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# PEER-REVIEW REPORT

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

**Manuscript NO:** 68685

**Title:** Insights into myelin dysfunction in schizophrenia and bipolar disorder

**Provenance and peer review**: Invited Manuscript; Externally peer reviewed

**Peer-review model:** Single blind

**Reviewer's code:** 02665114
**Position:** Peer Reviewer
**Academic degree:** MD
**Professional title:** Doctor
**Reviewer's Country/Territory:** United States
**Author's Country/Territory:** Mexico

**Manuscript submission date:** 2021-05-31
**Reviewer chosen by:** AI Technique
**Reviewer accepted review:** 2021-06-02 18:48
**Reviewer performed review:** 2021-06-07 23:39
**Review time:** 5 Days and 4 Hours

| | |
|---|---|
| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[ ] Minor revision [Y] Major revision [ ] Rejection |
| **Re-review** | [ ] Yes [Y] No |
| **Peer-reviewer** | Peer-Review: [Y] Anonymous [ ] Onymous |

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| **statements** | Conflicts-of-Interest: [ ] Yes [ Y] No |
|---|---|

**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. 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.

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. 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). 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.

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

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disorder.

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**Peer-review model:** Single blind

**Reviewer's code:** 02445242
**Position:** Editorial Board
**Academic degree:** MAMS, MBBS, MD

**Professional title:** Professor

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

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

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| | |
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| **Scientific quality** | [ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good<br>[ ] Grade D: Fair [ ] Grade E: Do not publish |
| **Language quality** | [ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing<br>[ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection |
| **Conclusion** | [ ] Accept (High priority) [ ] Accept (General priority)<br>[ ] Minor revision [Y] Major revision [ ] Rejection |
| **Re-review** | [ ] Yes [Y] No |
| **Peer-reviewer** | Peer-Review: [Y] Anonymous [ ] Onymous |

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**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. 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 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. I would also avoid the word "living". 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 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

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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). 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.