The strengths of the proposal are the importance of the investigated topic and the solid experimental plan that is likely to advance our understanding of neuronal mechanisms that operate in PTSD. Combining the manipulation of neuronal pathways activity with behavioral tests is a powerful approach for determining cause-and-effect relationships between specific brain activity and PTSD-like behavior. Additionally, as in my earlier email, the preliminary results and the group’s established track record in this field further strengthen the proposal. Below, I have outlined a few areas where the proposal could be improved and some suggestions for addressing these points.

1. Structure

The structure of several sections of the proposal does not follow the conventional structure of a grant proposal and requires a reviewer to spend time looking for specific information they might expect to be presented elsewhere. One noticeable omission is the lack of an overview of the experimental plan. The three aims of the project should be presented in the Scientific Abstract and again under section B: Research Objectives and Expected Significance.

Below, I have highlighted structural problems in various sections of the proposal.

SCIENTIFIC ABSTRACT

This section would be more effective if it followed the standard structure. In the attached document, ‘Scientific Abstract,’ please find a suggested revised version of this section. I used information from various sections of the proposal to construct the abstract, and because of the extensive revisions, it was impossible to use track changes in a meaningful way. Several points in the Scientific Abstract require your input: I have labeled these in blue font and square brackets.

A) SCIENTIFIC BACKGROUND

1. It is highly recommended to start this section with a clear (short) overview paragraph that sets the stage for the proposal. For example:

This study aims to substantially advance our understanding of the molecular mechanisms that contribute to […PTSD]. PTSD is […common and serious]. [The study is original and innovative…] This project builds on the strong track record of [the research group in this field].

1. It would be useful to introduce the HPA axis here.

B) RESEARCH OBJECTIVES AND EXPECTED SIGNIFICANCE

1. This is usually a shorter section that states the general hypothesis/ objective followed by the specific study aims. The preliminary experiments do not fit here very well. In the revised version, they have been moved to section C under Aim 1.
2. You could further modify this section by adding a specific subheading, ‘The expected significance.’ It is important to suggest how this project can lead to future studies, and although the ISF only funds basic science projects, it is reasonable to indicate potential clinical relevance.

C) DETAILED DESCRIPTION OF THE PROPOSED RESEARCH:

1. The subheadings in this section were labeled with capital letters and titles (for example, ‘A) The Neurobiological Basis of PSS-induced Resilient and Vulnerable Phenotypes Linked to the ZI). In the revised version, I suggested labeling the sections under ‘Aim 1,’ ‘Aim 2,’ etc.
2. The preliminary results that were presented under section C now appear here under Specific Aim 1a. The numbering of the following aims has been changed accordingly.
3. The structure of sections Aim 2 has been revised: Specific Aims B2, B3, B4, and B5 are now under Aim 2b to avoid repetition.
4. Formatting
5. Please change the page margins: it should be 2 cm on all sides. I have corrected it in the attached document, but if you use a different file, please correct the margins.
6. Some figures are too wide and do not fit into the page.
7. The indentations are inconsistent, with first-line indentations in some paragraphs and not others. This can be fixed when the document is closer to its final form.
8. Inconsistencies
9. The behavioral tests used in the study are the EPM, ASR, and freezing response to trauma reminders. However, when referring to behavioral outcomes, the text is inconsistent and mention*s ‘..fear, anxiety, and PTSD-related behaviors,’ ‘stress an*d anxiety responses to PSS,’ ‘PTSD-related behaviors,’ and other descriptors. It would be best to use the same nomenclature throughout.
10. PSS protocol—In several places, the duration of the exposure is 10 minutes, and in others, it is 15 minutes (including the red arrows in the figures).
11. Figures

**Figure 1**

1. The diagram is small and difficult to read. Consider increasing the diagram size and presenting the legend underneath it.
2. EMP should be corrected to EPM.
3. The published figure (Neuropharmacology 2012) had a horizontal line dividing sections A and B. It was easier to understand the figure with the line; without it, ‘A’ appears to refer only to the box on the left. I suggest you add the line here.

**Figure 6**

1. This is a helpful figure that could perhaps appear earlier under Specific Aim 2. The diagram could be improved.
2. Other comments
3. The knowledge gap the project aims to address could perhaps be specified more explicitly under section B (Research objectives and expected significance). The literature review quotes studies that found that ZI is involved in fear responses: ‘…suppress generalization and enhance fear extinction,’ ‘…discriminating fearful from non-fearful stimuli,’ and others. Could you specify what is already known about the ZI role in the pathophysiology of fear and what the gap is?
4. The proposal suggests that ZI operates in parallel to the prefrontal cortex-amygdala-hippocampus circuit in processing fear and anxiety. Is ‘in parallel’ specific enough? Do you hypothesize an upstream-downstream relation? Or a communication mechanism between the two pathways?
5. In several places, ZI is hypothesized to contribute to the pathophysiology of fear (or maladaptive responses to threat). Do you also hypothesize that it plays a role in normal physiology? Has this role already been established, and are you only testing pathophysiology here?
6. The proposal uses a long list of abbreviations. It is generally recommended to keep the number of abbreviations to a minimum, but I am not sure it is possible here.
7. The epidemiology of PTSD is only presented very briefly and generally(…millions of people globally.) It might be good to include some estimates of PTSD prevalence while acknowledging that this is a basic science project.