

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Psychiatry

**Manuscript NO:** 67091

**Title:** Differential Aberrant Connectivity of Precuneus and Anterior Insula May Underpin the Diagnosis of Schizophrenia and Mood Disorders

**Reviewer's code:** 02476743

**Position:** Editorial Board

**Academic degree:** PhD

**Professional title:** Associate Professor, Director, Statistician

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Bulgaria

**Manuscript submission date:** 2021-04-14

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-04-19 02:05

**Reviewer performed review:** 2021-04-25 09:18

**Review time:** 6 Days and 7 Hours

|                                 |   |
|---------------------------------|---|
| <b>Scientific quality</b>       | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>         | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>               | <input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| <b>Re-review</b>                | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No   |
| <b>Peer-reviewer statements</b> | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous<br>Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |



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## SPECIFIC COMMENTS TO AUTHORS

Overall comments: Thank you for opportunity for reviewing this paper “Differential Aberrant Connectivity of Precuneus and Anterior Insula May Underpin the Diagnosis of Schizophrenia and Mood Disorders”. Basically, the study designs and methods used are appropriate, and the interpretations of the results are reasonable. However, the methodological section was somewhat inadequate. There are several areas where the manuscript needs to be strengthened.

Specific comments:

1.The introduction reads rather descriptive. For example, it is not clear how the information presented in the introduction inform the aims of the study.

**Answer:**

2.Could you please give more information about the targeted population? Exactly, who are the targeted population?

**Answer:**

3.Please give the power of data collection.

**Answer:** *Michael Maes: Power of data collection?? Has the power of spDCM ever been established?*

4. A statement including the reference number of the ethics committee where appropriate should appear in the manuscript. In addition, the authors have not specified what these procedures are. I believe that these, which are also part of the methodology and normally require considerable bureaucracy, should be reflected.

**Answer:** The protocol of the study was approved by the University's Ethics Committee (ID: P-369/29.05.2015).

5. Describe any efforts to address potential sources of bias, if applicable.

**Answer:** [@Севдалина Севдалинова Кандиларова](#) Can you please answer?

6. P-values typically only need to be reported to 1 significant figure.

Answer: [@Севдалина Севдалинова Кандиларова](#), can you help answering this statement?

7. How was the normality of data distribution assessed in your study? Were all the variables in the study normally distributed, given that in your Table and text, you have them all reported as mean (SD)? If all variables were all normally distributed, please state this in the methods section. If not, please report them as median (range).

Answer: [@Севдалина Севдалинова Кандиларова](#) can you address this?

*Michael Maes: Normality of distribution is not an assumption to perform t-tests or ANOVAs, but homogeneity of variance is. I think you should check your t tests with the Levene tests and then we can mention this in the statistics. Also, I would follow this referee (to do something) and show median + range.*

Севдалина Севдалинова Кандиларова: All connectivity values were tested with Shapiro-Wilk's test and the significance was above 0.05. The relevant statement is added to the Methods section.

8. How physicians or policy makers can deliberate with patients or people based on the key findings of this paper?

Answer: *Michael Maes: You can put something at the end of the paper, e.g.*

*The findings of this study suggest that physicians treating patients with schizophrenia and MDE should communicate with their patients that their illness is characterized by alterations in brain connectome data, which in part may explain their symptoms.*

Totally, I would like to congratulate the authors for the enthusiasm invested in this study. However, the manuscript does not reach the level of quality required for publication as original research without major revision in World Journal of Psychiatry.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Psychiatry

**Manuscript NO:** 67091

**Title:** Differential Aberrant Connectivity of Precuneus and Anterior Insula May Underpin the Diagnosis of Schizophrenia and Mood Disorders

**Reviewer's code:** 00069192

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Chief Physician

**Reviewer's Country/Territory:** China

**Author's Country/Territory:** Bulgaria

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**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-04-16 11:06

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**Review time:** 10 Days and 2 Hours

|                                 |   |
|---------------------------------|---|
| <b>Scientific quality</b>       | <input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
| <b>Language quality</b>         | <input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing<br><input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection |
| <b>Conclusion</b>               | <input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority)<br><input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection             |
| <b>Re-review</b>                | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No   |
| <b>Peer-reviewer statements</b> | Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous<br>Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No   |

## **SPECIFIC COMMENTS TO AUTHORS**

This study performed resting state functional Magnetic Resonance Imaging (rs-fMRI) in Schizophrenia (SCH) and Major Depressive Episode (MDE) patients and using the consequent Dynamic Causal Modeling (DCM) to determine the direction and strength of connections nodes in the Default Mode Network (DMN), Salience Network (SN), and Central Executive Network (CEN). Finally, this study identified an excitatory connection from the anterior cingulate cortex to the anterior insula, and an inhibitory connection from the anterior insula to the precuneus, and from the precuneus to the prefrontal cortex in MDE, which is beneficial to distinguish SCH from MDE in clinical diagnosis. Overall this manuscript was well written and organized, however, there are several areas that may be of concern.

Here are our comments:

1. This study treated depression and bipolar disorder as a whole to explore the different brain connection patterns in SCH and MDE. It is interesting to explore the different connections of brain regions in SCH, depression, and bipolar disorder, e.g. SCH-depression, SCH-bipolar disorder.

**Answer: In future.**

2. In table 3, the numbers of MDD patients are 14, the numbers of BD patients are 18. However, there are 4 males and 6 females in MDD groups, and there are 5 males and 11 females in MDD groups.

**Answer: Addressed**

3. The results of this article are based on the rs-fMRI results, however, no rs-fMRI results are described in this article. The rs-fMRI results should be put in this article or supplementary materials.

**Answer: @[Росица Каменова Паунова](#)**

### Resting-state results

**We performed the analysis as described above (2.3). and received as a result various connection between the ROIs. The significant connections are described below in the different groups of patients (MDE, SCH) and between them.**

5. In the discussion section, the authors briefly described the difference in connection nodes in the Default Mode Network (DMN), Salience Network (SN), and Central Executive Network (CEN). However, lack of imaging results compared with other studies. Abnormal imaging signals in each separate brain area should be explained briefly in the discussion section. For the interesting results, the author can combine the previous research findings to further elaborate.

**Answer:** *Michael Maes: I think the referee asks for more comparisons with the results of previous studies. Perform a search on connectome data with respect to your ROIs only and review one by one.*

**Addressed.**

4. Abbreviations must be revised. For example, in the abstract section, the abbreviated "SCH" is wrong in the third line. In the introduction section, the abbreviations do not have full names. fMRI means Functional magnetic resonance imaging, however, this article appeared "functional fMRI".

**Answer:** Addressed.

5. The writing of the article should be refined, especially in the introduction section. Table 1, table 4 and table 5 are missing the final underscore. The annotations in table 2 and table 3 are duplicated.

**Answer:** Addressed.

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Psychiatry

**Manuscript NO:** 67091

**Title:** Differential Aberrant Connectivity of Precuneus and Anterior Insula May Underpin the Diagnosis of Schizophrenia and Mood Disorders

**Reviewer's code:** 05906528

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Assistant Professor, Staff Physician

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** Bulgaria

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**Review time:** 12 Days and 2 Hours

|                                 |   |
|---------------------------------|---|
| <b>Scientific quality</b>       | <input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good<br><input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish            |
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## SPECIFIC COMMENTS TO AUTHORS

Please see the attached word document comprising of the comments.

1. "The aim of this study is to investigate differential patterns of **effective connectivity**" (I would say patterns of aberrant or dysregulated or abnormal connectivity...since this paper is describing abnormal patterns of neuronal firing for these pathologies)

Answer:

2. "The results delineate **specific aberration patterns which correspond to the clinical presentations of the nosological units**" (this is confusing how its written, suggest change to: in neurological areas involved with MDE and SCH). "These findings may contribute to a better explanation of the underlying mechanisms of these disorders as well as to inform differential diagnosis and precise treatment targeting."

Answer: @Севдалина Севдалинова Кандиларова , can you please address this statement?

Севдалина Севдалинова Кандиларова: *Dear Reviewer, the term effective connectivity is used here which reflects the causal interaction between regions of interest as opposed to functional connectivity which reflects the correlations of activity of regions without any implication of causality. The method used in our study - Dynamic Causal Modeling produces effective connectivity measures.*

3. "As a result of their poor **biological validity**" (I would not say validity, suggest something on the lines of "as a result of mostly theoretical biological processes due to limited knowledge about the exact pathological process), "psychiatric assessment methods exist outside of the traditional medical framework. The need to identify diagnostic biomarkers in psychiatry is imperative due to the **low validity of the current diagnostic manuals**" (is this an accurate statement ? Do they truly have low validity or are the best current tools we have?)



Answer: Addressed in the text

4. "SCH is one of the most devastating and socially significant diseases as well as one of the most poorly understood mental conditions that affects people typically in the late adolescence/early adulthood and leads to a functional decline in the personal, social, and economic aspect of those affected." - Can we add a reference to support this statement?

Answer: Addressed in the text

5. "Those kinds of studies have been able to demonstrate an objective proof" (is this proof/evidence? This is just another method to aid in discerning the neurological process that occurs in SCH; BOLD changes are non-specific) "for impaired brain activity during cognitive tasks involving language, memory and concentration in patients with mental illness"

Answer: Addressed in the text

6. "we investigated the rs-fMRI effective connectivity in SCH patients with a paranoid syndrome and MDD and BD patients in a MDE" (confusing to say patients "in a MDE... since MDE is used to describe major depressive disorder as a category).

Answer: Corrected.

7. "The results from the tr-fMRI show that the areas which are activated in SCH patients during paranoid-specific items," - clarify what are you referring to?

Answer: Addressed in the text

8. "Furthermore, the observed DMN activation during the task might be indirect evidence from the inhibitory connection from the PFC to aI, which could interfere with the balancing function of the Salience network (SN) as a dynamic switch between the DMN and Central executive network (CEN)." (Was there a study looking at DMN activation in depressed patients? This should be mentioned. What is the basis of stating that DMN activation is related to inhibition between the PFC and aI?? Are

there papers that describe the interaction between these regions?)

Answer: Addressed in the text

9. “as the DMN is described as a network which must be active at rest” (are there studies that look at DMN activating during other times such as sleep or cognitive tasks?).

Answer: Addressed in the previous sentence.

10. “For the current study, we recruited 58 patients with a paranoid syndrome – in the context of SCH ( $n = 26$ , mean age  $39.2 \pm 13.2$  years, 13 males) and with a MDE ( $n = 32$ , mean age  $42.9 \pm 11.7$  years, 10 males)” - does this mean that patients with paranoid syndrome also had MDE? Unclear how it's written?

Answer: Addressed.

11. The main concern is that the beginning of the article discusses what could be the neurologic basis of schizophrenia, but the end of the paper focuses more on the differences in MDD and SCH brains based on MRI findings. If the paper intends to propose a neuro basis for SCH, it should have healthy participants as controls, not MDD patients. There could also be other confounding factors since Bipolar patients are also used, and the pathophysiology and pharmacological treatment in bipolar varies from MDD treatment. Recommend including past findings of resting state MRI on SCH, MDE, and bipolar patients and mention those findings.

Answer: @Севдалина Севдалинова Кандиларова @Росица Каменова Паунова Can we all address this comment?

Michael Maes: Best is to do what this referee asks, and make a review of previous findings with respect to your ROIs (see also above).

Done.

## EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

### **(1) Science editor:**

1 Scientific quality: The manuscript describes a Basic Study of the Abberant connectivity of precuneus. The topic is within the scope of the WJP.

(1) Classification: Grade B, C and C;

(2) Summary of the Peer-Review Report: The manuscript was well written and organized. The methodological section was somewhat inadequate and the manuscript is lack of imaging results compared with other studies **The questions raised by the reviewers should be answered;**

(3) Format: There are 5 tables and 3 figures;

(4) References: A total of 52 references are cited, including 6 references published in the last 3 years;

(5) Self-cited references: There are 4 self-cited references.

2 Language evaluation: Classification: Grade B, B and B. The manuscript is reviewed by a native English speaker.

3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form number. No academic misconduct was found in the Bing search.

4 Supplementary comments: No financial support was obtained for the study. The topic has not previously been published in the WJP.

5 Issues raised:

(1) The “Author Contributions” section is missing. **Please provide the author contributions;**

**Done**

(2) The authors did not provide original pictures. **Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;**

**Done**

(3) The “Article Highlights” section is missing. **Please add the “Article Highlights” section at the end of the main text;**

**Done.**

(4) For Institutional review board approval form or document. **Please upload the primary version (PDF) of the Institutional Review Board’s official approval, prepared in the official language of the authors’ country to the system;** for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc. Example: Download our sample of institutional review board approval, at <https://www.wjgnet.com/bpg/GerInfo/287>; and

**Not done!**

(4) For PMID and DOI numbers of references from English-language journals, **please ensure the PMID and DOI numbers in the square brackets**, PMCID numbers are not necessary.

**Done.**

6 Recommendation: Conditional acceptance.



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(2) *Company editor-in-chief*: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Psychiatry, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Before its final acceptance, **please upload the primary version (PDF) of the Institutional Review Board's official approval in official language of the authors' country to the system**; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.

**Not done!**