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RAMÓN DE LA FUENTE MUÑIZ

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Rajesh R Tampi, MD
Editor-in-Chief
World Journal of Psychiatry

In attention to the pre-acceptance notification received on July 14th, 2021 regarding our review article (manuscript No. 68685; invitation ID: 04062460), I am glad to submit the revised version of our manuscript now entitled **Insights into myelin dysfunction in schizophrenia and bipolar disorder**, by Marcela Valdés-Tovar, Alejandra Monserrat Rodríguez-Ramírez, Leslye Rodríguez-Cárdenas, Carlo E Sotelo-Ramírez, Beatriz Camarena, Marco Antonio Sanabrais-Jiménez, Héctor Solís-Chagoyán, Jesús Argueta and Germán Octavio López-Riquelme.

All suggestions kindly made by the reviewers were addressed and certainly, our manuscript was improved. Below you will find the answers to reviewers and to the Science Editor. We hope you would find our revised manuscript suitable for definitive acceptance for publication in the World Journal of Psychiatry.

Looking forward to hearing from you soon.

Best regards,

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Reviewer #1:

Specific Comments to Authors: This is a well researched review that brings together the evidence for myelin dysfunction in schizophrenia and bipolar disorder. The discussion about the features common to both the disorders such as psychosis, cognitive impairment, shared genes, and similar brain abnormalities provides an appropriate background to the topic of myelin dysfunction in these two disorders. The mention of the disconnection hypothesis was also very useful.

-However, I still thought that the manuscript could be organized in a better fashion. There are a lot of repetitions, which can be avoided.

As kindly suggested, the manuscript was re-organized emphasizing the alterations in myelination and oligodendrocytes.

-Certain portions such as the clinical details about schizophrenia (included in the section on -"Evidence of myelin dysfunction in schizophrenia") can be safely deleted.

The mentioned section was deleted.

-The whole section on - "White matter alterations evidenced by neuroimaging in living schizophrenia patients" can be shortened because it provides only indirect evidence for myelin dysfunction in schizophrenia.

This section was shortened and moved at the end of the manuscript.

-I would also avoid the word "living".

This word was deleted.

-Similarly, clinical details about bipolar disorder (section on -"Evidence of myelin dysfunction in bipolar disorder") can be omitted and the section on - "White matter alterations evidenced by neuroimaging in living bipolar disorder patients" can be shortened.

The clinical details regarding bipolar disorder were deleted and the other section was shortened.

-The authors must realize that this is a difficult topic for the ordinary clinician. Therefore, a more concise manuscript will only improve its readability. I have one question though. The authors have focused only on schizophrenia and bipolar disorder. But, is myelin dysfunction present only in these "psychotic" disorders and not in other neurodevelopmental disorders that do not have the element of psychosis? How would the authors explain the evidence for myelin dysfunction in autism spectrum disorders? In fact, a wide range of psychiatric disorders, including schizophrenia, chronic depression, bipolar disorder, obsessive-compulsive disorder and posttraumatic stress disorder, have been associated with white matter defects, as have neurodevelopmental cognitive and emotional disorders including autism, dyslexia and attention-deficit hyperactivity disorder (Fields RD. White matter in learning, cognition and psychiatric disorders. Trends Neurosci. 2008).

We agree with this thoughtful comment of the reviewer. Indeed, many mental illnesses share alterations in the myelination process and oligodendroglial physiology and it would be interesting to expand the scope of our work in the near future and further review the

current knowledge on myelin dysfunction in other psychiatric disorders. We include a phrase to clarify that oligodendroglial and myelin alterations are not exclusively present in schizophrenia and bipolar disorder and included the suggested reference.

-Neuroimaging and neuropathological studies have revealed myelin defects and microarray-profiling analysis demonstrated aberrant expression of myelin-related genes not only in schizophrenia and bipolar disorder, but also in major depressive disorder (MDD) and cocaine addiction (Feng, Y. Convergence and Divergence in the Etiology of Myelin Impairment in Psychiatric Disorders and Drug Addiction. Neurochem Res 2008; 33: 1940–1949). Thus, it appears that myelin dysfunction is not specific to "psychotic" disorders. The authors could consider adding a brief discussion on this issue.

We agree with this comment of the reviewer and this valuable information, and as told before a clarifying phrase and the suggested reference were added.

Reviewer #2:

-Specific Comments to Authors: The manuscript is very informative but, unfortunately, poorly structured and difficult to read, which makes a 'take home message' unclear. I suggest moving all information related to myelin and its biochemical structure (e.g., the information on p.14) to the beginning of the manuscript.

As kindly suggested, we re-organized the manuscript moving the information related to myelin and biochemical features to the beginning.

-Separating schizophrenia and bipolar disorder into separate sections seems unnecessary. The readers would benefit from the comparative analysis of these disorders that would describe common pathology as well as the differences between schizophrenia and bipolar disorder at the different levels of analysis.

We included a comparison of the anomalies occurred in these psychiatric disorders.

-It is really unclear why the authors decided to define bipolar disorder as a psychotic disorder. Many of bipolar patients (all patients with bipolar disorder type-II) never experience psychotic symptoms. Given that the current review includes work investigating bipolar disorder in general (not only that with psychotic features), the title as well as some statements regarding psychotic disorders are misleading.

We agree with this pertinent comment of the reviewer. Certainly, not all bipolar disorder patients experience psychotic symptoms. Hence, the manuscript is referred in the revised version as schizophrenia and bipolar disorder omitting the term 'psychotic disorders' in the tittle and along the text.

-Given that the myelin content can be most accurately assessed using post-mortem studies, it would make sense to start with postmortem studies and then proceed to the in vivo human neuroimaging (e.g., DTI).

As kindly suggested, the sections of the manuscript were re-ordered moving to the beginning the post-mortem studies and the brain imaging information at the end.

-Given that the FA value is not necessarily a good measure of myelin, it is important to discuss what else could be characterized by decreased FA (see Jones, D. K., Knösche, T. R. & Turner, R. White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. Neuroimage 73, 239–254 (2013).) Also, claiming that VBM or resting state functional connectivity reflect myelin level is a stretch.

We agree with this pertinent comment and a brief comment about this was included in the manuscript. The suggested reference was added.

-There are errors in Figure 1. Fronto-orbital and Dorsolater cortices are switched. The arcuate fasciculus that connects the Broca's and the Wernicke's areas is misplaced on the right figure of Fig.1.

Thanks for this comment. The errors in this figure were corrected (Figure 3 in the revised version).

-The review needs to generalize and discuss how and why the changes in myelin lead to specific symptoms characterizing schizophrenia and bipolar disorder.

As kindly suggested, we related the myelin anomalies with the connectivity of the CNS structures and this relationship with specific symptoms characterizing these psychiatric disorders.

(1) Science editor: 1 Scientific quality: The manuscript describes a review of the insights into myelin dysfunction in psychotic disorders. The topic is within the scope of the WJP. (1) Classification: Two Grades C; (2) Summary of the Peer-Review Report: This is a well-researched review that brings together the evidence for myelin dysfunction in schizophrenia and bipolar disorder. The discussion about the features common to both the disorders such as psychosis, cognitive impairment, shared genes, and similar brain abnormalities provides an appropriate background to the topic of myelin dysfunction in these two disorders. The mention of the disconnection hypothesis was also very useful. The questions raised by the reviewers should be answered; (3) Format: There is 1 table and 4 figures; (4) References: A total of 194 references are cited, including 62 references published in the last 3 years; (5) Self-cited references: There is no self-cited reference; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Two Grades B. A language editing certificate issued by AJE was provided. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by Fondo Sectorial de Investigación para la Educación, Fondo Sectorial de Investigación en Salud y Seguridad Social. 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;

The Authors Contributions section was included.

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Documents certifying our grants were uploaded.

(3) 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;

The original figures were provided as a Power Point file.

and (4) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Re-Review: Not required. 7 Recommendation: Conditional acceptance.