Author’s response to reviews

Title: Serum brain-derived neurotrophic factor concentrations and personality traits in patients with major depression

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Author’s response to reviews: see over
Reviewer 1: Dr. Alessandra Minelli

- Major Compulsory Revisions

1) Methods Subjects
   a) In the description of MDD sample the authors wrote “All patients were on antidepressant medication, but were not responding to their current medication.” Do you have enough treatment information for have the opportunity to define the patients (or a number of them) as treatment resistant depressed patients?
   
   **Reply to the comment:** All patients have been treated before admission the hospital. The adaptation of admission was determined by each psychiatrist. Thus, we do not have enough information to define the patients as treatment resistant depression.

   b) A clinical description such as presence of psychotic symptoms, comorbidity with anxiety or personality disorders, age of onset, Percentage of smokers etc., is needed.
   
   **Reply to the comment:** We described more clinical information suggested by reviewers. We added the sentence below in “Subjects” of “Methods”. A mean age of onset was described in Table 1. We do not have complete information of comorbidity with anxiety or personality disorders.
   “Psychotic symptoms were present in 19 patients. Twenty-five patients were smokers.”

   c) Insert in the description of the sample also chronic physical problems, such as hypertension, and relative treatments.
   
   **Reply to the comment:** We described clinical information about chronic physical problems. We added the sentence below in “Subjects” of “Methods”.
   “As chronic physical problems, 20 patients had hypertension (HT), 11 patients had hyperlipidemia (HL) and 8 patients had diabetes mellitus (DM).”

2) Results
   a) The authors should be include putative correlation with BDNF and TCI scales and subscales with all possible sociodemographic and clinical variables (presence of psychotic symptoms, comorbidity with anxiety or personality disorders, age of onset, education, percentage of smokers, physical problems, treatments, BMI and so on) in particular with well-known affecting variables (such as BMI).
   
   **Reply to the comment:** We analyzed correlations between BDNF and possible variables, and TCI subscales (HA and SD) and possible variables (ie, BDNF vs. presence of psychotic symptoms, age of onset, education, smoking, presence of HT, HL, DM and
BMI respectively by non-parametric analysis. The results showed that serum BDNF concentrations were negatively correlated with age and age of onset, and positively correlated with sex, daily dose of antidepressants and BMI. Then, we assumed age, sex, daily dose of antidepressants, BMI and HAM-D score as significant confounding factors. We reanalyzed the multiple regression analysis. The results were similar with previous results. We corrected and added paragraphs in “Methods”, “Results”, “Table 1” and “Table 2”.

b) Please show the results of all TCI scales and subscales

Reply to the comment:
We showed the results of all TCI scales in “Table 1”.

3) Discussion

a) This section is prevalently focused on the description of literature without an evaluation in relation to your results and without a possible explanation or speculation of your results.

Reply to the comment:
To clarify the relevance between previous reports and our results, we corrected the sentence as below.
“Inconsistent with results of these previous studies [33, 34], we found that serum BDNF concentrations were not correlated with HA score and negatively correlated with SD score in patients with MDD.”
And a sentence was corrected that "the discrepancy in these results may be caused by the differences in diagnosis of subjects".

b) The discussion is poor since the result is poor. Maybe that introducing more analysis your result could become more interesting.

Reply to the comment:
To clarify the relevance between previous reports and our results and to clarify the speculation, we corrected and added several sentences in the “Discussion”.

c) It is not clear your speculation when you compare current result with your previous results.

Reply to the comment:
To clarify the speculation, we added the sentence in the “Discussion”.
“From these previous studies, serum BDNF concentrations may reflect a
depression-related biological change.

- Minor Essential Revisions
  Authors should be check similar results in other psychiatric disorders

Reply to the comment:
We could not find similar study in other psychiatric disorders.
Reviewer 2: Dr. Harris Eyre

1. The authors state ‘The aim of the present study was to reveal the association between peripheral BDNF concentrations and personality traits evaluated by the TCI in patients with MDD.’ This is a leading aim... The authors are suggesting the aim is to reveal an association, but what if there is no association? The aim needs to be corrected to say the authors “explore’ for a possible association’

Reply to the comment:
Thank you for the kind suggestion. We corrected the sentence of aim as below in “Abstract” and “Background”.
“The aim of the present study was to explore for a possible association between peripheral BDNF concentrations and personality traits evaluated by the TCI in patients with MDD.”

2. Why did the authors not explore the associations between other personality traits and serum BDNF in the sample? Why focus just on HA and SD scores? It seems like a more appropriate method to explore the association with all personality traits (in TCI). If not, then there must be a very strong reason to only explore HA and SD scores.

Reply to the comment:
If all personality traits were analyzed without hypothesis, we thought that the results could be considered to be chance results. Therefore we considered meaningful to be investigated focus on items that are relevant to depression. We described more details of previous reports about TCI and depression, and mentioned the importance to focus on HA and SD in “Background” as follow as the next suggestion.

3. In the second para of the background section, could the authors please describe more details about the ‘number of studies suggest that depressed patients show high HA and low SD as measured on the TCI’. Is what populations are these findings – inpatient, community? How was depression diagnosed in these studies – self report, SCID? What numbers or size were these studies? Cross-sectional or prospective? The reader needs to be able to assess the size and quality of the existing literature, and at present this is too vague. This is a key part of the manuscript as only SD and HA are explored in association with serum BDNF. Note also the background section is generally 2 pages in length, so there is room to write in more details.

Reply to the comment:
Thank you for kind suggestions. We described more details of these previous reports
about TCI and depression. We added the sentences in “Background”. The sentences are so long, please see the revised manuscript.
At the end of the sentences, we mentioned as below.
“From these previous reports, it is suggested that associations of HA or SD scores with depression are more consistent and stronger than other dimensions of TCI.”

4. In the abstract, the method for diagnosing MDD should be mentioned. Covariates, if used, should be mentioned.

Reply to the comment:
We added “(DSM-IV)” after MDD in the “Methods” of the abstract and corrected a sentence as below in “Results”.
“Multiple regression analysis controlled age, sex, BMI, dose of antidepressant and depression severity showed that....”

5. Please reference the first sentence of the first para of the background section of the manuscript.

Reply to the comment:
We added a reference on the first sentence of the first para of the background.

6. In the third sentence of the first para of the background section, please describe if these studies are cross-sectional or longitudinal. This is important to know as it indicates the quality of this field.

Reply to the comment:
This sentence was referred from a review article. In the review article, both cross-sectional and longitudinal studies were referred as studies of acute and chronic stress. However, the effect of chronic stress to dysregulation of BDNF has been highlighted in the review article. We corrected the sentence as below.
“Animal models demonstrate stress -induced (especially chronic stress) dysregulation of BDNF expression.”

7. At the end of the first paragraph in the background section, could the authors please outline a reason why they think ‘not all depressed patients demonstrate decreased serum BDNF concentrations? This needs to then link to the second paragraph.

Reply to the comment:
We corrected the sentence as below.
“However, serum BDNF concentrations in depressed patients and controls showed a
large overlap [15], and not all depressed patients demonstrate decreased serum BDNF concentrations.

8. Please outline in more detail what the concepts of Harm-Avoidance and Self-Directedness refer to. The general psychiatry reader won’t know what these refer to.

Reply to the comment:
We added the sentences in the “Background” as below.

“HA score quantifies individual differences in the extent to which a person is anxious, pessimistic and shy versus risk-taking, optimistic and outgoing. SD score quantifies executive functions, such as being responsible, purposeful, and resourceful. Higher HA score indicates anxiety-prone, and lower SD score indicates immature. It has been reported that HA is a marker of emotional vulnerability to depression, and SD is a marker of executive functions that protect a person from depression.”

9. Is it true that no other temperament dimensions or character dimensions relate to depression?

Reply to the comment:
Some previous studies reported associations between another dimensions of TCI and depression. We described them in the “Background” as a response to your comment 3.

10. In the first sentence of the third paragraph of the background section, the authors state 'The relationships between BDNF and personality traits have been reported only in health subjects'. What does BDNF refer to here? Plasma, serum, CSF, genetics?

Reply to the comment:
In this sentence, we referred about plasma and serum BDNF. We corrected "BDNF" to “blood BDNF concentrations”

11. On the note of genetics, it is worth mentioning the VAL/MET polymorphism of the BDNF gene as a biomarker in psychiatry. Why have the authors chosen to look only at serum and not genetics? Why is serum better to explore here than genetics? A rationale must be given.

Reply to the comment:
Although we have considered the BDNF polymorphism is very important, we never examined it yet. We described it as a limitation of this study in the "Discussion" as below.
“On the note of genetics, it is very important to considering the VAL/MET polymorphism of the BDNF gene as a biomarker. Further investigations considering the genetic polymorphism will be needed.”

12. In the Subjects section of the Methods – please indicate who diagnosed the MDD. A senior psychiatrist, a medical student? It is relevant to the reader.

Reply to the comment:
In our university hospital, final diagnosis has been done by a professor or associate professors. We added the sentence as below.
“The diagnosis was done by senior psychiatrists.”

13. In the Methods section and under Personality Trait Measurements – please provide an overview of what data/domains the TCI covers.

Reply to the comment:
We added the paragraph in “Personality Trait Measurements” as below,
“The temperament dimensions measure individual differences in emotional responses to associatively conditioned stimuli. The four temperaments are HA (i.e., anxious versus risk-taking), NS (i.e., impulsive versus rigid), RD (i.e., approval seeking versus aloof), and P (i.e., overachieving versus underachieving). The character dimensions measure individual differences in higher cognitive processes that modulate emotional conflicts to satisfy a person’s goals and values. The character dimensions quantify the three branches of mental self-government: SD (executive functions, such as being responsible, purposeful, and resourceful), C (legislative functions, such as being tolerant, forgiving, and helpful), and ST (judicial functions, such as being intuitive, judicious, and aware)”

14. Covariates or confounding factors need to be very clearly stated in the methods section.

Reply to the comment:
We added the paragraph in the “Statistical analysis” as below.
“Correlations between serum BDNF concentrations, HA or SD and possible confounding factors (presence of psychotic symptoms, comorbidity with anxiety disorder, age of onset, education, presence of HT, HL, DM and BMI) were analyzed using Spearman's rank Correlation Coefficient test.”

15. The authors do a good job of reviewing the background literature in the second para of the discussion section. Could they please reflect on the relevance of each of these
studies to their own study? What is the link?

Reply to the comment:
We mentioned the relevance between the studies using TIC and our present study. We corrected the paragraph to reflect on the relevance between previous reports and our results. We corrected the sentence as below.
“Inconsistent with results of these previous studies [33, 34], we found that serum BDNF concentrations were not correlated with HA score and negatively correlated with SD score in patients with MDD.”

16. In the final sentence of the second para of the discussion section – please outline what ‘differences in subjects’ means. Differences in diagnosis, age, sex, comorbidities etc etc.

Reply to the comment:
We corrected the sentence as below.
“The discrepancy in these results may be caused by the differences in diagnosis of subjects.”

17. In the final para of the discussion section, can the authors outline evidence for and against antidepressant classes differential regulating BDNF levels. Do all antidepressants affect BDNF the same, or not?

Reply to the comment:
In the reference 19, Yoshimura et al. investigated the effects of paroxetine and milnacipran on serum BDNF levels in depressed patients. The results showed that serum BDNF levels in responders were significantly increased after treatment with both antidepressant, but the levels were not significantly different in either group. We added the paragraph above in the final para of the discussion.

18. Please comment on the sample size of this population in the limitations section. Please comment on the limitation of only exploring SD and HA, and not a wider array of personality traits. Outline pros and cons of serum BDNF vs. genetic BDNF testing VAL/MET.

Reply to the comment:
We added limitations in the “Discussion” as below.
“The small sample size of this population is also a limitation of the study. In the present study, we explored only SD and HA. A study exploring a wider array of personality trait using large sample should be done in the future.”
We described a limitation of no genetic examinations.
**Reviewer-3: Dr. María de las Mercedes Perez-Rodriguez**

Major Compulsory Revisions

1. After reading the paper, it is somewhat unclear what the authors’ model and hypotheses are. They discuss temperament features as “traits”, but then mention that they can be “altered” by the “state” of depression. Then in the discussion they seem to suggest that the temperament trait “self-directedness” influences the levels of BDNF. The paper would significantly improved if the underlying model and hypotheses were described in the introduction and discussed in the discussion section.

**Reply to the comment:**

We described the sentences below in “Backgroud” and discussed it in the “Discussion”.

“We considered two hypotheses. 1) Serum BDNF concentrations decrease greater in MDD patients with high HA or low SD personality traits because of their vulnerability to depression. 2) Serum BDNF concentrations do not decrease in MDD patients with high HA or low SD personality traits, because individuals with such anxiety-prone or immature personality may be more likely to fall into a depressive state even without strong-chronic stresses.”

2. Page 7, lines 13-15: The authors should highlight what in my opinion is the most intriguing result: the different (opposite) relationship between self-directedness and BDNF levels in depressed subjects and in healthy controls (i.e., comparing the study findings with Yasui-Furukori’s). This paragraph should be moved to the beginning of the discussion section.

**Reply to the comment:**

In this paragraph, we reviewed previous studies concerning the association between BDNF and personality trait from older reports. Yasui-Furukori’s paper is a newest report. To highlight the discussion against these opposite results, we corrected the sentence as below in this paragraph.

“Inconsistent with results of these previous studies [33, 34], we found that serum BDNF concentrations were not correlated with HA score and negatively correlated with SD score in patients with MDD.”

3. The conclusion that “serum BDNF concentrations tend to not decrease in MDD patients with 17 low SD personality trait” cannot directly be derived from the results, and should be removed or rephrased.
Reply to the comment:
We removed this sentence from the “Discussion”.

4. If the authors have any serum BDNF data available in healthy controls, it would be of interest to compare BDNF levels in MDD patients and HCs among those who have high vs low self-directedness levels.

Reply to the comment:
Thank you for important suggestion. We would like to analyze it in near future.

Minor Essential Revisions:
1. There are some minor typos throughout that should be corrected, for example:
   “trait” instead of “traits” in the title;

   Reply to the comment:
   We corrected “trait” to “traits” in the title and manuscript.

2. In the abstract, “reveal” seems to imply that an association will certainly be found. Please substitute for the more neutral “investigate”, or “examine”.

   Reply to the comment:
   We corrected the sentence as below in the abstract.
   “The aim of the present study was to explore for a possible association between peripheral BDNF concentrations and personality traits evaluated by the TCI in patients with MDD.”

3. Page 4, line 8 and Page 6, line 15: “influence” seems to imply causation, which cannot be inferred with the current, cross-sectional study design. Please rephrase using more neutral, non-causal terms (e.g., correlation, association or relationship).

   Reply to the comment:
   We rephrased “influence” to “association”.

4. Please clarify whether any comorbid psychiatric disorder was an exclusion criterion. The current phrasing, “Patients were excluded if they had a history of other psychiatric disorders including delusions,” is too vague (i.e., were they only excluded if they had a psychotic disorder?) If other comorbid disorders were present in the sample, the authors should report them in the descriptives table and in the statistical analyses.

   Reply to the comment:
One patient comorbid with Dementia with Lewy-bodies, one patient comorbid with Frontotemporal dementia, and 2 patients with cerebral vascular infarction were excluded. The final number of subjects was 123. The number of excluded subjects were so small, thus we did not described them.

5. Since HAMD scores likely changed throughout the admission, it would be of interest to report data about the number of days after admission (mean and range) when BDNF levels were obtained (i.e., number of days between HAMD and BDNF measures).

Reply to the comment:

HAM-D was evaluated at the day of admission as mentioned in the “Subjects”.

Blood samples were taken at the next day of admission. We added it in the “Serum BDNF Measurements” of the “Methods”.