**Author’s response to reviews**

**Title:** Association between NRGN Gene Polymorphism and Resting-State Hippocampal Functional Connectivity in Schizophrenia

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Technical Comments:

Title page: Please include the email addresses for all authors on the title page. The corresponding author should still be indicated. Please also ensure these email addresses match the email addresses provided in the editorial manager system.

We added the email addresses for all authors on the title page as follows:

ivanhey825@163.com, gongxh@fudan.edu.cn, zyyls@163.com, 13804071019@163.com, yangjian@cmu.edu.cn, Kyleonaz@163.com, zhou060117@126.com, jxw024@163.com,
Funding: Please state clearly the role the funder(s) had in your study in the "funding" section of the declarations.

We clarified the role the funders had in our study in the "funding" section of the declarations as follows: The funders had no influence on the research design, data collection, data analysis, interpretation of results, writing the manuscript or submitting for publication. (Funding section, line 17, page16)

Editor Comments:

BMC Psychiatry operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Marcos Santoro (Reviewer 1): The author addressed most of the issues raised in the last review. No further comments.

Gabriela Xavier (Reviewer 2): The authors solved all questions pointed in the last review. I have no further comments.

Kazutaka Ohi, M.D., Ph.D. (Reviewer 3): The current study investigated associations between hippocampal connectivity at rest and a genetic variant (rs12807809) in the NRGN gene in 59 patients with schizophrenia and 99 healthy controls. They found a gene-diagnosis interaction in a resting-state hippocampal connectivity with anterior and middle cingulate gyri. Although their sample size was too small, their findings were interesting. I have some suggestions that may, in my opinion, further improve the quality of the paper:
There were some concerns as follows;

1. In abstract and introduction section, please clarify which is a risk allele (T or C) for schizophrenia based on previous GWASs.

We apologise for the lack of clarity and appreciate the reviewer’s thorough reading of our manuscript. We have clarified this information in abstract and background section as follows:

A total of 158 participants were studied, including a C-carrier group carrying the non-risk C allele (29 individuals with SZ and 46 healthy controls) and a TT homozygous group carrying the risk T allele (30 SZ and 53 healthy controls). (Abstract, line 20, page 2)

In recent years, in genome-wide association studies, a single nucleotide polymorphism (SNP), rs12807809, in the NRGN gene was reportedly associated with SZ and the T allele conferred a high risk for SZ. (Background section, line 21, page 3)

2. In introduction 'Additionally, resting-state functional magnetic resonance imaging (fMRI) studies have shown aberrant activation in the hippocampus of individuals with SZ [27, 28].', the term 'aberrant' was ambiguous. Please specify whether the aberrant activation was increased or decreased.

We appreciate the reviewer’s thorough reading of our manuscript. We have clarified this information in the main text as follows: Additionally, resting-state functional magnetic resonance imaging (fMRI) studies have shown increased activation in the hippocampus of individuals with SZ. (Background section, line 16, page 5)

3. In method 'Most participants were Han Chinese (n=134, 85% of total participants; n=52, 88% of patients with SZ; n=82, 83% of HCs),' please add information about other ethnicities except for Han Chinese.

We agree with the reviewer that this information is important. We have clarified this information in the revised manuscript as follows: Most participants were Han Chinese (n=137, 87% of total participants; n=53, 90% of patients with SZ; n=84, 85% of HCs), and ethnic information of other participants included Manchu (n=13, 8% of total participants; n=4, 7% of patients with SZ; n=9, 9% of HCs), the Hui nationality (n=3, 2% of total participants; n=3, 3% of HCs), the Mongol
nationality (n=3, 2% of total participants; n=1, 2% of patients with SZ; n=2, 2% of HCs), the Korean nationality (n=1, 1% of total participants; n=1, 2% of patients with SZ) and the Zhuang nationality (n=1, 1% of total participants; n=1, 1% of HCs). (Method section, line 19, page 6)

4. In method 'cluster size >22', how did the authors decide the criteria?

We appreciate the reviewer’s thorough reading of our manuscript. The cluster size was determined by Gaussian random field (GRF) correction in Data Processing & Analysis for Brain Imaging (DPABI, 2.3 version) toolbox based on MATLAB 2011a.

5. In method 'Statistical significance was defined as p < 0.05 to perform the Bonferroni correction.', how did they perform the Bonferroni?

We apologise for the language issues. We have modified the concerning text as follows: Bonferroni correction was used for post hoc comparisons with a p < 0.0083 (0.05/6) considered as the threshold for significance. (Method section, line 12, page 10)

6. In figure1, please separate increased and decreased connectivity regions with diagnosis effects.

We apologise for the lack of clarity and appreciate the reviewer’s thorough reading of our manuscript. We have modified the figure and clarified this information in the revised manuscript as follow: Figure 1: The main effect of diagnostic group. (a) Regions (white box) with main effect of diagnostic group include (A) left fusiform gyrus, left lingual gyrus, left inferior temporal gyrus, (B) right lingual gyrus, right fusiform gyrus, (C) left caudate nucleus, (D) left thalamus, right thalamus, (E) left anterior cingulate gyrus, right anterior cingulate gyrus (cluster-level threshold of p<0.05 after GRF correction and cluster size =35). The coloured bar represents the range of F values. (b) Shown here are the FC values (mean ± standard deviation) extracted from regions with main effect of diagnostic group. The Y-axis represents FC values. The X-axis represents regions with main effect of diagnostic group. (line 1, page 21) An improved figure was provided in Figure1.