Author’s response to reviews

Title: Variation in the CACNB2 Gene is Associated with Functional Connectivity of the Hippocampus in Bipolar Disorder

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Author’s response to reviews:

Dear editors and reviewers,

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Variation in CACNB2 Gene is Associated with Functional Connectivity of the Hippocampus in Bipolar Disorder.” These comments are all valuable and helpful for revising and improving our paper, as well as for guiding the significance of our research. We have studied the reviewers’ comments carefully and have made corrections which we hope will be met with approval. Revised portions are marked in yellow throughout the paper. The primary corrections to the paper and our responses to the reviewer’s comments are as follows:

Response to the referee’s comments

Reviewer #1:

Comment: Materials and Methods: clarify how many patients are Bipolar 1 or Bipolar 2 and the mood stabilizer therapy (in particular Lithium). If these data are not available, please put this point as limitation of the study in the Discussion section.
Response: Thank you for your valuable advice. We have added information about the BD-I and BD-II on page 6, lines 20-22. Information about patient medication has been added to Table 1, including one patient who was treated with lithium. In our opinion, the distinction between BD-I and BD-II is rarely related to whether patients have taken lithium. Hence, we do not have any such special records regarding this in our study.

Reviewer #2:

1. Comment: rs11013860 is the ID for a single nucleotide polymorphism but not for CACNBs. Please correct.

Response: We apologize for not describing the CACNB2 gene clearly. We have rewritten the background section of the abstract to include this description (page 3, line 3-6).

2. Comment: The results are confusing in their current form. Please correct.

Response: Thank you for your careful reading of our manuscript. We've combed the results and re-described them in an orderly fashion (page 3, line 19-22 and page 4, line 1).

3. Comment: As a general comment I would suggest a correction of English throughout the whole text.

Response: We apologize for any language-related issues. The manuscript has now been revised with professional language editing.

4. Comment: What is the exact significance (P-value) of rs11013860 in the CACNB2 gene in the mentioned GWAS in Han Chinese population (reference 4).

Response: Thank you for your careful work. We have added a description of this significance in page 5, line 15.


Response: Thank you for your valuable advice. We have added relevant information on page 5, line 9-12. Detailed information about the CACNB2 gene can be found in the UCSC database, and related links are attached (https://genome.ucsc.edu/cgi-bin/hgGene?db=hg38&hgg_gene=CACNB2).

6. Comment: Please be more specific on the observed effect of CACN2B SNPs mentioned in references 8, 9, 10.

Response: Thank you for your valuable comments. In reference 8, Hariri et al, outlined the rationale for investigating genetic effects on brain function via neuroimaging. In reference 9,
Bearden et al considered that genetic investigation of endophenotypes offered great promise as an alternative or complement to studies of categorical disease phenotypes, which was the direction of our future research. In reference 10, Meyer-Lindenberg et al suggest that functional and structural brain imaging could identify neurotransmitter systems involved in schizophrenia, as well as their link to cognitive and behavioral disturbances such as psychosis. Hence, the references of 8, 9, and 10 provide a strong rationale for our method of using functional imaging techniques to explore the genetic mechanism of CACNB2. However, none of the three references provided a specific description on the observed effect of CACN2B SNPs.

7. Comment: What is the rationale to group subjects as CC versus A-carriers? Not really clear why this has been done.

Response: Thank you for your thoughtful comments. According to the GWAS results published by MP et al (2011), the association of rs11013860 with bipolar disorder was most significant under the dominant genetic model (CC: AC+CC), that is why we subgrouped our cohort in the way that we did for our study.

8. Comment: Was there any power analysis done before doing analyses?

Response: Thank you for your insightful comments. We are sorry for not calculating power analysis before. Based on your suggestion, we have now made power analysis and found power \((1-\beta_{err \ prob})=0.96.\)

9. Comment: It's difficult to understand which are the areas showing differences in each analysis. Please rewrite the whole results section for clarity.

Response: Thank you for your careful reading of our manuscript. We've combined the results and re-described them in an orderly fashion (page10, line 10-13).

10. Comment: I would suggest significantly shortening (to half the current length) the discussion section but keeping the current concepts.

Response: Thank you very much. We have shortened the length of the discussion as required.

We greatly appreciate all of your insightful and helpful comments.

We did our best to improve the manuscript by making several changes based on the reviewers’ comments. However, these changes will not influence the overall content and framework of the paper. We appreciate the editor’s/reviewers’ kind work earnestly, and hope that our corrections will be met with approval.
Once again, thank you very much for your comments and suggestions.

Thanks and best regards,

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