PEER-REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-18-00399
Title: Distinguishing normal brain aging from the development of Alzheimer's disease: inflammation, insulin signaling and cognition
Reviewer's Name: Nobuyuki Ishibashi
Reviewer's country: USA
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COMMENTS TO AUTHORS

Introduction:

This mini-review starts discussing the limited relation between Aβ depositions and cognitive function in AD. Although these sentences imply that distinguishing normal brain aging from AD development is required, the main topic of this article (assume differences between normal aging and AD from the title) is not clearly displayed in the introduction. To improve the section the reviewer suggests including: 1) aims of this article; 2) why the article is important; and 3) how the article differs from other reviews.

Spatial learning and synaptic loss in the hilus:

In these two sections, authors mostly discuss one recent publication from their group. If spatial learning is especially defective in AD, the reviewer suggests discussing previous works from other groups and including clinical data in order to support their results. Similarly, if synaptic loss in the hilus region is more specific and sensitive for distinguishing AD development from normal aging compared with other brain areas, more robust evidence should be demonstrated.

Inflammation:

Authors discuss that IFNγ and IL-4 are specifically increased in the AD brain but not in aging brain. Similar with previous two sections, authors should demonstrate more robust evidences if they suggest that within a wide range of cytokines/chemokines IFN and IL-4 are highly specific in the AD pathology. In my view, the evidence described here (results from one mouse line) is not enough and there are many other possibilities to distinguish neuro-inflammatory responses between AD and normal aging.

Insulin signaling:

Authors describe difference between brain and peripheral tissues in insulin resistance but, in my view, discussions in the section are not related with their main topic - difference between normal aging and AD.

In summary, authors should not rely only on own works (from one line of mice) to discuss their opinion in the AD pathology. Aims of this article should be clarified. If their intension is

to distinguish normal brain aging from AD development in inflammation, insulin signaling, and cognition, robust evidences and extensive discussion from previous works should be included. Authors discuss a wide range of topics - behavioral phenotype, brain region, inflammation, and insulin signaling in the AD pathology. If comprehensive review is not their purpose, authors may select one or two topics in the short review article.