

OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-22-01237

Title: Trans-synaptic degeneration as a mechanism of neurodegeneration in multiple sclerosis

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Reviewer's country: Germany

COMMENTS TO AUTHORS

In the current manuscript "Trans-synaptic degeneration as a mechanism of neurodegeneration in multiple sclerosis", the authors provide a state-of-the-art overview on current concepts of antero- and retrograde neurodegeneration within the visual system. The manuscript is very well written and sounds and covers / includes the most relevant papers on this topic.

I have only a few minor comments which should be addressable by the authors within a minor revision.

MINOR

- A figure reflecting the different concepts of antero- and retrograde neurodegeneration within the visual system would be very valuable

- I suggest to add a reasonable limitation to the statement "In the era of the precision medicine approach to MS, the tracking of trans-synaptic degeneration with advanced quantitative imaging techniques represents one potential biomarker that could contribute to the multimodal clinical, laboratory, and radiological assessment used to inform prognostication, therapeutic decision making, and disease monitoring." (page 6). Based on the limitations of retinal layer thickness measures (inter-rater reliability, repeatability GCIP $\sim 0.5-1.0 \mu\text{m}$) and the influence of certain environmental and genetical factors ($\sim 0.1-0.3 \mu\text{m}/\text{year}$), intra-individual longitudinal tracking of retinal (or MRI) measures is still away from the introduction into the clinical practice and significant both technical and analytical improvements are an urgent need. I agree that longitudinal tracking of trans-synaptic degeneration may be suitable when focusing whole patient cohorts, but not when evaluating single patients.