3-Dec-2017
Dear Dr. OLIVEIRA:

ACN-17-1476 entitled "Cannabinoid signalling in embryonic and adult neurogenesis: possible implications for psychiatric and neurological disorders" which you submitted to the Acta Neuropsychiatrica, has been reviewed. We are not able to accept the manuscript in its present form but would be willing to consider a revised version that addresses the comments of the reviewers. The comments of the reviewer(s) are included at the bottom of this letter. Note that the revised manuscript will most likely be reassessed by one of the reviewers.

To revise your manuscript, log into <https://mc.manuscriptcentral.com/acn> and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text. Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

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Because we are trying to facilitate timely publication of manuscripts submitted to the Acta Neuropsychiatrica, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission. Your revision is due before 03-Mar-2018.

Once again, thank you for submitting your manuscript to the Acta Neuropsychiatrica and I look forward to receiving your revision.

Sincerely,
Prof. Gregers Wegener.

Editor in Chief, Acta Neuropsychiatrica. wegener@clin.au.dk.

Associate Editor

 Dear editor and reviewers,

 We are very thankful for your valuable and accurate comments on the Manuscript ACN-17-1476 entitled "*Cannabinoid signalling in embryonic and adult neurogenesis: possible implications for psychiatric and neurological disorders".*

 In the current version of this Manuscript we have included all suggestions and information requested by the reviewers. We performed a careful review of the references. Reviewer#2 mentioned that the section "*Neurogenesis"* did not add value to the Manuscript. With all due respect to the reviewer´s comment, we would like to keep this section *(*now "*Neurogenesis in embryonic and adult central nervous system")* in the current version of the Manuscript*,* because webelieve the information it contains may help readers unfamiliar to this subject to have a better understanding of the text. Timely, this section was reorganized and properly corrected taking in account the suggestions made by reviewers. Also the section "*Cannabinoids neurogenesis and Alzheimer's disease*", which was indeed confusing and incomplete in the first version, was rewritten and now includes more information.

 We believe now the Manuscript is much better and may be suitable for publication in the Acta Neuropsychiatrica. Please, see below our answers and comments.

 With our best regards,

 Rúbia Maria Weffort de Oliveira

Response to reviewers

Reviewer: 1

Comments to the Author

The manuscript by Rubia et al., appropriately reviews the topic. Some minor suggestions and corrections are detailed below. In addition, authors are requested to include some aspects of the literature regarding cannabinoid actions in Alzheimer’s disease models or the early studies in ischemia.

Answer: According to the reviewer’s suggestion, in the current version we have included more information about cannabinoid actions in Alzheimer´s disease models (the section *Cannabinoids neurogenesis and Alzheimer's disease* was rewritten) and the pioneer studies on cannabinoids and brain ischemia (Nagayama et al., 1999 – reference 180). Please see page 22, lines 18-22.

Suggestions for improvement and more accuracy.

1. p. 9, l. 13. Include a mention that adult neurogenesis magnitude in humans is very reduced, if any, compared to other mammalian species.

Answer: Adult neurogenesis has been reported in humans (Ericksson et al., 1998; Reif et al., 2006; Manganas et al., 2007; Spalding et al., 2013) and the magnitude of renewing cell population exhibits variations when compared across species and age of the subjects (Ihunwo et al., 2016). To make comparisons between species is difficult because of the markers and methods used to measure the phenomenon are not the same. For instance, immunohistochemistry for DCX, TUC-4, Ki-67 or BrdU only provide a snapshot of a point in time of the neurogenesis process, since they label transient expression of neurons. Using stereological methods, it has been shown that the turnover rates in human is about 0.004% per day (Spalding et al., 2013), but exhibits an age dependent decline of neuroblasts, indicating that part of neurons undergoing apoptosis (Eriksson et al, 1998; Bergami et al., 29015). In 2-month-old mice is 0.03% to 0.06% and for the 5-16 year old macaque it is 0.04% per day (Bergami et al., 2015). Between 2-9 months, mice also experience a 10-fold decline in neurogenesis (Bergami et al., 2015). Because of the difficulties on making comparisons and conclusions, we included a brief sentence in the Manuscript about the differences between species and ages, but not discussed the magnitude, extent of neurogenesis and neuronal turn-over. See page 8, 19-25.

2. p. 9, l. 35, Radial glial cell development is not a classical or typical gliogenic process. I suggest to edit the rational of the sentence. Other important contributions of glial cells in neurogenesis are better examples of the crosstalk between both processes.

Answer: The sentence was re-written.

3. p.10, l. 37 diffusible (and membrane bound) factors.

Answer: Thank you for this correction. We added and membrane bound factors to the sentence.

4. p.11, l. 22; some references are not numbered and provided with authors name, please unify (also p17., l20).

Answer: Thank you for this correction. We checked all the references in the text and the reference list accordingly.

5. p.14, l. 35; please specify is in human early development.

Answer: It was specified as required.

6. p.15, l. 4, potential.

Answer: Thank you for this correction.

7. p.15, l.11 please replace reference 82 a review article by the original demonstration that ECBs are produced in NSCs (Aguado et al., 2005 = reference 72)

Answer: Thank you. The correct reference was included (now reference 63).

8. p.15, l. 53 Authors should take in account and discuss new studies beyond reference 82 (i.e. the recent report by Diaz-Alonso et al., Cer Cor 2017).

Answer: The reference Diaz-Alonso et al., 2015 (now reference 66) was included in the text.

9. p.15. l. 55 CB1 receptors are expressed in Tbr2 cells. Add original contribution 76.

Answer: This was included in the text (now reference 65)

10. p.20, l. 11 … therefore it is likely that some BEHAVIORAL/FUNCTIONAL actions of cannabinoids.

Answer: The sentence was changed accordingly. Please see page 17, lines 10-11.

11. p.22, l. 40 When referring to the work of Zhang et al (146) it is important to mention, that so far these results have not been confirmed by other groups.

Answer: This sentence was included (please see page 18, lines 3-4).

12. p.25, l.24 There is no proof at this moment of any influence of CB signaling in interneuron differentiation. Harkany papers and others relate to their development, positioning or morphogenesis.

Answer: Thank you for this information. We corrected the sentence and included Harkany´s important references (references 39 and 71).

13. p.27, l.46, reference is 198 not 199.

Answer: It was corrected. Caltana et al., 2015 is now reference 182.

14. p.27, when discussing neuroprotective actions of cannabinoid signaling in ischemia please mention the original studies as this is a domain with a long history of cannabinoid research (i.e.. Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. Nagayama T, Sinor AD, Simon RP, Chen J, Graham SH, Jin K, Greenberg DA. J Neurosci. 1999 Apr 15;19(8):2987-95).

Answer: This important work was included in the text (reference 180). Please see page 22, lines 18-22.

15. p.29, When discussing cannabinoid actions in AD models please include some mention to the numerous studies by Aso et al (i.e. J Alzheimers Dis. 2012;30(2):439-59. doi: 10.3233/JAD- 2012-111862. CB1 agonist ACEA protects neurons and reduces the cognitive impairment of AβPP/PS1 mice. Aso E1, Palomer E, Juvés S, Maldonado R, Muñoz FJ, Ferrer I.; J Alzheimers Dis. 2015;43(3):977-91. doi: 10.3233/JAD-141014. Cannabis-based medicine reduces multiple pathological processes in AβPP/PS1 mice. Aso E1, Sánchez-Pla A2, Vegas-Lozano E3, Maldonado R4, Ferrer I1.)

Answer: Thank you again. Indeed, there was incorrect references and missing information in the first version of the Manuscript. We rewritten the section "*Cannabioids, neurogenesis and Alzheimer´s disease"* and we believe the current version is more complete and suitable.

16. Figure 1. Is not accurate and must be improved to provide accurate scientific content. I.e. Asymmetric and symmetric divisions are not correctly labeled.

Answer: Thank you for this observation. The figure was corrected.

**Reviewer: 2.**

Comments to the Author.

In the present paper Oliveira and colleagues provide a review on the relevance of cannabinoid signaling for adult neurogenesis and for psychiatric and neurologic disorders. This is an ambitious task. While the topic is interesting and timely, this review is a lost opportunity to explore some provocative thoughts on the topic. It is largely descriptive and a through list of the published papers on the topic; however, it does not open new perspectives neither provides a mechanistic insight on how cannabinoids might influence adult neurogenesis. Therefore, this serves better as a guide for newcomers into the field.

1. The first section of the review “Neurogenesis” is superficial, confusing, and without adding value to the review. The last two paragraphs of this section would be enough to introduce the readers to the topic.

Answer: With all due respect to the reviewer´s comment, we would like to keep the section "*neurogenesis'' (*now "*Neurogenesis in embryonic and adult central nervous system")* in this current version of the Manuscript. In the (Abstract) we emphasized that it is a narrative review. We reorganized section, included more information and believe the beginning of this section may help readers unfamiliar to this subject to have a better understanding of the text.

2. In page 19, lines 40-42, the authors start by mentioning animal models of AD and PD and then jump to studies in psychiatric patients as if there were no studies in animal models of psychiatric disorders revealing extensive impairments in adult neurogenesis. The last section on neurodegenerative (mostly focus on AD) provides little information to the field.

Answer: We agreed with the reviewer. In the current version of the Manuscript we have included more information revealing changes in adult neurogenesis in the different animal models of neuropsychiatric disorders. We presented evidence of changes in neurogenesis in each respective subsection. We also re-written the section *Cannabinoids, adult neurogenesis and Alzheimer’s disease.* We believe nor the current version is clearer and more suitbale for publication.

Minor points.

3. References 142-144 are inappropriate for the statement.

Answer: A careful review of references was done and appropriate references were included accordingly.

4. Lines 49-55 in page 26 seem totally out of context. Actually, the entire paragraph could be deleted.

Answer: According to the Reviewer´s suggestion, the paragraph was removed from the text.

5. In page 9 (line 27) and page 11 (line 22) there are references in extent.

Answer: We corrected the references.

6. Typo in page 10 line 11 “precursors”

Answer: It was corrected. Thank you.