Qeios

Peer Review

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

Fanny Saulnier[1]

1. Université Paris Cité, Paris, France

Dear Authors,

This manuscript, "The Scarred Circuitry of Fear: A computational-Clinical Synthesis of PTSD Neurobiology", in which you develop a computational model of PTSD neurobiology targeting individual patients' symptoms to address specific adapted treatments. This work is therefore significant and original but needs to be rewritten and greatly improved with major revisions:

1. **Lack of biological precision (chapters 2-5)**

I understand that the author comes from a clinical and computational background and not a preclinical one. All over the manuscript, the author should disclaim if the results are found in patients or rodents. Indeed, studies in rodents could not properly be directly linked with clinical data. It leads to a considerable lack of precision when discussing the neurobiology. However, these approximative links are not my only problematic concerns.

If I understood correctly, chapters 2-5 serve as an introduction to the computational model and define the biological variables used in the following chapters. However, when reading, it is not very clear which variables are going to be used and which parts are only observations. Those chapters are closer to a non-exhaustive list of subjects of interest in the field of PTSD than to a biological discussion on PTSD fear circuitry, as claimed. Moreover, not every biological variable discussed is used in the following computational framework. Why are they used? My advice would thus be to focus on the variables that matter biologically and that are used in the clinical framework, and to discuss them more accurately.

For example:

doi.org/10.32388/4BLJE9

- In PTSD patients, amygdala activity is indeed heightened in response to contextual-fear cues. However, multiple reviews argue that we observe more differences in amygdala functional connectivity than in its reactivity itself (*Davis, 2024*). It would have been essential to discuss it.
- The prefrontal cortex is a key structure in the fear extinction circuitry, but it is also involved in fear expression, in relation with the amygdala (as hinted in the manuscript). Its role in fear expression (in relation with the periaqueductal grey) should have been mentioned. Moreover, the vmPFC and the dACC have opposite roles in fear extinction memory (*Pizzimenti and Lattal, 2025; Pitman et al., 2012)*. Not discussing it considerably weakens the argument about the role of the PFC in memory extinction.
- As stated, only some of the mechanisms explained in the manuscript are used in the computational frameworks that follow. Thus, why discuss them? Why discuss polygenic risk factors? Why FKBP5 as an example and not another one? Similarly, while it is written that early life adversity is a PTSD risk factor, it is then not used in the computational model, nor put in relation with the HPA axis modulation in PTSD, while it is known that early life adversity modulates adult cortisol responses (*Jopling and Le Moult, 2023)*.
- In the discussion regarding the modulation of NMDA signalling in PTSD physiopathology, only one trial with ketamine is discussed. However, these results are not exploited conceptually. What does this result tell us about glutamatergic signalling in PTSD patients? How does NMDA signalling influence fear learning? How is it linked with fear circuitry? How to implement it in the following clinical framework?
- The discussion on sex differences is interesting and significant, as women are more at risk of developing PTSD than men. However, while PACAP signalling is mentioned, its role in PTSD physiopathology should be explained. Moreover, sex differences have also been identified in brain structures and connectivity linked to PTSD, and estradiol levels have been shown to modulate fear extinction in women (*Day and Stevenson, 2020*). Thus, the discussion on sex differences should have either been more precise (and the role of PACAP developed) or more extensive.
- In the abstract, the author claims to "*formalize how these components jointly generate hallmark clinical phenomena*". This is, however, not the case, as the author only describes circuitry modification in PTSD but never links them with any behaviour nor symptom. I suggest creating a table classifying circuitry modification, imaging results in PTSD patients, and the symptoms and clinical subtypes they are linked to, with appropriate references (see *Lanius et al., 2018 and Ferrera et al., 2023* for review).

Moreover, chapters 2-5 lack critical references. The author only uses 25 references, which is not sufficient for a review on such a broad subject. Every claim must be justified by a reference, which is not always the case in this manuscript: for example, "*In PTSD noradrenergic hyperreactivity has been linked to hyperarousal, sleep disturbance and heightened startle...*" is not backed up by any reference. There are no references in Table 1; every link between the interpretation, the predicted signature, and the measurement proxy should be backed up by at least one reference per line. I urge you to add one column titled "References".

Almost all the references are older than 2020. However, precious reviews have since been written on the biology of fear consolidation, extinction, and its role in PTSD (*i.e., Bouton et al., 2021; Ferrara et al., 2023; Ressler et al., 2022; Shalev et al., 2024...*). Using and quoting them would have allowed for more accurate and precise arguments, as explained above. Lastly, there is a formatting mistake in the citations, as the author mixes two different citation patterns.

2. **Lack of clarity in the computational part (chapters 6-11)**

The computational-clinical framework is out of my scope of expertise. I highly advise that this paper be reviewed by a biostatistician or a computational neuroscientist. However, here are some suggestions to make it easier to understand:

- The overall aim of the framework should be extensively explained before Table 1 and in greater detail.
- All of the variables should be in Table 1. It would be less confounding than to have half of the variables in the table and the other half in the text.
- The author never suggests that his model should be tested. The author should test his model with available datasets or suggest others to do so.

Moreover, the framework allows the identification of clinical subtypes. Do they really exist in the clinic? Could the author provide references accounting for them? Moreover, the author seems to only account for two of them. However, multiple other subtypes exist, and it has been reviewed that each type could trigger different brain regulation, notably regarding the brain structures (*Lanius et al., 2018*). Why does this paper only account for two? How to implement them in your model?

Resilience factors are thoroughly discussed at the beginning of the paper but are not part of the computational model. How could the author account for them?

3. **Formulation**

The English could be overall improved. Some formulations, such as "*failure to terminate the stress response*", do not make sense biologically nor grammatically. Many other sentences are not understandable; please rewrite them. Lastly, many formulations are assertive without any references, such as "*this paper rejects biomarker determinism*". This sentence is more a prejudice than a scientific conclusion.

Conclusion:

This manuscript provides an interesting framework on PTSD neurobiology to identify clinical subtypes. However, chapters 2-5 should be thoroughly rewritten with more precise arguments and adequate references.

Declarations

Potential competing interests: No potential competing interests to declare.