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Format for ANSWERING REVIEWERS



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9160-review.doc).

Title: The burden of white matter abnormalities in the pathophysiology of major affective disorders

Authors: Gianluca Serafini, Xenia Gonda, Zoltan Rihmer, Mario Amore, Paolo Girardi

Name of Journal: *World Journal of Radiology*

ESPS Manuscript NO: 9160

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

Reviewer 1.

Re: 20140123224659, The impact of white matter abnormalities in the pathophysiology of major affective disorders

Dr. Serafini et al. prepared an essay review on the white matter hyperintensities (WMHs) among patients with major affective disorders. I think WMHs is an important issue for radiologist as well as psychiatrist and other professions. This paper could revise to a good and educational commentary. I have some comments listed below.

Question 1. I suggest the authors revised the infrastructure and trimmed the text of this paper. This version has only three Sections (Introduction, Discussion, and Conclusion). I suggest the authors adjust the text and use more concrete subtitles for the benefit of readers. Meanwhile, I am not sure what the aim of this essay is. I suggest the authors state the aim of this essay and adjust the text to follow the aim of this paper.

Answer to question 1. Thank you for this suggestion, now the manuscript has been modified based on the Reviewers' indication. The main text of the paper has been carefully revised and the aim of the manuscript has been specified.

Question 2. The title and abstract focused on "major affective disorders", whereas the text (and Table



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1) focuses on the bipolar disorder. I suggest the authors adjust the title and abstract, as the paper is focus on one kind of major affective disorders.

Answer to question 2. Thank you for this suggestion. In the revised version of the manuscript we have carefully reviewed both the title, abstract and main text that now appear more focused on major affective disorders as in the initial intention of the authors.

Question 3. It seems to me that the papers in the Table 1 were all from the authors' team. I acknowledge the authors' expertise on this issue, but I think the authors should provide the rationale why only the papers from your lab were reviewed.

Answer to question 3. In the revised version of the manuscript, we included a specific Methods section in which we provided the rationale why only the manuscript of our research group has been critically reviewed. We understand that the mentioned Table would be more complete if it contains based on the current literature all the most relevant publications about the specified topic but this does not meet our primary aim which is to critically review all the studies of our research group that have been published to date about the association between WMHs and major affective disorders. For a more comprehensive review, please see the Table that has been reported in a recently published article (Serafini et al., CNS Spectrums, 2014). This Table clearly summarized the current literature about all the available MRI studies concerning the impact of WMHs in adult patients with major psychiatric disorders.

Question 4. Two minor points:a. As an educational commentary, I suggest the authors prepare an illustration to show the WMHs to enhance the knowledge of potential reader from other discipline.b. Since all the papers in Table 1 using "The modified Fazekas four-point rating scale" as evaluation instrument. This column would be a redundant one.

Answer to question 4. Thank you very much for your suggestions. An appropriate illustration on WMHs has been now included in the revised version of the manuscript in order to make more clear the significance of WMHs for the general readership. Also, the mentioned column in Table 1 has been deleted as redundant according to Reviewer's indications.

Reviewer 2.

This manuscript reviews the evidence for white matter abnormalities in major affective disorders.

Question 1. The manuscript emphasizes publications of the authors. The manuscript could be enhanced by including contributions by other authors. Several revisions would clarify the meaning, improve the flow among sections of the manuscript, and enhance the value for clinicians.

Answer to question 1. We really understand that the mentioned Table would be more complete if it contains, according to the current literature, all the most relevant publications about the topic but this does not meet our primary aim which is to critically review our research manuscripts that have been published to date about the specified topic. For a more comprehensive review, please see the Table that has been reported in a recently published article (Serafini et al., CNS Spectrums, 2014). This Table clearly summarized the current literature about all the available MRI studies concerning the impact of WMHs in adult patients with major psychiatric disorders.

However, based on the Reviewers' suggestions, some revisions have been performed in order to clarify the general meaning and improve the flow of the main text enhancing the predictive value of WMHs in grouping subjects with mood disorders potentially helping in optimizing valid treatment strategies.

Question 2. Page 3 The second paragraph about omits a discussion of the hyperintensities in demyelinating disorders. Please include a discussion of these common findings. This is particularly relevant because depression is extremely common in multiple sclerosis.

Answer to question 2. Thank you for this comment, now we included some statements about WMHs and demyelinating disorders in the revised version of the manuscript. We agree with Reviewer's suggestion, WMHs are also frequent in multiple sclerosis.

Question 3. Page 4 \Paragraphs 4 and 5. Please define acronyms, e.g., LOBD, TEMPS-A, BHS, and MINI, when first used. Also please provide a description of instruments; readers may be unfamiliar. Paragraph 5 Please provide references for the statements in the text.

Answer to question 3. Ok, in the revised version of the manuscript all the acronyms have been correctly used. Also, psychometric instruments have been defined and references on paragraph 5 have been adequately provided as suggested.

Question 4. Page 6 Paragraph 1 Please provide references for the statements in the text. Paragraph 3 Some readers may be unfamiliar with the Fazekas modified scale. Please provide a description of the instrument and its properties. Please provide a reference.

Answer to question 4. Thank you for this suggestion, now we provided the indicated missing references in the revised version of the manuscript. Also, we added a short description and appropriate citation of the Fazekas modified scale as well as its main properties.

Question 5. Pages 11 and 12 Table 1 Please provide a more general title, e.g., "Salient publications about white matter hyperintensities in affective disorders." The table must be self-explanatory. Some readers may skim the article to read the table without reading the rest of the article. Therefore, please add a legend at the bottom of the table with definitions of all abbreviations.

Answer to question 5. Ok, now the title of Table 1 has been revised and a specific legend including definitions and all abbreviations of the included studies has been reported at the bottom of the Table.

Question 6. Do any of the publications in Table 1 describe the same cohort of patients? In other words, is a single patient reported in more than one of the publications?

Answer to question 6. Thank you for this comment, all the publications reported in Table 1 derived as indicated by the same cohort of patients with the exception of the following studies: Serafini et al. [18,19].

Question 7. Are there any publications about white matter hyperintensities in affective disorders omitted from Table 1? If so, why are they omitted?

Answer to question 7. In the current version of the manuscript, there are no studies of our research group about WMHs in affective disorders that have been omitted from Table 1.

Question 8. The table would be more complete if it contains all publications about the topic. The manuscript likely merits publication after revision with the correction of the points addressed above.

Answer to question 8. We really understand that the mentioned Table would be more complete if it contains, according to the current literature, all the most relevant publications about the topic but this does not meet our primary aim which is to critically review our research manuscripts that have been published to date about the specified topic. For a more comprehensive review, please see the Table that has been reported in a recently published article (Serafini et al., CNS Spectrums, 2014). This Table clearly summarized the current literature about all the available MRI studies concerning the impact of WMHs in adult patients with major psychiatric disorders.

However, based on the Reviewers' suggestions, some revisions have been performed in order to clarify the general meaning and improve the flow of the main text enhancing the predictive value of WMHs in grouping subjects with mood disorders potentially helping in optimizing valid treatment strategies.



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3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Radiology*

Sincerely yours,

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