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Peer Review

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

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Thank you for the invitation to review the manuscript “The Scarred Circuitry of Fear: A Computational–Clinical Synthesis of PTSD Neurobiology”.

This article synthesizes convergent findings across fear-circuit neurobiology — including amygdala reactivity, ventromedial prefrontal and anterior cingulate regulatory control, hippocampal context processing, and relevant stress-system and neuromodulatory mechanisms. Its aim is to formalize how these components jointly produce hallmark clinical phenomena: cue-triggered intrusions, hyperarousal, avoidance, and fear generalization with context-dependent relapse. To that end, the paper proposes a minimal, multi-scale computational framework that yields falsifiable hypotheses and can explain differential responses to treatment. The authors have done an excellent job presenting an interesting and useful theoretical proposal.

To strengthen the manuscript, I recommend adding the following clarifications and explanations:

1. Expand the explanation of HPA-axis dysregulation and note that some studies report hypocortisolemia while others report hypercortisolemia. Distinguish between basal cortisol concentrations and cortisol responses elicited by an acute stressor.
2. The dissociation between implicit and explicit memory is missing. Facilitation of implicit memory can lead to unconscious recall of stimuli, sometimes when explicit memory is impaired due to reduced hippocampal volume.



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3. In Section 5.1, “Genetic and epigenetic susceptibility,” explain what FKBP5 is. Is it the only genetic mechanism implicated?
4. In Section 5.3, clarify which ligand the “PACAP/PAC1 receptor system” responds to. The sexual dimorphism in this receptor system and how it increases female vulnerability to PTSD are not made clear.
5. At the bottom of Table 1, define the abbreviations: W_PA (P – A inhibition); W_PA (P – A suppression); g_LC; HRV; y_E; a_ext a_thre…; h; EMA.
6. Using Greek symbols to denote relationships is difficult to remember. Consider using Latin letters that more intuitively correspond to the processes represented in the equations.

Thank you for the invitation to review the manuscript “The Scarred Circuitry of Fear: A Computational–Clinical Synthesis of PTSD Neurobiology”.

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1. Expand the explanation of HPA-axis dysregulation and note that some studies report hypocortisolemia while others report hypercortisolemia. Distinguish between basal cortisol concentrations and cortisol responses elicited by an acute stressor. Here are several studies that have documented this discrepancy in cortisol concentrations:


- M. Kellner, R. Yehuda, J. Arlt, and K. Wiedemann, “Longitudinal course of salivary cortisol in post-traumatic stress disorder.,” *Acta Psychiatrica Scandinavica*, vol. 105, no. 2, pp. 153–156, Feb. 2002, doi: 10.1034/J.1600-0447.2002.01012.X.
- S. A. M. Rauch *et al.*, “Biological and symptom changes in posttraumatic stress disorder treatment: a randomized clinical trial.,” *Depression and Anxiety*, vol. 32, no. 3, pp. 204–212, Mar. 2015, doi: 10.1002/DA.22331.

- P. Pervanidou and G. P. Chrousos, “Posttraumatic Stress Disorder in Children and Adolescents: Neuroendocrine Perspectives,” *Science Signaling*, vol. 5, no. 245, p. 2003327, Oct. 2012, doi: 10.1126/SCISIGNAL.2003327.
- S. Schumacher, H. Niemeyer, S. Engel, J. C. Cwik, and C. Knaevelsrud, “Psychotherapeutic treatment and HPA axis regulation in posttraumatic stress disorder: A systematic review and meta-analysis,” *Psychoneuroendocrinology*, Dec. 2018, doi: 10.1016/J.PSYNEUEN.2018.08.006.
- J. W. Mason, E. L. Giller, T. R. Kosten, R. B. Ostroff, and L. Podd, “Urinary free-cortisol levels in posttraumatic stress disorder patients.,” *Journal of Nervous and Mental Disease*, vol. 174, no. 3, pp. 145–149, Mar. 1986, doi: 10.1097/00005053-198603000-00003.
- Mason *et al.*, “Marked lability in urinary cortisol levels in subgroups of combat veterans with posttraumatic stress disorder during an intensive exposure treatment program.,” *Psychosomatic medicine*, 2002, doi: 10.1097/00006842-200203000-00006.
- L. M. Bierer *et al.*, “Clinical Correlates of 24-H Cortisol and Norepinephrine Excretion Among Subjects Seeking Treatment Following the World Trade Center Attacks on 9/11,” *Annals of the New York Academy of Sciences*, vol. 1071, no. 1, pp. 514–520, July 2006, doi: 10.1196/ANNALS.1364.055.
- R. Yehuda, B. Kahana, K. Binder-Brynes, S. M. Southwick, J. W. Mason, and E. L. Giller, “Low Urinary Cortisol Excretion in Holocaust Survivors With Posttraumatic Stress Disorder,” *American Journal of Psychiatry*, vol. 152, no. 7, pp. 982–986, July 1995, doi: 10.1176/AJP.152.7.982.
- M. E. Pierce, “The Neuroendocrine and Performance Correlates of Posttraumatic Stress Disorder in Males and Females,” Jan. 2015, doi: 10.34917/7646024.
- Rohleder, Joksimovic, Wolf, and Kirschbaum, “Hypocortisolism and increased glucocorticoid sensitivity of pro-Inflammatory cytokine production in Bosnian war refugees with posttraumatic stress disorder.,” *Biological psychiatry*, 2004, doi: 10.1016/j.biopsych.2003.11.018.
- R. Yehuda, S. M. Southwick, G. Nussbaum, V. Wahby, E. L. Giller, and J. W. Mason, “Low urinary cortisol excretion in patients with posttraumatic stress disorder.,” *Journal of Nervous and Mental Disease*, vol. 178, no. 6, pp. 366–369, June 1990, doi: 10.1097/00005053-199006000-00004.
- M. van Zuiden *et al.*, “Associations Among Hair Cortisol Concentrations, Posttraumatic Stress Disorder Status, and Amygdala Reactivity to Negative Affective Stimuli in Female Police Officers,” *Journal of Traumatic Stress*, vol. 32, no. 2, pp. 238–248, Apr. 2019, doi: 10.1002/JTS.22395.
- J. Gill, M. Vythilingam, and G. G. Page, “Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD.,” *Journal of Traumatic Stress*, vol. 21, no. 6, pp. 530–539, Dec. 2008, doi: 10.1002/JTS.20372.

- R. Yehuda, “HPA Alterations in PTSD,” pp. 359–364, Jan. 2007, doi: 10.1016/B978-012373947-6.00737-6.
- Thaller, Vrkljan, Hotujac, and Thakore, “The potential role of hypocortisolism in the pathophysiology of PTSD and psoriasis.,” *Collegium antropologicum*, 1999, [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/1064623.

2. The dissociation between implicit and explicit memory is missing. Facilitation of implicit memory can lead to unconscious recall of stimuli, sometimes when explicit memory is impaired due to reduced hippocampal volume. For example, Lyttle et al. (2010) Conceptual and perceptual priming and dissociation in chronic posttraumatic stress disorder. The study measured perceptual priming (word-stem completion), conceptual priming (word-cue association), and related explicit symptom measures in N = 50 trauma-exposed participants and reported enhanced perceptual priming for trauma words together with reduced conceptual priming and explicit memory disturbances associated with PTSD severity and dissociation.

Brewin (2014) synthesizes multiple experiments and concludes that a functional dissociation—enhanced perceptual memory/priming for trauma material with impaired episodic/declarative memory for the same events—is consistently supported across experimental paradigms.

Wessa and Flor (2002) propose and present initial empirical confirmations of a model in which strong implicit emotional memory coexists with insufficient explicit trauma encoding, producing a dissociation that maintains PTSD symptoms.

The references are:

Lyttle NL et al. (2010) Conceptual and perceptual priming and dissociation in chronic posttraumatic stress disorder. *Journal of Abnormal Psychology.* DOI 10.1037/A0020894.

Brewin CR (2014). Episodic Memory, Perceptual Memory, and Their Interaction. *Psychological Bulletin.* DOI 10.1037/A0033722.

Wessa M & Flor H (2002). [Posttraumatic stress disorder and trauma memory--a psychobiological perspective]. *Zeitschrift Fur Psychosomatische Medizin Und Psychotherapie.* DOI 10.13109/ZPTM.2002.48.1.28.

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6. Using Greek symbols to denote relationships is difficult to remember. Consider using Latin letters that more intuitively correspond to the processes represented in the equations.

**In conclusion**, this manuscript makes a meaningful contribution to the understanding of PTSD and merits publication. The manuscript requires minor revisions.

## Declarations

**Potential competing interests:** No potential competing interests to declare.