Author’s response to reviews

Title: Hypothalamic-pituitary-adrenal axis functioning and dysfunctional attitude in depressed patients with and without childhood neglect

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Author’s response to reviews: see over
Cover letter

Dear Editor,

Please find our point-by-point responses to each of the reviewers’ suggestions and comments below. We thank you and the reviewers for your helpful comments, which we feel have substantially improved the manuscript.

We have highlighted all changes in red in the revised manuscript.

We have ensured the revised manuscript conforms to the journal style.

We have edited our revised manuscript in language to improve the style of written English by the branch office of Edanz editing company which advised by Elsevier company in China (www.liwenbianji.cn). It is more easy and convenient for us to pay for the editing.

We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Hongjun Peng

Responding to the reviewer #1 Sarah Doucette

Thank you very much for your careful review.

The major revisions are shown in red in the revised manuscript.
The authors present a study examining the relationship between self-reported childhood neglect, the cortisol awakening response, and dysfunctional attitudes in patients with depression compared to controls with no depression. The design and methodology appear sound; however, several aspects could be elaborated on to help the reader interpret the findings.

Major Compulsory Revisions:

Comment 1:

The authors make no mention of the age, sex, or any other demographic component of the study sample. Although it is reported that there is no difference on these variables between the groups and that the control group was age and sex matched, it is still important to report these variables for comparisons across other studies. Was the sample an elderly sample or in early adulthood? This makes a large difference when interpreting the findings. A mean age, and distribution of sex must be reported.

Response: Thank you for your helpful suggestions, the authors have supplemented the description of the age, sex and other demographic component of the study sample. See the words in red in the section of Methods. The ages of the depressed patients and healthy controls are between 18 and 45 years old in our study. We eventually had
28 patients with childhood neglect (mean age, 28.87 ± 6.28 years; mean disease course, 21.68 ± 22.12 months; male/female, 15/13) and 30 patients without childhood neglect (mean age, 28.37 ± 8.27 years; mean disease course, 25.48 ± 19.06 months; male/female, 16/14). 29 sex- and age-matched healthy controls without childhood neglect (mean age, 27.87 ± 4.28 years; male/female, 15/14) and 22 healthy controls with childhood neglect (mean age, 28.37 ± 5.28 years; male/female, 12/10).

2) How many patients were originally recruited, and was there attrition? Do the authors have any information on those subjects who dropped out (if any)?

**Response:**

We originally recruited 124 depressed patients. The Childhood Trauma Questionnaire (CTQ) was used to evaluate childhood trauma. Childhood neglect included emotional and physical neglect and the co-occurrence of both of them according to the subscale scores of the Childhood Trauma Questionnaire (CTQ). The cutoff score for moderate-severe exposure was set at ≥15 for emotional neglect, ≥10 for physical neglect, and ≥20 for the coexistence of both of them. We excluded any other type of child trauma (any other CTQ subscale scores were required to be lower than 8). According to the cutoff values, after excluding subjects whose salivary samples were polluted by minor bleeding in the oral cavity, or samples that were collected after having breakfast, drinking something or brushing teeth during the first half hour after awakening, we had a total of 28 patients with childhood neglect and 30 patients without childhood neglect (excluding any other type of trauma). See the
words in red in subjects section.

3) Tables 1 and 2 require major revisions.

TABLE 1: It is not clear which groups the authors are comparing. Please indicate what the p-value is representing. Please revise accordingly. For clarity, could the authors please re-label the groups to something more informative than G1, G2, etc. The title of the table could also be revised to be clearer. For example, differences in HPA axis functioning, DAS, and SSRS between depressive and control groups with and without childhood neglect.

TABLE 2: It is not clear what values the authors are presenting under each column. Is it the difference in scores between the groups? A more clear way of presenting these findings would be to present the mean values for each group separately then the p-value following these estimates horizontally. Please revise this table to more clearly articulate the results.

**Response:**

Thank you for your good suggestions. We have revised the Table1 and Table2 in the revised manuscript.

**Table1. Differences in HPA axis functioning, DAS, and SSRS between depressed and control groups with and without childhood neglect**

<table>
<thead>
<tr>
<th></th>
<th>CWOCN (n=29)</th>
<th>DWCN (n=28)</th>
<th>DWOCN (n=30)</th>
<th>CWCN (n=22)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA axis</td>
<td>6.82±2.81</td>
<td>8.76±2.43</td>
<td>4.84±2.73</td>
<td>7.68±1.66</td>
<td>5.92</td>
<td>0.001</td>
</tr>
<tr>
<td>functioning(n mol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS</td>
<td>114.21±21.38</td>
<td>159.72±31.28</td>
<td>139.17±28.87</td>
<td>142.20±26.3</td>
<td>25.42</td>
<td>0.000</td>
</tr>
<tr>
<td>SSRS</td>
<td>40.18±6.33</td>
<td>31.72±6.94</td>
<td>30.36±6.72</td>
<td>41.23±8.52</td>
<td>9.01</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Table 2. Differences in HPA axis functioning, DAS scores between any two groups of healthy control groups, depressed groups with and without childhood neglect

<table>
<thead>
<tr>
<th>Comparison between the two groups</th>
<th>HPA axis functioning (nmol/l)</th>
<th>p</th>
<th>DAS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CWOCN</td>
<td>6.82±2.81</td>
<td></td>
<td>114.21±21.38</td>
<td></td>
</tr>
<tr>
<td>DWCN</td>
<td>8.76±2.43</td>
<td>0.067</td>
<td>159.72±31.28</td>
<td>0.000</td>
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<td>DWOCN</td>
<td>4.84±2.73</td>
<td>0.048</td>
<td>139.17±28.87</td>
<td>0.000</td>
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<tr>
<td>CWCN</td>
<td>7.68±1.66</td>
<td>0.29</td>
<td>142.20±26.3</td>
<td>0.000</td>
</tr>
<tr>
<td>DWCN</td>
<td>8.76±2.43</td>
<td></td>
<td>159.72±31.28</td>
<td></td>
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<tr>
<td>DWOCN</td>
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<td>0.000</td>
<td>139.17±28.87</td>
<td>0.000</td>
</tr>
<tr>
<td>CWCN</td>
<td>7.68±1.66</td>
<td>0.59</td>
<td>142.20±26.3</td>
<td>0.006</td>
</tr>
<tr>
<td>DWOCN</td>
<td>4.84±2.73</td>
<td></td>
<td>139.17±28.87</td>
<td></td>
</tr>
<tr>
<td>CWCN</td>
<td>7.68±1.66</td>
<td>0.007</td>
<td>142.20±26.3</td>
<td>0.881</td>
</tr>
</tbody>
</table>

CWOCN=healthy control without childhood neglect; DWCN=depression with childhood neglect; DWOCN =depression without childhood neglect; CWCN=healthy control with childhood neglect; HPA axis functioning= cortisol concentrations at 30 minutes after awakening -cortisol concentrations at awakening; SSRS=Social Support Rating Scale; ANOVA= Analysis of Variance; p<0.001 represent significant differences statistically.

4) Do figures 1 and 2 represent the entire sample? Please indicate which subjects these figures represent?

Response: Yes, figures 1 and 2 represent the entire sample; we have indicated it clearly in the title of the figures in the revised manuscript.

5) The authors need to be careful in over interpretation of the findings. The findings and the nature of the analysis do not lend knowledge of effect modification of SSRS. Suggesting that SSRS might modify the severity of depression resulting from
childhood neglect is incorrect. A correlation between SSRS and HAMD scores does not indicate this. Similarly in your conclusions, please omit the statement “social support can adjust depression associated with childhood neglect”, as this is not valid based on the results.

**Response:** Thank you, the authors have revised the interpretation of the findings in the corresponding section according your suggestions. See the words in red. In addition, we have omitted the statement “social support can adjust depression associated with childhood neglect”.

6) Please elaborate your limitations section. There are several limitations that need mentioning including the following:

a) The self report nature of the measures used, particularly the measure of childhood neglect. Were the patients in depressive episodes when completing these measures? The authors need to comment on how this may have biased the findings as well as the limitations of using a self report measure of early trauma.

b) The very simple unadjusted analyses.

c) Potential unmeasured confounders, particularly associated with the cortisol collection.

**Response:** Thank you for your helpful suggestions; we have revised the limitations section. See the words in red in limitations section.

Further research should duplicate the results of the current study in a larger sample and with an optimized method of sampling over five time points (0 min, 15min, 30 min, 60 min, and 120 min).
45min, 60min after awakening) for cortisol collection. There are several potential unmeasured confounders known to be associated with cortisol collection, for example, compliance and sleep quality. In addition, the CTQ was used to measure childhood trauma; the self-report nature of this measure may have caused recall bias. We tried to overcome this problem by obtaining information about the subjects’ early life experiences from their first relatives. Finally, we suggest that more advanced statistical methods and a more powerful p-value correction should be performed in future research of this topic.

Minor Essential Revisions

1) The authors label the control groups as “normal subjects” in their abstract.

Please change this to control subjects. Labeling groups as normal and not normal runs into issues of ethics.

Response: Thank you, the authors have change “normal” to “control” in the revised manuscript.

2) Please state where the sample was from in the methods and in the abstract.

Response: The authors have supplemented the description in the methods and in the abstract. See the words in red.

3) Can the authors please explain how the controls were recruited in the methods section? Are there any possible selection biases associated with how they were recruited?

Response: The healthy controls were recruited in local community by advertisement;
each healthy subject was selected randomly and must meet the inclusion criterion.

4) Are there any validation studies available on the social support rating scale used? The authors do not comment on the reliability or validity of this scale is there a reason for this?

Response: yes, SSRS has been used widely, and has good reliability or validity in china[1-3], therefore, we did not comment on the reliability or validity of this scale in this study.

References:


5) Cortisol methodology: Do the authors have any information on the sleep quality, or current mood state when subjects were completing the cortisol collection? These are major potential confounders. Were the depressive patients in a current episode, or were they in remission? What about BMI, as this is also associated with elevated cortisol.

Response: Yes, the depressed patients were in a current episode from the inpatient
and outpatient units of Guangzhou Psychiatric Hospital, Affiliated Hospital of Guangzhou Medical University. We had asked the information on the sleep quality, or current mood state when subjects were completing the cortisol collection. The subjects suffering from insomnia, serious mood disorder or working the night shift had been excluded. Yes, BMI is also associated with elevated cortisol, further related analysis would be done in future study.

6) The legend of table 2 indicates healthy control without childhood trauma. I am assuming this is a typo and should be neglect?

Response: the authors have changed “trauma” to “neglect” according to your suggestion.

7) The manuscript should be edited by a native English speaking individual.

There are several grammatical errors, and the language could be improved for clarity.

Response:
Thank you, the revised manuscript has been revised by the branch office of Edanz editing company which advised by Elsevier company in China (www.liwenbianji.cn).

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published
**Response:**

Thank you, the revised manuscript has been revised by the branch office of Edanz editing company which advised by Elsevier company in China (www.liwenbianji.cn).

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests related to this manuscript.

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**Responding to the reviewer** Qingrong Tan

Thank you very much for your careful review of our manuscript.

The major changes in the revised version of the manuscript are shown in red.

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**Reviewer's report**

**Title:** Hypothalamic-pituitary-adrenal axis functioning and dysfunctional attitude in depressive patients with and without childhood neglect

**Version:** 1 **Date:** 2 January 2014

**Reviewer:** Qingrong Tan

**Reviewer's report:**
Major points

Comment 1:
The description was very confused and lack of English logic, for example, author described “At present, many studies have shown that patients with depression have hyperactivity in HPA axis functioning, suggesting that HPA axis hyperactivity may be the outcome of childhood trauma and a predisposing factor to depression rather than the outcome of depression [1].” In addition, they only cited one reference to present “many studies”.

Response:
Thank you for your helpful suggestions, we have revised the description you mentioned. See the words in red in the first paragraph.

Comment 2:
one study reported decreased cortisol awakening response after early loss experience [12], but another that found parental loss was associated with increased cortisol awakening responses[13].” is a grammatically wrong sentence. It might be “one study reported that the cortisol awakening response was decreased after early loss experience [12], but another study found that parental loss was associated with increased cortisol awakening responses[13] ”.There were so many similar errors in the whole manuscript!

Response: Thank you. We have revised the grammatically wrong sentence according to your suggestion. See the words in red in the first paragraph.
Comment 3:

Two-way ANOVA may be more suitable for the analysis of results, and the analysis method of ANOVA should be mentioned. The method of Pearson correlations was used only when the data was normal distributed, so the authors should testify the normal distribution of the data.

Response:

Thank you for your helpful suggestions, we have revised it according to your suggestion. See the words in red in the section of Statistical analysis. In our study, we have testified the distribution of the data, and found it was normal distributed.

Minor points:

Comment 4:

The references were not consistent in the manuscript, such as page 3, line 2 “adulthood[1-6].” and line 4 “in depression [7, 8].” I think there should be a space between “adulthood” and “[1-6].”

Response:

The citations have been improved in the revised manuscript according to your suggestion. Thank you!

Comment 5:

There are many grammar mistakes in the manuscript.
Response: Thank you for your careful review; we have corrected the mistakes in the revised manuscript.

Level of interest: An article of limited interest

Comment6:

Quality of written English: Not suitable for publication unless extensively edited

Response:

Thank you, the revised manuscript has been revised by the branch office of Edanz editing company which advised by Elsevier company in China (www.liwenbianji.cn).

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: