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Research Highlight

Neuroimmune suppression and anhedonia in post-traumatic stress disorder: connecting central and peripheral immunity

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Immune dysregulation and anhedonia in PTSD

Post-traumatic stress disorder (PTSD) is a trauma-exposure-induced psychiatric disorder with symptoms of intrusions, avoidance, negative mood, and cognitive changes (Miao *et al.*, 2018; Compean & Hamner, 2019). The lifetime prevalence of PTSD is as high as 7% (Read *et al.*, 2005). Anhedonia is a manifestation of the lack of response to pleasurable stimuli caused by chronic stressors in PTSD (Pizzagalli, 2022). A dysregulated immune response is widely observed in PTSD patients and causes deterioration of mental health (Dh *et al.*, 2022). The evidentiary basis for the assertion that immune cells, including microglia, play a pivotal role in PTSD progression is that they release inflammatory factors and modulate neuroplasticity (Borst *et al.*, 2021). The study of the relationship between PTSD symptoms and the immune response is fundamental to the understanding of pathogenesis and drug development. A recent study by Bonomi *et al.* (2024) discovered a correlation between immune response and pleasure deficit in patients diagnosed with PTSD.

Neuroimmunosuppression linked to anhedonia

Bonomi and colleagues utilized the magnitude of the microglia marker, 18 kDa translocator protein (TSPO), as a measure of neuroimmune functionality after stimulation with the immune activator (Bonomi *et al.*, 2024). In their study, 15 PTSD patients and 15 age-matched controls were administered lipopolysaccharide (LPS) injections (Bonomi *et al.*, 2024). TSPO expression was detected by radiolabeled [^{11}C] PBR28 and positron emission tomography (PET) later (Bonomi *et al.*, 2024). The result revealed a significant reduction in TSPO response in the prefrontal–limbic circuits of PTSD patients compared to controls (Bonomi *et al.*, 2024). Lower peripheral responses to granulocyte-macrophage colony-stimulating factor (GM-CSF) were observed (Bonomi *et al.*, 2024). Moreover, peripheral C-reactive protein (CRP) levels were negatively correlated with TSPO levels, indicating an interplay between peripheral and central immune systems (Bonomi *et al.*, 2024). A noteworthy finding was that individuals experiencing anhedonia exhibited lower levels of TSPO availability in the prefrontal limbic system, both at baseline and after LPS administration (Bonomi *et al.*, 2024).

In their study, the authors used PET for *in vivo* imaging and radiolabeled [^{11}C] PBR28 to measure TSPO availability as a marker of microglial activation and dynamically observed the changes in the central nervous system (CNS) immune response in PTSD after LPS stimulation. Such *in vivo* immune response studies provide an in-depth dynamic analysis for understanding the role of neuroimmunity in PTSD. The observed suppression of TSPO availability challenges the traditional notion of PTSD as a pro-inflammatory condition (Hori & Kim, 2019), suggesting a neuroimmune suppression model that links immune dysfunction to anhedonia. These findings offer new dimensions for mechanistic research and therapeutic exploration in PTSD.

Neuroimmune–peripheral interactions

The analysis or intervention in the CNS microglia-dominated immune response is challenging due to the infiltrative nature of cells in the brain and ethical constraints regarding research. However, Bonomi *et al.*'s discovery of a correlation between neuroimmunity and peripheral immunity provides new ideas for pharmacological interventions in PTSD and for modeling the disease. The convenience of sampling peripheral blood and even pharmacological interventions far outweighs the direct modulation of the neuroimmune system.

Their study revealed a negative correlation between peripheral CRP levels and central TSPO availability, suggesting that high levels of peripheral inflammation may limit microglial activation and impair neuroimmune function. Peripheral cytokines in the blood can communicate with the brain via the vagus nerve (Jin *et al.*, 2024). Of greater concern is peripheral–central immune communication across the blood–brain barrier (BBB). In stressful environments, the permeability of the BBB is altered, allowing cytokines and immune cells (e.g. monocytes, T-cells) to cross into the brain and influence astrocyte and microglial functions (Chesnokova *et al.*, 2016; Morris *et al.*, 2015).

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GM-CSF is a key cytokine normally produced by peripheral immune cells in response to immune activation, stimulating the proliferation and activation of macrophages and dendritic cells (Bhattacharya *et al.*, 2015; Dougan *et al.*, 2019). After diffusion across the BBB, GM-CSF can bind to the GM-CSF receptor and directly activate the proliferation and immune function of microglia (Chitu *et al.*, 2021). GM-CSF also enhances the expression of TLR4 and CD14 receptors on microglia, amplifying LPS-induced pro-inflammatory responses (Parajuli *et al.*, 2012). In addition, GM-CSF induces CCR2 expression in monocytes, facilitating their migration across the BBB to brain inflammatory sites (Lotfi *et al.*, 2019; Vogel *et al.*, 2015). The study's finding of reduced GM-CSF levels in PTSD patients following LPS stimulation highlights a potential mechanism limiting both microglial activation and immune cell migration to the CNS.

Neuroimaging of PTSD anhedonia

Using radiolabeled [^{11}C] PBR28 and PET techniques, Bonomi *et al.* found that the more severe the pleasure deficit, the lower the availability of TSPO in the limbic system. The amygdala and hippocampus act as emotional control centers, working with the prefrontal cortex (PFC) to perceive, generate, and regulate emotions (Yavas *et al.*, 2019). In 2019, a study revealed a reduction in the volume of the hippocampus and amygdala in patients with PTSD anhedonia, as evidenced by magnetic resonance imaging (MRI) (Bae *et al.*, 2020). Blood oxygen level-dependent (BOLD)—functional MRI (fMRI) is an imaging technique that indirectly infers the intensity of neural activity based on changes in oxygenated hemoglobin levels (Glover, 2011). The BOLD-fMRI results suggest that there are abnormalities in amygdala–hippocampal functional connectivity and PFC activity (Lee *et al.*, 2021).

Microglia express a high level of TSPO in mitochondria upon activation (Kreutzberg, 1996). TSPO PET detection of brain inflammation is used in a variety of diseases. An increased TSPO PET signal in gray matter and the limbic system has been observed in, for example, Alzheimer's disease and mood disorders (De Picker *et al.*, 2023). PET technology uses radioligands to bind TSPO and therefore needs to take into account brain permeability, affinity, and safety. Bonomi *et al.* used a high-affinity radioligand developed by Brown *et al.* (2007). The radiotracer [^{18}F]-FEPPA, based on high brain permeability, allows higher resolution image analysis (Ko *et al.*, 2013). TSPO expression in, for example, endothelial cells and smooth muscle cells must be excluded when detecting brain TSPO. Atrial dynamics modeling is now available to exclude vascular TSPO expression (Wimberley *et al.*, 2021).

Limitations and future directions

The immunosuppressive milieu of PTSD suggested by the study results challenges views of PTSD as a pro-inflammatory disorder. Previous serum analyses and genome-wide association studies have shown elevated levels of inflammatory factors such as interleukin (IL)-1β and IL-6 in patients with PTSD (Passos *et al.*, 2015; Stein *et al.*, 2016). PTSD has also been identified as a paradigmatic example of stress sensitization, with central inflammation characterized by microglia (Biltz *et al.*, 2022). These conflicting results may stem from methodological differences. The mechanism of LPS as an immunostimulant is different from psychological stress in PTSD. A transcriptomic analysis of post-mortem PTSD patients showed significantly lower expression of the TSPO and microglia-associated genes TNFRSF14 and TSPOAP1 in women (Bhatt *et al.*, 2020). Gender differences result in different baseline levels of genes. The immune response is a dynamic process and the pathogenic loci in the PTSD brain form an immune microenvironment with differences in inflammatory state.

TSPO is a microglia-specific targeted transport protein (Uzuegbunam *et al.*, 2023). Non-invasive quantification of neuroinflammatory processes has been achieved by analyzing TSPO expression using contrast and neuroimaging techniques (Haider *et al.*, 2023). However, TSPO expression revealed only reduced levels of microglial activation, which is not yet sufficient to draw definitive conclusions about immunosuppression within the prefrontal–limbic system region. Intrinsic nerve damage in patients with PTSD reduces the selective permeability of the BBB (Sivandzade *et al.*, 2020). The variability in microglial exposure to LPS between PTSD patients and healthy controls due to factors such as the BBB was not considered in the study by Bonomi *et al.* For data processing, brain penetration should be measured with other radiotracers or other methods should be used to standardize and normalize the data.

The experiment did not include analysis of genetic or pathway differences, and future studies could collect blood samples before and after stress for metabolomics and other multi-omics analyses.

Conclusion

The innovative study by Bonomi *et al.* provides a new perspective on the study of intracerebral mechanisms of PTSD by combining neuroimmunity with peripheral immunity. The *in vivo* dynamic analysis helped to understand abnormal microglia activation in anhedonia symptoms. Future studies need to incorporate considerations such as gender, PTSD progression, data normalization, and multi-omics studies.

Conflict of interest

None declared

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