

Peer Review

Review of: "From Circuit Descriptions to Testable Mechanism Space in PTSD: A Minimal, Identifiability-Aware Computational Framework for Heterogeneous Threat Inference"

Santosh Kumar Prajapati¹

1. University of South Florida, United States

Title: From Circuit Descriptions to Testable Mechanism Space in PTSD: A Minimal, Identifiability-Aware Computational Framework for Heterogeneous Threat Inference. The manuscript provides a thoughtful and intellectually rigorous synthesis of PTSD neurobiology, integrating circuit-level mechanisms with a computational framework. The effort to formalize threat-control dynamics and contextual learning into a multi-scale model is commendable and reflects strong theoretical maturity. However, several important points need to be carefully addressed before the manuscript can be considered further.

Major Comments

1. Integration of the Orexinergic System Is Missing

While the manuscript extensively discusses noradrenergic gain (LC system) and HPA-axis modulation, it does not sufficiently address the orexin (hypocretin) system, which plays a critical role in arousal regulation, stress reactivity, and sleep-wake stabilization in PTSD.

2. I would recommend that the author explicitly integrate orexinergic projections from the lateral hypothalamus into the gain-control framework (Layer 1), particularly given orexin's functional interaction with LC-noradrenergic signaling and amygdala reactivity.

3. The pharmacological section discusses prazosin and ketamine but omits dual (non-selective) orexin receptor antagonists (DORAs), which are highly relevant in PTSD-related sleep disturbance and hyperarousal.

4. I would recommend that the author cite emerging evidence on non-selective orexin antagonists such as suvorexant and discuss their mechanistic implications within the proposed model.
<https://pubmed.ncbi.nlm.nih.gov/38185385/>. <https://pubmed.ncbi.nlm.nih.gov/33212086/>.
 5. Sleep disturbance is central to PTSD pathophysiology but is only indirectly referenced. Given the strong bidirectional relationship between sleep, extinction consolidation, hippocampal context precision (π_H), and noradrenergic gain, the manuscript would benefit from a dedicated subsection on sleep–memory–arousal interactions.
 6. The limitation section briefly mentions inflammation, but given the growing literature linking immune signaling (e.g., IL-6, CRP, microglial activation) with PTSD symptom severity and threat processing, the omission is notable. Please add a brief integrative paragraph explaining how inflammatory signaling could modulate gain parameters, synaptic plasticity, or HPA-axis feedback.
 7. The pharmacologic section is relatively narrow. I would recommend briefly discussing:
<https://pubmed.ncbi.nlm.nih.gov/40493868/>.
- SSRIs/SNRIs as first-line treatments and their possible modulation of learning parameters.
 - The interaction between noradrenergic and orexin systems in arousal regulation.
 - Emerging adjunctive strategies targeting plasticity windows.

Declarations

Potential competing interests: No potential competing interests to declare.