflammatory cytokines (Michopoulos et al., 2017). Data also suggests that a PTSD score, as measured by the Clinician-Administered PTSD Scale (CAPS), may correlate with particular elevated pro-inflammatory cytokines such as IL-6 and CRP, as well as increased sympathetic signatures (Kim et al., 2020; Somvanshi et al., 2020). However, as evidenced by one such study, even if the psychiatric manifestations improve over the long term, inflammation and the risk for inflammatory comorbidities may still persist (Himmerich et al., 2016). In this study, various groups of soldiers with PTSD were treated with psychotherapy, eye movement desensitization and reprocessing (EMDR), and/or traditional antidepressants, and levels of TNFα and its soluble receptors were examined both before and after therapy. Interestingly, while PTSD symptoms (as measured by the post-traumatic stress diagnostic scale) improved with these therapies, the TNFα system in these patients was mostly unchanged. This observation is imperative, as it implies that not all inflammatory and physiological sequelae of PTSD are fully coupled with the behavioral manifestations. Indeed, a newer study recently reported significant elevations in circulating inflammatory proteins in trauma exposed individuals with and without the development of PTSD compared to health controls, which further supports the notion of a disconnect between behavior and inflammatory outcomes (Koirala et al., 2023). Therefore, understanding the exact cause of the behavioral, autonomic, and inflammatory consequences is paramount for uncovering the source of the disease in which appropriate therapeutic modalities may be applied. A summary of this section, which describes both innate and adaptive immune interactions in PTSD, may be found in Table 1.

4.1. Cytokine dysregulation in PTSD

The majority of research examining immune dysregulation and inflammation in PTSD has simply measured levels of circulating cytokines and chemokines. Traditionally, these inflammatory proteins play a crucial role in modulating both the innate and adaptive immune cell populations as signaling molecules, but their specific role in the context

Table 1
Immune system alterations in PTSD.

Cell type		Phenotype	Species	References
Innate immune cells	Neutrophils	- ↑ IL-6, IL-1β, TNFα - Pro-inflammatory - Attenuated phagocytic activity - ↑ Neutrophil Extracellular Traps (NETs)*	- Human - *Rat	- 133–136 - 130, 144 - 156
	Monocytes	- Impaired response to mitogens - Elevated in circulation in some studies, no elevation in others - ↑ IL-1β*	- Human - *Mouse	- 126, 129, 130 - 141 - 123
	Microglia	- ↑ IL-1β, CD14, CD86, TLR4 - Pro-inflammatory - Implicated in behavioral[†] and physiological effects of PTSD[$]; Possible anti-inflammatory response in some cases*	- Mouse - *Human - [†,$]Rat	- 121 - 151 - 152, 153 - 155
	NK Cells	- Reduced functionality and cytokine production	- Human	- 140, 142, 143
	Dendritic Cells	- Increased apoptosis in trauma patients - Imbalance in subtypes observed	- Human	- 137 - 138
	Innate Lymphoid Cells	- Sparse research on their role in mental health	- Human	- 139
Adaptive immune cells	B-Lymphocytes	- No significant differences observed in PTSD patients	- Human	- 159–161
	T-Lymphocytes	- ↑ TNFα, IL-6, IL-17A, IL-22* - Pro-inflammatory* - Increased activation - Decrease in naïve T-lymphocytes and Tregs; Increase in memory T-lymphocytes - Decrease in CD4: CD8 ratio - Limited studies suggesting T-lymphocyte numbers may be depressed after PTSD	- Human - *Human, mouse	- 161–164 - 142

of PTSD is still unclear (Holtmann and Resch, 1995). The increased cytokine and chemokine levels observed in individuals experiencing PTSD (Boscarino, 2008) may be a key factor contributing to long-term pathophysiology, including an elevated risk for autoimmune and cardiovascular diseases (O'Donovan et al., 2015; Remch et al., 2018), but additional studies are highly warranted to understand the mechanistic role of specific cytokines in this disorder.

One important facet of PTSD is that not all cytokines and chemokines are elevated indiscriminately in this disease, but specific subsets have been repeatedly identified as dysregulated (Breen et al., 2018; Uddin et al., 2010). For example, pro-inflammatory cytokines such as IL-6, CRP, IL-1β, and TNFα have been consistently implicated in PTSD (Spivak et al., 1997; von Känel et al., 2007; Tucker et al., 2010; von Känel et al., 2010; Baker et al., 2001). Other studies, though not as prevalent as the aforementioned, have also identified IL-17A increases in PTSD (Maloley et al., 2019). This cytokine has been highly implicated in autoimmune diseases (Bedoya et al., 2013), which makes it an attractive target for investigations studying the links between psychological trauma and autoimmunity. Conversely, several studies have also shown elevated levels of anti-inflammatory cytokines IL-4 and IL-10 in PTSD patients, indicating that PTSD is not solely characterized by a pro-inflammatory response and likely involves multiple immune pathways (Guo et al., 2012; Renner et al., 2022a; Renner et al., 2022b).

Of the cytokines that have been identified in PTSD, IL-6 and CRP appear to show the greatest association with PTSD behavioral manifestations (Marsland et al., 2017; Passos et al., 2015; Lima et al., 2019). In fact, baseline plasma CRP concentrations have been indicative of PTSD diagnosis and severity in pre-deployment Marines (Eraly et al., 2014). Additionally, both IL-6 and CRP levels in the periphery have been associated with PTSD following a traumatic event (Cohen et al., 2011). Interestingly, peripherally elevated levels of IL-6 have been reported to independently contribute to PTSD severity and are associated with enhanced fear and anxiety responses, as well as increasing brain activity in the regions responsible for this behavior (Kim et al., 2020; Inagaki et al., 2012; Muscatell et al., 2015). Moreover, non-pharmaceutical based PTSD therapies, such as vagal nerve stimulation, have also demonstrated the ability to lower IL-6 levels in both acute and chronic settings (Bremner et al., 2020; Bremner et al., 2021). At this time, it is unclear if the nerve stimulation directly acts on the immune system to lower IL-6 levels which in turn attenuates PTSD behavioral manifestations, or conversely acts first on the brain which triggers a downstream reduction in IL-6. In either situation, these novel therapeutic approaches that address both behavior and inflammation show incredible promise, and may become the standard of therapy for mental health disorders in the future. Indeed, direct targeting of specific cytokines in mental health disorders is also being investigated, with several clinical trials currently underway targeting pro-inflammatory cytokines (primarily IL-6) in mental health disorders (Tyring et al., 2006; Abbasi et al., 2012).

While the previous investigations have undoubtedly demonstrated that PTSD is associated with elevated levels of cytokines and chemokines, mechanistic insight into the source, timing, and effects of these pro-inflammatory proteins are currently lacking in these human studies. Due to this, many investigators have turned to preclinical animal models that recapitulate aspects of PTSD. There are approximately a half a dozen animal models that are currently accepted to mimic various features of PTSD (Aspesi and Pinna, 2019; Deslauriers et al., 2018). Interestingly, only one model has been shown to recapitulate peripheral elevations in cytokines and chemokines similar to human PTSD (Aspesi and Pinna, 2019; Deslauriers et al., 2018). This model is known as repeated social defeat stress (RSDS), and incorporates aspects of both physical and psychological trauma (Reader et al., 2015; Moshfegh et al., 2019; Weber et al., 2017). Animals undergoing RSDS possess elevated levels of circulating IL-6, IL-17A, TNFα, and IL-10, which is highly similar to human PTSD (Moshfegh et al., 2019; Elkhatib et al., 2020). Further, investigations have also found that specific subsets of cytokines associate with RSDS behavioral manifestations such as anti-social behavior (Hodes et al., 2014) or anxiety-like behavior (Elkhatib et al., 2020). Other preclinical models of PTSD, such as predator stress or social disruption stress (SDR), have observed increased pro-inflammatory cytokines such as IL-1β, IL-6, CRP, and TNFα in the brain after psychological trauma, suggesting neuroinflammatory mechanisms at play as well (Wohleb et al., 2014b; Wilson et al., 2013; Deslauriers et al., 2017). Together, these studies confirm that psychological trauma, even in rodents, is able to produce a pro-inflammatory phenotype, suggesting a conserved evolutionary immune response to stress.

However, the question still remains as to how these cytokines and chemokines affect behavior and physiology after psychological trauma. To address this question, pharmacological and genetic manipulations of inflammation in animal models have been primarily utilized. For example, treatments with generalized non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to effectively reduce levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNFα in a rat model of PTSD (Levkovitz et al., 2015; Gamble-George et al., 2016) as well as being generally neuroprotective for their effects on neuroinflammation (Ajmone-Cat et al., 2010). Other more specific NSAIDs, such as COX-2 inhibitors, significantly improved locomotor activity, antianxiety effect, memory retention, and attenuated oxidative damage in mouse and rat PTSD models (Kumari et al., 2007; Wang et al., 2018). Additionally, the application of NSAIDs has not only diminished anxious behaviors but has also alleviated general anxiety symptoms in animals subjected to stress (Levkovitz et al., 2015; Gamble-George et al., 2016; Lee et al., 2016). However, in stark contrast, NSAIDs have shown little benefit in the context of human PTSD (Grau et al., 2022) with very few studies to validate their efficacy in this disease. Therefore, additional studies are required in order to better understand the impact of PTSD treatments on inflammation in humans.

On the opposite end of the spectrum to NSAIDs, steroidal anti-inflammatory drugs have also been examined in the context of PTSD. Interestingly, PTSD has a complex presentation regarding endogenous corticosteroid production compared to other mental health disorders (which often present with elevated levels), with disparate findings showing either unchanged or reduced levels in patients with PTSD (Yehuda, 2002). This raises the question as to the role of corticosteroids in PTSD, as well as how they may regulate post-psychological trauma inflammation. Regarding exogenous supplementation of corticosteroids, studies have shown that a single treatment with corticosterone shortly after stress exposure reduced behavioral symptoms in animal PTSD models (Cohen et al., 2008; Jia et al., 2015). Additionally, steroidal treatments have been effective for their enhanced memory retrieval effects in humans (Wingenfeld et al., 2012), their usage to confront traumatic memories in veterans with PTSD (Surís et al., 2010), as well as being protective against the development of PTSD in certain contexts (Schelling et al., 2001). While these results are promising, there have been minimal examination as to how corticosteroids exert these positive effects, and if modulating the immune system is a primary target. Moreover, these broad anti-inflammatory drugs are highly non-specific, and therefore provide minimal information as to which specific inflammatory proteins or cells are important in the context of PTSD-induced inflammation and pathology.

Given this limitation in generalized anti-inflammatories, several investigations have attempted to target specific cytokines implicated in PTSD. For example, administration of antibodies specifically targeting TNFα resulted in diminished peripheral inflammation and prevention of anxiety-like behaviors in a preclinical rat model of PTSD (Dib et al., 2021). Furthermore, the targeting of IL-6 by using antibodies or genetic knock-out animals has also shown that blockade of IL-6 reverses psychological trauma-induced behavioral changes such as social avoidance or anxiety-like phenotypes (Hodes et al., 2014; Niraula et al., 2019). Intriguingly, while the genetic knock-out of IL-6 appeared to reverse negative behavior changes as well as limit pro-inflammatory gene signatures in innate immune cells, it had minimal impact on innate immune cell release from the periphery and recruitment to the brain (Niraula

et al., 2019). This suggests the possibility of multiple mechanisms involved in the regulation of immunity and inflammation after psychological trauma. With that, IL-1β has also been investigated due to its repeated characterization and importance in the stress response (Shintani et al., 1995; Goshen and Yirmiya, 2009). For example, systemic pharmacological or genetic blockade of the IL-1β receptor has been shown to reverse the antineurogenic, anhedonic, and anxiety-like behavior caused by chronic stress exposure (Koo and Duman, 2008; Wohleb et al., 2011). Interestingly, blockade of the IL-1β receptor specifically in endothelial cells is sufficient to prevent stress-induced behavioral deficits such as anxiety-like behavior (Wohleb et al., 2014c). This endothelial effect is believed to begin with microglia in the brain becoming activated during chronic stress, which causes the recruitment of IL-1β expressing monocytes to the brain (McKim et al., 2018). These proinflammatory monocytes appear to be causal in driving stress-induced behavioral manifestations, but are trafficked to the brain via IL-1β receptor expressing-endothelial cells (McKim et al., 2018; Liu et al., 2019). This multicellular cascade demonstrates the complexity of psychological trauma-induced immune perturbations, but illuminates new potential targets in the treating of PTSD behaviors. However, given the limitations of performing mechanistic studies in humans, much of this work still remains to be validated in human PTSD patients.

Overall, the presence of a unique cytokine milieu in PTSD suggests that specific immune cells may be a central element in the development and progression of PTSD (Lindqvist et al., 2014). However, static levels of circulating cytokines and chemokines in the absence of any other immune system examination, which is how the majority of PTSD studies have been performed, provide little evidence as to the source of these proteins, the root cause of the actual elevation, or how these inflammatory mediators after affecting specific cell types in and out of the immune system. Reports of specific immune mechanisms in PTSD are currently sparse in the literature, but are beginning to be investigated. These types of studies will prove quintessential in unraveling the regulatory pathways involved that link psychological trauma to altered immune function.

4.2. Innate immune alterations in PTSD

As earlier mentioned, the changes in inflammatory proteins observed among individuals with PTSD suggest the potential for immune dysregulation and malfunction. However, the available evidence regarding these immune alterations in humans remains limited. Most studies have simply explored population shifts of innate immune cells associated with PTSD, primarily focusing on monocytes, natural killer (NK) cells, and granulocytes due to their abundance in circulation and their potential role in altered cytokine production of IL-1β and TNFα following psychological trauma.

Investigations into the proportions and quantities of these innate immune cells have yielded inconsistent findings among PTSD patients. Certain studies, including one involving prisoners of war with PTSD, have reported increased circulating monocyte cell counts (Skarpa et al., 2001), while lifetime prevalence of PTSD has shown elevated monocyte proportions in males (Kim et al., 2019). Additionally, others have demonstrated that stress (not PTSD per se) leads to elevated circulating monocyte levels in healthy female volunteers (van de Wouw et al., 2021). In contrast, other investigations have failed to identify elevated levels of monocytes or NK cells in the circulation of individuals with PTSD (Laudenslager et al., 1998; Rohleder et al., 2004). Additionally, while the proportion of neutrophils greatly increases in peripheral blood following acute stress (Dhabhar, 2014; Tang et al., 2022), chronic stress and PTSD contrastingly suppresses these innate cells (Dhabhar, 2014). For example, in studies investigating acute stress with participants undergoing a 10-minute paced auditory serial addition stress test or being stressed about an upcoming academic examination, participants showed enhanced neutrophil release (Khanfer et al., 2010; Tsukamoto and Machida, 2014). However, in instances of chronic stress, such as individuals who have been kept as prisoners of war or children who have delt with parental separation/divorce, neutrophil numbers were attenuated (Dekaris et al., 1993; Bartlett et al., 1997). Literature on other innate immune cells such as dendritic or innate lymphoid cells is even more sparse. For instance, dendritic cells in trauma patients exhibited increased levels of apoptosis compared to healthy controls (Maier et al., 2009) while another study demonstrated trauma led to an imbalance in dendritic cell subtypes (Henrich et al., 2009), but given these patients suffered significant physical trauma, it is unclear if psychological factors contributed to these dendritic cell effects. Research on a relatively newer class of innate immune cells known as innate lymphoid cells is even more scarce, with only speculation at this time as to how these cells may contribute to mental health (Barichello, 2022).

Beyond merely characterizing cell numbers, select studies have attempted to characterize human innate immune cell function in the context of PTSD. For instance, the response of NK cells and monocytes to mitogens appears to be impaired in PTSD given that patients who developed PTSD showed reduced cell proliferation and cytokine release from these cells compared to controls (Gotovac et al., 2010; Wutzler et al., 2009). This diminished NK functionality has been consistently replicated in survivors of natural disasters with PTSD (Kawamura et al., 2001; Inoue-Sakurai et al., 2000). However, a single study (Laudenslager et al., 1998) presented contrasting results, indicating increased cytotoxic NK cell activity among Vietnam War veterans. Neutrophil function shows a similar pattern to that of their numbers; acute stress leads to increases, while chronic stress decreases, phagocytic activity (Khanfer et al., 2010; Tsukamoto and Machida, 2014; Dekaris et al., 1993; Bartlett et al., 1997). Other studies have demonstrated that peripheral blood mononuclear cells (PBMC) have potentiated functional responses. For example, when subjected to cytokine response tests using mitogens like LPS, PBMCs from individuals with PTSD have demonstrated heightened production of pro-inflammatory cytokines such as IL-6, IL-1β, and TNFα (Rohleder et al., 2004; Gola et al., 2013). However, studies utilizing PBMCs are convoluted by the fact they contain an array of cell types including adaptive immune cells, which precludes any definitive conclusions regarding specific cell types.

Together, it is clear that additional and more controlled studies are highly needed to better understand the timing, distribution, and function of innate immune cells in PTSD. The disparity in the aforementioned studies likely stems from one of the most significant limitations in the field of psychological trauma: an incredibly broad definition of PTSD. Currently, the diagnosis of PTSD in the United States is made using the Diagnostic and Statistical Manual of Mental Disorders volume 5 (DSM-5), which discusses an array of symptomology that may be characteristic of PTSD. However, using these extensive diagnostic criteria, it has been estimated that there are over 630,000 potential permutations of being diagnosed with PTSD (Galatzer-Levy and Bryant, 2013). This vast diversity in presentation, time since trauma, and etiology of trauma all likely contribute to the impact on the immune system, and thus convolute cross-sectional studies of patients simply categorized with a PTSD diagnosis. The nuance of the patients' psychological trauma needs to be considered along with other factors relating to the PTSD diagnosis that has been previously discussed (Reed and Case, 2023).

Therefore, with the dearth of in-depth immune profiling in human PTSD as well as the limitation of studying mechanistic immune interactions in the brains of human patients, many researchers have again turned to animal models to obtain a better understanding of immune perturbations after psychological trauma. Given that RSDS is one of the only preclinical PTSD models that produces systemic inflammation, many animal studies have utilized this paradigm to study innate immune function. For example, studies have shown that RSDS induces increases in pro-inflammatory monocyte and macrophage populations, which produce IL-1β and the chemokine CCL2, and increased brain trafficking to promote anxiety-like behavior (Wohleb et al., 2013; McKim et al., 2018). Additionally, psychological trauma has also shown an

association between increased trafficking of the innate cells to the brain and the causal emergence of anxiety-like behaviors (Wohleb et al., 2014a; Reader et al., 2015). Monocyte trafficking is believed to be in response to the abundant norepinephrine release after psychological trauma, which promotes migration into circulation, the brain, and lymphoid organs (Wohleb et al., 2013; Saint-Mezard et al., 2003; McKim et al., 2016). As mentioned previously, these monocytes interact with brain-resident microglia, which are major contributors to cytokine production and are implicated in various psychiatric disorders (Calcia et al., 2016). For example, one study identified an increase in the ratio of microglia to other immune cell types in the brain after electric foot-shock-induced psychological stress in mice, and that both depletion and pharmacological blockade of microglia improved stress-induced memory deficits (Li et al., 2021). Other animal models of PTSD, such as the predator scent-stress model, demonstrated a direct correlation between microglial activation and the levels of anxiety-like symptoms developed (Nahum et al., 2022). Notably, the social defeat model has shown to significantly elevate the microglial inflammatory surface markers CD14, CD86, and TLR4, as well as increased IL-1β expression (Wohleb et al., 2011). In addition to behavioral effects, there is evidence to suggest that microglia are also implicated in the physiological comorbidities that afflict PTSD patients. For example, activation of microglia in the hippocampus following a single prolonged stress induction in rats has been shown to be positively correlated with chronic pain that is associated with the onset of PTSD (Sun et al., 2016). Moreover, this activation of hippocampal microglia in the same model was correlated with increased cognitive impairment as well as increased permeability of the blood-brain barrier (BBB) after stress induction (Ni et al., 2022). The compromised integrity of the BBB may lead to numerous pathologies of the CNS, including inflammatory diseases and strokes (Liu et al., 2015), both of which show enhanced risk among PTSD patients.

While the concept of activated microglia driving neuroinflammation and pathology in the brain is easy to understand, these findings are possibly refuted by a recent study that suggests an anti-inflammatory microglial response in PTSD. In this study, levels of the microglial translocator protein (TSPO) in the frontal circuits of human PTSD patients via positron emission tomography (PET) scans demonstrated a negative correlation between the levels of heightened peripheral inflammation in PTSD patients. These data were further confirmed via demonstration of lowered expression of microglia-associated genes in postmortem brains of PTSD patients (Bhatt et al., 2020). These findings will need to be validated by other groups, but provide a provocative alternative view of microglia in PTSD that is not recapitulated in animal models. While this may be a fundamental difference between humans and rodents, another possible explanation is simply the temporal factor. Virtually every preclinical model of PTSD examines the behavioral, molecular, and physiological effects shortly after a relatively acute psychological trauma. While these findings have illuminated potential mechanisms of how the immune system is initially perturbed after psychological trauma, they provide little insight into the long-term ramifications of ongoing PTSD that may last decades in humans. Therefore, there is a significant need to 1) examine the consequences of psychological trauma in animal models at significantly later timepoints than is currently being performed and 2) investigate mechanisms of immune system activation in human patients at timepoints closer to the exposure to psychological trauma and potentially even prior to the onset of overt PTSD. Together, these experiments may illuminate how the immune system evolves over the course of PTSD from an acute traumatic experience into a long-term chronic disease.

Outside of monocytes and microglia, granulocyte responses have also been investigated in animal models of psychological trauma, which appear to somewhat mimic the aforementioned human responses. For example, in a mouse model of acute restraint stress, neutrophils were found to be elevated in the blood, which corresponds to what is seen in humans after transient stress (Tang et al., 2022). Additionally, elevated neutrophil extracellular traps (NETs) were also found in another acute rat stress model that utilized foot shock followed by 3 restraint stress sessions (Corsi-Zuelli et al., 2022), again mimicking enhanced granulocytic responses after acute stress. However, in a different murine study that employed 1- or 2-hour water immersion restraint stress (WIR), neutrophil count and bactericidal activity were significantly reduced (Kinoshita et al., 2019). This finding is counterintuitive given that this model appears to be acute stress. Moreover, in a mouse model of RSDS that is thought to recapitulate chronic psychological trauma, the numbers of neutrophils and monocytes significantly increased in the bone marrow, blood, and spleen following stress (Ishikawa et al., 2021). Together, these animal findings show paradoxical results compared to humans, but these inconsistent findings could simply be due to the use of models that simply do not recapitulate specific phenomena that are characteristic of psychological trauma in humans. One factor that is often not considered when studying PTSD is severity of the psychological trauma, which is difficult to objectively assess, but may be a critical factor in understanding how the immune system is affected (even more so than time). Additionally, another critical issue lies in the fact that there are many mechanisms of trauma, both physical and emotional, that may lead to PTSD. Therefore, it would be near impossible to develop one uniform animal model that encapsulates every form of trauma and the different ways in which they may alter physiological sequalae. As discussed before, in order to overcome this hurdle, additional human studies need to be performed that separate PTSD patients based on the type of trauma experienced and their resultant physiology. This would allow for the development of more nuanced models that can be used to study different forms of PTSD and understand the variable pathophysiology that may follow, which includes not only in-depth evaluation of the innate immune system, but also the adaptive branch as well.

4.3. Adaptive immune alterations in PTSD

Similar to monocytes and NK cells, studies examining B- and T-lymphocyte populations in PTSD are more common given their relative abundance in circulation. Several studies have compared B-lymphocyte populations between PTSD patients and their non-PTSD counterparts, and have concluded no differences in these cell types (Boscarino and Chang, 1999; Vidović et al., 2007; Wilson et al., 1999). In contrast, T-lymphocytes do appear to be impacted more robustly by the effects of PTSD. First, PTSD patients have been demonstrated to have increased markers of activation in circulation compared to health controls (Wilson et al., 1999). Additionally, patients with PTSD exhibit a downward shift in the proportion of naive and regulatory T-lymphocytes with a concurrent increase in memory T-lymphocytes as compared to controls; a finding that was unable to be reversed when utilizing standard therapies for PTSD (Sommershof et al., 2009; Morath et al., 2014). More in depth characterization of T-lymphocytes has demonstrated PTSD is associated with a decrease in CD4 to CD8 ratio as well as an increase in the ratio of CD8 effector to naïve T-lymphocytes (Aiello et al., 2016). Interestingly, these effects were observed in patients diagnosed with PTSD within 1 year previous as well as those with lifelong PTSD (Aiello et al., 2016), suggesting adaptive immune effects occur relatively quickly after psychological trauma and are long lasting. While limited studies exist suggesting T-lymphocyte numbers are depressed after PTSD (Kawamura et al., 2001), the overwhelming majority suggest PTSD impacts T-lymphocytes to drive increased numbers, activation, and a pro-inflammatory phenotype.

Regarding function of the adaptive immune system, studies have primarily encompassed a variety of tests, including evaluations of vaccine response, antibody titer, and delayed hypersensitivity tests (DTH) within patients with PTSD. In contrast to chronic stress, which has been demonstrated to impair B-lymphocyte mediated immune response to vaccinations (Vedhara et al., 1999; Kiecolt-Glaser et al., 1996; Glaser et al., 1998), PTSD does not appear to demonstrate this similar kind of

antibody depression (Kosor Krnic et al., 2007). These studies may elucidate a clear difference between chronic stress and traumatic stress as it pertains to the adaptive immune system, and may suggest differential mechanisms between the respective conditions. In contrast, in this same study it was observed PTSD patients appeared to have lower numbers of antigen-specific T-lymphocytes prior to vaccination compared to healthy controls, but after vaccination these numbers were not statistically different (Kosor Krnic et al., 2007). This may suggest a potentiated T-lymphocyte response by PTSD patients given the ability to reach healthy control levels even though starting at a lower point, but this observation will need additional follow-up studies to confirm this observation. Other investigations have studied the response of T-lymphocytes in PTSD patients using both skin-applied antigens and direct in vitro stimulation. In the skin application study, an increased number of T-lymphocytes was observed after antigen application, accompanied by an enhanced skin response, indicating the presence of more reactive T-lymphocytes from patients with PTSD (Boscarino and Chang, 1999; Altemus et al., 2006). Moreover, subjecting whole blood PBMCs to a CD3 antibody to induce a T-lymphocyte receptor-mediated response resulted in amplified proliferation of pro-inflammatory T-lymphocyte subtypes and a 50 % reduction in the availability of regulatory or anti-inflammatory T-lymphocytes (Sommershof et al., 2009). While one study did demonstrate that through ex vivo mitogen-induced cytokine assays that T-lymphocytes from individuals with PTSD exhibited lowered production levels of IFNy and IL-4, coupled with reduced T-lymphocyte proliferation (Kawamura et al., 2001), this study was performed in only 12 individuals, which does not reach the rigor to make any definitive conclusions. Taken together, these studies highly support minimal impact on B-lymphocytes in PTSD, but much stronger and likely pro-inflammatory effects on T-lymphocytes in these patients. Given these observations, it is imperative to delve into the mechanisms that underlie immune cell function in order to shed light on these processes.

While animal models have provided the means to study mechanisms linking psychological trauma to adaptive immune alterations, the literature is still conflicted as to the specifics of these neuroimmune interactions. Several early studies demonstrated that psychological trauma led to a suppression of adaptive immunity. For example, when utilizing restraint stress, investigators observed reductions in the number of lymphocytes in the spleen and mesentery as well as levels of circulating antibodies after an immune challenge (Fukui et al., 1997; Domínguez-Gerpe and Rey-Méndez, 2001). A similar result was observed in rats where increased levels of psychological trauma equated to decreased levels of lymphocyte and their functional capacities (Keller et al., 1981). Another study mimicked these effects by demonstrating decreased numbers of lymphocytes and antibody production in a different model of stress (Esterling and Rabin, 1987). However, this latter study uncovered an additional layer in that removal of the adrenal gland had no effect on this reduction in adaptive immunity (Esterling and Rabin, 1987). This observation is incredibly important, as it eliminates a major stress-related organ as the potential signal leading to decreased lymphocytes and their function. However, the question remains as to why these studies demonstrate marked adaptive immune suppression whereas PTSD patients appear to have potentiated effects and increased inflammation.

The answer to this question likely lies in the etiology of the stressor as well as the timing. Many of these early studies examined immune populations and function immediately following a short-term stressor, which likely examines the effect of acute stress on the immune system. Indeed, many studies have demonstrated that short-term acute stress induces immunosuppression as opposed to activation. Therefore, significant caution needs to be taken when examining “stress models” in rodents, as they may not replicate true psychological trauma nor have the chronic nature needed to induce a long-term inflammatory state. With that, given the more chronic (10 day) nature of the RSDS paradigm combined with its reproducible production of systemic inflammation, this model serves as an important model in understanding the response of peripheral immunity to longer-term psychological trauma. Notably, our laboratory has unveiled that RSDS consistently leads to an increase in the levels of both systemic and T-lymphocyte-produced TNFα, IL-6, IL-17A, and IL-22 (Moshfegh et al., 2019; Elkhatib et al., 2020), and that this inflammation lasts at least 3 months past the initial psychological trauma (unpublished work). Intriguingly, blocking sympathetic transmission to the spleen through splenic denervation resulted in a complete abrogation of the T-lymphocyte response in this lymphoid organ (Elkhatib et al., 2021). Notably, systemic inflammation was not totally attenuated, suggesting RSDS induces inflammation at multiple sites throughout the body likely through autonomic innervation. Additionally, utilizing a T-lymphocyte-specific knock-out of tyrosine hydroxylase, which inhibits the ability for T-lymphocytes to produce their own catecholamines, specifically inhibited these cells from producing IL-17A and IL-22 (Elkhatib et al., 2022). This finding adds an additional layer of complexity to the signaling cascade, as it suggests the brain and immune system both produce neurotransmitters during psychological trauma necessary for the production of pro-inflammatory cytokines. In addition to our work, others have confirmed a pro-inflammatory T-lymphocyte signature after RSDS, even delineating that animals with worsened behavioral outcomes may have increased levels of T-lymphocyte inflammation (Ambrée et al., 2019). Additionally, a recent study has shown the potential for B-lymphocytes to also be involved in inflammation post-RSDS, but this work is still in its infancy and may not recapitulate human PTSD as previously discussed (Shimo et al., 2022).

In summary, the intricate relationship between psychological trauma and the adaptive immune system has only begun to be explored through various cellular and functional assays, both in human subjects and animal models. From these studies, T-lymphocytes have emerged as a key player in the immune dysregulation associated with PTSD. These human studies, supported with insights from animal models, shed light on the potential mechanisms underlying adaptive immune alterations in PTSD. The role that the autonomic nervous system could have in driving these immune changes highlights a potential therapeutic target for intervention. Further unraveling the complex interplay between psychological trauma and immune cell function holds promise for understanding the increased risk of immune dysregulation and disease in individuals with PTSD and developing new therapies for their treatment.

5. Conclusions and considerations moving forward

Current therapies for PTSD focus solely on the behavioral manifestations of the disease, with no consideration for the consequences of inflammation. In fact, while it is well-accepted that elevated inflammation is often associated with somatic diseases such as cardiovascular and autoimmune diseases, it still remains unclear if the elevated inflammation associated with PTSD is mechanistic to the development of these physiological diseases after psychological trauma. Furthermore, studies that have examined inflammation before and after standard therapies for PTSD are virtually non-existent. Of the few studies that have attempted such investigation, the results are mixed as to the impact on inflammation with standard PTSD treatment (Himmerich et al., 2016; Sagarwala and Nasrallah, 2019). This provocative observation suggests the potential for the uncoupling of PTSD behavioral manifestations from physiological/inflammatory consequences. Moreover, this finding may also suggest that psychological trauma alone (independent of the development of clinical PTSD based on behavior) may lead to physiological and immune alterations (as demonstrated recently (Koirala et al., 2023)), which may often go undiagnosed due to a lack of seeking help in the absence of behavioral changes. We have observed this exact phenomenon in our own laboratory in that not all behavior manifestations of psychological trauma correlate with inflammation, which again, suggests multiple mechanisms at play (Elkhatib et al., 2020).

Given this, we propose three areas of research that need further

investigation and research. First, as described previously, in depth immunological analyses need to be performed on patients with PTSD. However, cross sectional studies are not appropriate for these types of analyses due to the variability of psychological trauma, time since the trauma, and existing development of PTSD. Instead, patients should be recruited at the time of psychological trauma before the development of PTSD, and followed over time to understand how/when inflammation begins, how it may contribute or be predictive of PTSD, and how it may lead to other inflammatory diseases later in life. This type of recruitment is already being performed and investigated for potential interventions that can prevent the development of PTSD after a traumatic incident (Rothbaum et al., 2012; Iyadurai et al., 2018; Kanstrup et al., 2021; Horsch et al., 2017). In these studies, patients are screened for traumatic incidents at intake of emergency rooms, and then enrolled in prevention studies in attempts to limit the development of PTSD. Using this same kind of model, these patients could also be screened temporally for immunological and inflammatory parameters, and even assess how these change with different therapeutic modalities. Alternatively, pre- and post-deployment studies of military personnel would also be appropriate, as they allow for the assessment of inflammation even prior to psychological trauma. While these types of studies have been performed in the past, the assessment of inflammation and immune function have often been significantly limited to only one or a few inflammatory proteins, and should be expanded to include additional inflammatory proteins, cellular targets, and the association with the known symptom clusters of PTSD. Second, comprehensive assessments of inflammation before and after standard PTSD therapies need to be performed. It is imperative that we fully understand if attenuation of the behavioral manifestations of PTSD are sufficient to reverse the physiological consequences of the disease. We would suggest not limiting these types of examinations only to the immune system, but to other organ systems that are also affected by PTSD, such as the cardiovascular and gastrointestinal systems. Last, research into the mechanisms linking psychological trauma to inflammation and physiological diseases is highly warranted. While these studies will likely first occur in animal models, in depth neural, immunological, and inflammatory mechanisms need to be elucidated to understand how psychological trauma affects downstream pathology. In doing so, these investigations will likely produce novel targets for therapeutic intervention that may alter our thinking of PTSD as a disease and how we treat it. In summary, based on the emerging literature, it is our belief that PTSD patients need evaluation and treatment beyond the scope of psychiatry, and should be considered complex internal medicine patients that require complete somatic workups with comprehensive medical therapies. However, we understand that to get to this point, the field needs to fully appreciate and understand the mechanisms underlying this complex disorder so that we may view it not only as a behavioral disorder, but a systemic one.

CrediT authorship contribution statement

Tatlock H. Lauten: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Tamara Natour:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Adam J. Case:** Conceptualization, Data curation, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors have declared that no conflict of interest exists.

Data availability

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

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