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Peer Review

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

Jonas Wolf[1]

1. Hospital Moinhos de Vento, Porto Alegre, Brazil

This manuscript presents compelling evidence for the role of caspase-3 in mediating activity-dependent synapse elimination during neural development and in the context of neurodegeneration. One of the most significant strengths of the study is its ability to connect two major neurobiological processes—synaptic pruning during development and pathological synapse loss in Alzheimer's disease—through a shared molecular mechanism. By identifying caspase-3 activation as a necessary signal for microglia-mediated synapse elimination, the authors establish a unifying framework that has both developmental and translational relevance.

The experimental design is a key strength, incorporating a combination of genetic, molecular, and imaging techniques to dissect the relationship between synaptic activity, caspase-3 activation, and glial cell involvement. The use of the developing mouse visual system as a model is particularly appropriate, given its well-characterized synaptic refinement timeline and accessibility to both spontaneous and experience-driven activity paradigms. This choice lends temporal and anatomical specificity to the findings, enhancing their credibility.

Another notable strength is the study's clear differentiation between the roles of microglia and astrocytes in synaptic elimination. The finding that caspase-3 activation selectively enables microglial—but not astrocytic—targeting of weakened synapses adds granularity to our understanding of glia-specific mechanisms in synaptic remodeling. This distinction will be valuable for future studies aiming to modulate specific glial pathways in therapeutic contexts.

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Furthermore, the translational extension of the findings into a mouse model of Alzheimer's disease broadens the significance of the study. Demonstrating that caspase-3 deficiency confers synaptic protection in the presence of amyloid-β strengthens the argument for caspase-3 as a viable therapeutic target. The convergence of developmental biology and disease pathology in this context enhances the study's impact and raises important questions about the reactivation of developmental pathways in neurodegeneration.

However, one area that could be improved is the mechanistic detail underlying caspase-3 activation in response to synaptic weakening. While the study convincingly shows that reduced activity triggers caspase-3 activation, it does not explore upstream signaling pathways or the molecular sensors that detect synaptic inactivity. A discussion or preliminary data addressing these upstream events would enrich the model and offer targets for intervention at earlier stages of the pathway.

In addition, although the study demonstrates caspase-3's necessity for synapse elimination, it does not assess whether its activation is sufficient to induce pruning in the absence of decreased activity. Establishing sufficiency, perhaps via optogenetic or chemogenetic tools, would strengthen the causal framework and clarify whether caspase-3 acts as a gatekeeper or merely a permissive factor.

The role of caspase-3 in cell death versus synapse elimination is also a point that warrants more detailed discussion. While the non-apoptotic functions of caspases are increasingly recognized, the boundary between synaptic pruning and neuronal viability can be subtle. The manuscript would benefit from additional controls or clarifications to distinguish low-level, localized caspase activity in synapses from broader apoptotic signaling cascades.

From a methodological standpoint, the study is largely robust, but details on the quantification of synapse elimination and microglial engagement could be expanded. For example, a discussion on the resolution limits of the imaging methods and the criteria used to define engulfment events would improve reproducibility and transparency. Inclusion of these technical aspects would be especially helpful for researchers seeking to replicate or build upon the findings.

The manuscript's writing is generally clear and concise, but there are sections where more contextualization could aid interpretation. For instance, brief background on caspase-3's established roles outside of apoptosis would help frame the novelty of the findings. Similarly, elaborating on the implications for neurodevelopmental disorders (e.g., autism or schizophrenia), where synaptic pruning abnormalities are implicated, could broaden the relevance of the work.

In conclusion, this study makes a valuable contribution to the field by identifying caspase-3 activation as a central determinant of synapse specificity in microglia-mediated pruning during development and in Alzheimer's disease. Its strengths lie in its elegant use of in vivo models, its glia-specific insights, and its translational scope. Future work could build upon this foundation by elucidating upstream regulators of caspase-3 and exploring its therapeutic modulation in neurodevelopmental and neurodegenerative conditions alike.

Declarations

Potential competing interests: No potential competing interests to declare.