Review of: "Synapse Weakening-Induced Caspase-3 Activity Confers Specificity to Microglia-Mediated Synapse Elimination"

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Potential competing interests: No potential competing interests to declare.

The manuscript "*Synapse Weakening-Induced Caspase-3 Activity Confers Specificity to Microglia-Mediated Synapse Elimination"* by Yu and colleagues provides extensive and well-discussed work about the involvement of caspase-3 activation in the elimination of inactive synapses in the visual pathway, describing also the involvement of the caspase in the context of Alzheimer's disease.

Even though this represents valuable work, in my opinion, the paper needs extensive revision, and the results need to be re-organized or even split, in order to enhance every part of the work done by the research group.

Here are some key points I would highlight:

- Please consider the possibility of preparing two different manuscripts, one focusing on the experiments related to the visual pathway and the other related to the results obtained on the Alzheimer's disease (AD) model.
- Chapter "Synapse inactivation induces postsynaptic caspase-3 activity": the data described in this chapter are not sufficient to state that caspase-3 activity is post-synaptic. Please rephrase or provide further evidence for this.
- Figures S1 to S3 are essential to understand the results presented so far, so I suggest incorporating them in the main body (maybe in the Materials and Methods part). I also suggest merging S1 and S2; the huge number of supplementary figures compromises the readability of the manuscript.
- Figure S7 should be merged with Figure 4.
- Figure S9: Please consider studying the presence of inflammatory markers to confirm the absence of microglia activation.
- Figure S10 should be merged with Figure 5.
- Figure S12 should be merged with Figure 6.
- I will not go into details about the part of the manuscript on AD, but I strongly suggest putting these results in a novel manuscript and reorganizing figures. This will allow for more detail in studying the involvement of caspase-3 in ABeta-induced synaptic loss.

Minor points:

- Some figure legends include parts of the discussion that should be moved to the main text (e.g., Figure S12).

- Please carefully check for typos and for the abbreviations.