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Peer Review

Review of: "The Scarred Circuitry of Fear: A Computational–Clinical Synthesis of PTSD Neurobiology"

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This is an intriguing computational construct for PTSD that attempts to minimize the multiple parameters and complexity of PTSD to add translational mapping using four core elements. It compresses heterogeneity into four composite dimensions: Control (stress-fragile regulation), Context (imprecise or biased context inference), Gain (arousal-amplified expression), and Recovery (feedback and return-to-baseline). The authors should be applauded for this attempt, and the manuscript writing is quite sophisticated. There are a few key issues that should be considered.

1. How does threat processing fit into their four major concepts? Additionally, how do major features of the illness fit into their model, or are they ignored, such as fear intrusions, avoidance behaviors, social isolation, negative cognitions, and depression?
2. It would be useful in this theoretical paper to include a clinical example or two and explain how features in these examples specifically fit the model.
3. Some of the concrete examples they provide using prazosin and ketamine treatment in their models have some flaws. For example, prazosin is used as an example relating to hyperarousal and associated sleep disruption. But many studies have shown that prazosin has complex effects on PTSD. Since the publication of the Raskind large-scale RCT that showed no evidence for prazosin efficacy for distressing dreams in military veterans, a post hoc analysis of previously published data collected in veterans from Iraq and Afghanistan (Reference: Hendrickson RC, Millard SP, Pagulayan KF, Peskind ER, Raskind MA. The Relative Effects of Prazosin on Individual PTSD Symptoms: Evidence for Pathophysiologically-Related Clustering. Chronic Stress. 2021;5:2470547020979780. doi:10.1177/2470547020979780) attempted to clarify prazosin efficacy for individual PTSD symptoms on the CAPS, as defined by DSM-IV. Prazosin showed a variety of effects, with the largest significant

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effect (>1 effect size beyond placebo) for distressing dreams, insomnia, and other parameters including difficulty concentrating and anhedonia; it also trended toward efficacy for irritability. Notably, these symptoms were also of higher baseline severity in the studied population and were more likely to remain elevated after treatment with placebo. This study suggests that baseline characteristics of the patient population may determine trial outcome.

4. The referenced ketamine study also impacted parameters outside of their model. Treatment reduced PTSD symptom scores, arousal, depression, fear intrusions, avoidance behaviors, and negative ideation. They should highlight the example of how ketamine has more effects that require structured learning in the referenced study.
5. They thoughtfully included a section on a Practical roadmap: what datasets and analyses would make this

   real? Before large efforts are made using this approach, to confirm some utility of the model can be made in this manuscript using some clinical examples.

Declarations

Potential competing interests: No potential competing interests to declare.