Author's response to reviews

Title: The relationship between glucocorticoid receptor polymorphisms, stressful life events, social support, and post-traumatic stress disorder

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Author's response to reviews: see over
Dear Professor Chua:
Thank you for sending us the reviewers’ comments regarding our manuscript (MS: 9653087361251514), entitled “The relationship between glucocorticoid receptor polymorphisms, stressful life events, social support, and post-traumatic stress disorder”. In particular, I would like to express our appreciation to you and the referees for suggesting how to improve our manuscript according to the valuable comments and criticisms, as well as providing important guidance for our research. We have studied the comments carefully and have made corrections which we hope will meet with your approval. The revised parts are underlined in red. We hope the revised manuscript is acceptable for publication. The revisions are addressed point-by-point below.

Response to the reviewer’s comments:
Reviewer #1:
1. The formatting of this article is a disaster, there are spaces lacking between words and it is almost impossible to read. Please correct this.
Response: First, we would like to thank the reviewer for the critical and insightful comments. We have made corrections with assistance from a professional editing service.
2. Major drawback of this study is the lack of replication of the results. It is a golden standard to replicate genetic findings in an independent sample to confirm the results especially for GxE studies, the authors should consider replicating these results in another sample.
Response: We would like to thank the reviewer for the comments. The lack of replication of the results is a major limitation in our study. Because we could not collect an independent representative sample over a short period of time, we could not confirm the results. We are currently collecting more samples in collaboration with other clinical institutions.
3. Page 6 "Trauma exposure" - the TLEQ combines different types of trauma exposure. It is clear from recent seminal studies that the timing and timing of the trauma exposure is essential for etiology of PTSD. The authors should divide the trauma exposure into early/childhood trauma and late/adult trauma. It would be interesting to see if these results remain consistent even after this distinction.
Response: We followed this suggestion and divided trauma exposure into childhood trauma and non-childhood trauma (primary adult trauma). We found that adults with childhood trauma or non-childhood trauma in the high- and medium-risk groups were significantly more likely to have PTSD that those in the low-risk group, which is consistent with reports in the entire population.
4. Page 7 lines 191-197 - Criteria for selecting these SNPs needs to be better justified. It is not clear to me why these 3 SNPs were used and why not others.
Response: We apologize for the confusion and have revised the details regarding the selection of the SNPs.
5. Page 10.11 lines 282-289 - the authors have divided the findings into 3 groups with the last group being "all others", however this is a large group with over 600 samples,
so it would still be worthwhile further stratifying this group into distinct combinations of risk genotypes and environmental factors and these results are of interest to the reader.

Response: We re-analyzed the data of the last group "all others" and added the results of combinations of risk genotypes and environmental factors in the revised manuscript.

6. Page 7 line 179-80 - "75% percentile used as a cutoff.." - based on what criteria? Authors should provide appropriate references here.

Response: The criteria were based on the previous study. We added the references in the Methods section.

7. Page 7 line 248 - "It is noteworthy..." - I believe this is not noteworthy but rather expected and has been described in many previous studies.

Response: We apologize for the errors and have made corrections.

Reviewer #2:

1. The authors used DSM-IV criteria for PTSD. They should update their text to relate the findings to DSM-V criteria and in the description of PTSD by DSM-V standards.

Response: We would like to thank the reviewer for the comments. We reappraised the PTSD patients using DSM-V standards, and revised the description of PTSD diagnosis.

2. There is a bias toward significantly more males in the PTSD group and more females in the controls. The authors should address whether this is a problem for the validity of the findings. Is there any gender bias in stress/gene/environment interactions?

Response: Although the number of participants by gender was different in the two groups, no significant difference existed based on a chi-square test. We considered no gender bias and did not address the limitation in our study.

3. It's not clear to me how or why the factors in Table 1 are adjusted for age.

Response: Most previous studies have shown that the likelihood of encountering traumatic events increases with age. Thus, we adjusted the confounding factor when we analyzed the effect of the number of traumatic events.

4. There is no information about the trauma type. It would be helpful to know if, for example, there is a differential gene/environment effect of assault/rape based PTSD versus combat PTSD. Indeed, there is no mention of how PTSD occurred in this population. Some mention of the nature of the trauma events would be helpful.

Response: We would like to thank the reviewer for the critical and insightful comments. Considering the reviewer’s suggestion, we have added information regarding the trauma type in the Results section. Because of the small sample size for each type of trauma, we did not analyze the differential gene–environment effect by different trauma types and we have addressed this limitation in the Discussion section.

5. I find it odd, and perhaps a bit curious, that 18.2% of the PTSD subjects described their trauma as "moderate", not severe. Perhaps a post-hoc analysis of this PTSD subgroup versus the remaining PTSD subjects that described their trauma as "severe" might reveal a relation between genetics, life history and the magnitude of their...
perceived trauma intensity.
Response: We would like to thank the reviewer for the critical and insightful comments. As per your comments, we re-analyzed the data and found an existing relationship between genetics, early trauma exposure, and the number of traumatic events. Another explanation was that the stressful life event questionnaire only measures daily negative life events, not including major trauma events, such as combat and natural disasters.

Reviewer #3:
1. The authors provide evidence for connections between GR polymorphisms, trauma, social support and PTSD. This paper exhibits sound methodology and results and provides new information to the field.
Response: We would like to thank the reviewer for the comments.

We have tried to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We have not listed the changes, but have marked the changes in red in the revised paper. We greatly appreciate the Editor/reviewers’ suggestions and comments, and hope that the corrections will meet with approval.

Warmest regards
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