March 24, 2018

Dr. Larry Cahill  
Associate Editor  
Journal of Neuroscience Research

Resubmission: MS number JCP-FA 16-95

Dear Dr. Cahill,

We are pleased to send you our revised manuscript, “A role for gonadal hormones in HPA-axis and SNS reactivity to psychosocial stress.” We are grateful for the reviews and happy to learn that the reviewers acknowledged the potential contribution of our manuscript.

We followed the reviewers’ recommendations and made the following changes in the manuscript using the Track Changes format:

Associate Editor:

* We have addressed the need for providing a clear definition of "responders" (see our reply to reviewer X)
* We corrected the typographical error in the axis label of Fig. 2. (p. )

Editor in Chief:

* We have described the demographics of the participants and reported the exclusion criteria to participate in the study (p. )
* We included a full title page with contact information
* We uploaded figures separately using the TIF format
* We uploaded a graphical abstract
* We added a conflict of interest statement and a statement regarding the authors' contributions (p. )
* We will be happy to present our data upon acceptance

First reviewer:

* We added more background literature on the SNS response to stress (p. 3)
* We provided a rationale for the relationship between progesterone and the HPA-axis/SNS response to stress (p. 5–6)
* We clarified the number of responders and non-responders (p.
* We have omitted the correlations between sex hormones and cortisol in each group given the small N in each group
* Given the change of the transformation method, the correlation between sex hormones and sAA reactivity to stress was insignificant; therefore, the correlation was not presented in a table or a figure
* Reviewer 1 suggested discussing our finding in the context of the Jacobs and Goldstein et al. findings "on the lower brain response to stress in high versus low estrogen group of women". We followed the reviewer's recommendation and further discussed this issue in the discussion (p. 19)
* We provided an explanation for the differences in cortisol versus sAA response to stress (p. 21–22)
* We replaced the word “however” in another suitable phrase (p. 5)
* We corrected the mistaken double use of the word “second” (p. 21)
* We corrected “similary” into 'similar' (p. 22)

Second reviewer:

* In the abstract, we have changed the report regarding the current findings in alignment to the statistical changes recommended by the reviewers (p. 1)
* We cited the suggested studies and meta-analysis regarding the HPA-axis activity among different groups (p. 4)
* We added “axis” wherever we referred to HPA
* We corrected the order of the presentation of the end products of both stress systems (p. 3)
* We added a suitable citation to the report regarding cortisol and the HPA-axis (p. 3)
* We specified the results that decreased, increased, and did not change (p. 4)
* We cited another study regarding the sAA reactivity to stress and the role of sex and the menstrual cycle (p. 5–6)
* We clarified ADHD (p. 7)
* We have addressed the choice of testing early in the morning as the sampling schedule in the present study (p. 7) and addressed the choice as a limitation in the discussion (p. 22)
* We addressed the absence of a control group as a limitation (p. 23)
* We have elaborated on the lab analyses (p. 8–9)
* We clarified JCI (p. 9)
* We omitted the report regarding state anxiety
* We reanalyzed the data using log transformations (p. 10–17)
* We used 1-tailed significant values in Pearson's correlations since we had a rationale for direction in our hypotheses regarding the role of sex hormones on HPA-axis and SNS reactivity to stress
* We italicized p throughout the MS
* Reviewer 2 suggested presenting cortisol reactivity results for all participants first followed by separate results for responders and non-responders. We followed this suggestion and provided these analyses in the result section (p. 12–14)
* Given the change in the transformation method, the timeXgroupXprogesterone interaction was no longer significant; therefore, the interaction was omitted from the report
* We performed the correlations between sex hormones and cortisol reactivity for the total sample and separately for responders and non-responders (p. 14–15)
* We changed "insignificant" into "not significant" (p. 15)
* We aligned the discussion to the changes performed in the introduction
* We corrected Reschke-Hernández et al., 2017 citation (p. 17)
* We corrected the mistaken double use of the word “second” (p. 21)
* We clarified HRT (p. 23)
* We changed the data presented in table 1 into raw data (p. 12)
* We changed the cortisol units from ug/dL into nmol/L throughout the Methods and fResults sections

Third reviewer:

* Given the change in results section regarding the presentation of the whole sample findings and then separately for responders and non-responders, the abstract has been changed accordingly (p. 1)
* Reviewer 3 pointed out that the introduction is too long. However, given the elaborations requested by the reviewers, we were unable to address this comment
* Reviewer 3 provided suggested studies to cite regarding stress responses in different groups. We accepted these suggestions and incorporated the studies in the Introduction (p. 4–5)
* We provided the relevant information regarding the OC women (p. 7)
* We addressed the sampling schedule in the methods (p. 7)
* Reviewer 3 indicated that the intra-assay CV was higher than the inter-assay CV for testosterone. He was right; it was a mismatch between the values and was corrected (p. 8–9)
* Reviewer 3 asked whether saliva samples assayed in duplicates. No, only the calibration curve in every run was performed with duplicates.
* We addressed the single measure of sex hormones as a limitation (p. 22)
* We provided further details for the TSST and included the suggested meta-analysis for more details (p. 10–11)
* We used a liberal definition of responders, whereas some studies used more conservative definitions of responders. We have performed the analyses following the conservative definition of 1.5 nmol/L (following Miller et al., 2013 findings) and replicated the results. Given the small N in responders, we have adopted the liberal definition. Furthermore, we applied reviewer 3’s comment and provided the requested statistics regarding the responders in the results (p. 12–15)
* We included the suggested references for cortisol peaks (p. 11)
* We added the relevant tests and statistics for the Post-hoc analyses (p. 12–15)
* We changed all tables and figures into raw data (instead of transformed data)
* We computed Chi2 to examine the distribution of responders among groups (p. 11)
* Given the change in the transformation method, the timeXgroupXprogesterone interaction was no longer significant and therefore omitted from the report
* We accepted reviewer 3’s suggestion and omitted the correlations between sex hormones and cortisol reactivity among groups
* We omitted the report regarding state anxiety

We believe that we have addressed all the issues raised in the reviews and hope that you will find the article acceptable for publication in the *Journal of Neuroscience Research*.

We thank you again and look forward to hearing from you,

## Efrat Barel, Randa Abbu-Shkara, Raul Colodner, Rifat Masalha, Lila Mahagna, Or Chen Zemel, and Ami Cohen