OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-21-00805
Title: Lipopolysaccharide mouse models for Parkinson's research: a critical appraisal
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COMMENTS TO AUTHORS

The topic of the manuscript is highly relevant and the authors give a critical appraisal with clear suggestions for future research, this will be well-appreciated by the readers. However, they fully focus on their own work and seem to pass research using the same models by other researchers. It would be more objective and helpful to understand the state of the art in this field, if they would also discuss work from other research groups.

Overall, this is a very interesting and timely perspective on emerging models in PD research, by experts in the field. The scope is well-defined and the article is written in an intelligible fashion. In addition to some minor comments (cfr. below), my only major concern is that the authors largely focus on their own research and hence don't give a comprehensive overview of this research domain. This should be mitigated in the revised manuscript.

- I suggest rephrasing the first subtitle "Animal models in Parkinson's research" to "Introduction" or even "Abstract".
- On p. 1, line 33, it is unclear what is meant with "and utilize variety of treatment regimens which require further evaluation."
- In general, when using LPS to induce inflammation, different types of LPS from different bacteria are being used and tend to have varying effects. Can the authors please comment on this?
- The authors conclude that "a single systemic injection of LPS induced a delayed progressive degeneration while repeated systemic injections may not induce progressive degeneration". However, did they consider the different time windows of these experiments? I understand that they looked at day 19 post LPS injection for the repeated systemic injections while a single dose took 7-10 months to develop into SN degeneration. Furthermore, the authors write "We did not find dopaminergic degeneration in the midbrain after repeated systemic LPS injections (possibly due to the development of tolerance to LPS and the relatively short time-frame)." Can they briefly explain what this tolerance to LPS entails?
- It would be informative for the reader if the authors could briefly explain the relevance of inflammation in the olfactory bulb and hippocampus for PD.
- Especially for the section on systemic LPS models, it is unclear which other studies - besides the self-cited studies of the authors - have been using this model and what their findings were. Overall, the manuscript should combine the personal experience and critical appraisal of the authors with a literature overview. The latter seems to be somewhat missing or incomplete.
- Please explain (p. 3, line 24): "Our model mimics the inflammatory effects of an environmental agent"
- In the introductory alinea, the authors write "There are three common routes of administration of LPS that are used to model PD: intranasal, intraperitoneal, and stereotaxic (localised injection into the SN or striatum)." It is a missed opportunity that they only discuss two of these three options in the remainder of the manuscript. Even if the authors don't have any hands-on experience with the nasal LPS model, they could still give a literature overview and reflect on the pros and cons of this model.