Synaptic Pruning and Learning/Adaptation in the Adult Brain: A Comprehensive Review

1. Introduction

Synaptic pruning—the selective elimination of synapses—is increasingly recognized as a dynamic and ongoing process in the adult brain, not just a developmental phenomenon. Recent research demonstrates that synaptic pruning, mediated by glial cells (especially microglia and astrocytes), is crucial for experience-dependent plasticity, learning, memory formation, and cognitive adaptation throughout adulthood (Cornell et al., 2021; Morizawa et al., 2022; Hösli et al., 2022; Basilico et al., 2021; Ball et al., 2022; Vardalaki et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; De Luca et al., 2020; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Basilico et al., 2022). Pruning helps refine neural circuits by removing less active or redundant synapses, thereby enhancing the efficiency and flexibility of information processing. This process is tightly regulated by molecular signals, neuronal activity, and glial-neuronal interactions, and is implicated in both healthy cognitive function and the pathophysiology of neuropsychiatric and neurodegenerative disorders (Cornell et al., 2021; Morizawa et al., 2022; Hösli et al., 2022; Basilico et al., 2021; Ball et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; De Luca et al., 2020; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Basilico et al., 2022). The following review synthesizes the current understanding of synaptic pruning's role in adult learning and adaptation, highlighting key mechanisms, evidence, and open questions.

2. Methods

A comprehensive search was conducted across over 170 million research papers in Consensus, including Semantic Scholar, PubMed, and other databases. The search strategy targeted foundational concepts, mechanistic studies, glial involvement, molecular pathways, computational models, and clinical implications of synaptic pruning in adult learning and adaptation. In total, 1047 papers were identified, 690 were screened, 568 were deemed eligible, and the top 50 most relevant papers were included in this review.

Search Strategy

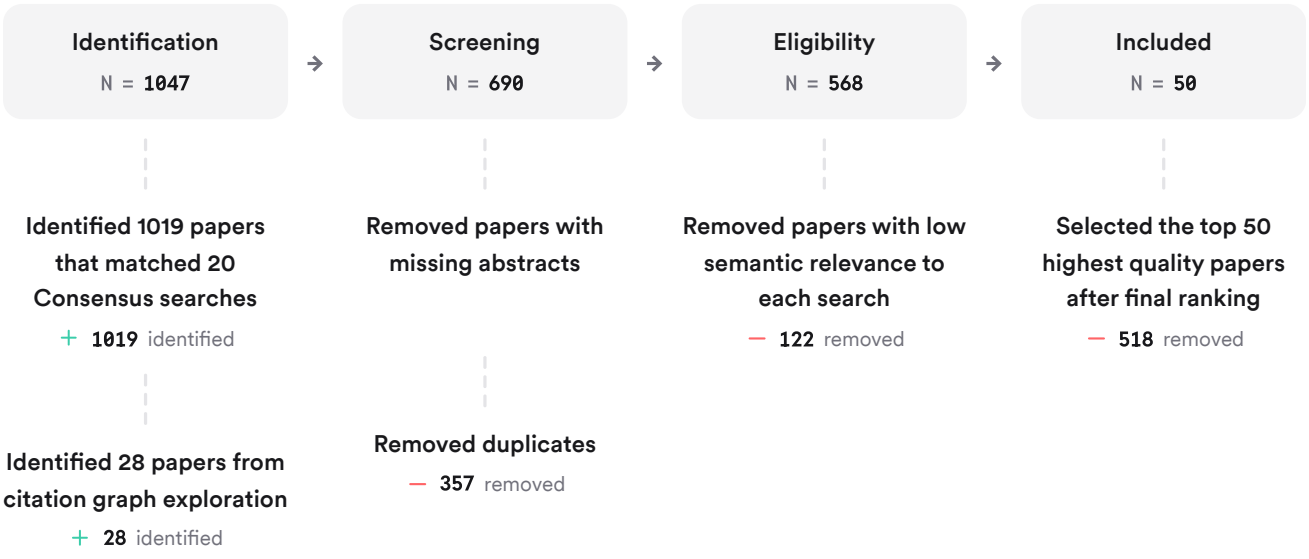

FIGURE 1 Flow of papers through the search and selection process.

Eight unique search groups were used, spanning foundational, mechanistic, and interdisciplinary perspectives.

3. Results

3.1 Glial-Mediated Synaptic Pruning in Adult Plasticity

Microglia and astrocytes are central to synaptic pruning in the adult brain. Microglia monitor synaptic activity and selectively engulf less active synapses via complement pathways (e.g., C1q, C3, CR3) and “Eat Me/Don’t Eat Me” signals, thereby regulating synaptic plasticity, learning, and memory (Cornell et al., 2021; Morizawa et al., 2022; Hösli et al., 2022; Basilico et al., 2021; Ball et al., 2022; Wang et al., 2021; Kurematsu et al., 2022; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Basilico et al., 2022). Astrocytes also modulate synaptic pruning and plasticity through gap junctions, cytokine release (e.g., IL-33), and direct synaptic contact (Hösli et al., 2022; Wang et al., 2021; Wang et al., 2020; Nguyen et al., 2020). Disruption of glial function impairs synaptic homeostasis, plasticity, and cognitive performance (Hösli et al., 2022; Basilico et al., 2021; Wang et al., 2021; Kurematsu et al., 2022; Liu et al., 2020; Nguyen et al., 2020).

3.2 Synaptic Pruning and Experience-Dependent Learning

Experience-dependent synaptic pruning is observed in multiple adult brain regions, including the hippocampus, cortex, and cerebellum. Learning tasks (e.g., motor adaptation, spatial navigation) induce glial-mediated synaptic engulfment, dendritic spine remodeling, and selective elimination of less active synapses, which are essential for memory consolidation and circuit refinement (Morizawa et al., 2022; Schmidt et al., 2020; Vardalaki et al., 2022; Donato et al., 2013; Kurematsu et al., 2022; De Luca et al., 2020; Liu et al., 2020; Nguyen et al., 2020). Both the formation of new synapses and the pruning of existing ones contribute to the dynamic reorganization of neural circuits during learning (Schmidt et al., 2020; Vardalaki et al., 2022; Donato et al., 2013; Kurematsu et al., 2022; De Luca et al., 2020; Liu et al., 2020; Nguyen et al., 2020).

3.3 Molecular and Cellular Mechanisms

Synaptic pruning in adulthood is regulated by a complex interplay of molecular signals, including complement proteins, neurotrophic factors (e.g., BDNF, netrin-1), cytokines (e.g., IL-33), and neurotransmitter systems (e.g., dopamine, serotonin) (Cornell et al., 2021; Glasgow et al., 2020; Wang et al., 2021; Johnstone & Mobley, 2020; Wang et al., 2020; Nguyen et al., 2020; Zhang et al., 2021; Bijata et al., 2017). Activity-dependent mechanisms, such as Hebbian plasticity, long-term potentiation (LTP), and long-term depression (LTD), interact with pruning processes to shape synaptic strength and connectivity (Mansvelder et al., 2019; Donato et al., 2013; Piochon et al., 2016; Yasuda et al., 2022; Bazzari & Parri, 2019; Zhang et al., 2021; Bijata et al., 2017; Fuchsberger & Paulsen, 2022). Silent synapses and dendritic spine turnover provide a reservoir for circuit remodeling and learning in the adult brain (Vardalaki et al., 2025; Vardalaki et al., 2022; Xu et al., 2020).

3.4 Synaptic Pruning in Health, Aging, and Disease

Proper synaptic pruning supports cognitive flexibility and memory, while dysregulation is linked to aging, neurodegeneration, and psychiatric disorders (Cornell et al., 2021; Hösli et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; Navakkode & Kennedy, 2024; De Luca et al., 2020; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Zhang et al., 2021; Basilico et al., 2022). Excessive or insufficient pruning can impair learning, memory, and adaptation, and is implicated in conditions such as Alzheimer's disease, schizophrenia, and depression (Cornell et al., 2021; Hösli et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; Navakkode & Kennedy, 2024; De Luca et al., 2020; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Zhang et al., 2021; Basilico et al., 2022). Manipulating glial activity or pruning pathways is being explored as a therapeutic strategy for cognitive enhancement and neuroprotection (Cornell et al., 2021; Morizawa et al., 2022; Hösli et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Basilico et al., 2022).

Key Papers

Paper	Methodology	Key Findings
(Cornell et al., 2021)	Review, animal/human	Microglia regulate synaptic pruning and plasticity, essential for learning/memory in adults
(Morizawa et al., 2022)	In vivo imaging, mouse	Glial synaptic engulfment increases with motor learning; blocking pruning impairs adaptation
(Hösli et al., 2022)	Genetic knockout, mouse	Astrocyte gap junctions vital for synaptic plasticity and spatial learning in adults
(Vardalaki et al., 2022)	Super-resolution imaging, mouse	Silent synapses abundant in adult cortex; can be unsilenced for learning via plasticity
(Donato et al., 2013)	Behavioral, mouse	PV-interneuron network plasticity and synaptic remodeling regulate adult learning/memory

FIGURE 2 Comparison of key studies on synaptic pruning and adult learning/adaptation.

Top Contributors

Type	Name	Papers
Author	S. Donato	(Donato et al., 2013)
Author	Dimitra Vardalaki	(Vardalaki et al., 2025; Vardalaki et al., 2022)
Author	J. Cornell	(Cornell et al., 2021)
Journal	*Nature*	(Morizawa et al., 2022; Vardalaki et al., 2022; Donato et al., 2013; Piochon et al., 2016)
Journal	*Glia*	(Basilico et al., 2021; Ball et al., 2022)
Journal	*Cell reports*	(Hösli et al., 2022; Horn et al., 2013; Bijata et al., 2017)

FIGURE 3 Authors & journals that appeared most frequently in the included papers.

4. Discussion

The evidence robustly supports that synaptic pruning is an active, regulated process in the adult brain, essential for learning, memory, and adaptation (Cornell et al., 2021; Morizawa et al., 2022; Hösli et al., 2022; Basilico et al., 2021; Ball et al., 2022; Vardalaki et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; De Luca et al., 2020; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Basilico et al., 2022). Glial cells, especially microglia and astrocytes, are key mediators, responding to neuronal activity and experience to sculpt neural circuits (Cornell et al., 2021; Morizawa et al., 2022; Hösli et al., 2022; Basilico et al., 2021; Ball et al., 2022; Wang et al., 2021; Kurematsu et al., 2022; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Basilico et al., 2022). Pruning is tightly linked to synaptic plasticity mechanisms (LTP, LTD, Hebbian rules), and both the elimination and formation of synapses are required for optimal cognitive function (Mansvelder et al., 2019; Vardalaki et al., 2022; Donato et al., 2013; Piochon et al., 2016; Yasuda et al., 2022; Bazzari & Parri, 2019; Zhang et al., 2021; Bijata et al., 2017; Fuchsberger & Paulsen, 2022). The presence of silent synapses and ongoing dendritic spine turnover in adults provides a substrate for rapid circuit remodeling and learning (Vardalaki et al., 2025; Vardalaki et al., 2022; Xu et al., 2020).

However, the relationship between synaptic pruning and behavior is complex. While pruning is necessary for certain types of learning and memory, not all forms of cognitive adaptation require extensive synaptic elimination (Basilico et al., 2022). The balance between pruning and synaptic stabilization is critical; dysregulation can lead to cognitive deficits or neuropsychiatric disease (Cornell et al., 2021; Hösli et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; Navakkode & Kennedy, 2024; De Luca et al., 2020; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Zhang et al., 2021; Basilico et al., 2022). There are also open questions about the specificity of pruning mechanisms across brain regions, cell types, and learning paradigms.

Claims and Evidence Table

Claim	Evidence Strength	Reasoning	Papers
Synaptic pruning occurs in the adult brain and is experience-dependent	Strong	In vivo imaging, molecular, and behavioral studies	(Cornell et al., 2021; Morizawa et al., 2022; Hösli et al., 2022; Basilico et al., 2021; Ball et al., 2022; Vardalaki et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; De Luca et al., 2020; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Basilico et al., 2022)
Glial cells (microglia, astrocytes) mediate adult synaptic pruning	Strong	Genetic, pharmacological, and imaging evidence	(Cornell et al., 2021; Morizawa et al., 2022; Hösli et al., 2022; Basilico et al., 2021; Ball et al., 2022; Wang et al., 2021; Wang et al., 2020; Kurematsu et al., 2022; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Basilico et al., 2022)
Pruning is essential for learning, memory, and adaptation	Strong	Blocking pruning impairs learning/adaptation; pruning increases with learning	(Morizawa et al., 2022; Hösli et al., 2022; Vardalaki et al., 2022; Donato et al., 2013; Kurematsu et al., 2022; De Luca et al., 2020; Liu et al., 2020; Nguyen et al., 2020)
Silent synapses and spine turnover enable adult circuit remodeling	Moderate	Super-resolution imaging, physiological studies	(Vardalaki et al., 2025; Vardalaki et al., 2022; Xu et al., 2020)
Dysregulated pruning is linked to cognitive and neuropsychiatric disorders	Moderate	Animal models, human pathology	(Cornell et al., 2021; Hösli et al., 2022; Donato et al., 2013; Wang et al., 2021; Kurematsu et al., 2022; Navakkode & Kennedy, 2024; De Luca et al., 2020; Liu et al., 2020; Sominsky et al., 2018; Nguyen et al., 2020; Zhang et al., 2021; Basilico et al., 2022)
Pruning and synaptogenesis are both required for optimal adaptation	Moderate	Both elimination and formation observed during learning	(Schmidt et al., 2020; Vardalaki et al., 2022; Donato et al., 2013; Kurematsu et al., 2022; De Luca et al., 2020; Liu et al., 2020; Nguyen et al., 2020)

FIGURE Key claims and support evidence identified in these papers.

5. Conclusion

Synaptic pruning is a dynamic, experience-dependent process in the adult brain, essential for learning, memory, and adaptation. Glial cells orchestrate the selective elimination and maintenance of synapses, enabling flexible and efficient neural circuit function. Dysregulation of pruning contributes to cognitive decline and neuropsychiatric disease, making it a promising target for therapeutic intervention.

5.1 Research Gaps

Key gaps include the precise molecular signals governing adult pruning, the interplay between pruning and synaptogenesis, and the behavioral specificity of pruning across learning paradigms.

Research Gaps Matrix

Topic/Attribute	Microglia	Astrocytes	Molecular Pathways	Behavioral Studies	Disease Models
Adult Pruning Mechanisms	12	8	7	9	6
Experience-Dependent Pruning	10	6	5	8	4
Pruning & Synaptogenesis	7	5	4	6	3
Pruning in Disease	8	5	6	5	10

FIGURE Distribution of research across topics and study attributes, highlighting underexplored areas.

5.2 Open Research Questions

Future research should clarify the molecular and cellular rules of adult synaptic pruning, its behavioral specificity, and its therapeutic potential.

Question	Why
What molecular signals determine which synapses are pruned versus maintained in the adult brain?	Understanding this will enable targeted interventions for cognitive enhancement and disease.
How do synaptic pruning and synaptogenesis interact during different forms of adult learning and adaptation?	Clarifying this interplay is key to understanding circuit remodeling and optimizing learning.
Can manipulating glial-mediated pruning improve cognitive function or treat neuropsychiatric disorders in adults?	This could lead to novel therapies for cognitive decline and mental illness.

FIGURE Key open questions for advancing research on synaptic pruning and adult learning/adaptation.

In summary, synaptic pruning is a vital, ongoing process in the adult brain, enabling learning and adaptation through glial-mediated circuit refinement. Further research will deepen our understanding and therapeutic use of this fundamental mechanism.

These papers were sourced and synthesized using Consensus, an AI-powered search engine for research. Try it at https://consensus.app

References

Cornell, J., Salinas, S., Huang, H., & Zhou, M. (2021). Microglia regulation of synaptic plasticity and learning and memory. *Neural Regeneration Research*, 17, 705 - 716. https://doi.org/10.4103/1673-5374.322423

Mansvelder, H., Verhoog, M., & Goriounova, N. (2019). Synaptic plasticity in human cortical circuits: cellular mechanisms of learning and memory in the human brain?. *Current opinion in neurobiology*, 54, 186-193. https://doi.org/10.1016/j.conb.2018.06.013

Morizawa, Y., Matsumoto, M., Nakashima, Y., Endo, N., Aida, T., Ishikane, H., Beppu, K., Moritoh, S., Inada, H., Osumi, N., Shigetomi, E., Koizumi, S., Yang, G., Hirai, H., Tanaka, K., Tanaka, K., Ohno, N., Fukazawa, Y., & Matsui, K. (2022). Synaptic pruning through glial synapse engulfment upon motor learning. *Nature Neuroscience*, 25, 1458 - 1469. https://doi.org/10.1038/s41593-022-01184-5

Glasgow, S., Ruthazer, E., & Kennedy, T. (2020). Guiding synaptic plasticity: Novel roles for netrin-1 in synaptic plasticity and memory formation in the adult brain. *The Journal of Physiology*, 599. https://doi.org/10.1113/JP278704

Hösli, L., Binini, N., Ferrari, K., Thieren, L., Looser, Z., Zuend, M., Zanker, H., Berry, S., Holub, M., Möbius, W., Ruhwedel, T., Nave, K., Giaume, C., Weber, B., & Saab, A. (2022). Decoupling astrocytes in adult mice impairs synaptic plasticity and spatial learning.. *Cell reports*, 38 10, 110484. https://doi.org/10.1016/j.celrep.2022.110484

Basilico, B., Ferrucci, L., Ratano, P., Golia, M., Grimaldi, A., Rosito, M., Ferretti, V., Reverte, I., Marrone, M., Giubettini, M., De Turris, V., Salerno, D., Garofalo, S., St-Pierre, M., Carrier, M., Renzi, M., Pagani, F., Raspa, M., Scavizzi, F., Gross, C., Marinelli, S., Tremblay, M., Caprioli, D., Maggi, L., Limatola, C., Di Angelantonio, S., & Ragozzino, D. (2021). Microglia control glutamatergic synapses in the adult mouse hippocampus. *Glia*, 70, 173 - 195. https://doi.org/10.1002/glia.24101

Vardalaki, D., Yaeger, C., & Harnett, M. (2025). Silent Synapses in the Adult Brain.. *Annual review of neuroscience*. https://doi.org/10.1146/annurev-neuro-112723-032924

Ball, J., Green-Fulgham, S., & Watkins, L. (2022). Mechanisms of microglia-mediated synapse turnover and synaptogenesis. *Progress in Neurobiology*, 218. https://doi.org/10.1016/j.pneurobio.2022.102336

Schmidt, S., Gull, S., Herrmann, K., Boehme, M., Irintchev, A., Urbach, A., Reichenbach, J., Klingner, C., Gaser, C., & Witte, O. (2020). Experience-dependent structural plasticity in the adult brain: How the learning brain grows. *NeuroImage*, 225. https://doi.org/10.1016/j.neuroimage.2020.117502

Vardalaki, D., Chung, K., & Harnett, M. (2022). Filopodia are a structural substrate for silent synapses in adult neocortex. *Nature*, 612, 323-327. https://doi.org/10.1038/s41586-022-05483-6

Donato, F., Rompani, S., & Caroni, P. (2013). Parvalbumin-expressing basket-cell network plasticity induced by experience regulates adult learning. *Nature*, 504, 272-276. https://doi.org/10.1038/nature12866

Wang, Y., Fu, A., & Ip, N. (2021). Instructive roles of astrocytes in hippocampal synaptic plasticity: neuronal activity-dependent regulatory mechanisms. *The Febs Journal*, 289, 2202 - 2218. https://doi.org/10.1111/febs.15878

Johnstone, A., & Mobley, W. (2020). Local TrkB signaling: themes in development and neural plasticity. *Cell and Tissue Research*, 382, 101 - 111. https://doi.org/10.1007/s00441-020-03278-7

Wang, Y., Fu, W., Cheung, K., Hung, K., Chen, C., Geng, H., Yung, W., Qu, J., Fu, A., & Ip, N. (2020). Astrocyte-secreted IL-33 mediates homeostatic synaptic plasticity in the adult hippocampus. *Proceedings of the National Academy of Sciences of the United States of America*, 118. https://doi.org/10.1073/pnas.2020810118

Kurematsu, C., Sawada, M., Ohmuraya, M., Tanaka, M., Kuboyama, K., Ogino, T., Matsumoto, M., Oishi, H., Inada, H., Ishido, Y., Sakakibara, Y., Nguyen, H., Thai, T., Kohsaka, S., Ohno, N., Yamada, M., Asai, M., Sokabe, M., Nabekura, J., Asano, K., Tanaka, M., & Sawamoto, K. (2022). Synaptic pruning of murine adult-born neurons by microglia depends on phosphatidylserine. *The Journal of Experimental Medicine*, 219. https://doi.org/10.1084/jem.20202304

Piochon, C., Kano, M., & Hansel, C. (2016). LTD-like molecular pathways in developmental synaptic pruning. *Nature Neuroscience*, 19, 1299-1310. https://doi.org/10.1038/nn.4389

Horn, K., Glasgow, S., Gobert, D., Bull, S., Luk, T., Girgis, J., Tremblay, M., McEachern, D., Bouchard, J., Haber, M., Hamel, E., Krimpenfort, P., Murai, K., Berns, A., Doucet, G., Chapman, C., Ruthazer, E., & Kennedy, T. (2013). DCC expression by neurons regulates synaptic plasticity in the adult brain.. *Cell reports*, 3 1, 173-85. https://doi.org/10.1016/j.celrep.2012.12.005

Navakkode, S., & Kennedy, B. (2024). Neural ageing and synaptic plasticity: prioritizing brain health in healthy longevity. *Frontiers in Aging Neuroscience*, 16. https://doi.org/10.3389/fnagi.2024.1428244

De Luca, S., Soch, A., Sominsky, L., Nguyen, T., Bosakhar, A., & Spencer, S. (2020). Glial remodeling enhances short-term memory performance in Wistar rats. *Journal of Neuroinflammation*, 17. https://doi.org/10.1186/s12974-020-1729-4

Liu, Y., Spangenberg, E., Tang, B., Holmes, T., Green, K., & Xu, X. (2020). Microglia Elimination Increases Neural Circuit Connectivity and Activity in Adult Mouse Cortex. *The Journal of Neuroscience*, 41, 1274 - 1287. https://doi.org/10.1523/jneurosci.2140-20.2020

Yasuda, R., Hayashi, Y., & Hell, J. (2022). CaMKII: a central molecular organizer of synaptic plasticity, learning and memory. *Nature Reviews Neuroscience*, 23, 666 - 682. https://doi.org/10.1038/s41583-022-00624-2

Sominsky, L., De Luca, S., & Spencer, S. (2018). Microglia: Key players in neurodevelopment and neuronal plasticity.. *The international journal of biochemistry & cell biology*, 94, 56-60. https://doi.org/10.1016/j.biocel.2017.11.012

Bazzari, A., & Parri, H. (2019). Neuromodulators and Long-Term Synaptic Plasticity in Learning and Memory: A Steered-Glutamatergic Perspective. *Brain Sciences*, 9. https://doi.org/10.3390/brainsci9110300

Zhang, H., Zablah, Y., Zhang, H., & Jia, Z. (2021). Rho Signaling in Synaptic Plasticity, Memory, and Brain Disorders. *Frontiers in Cell and Developmental Biology*, 9. https://doi.org/10.3389/fcell.2021.729076

Nguyen, P., Dorman, L., Pan, S., Vainchtein, I., Han, R., Nakao-Inoue, H., Taloma, S., Barron, J., Molofsky, A., Kheirbek, M., & Molofsky, A. (2020). Microglial Remodeling of the Extracellular Matrix Promotes Synapse Plasticity. *Cell*, 182, 388-403.e15. https://doi.org/10.1016/j.cell.2020.05.050

Zhang, Y., Lin, W., Huang, L., Zhao, B., Zhang, C., & Yin, D. (2021). Dopamine D2 receptor regulates cortical synaptic pruning in rodents. *Nature Communications*, 12. https://doi.org/10.1038/s41467-021-26769-9

Bijata, M., Labus, J., Guseva, D., Stawarski, M., Butzlaff, M., Dzwonek, J., Schneeberg, J., Böhm, K., Michaluk, P., Rusakov, D., Dityatev, A., Wilczynski, G., Włodarczyk, J., & Ponimaskin, E. (2017). Synaptic Remodeling Depends on Signaling between Serotonin Receptors and the Extracellular Matrix.. *Cell reports*, 19 9, 1767-1782. https://doi.org/10.1016/j.celrep.2017.05.023

Xu, W., Löwel, S., & Schlüter, O. (2020). Silent Synapse-Based Mechanisms of Critical Period Plasticity. *Frontiers in Cellular Neuroscience*, 14. https://doi.org/10.3389/fncel.2020.00213

Basilico, B., Ferrucci, L., Khan, A., Di Angelantonio, S., Ragozzino, D., & Reverte, I. (2022). What microglia depletion approaches tell us about the role of microglia on synaptic function and behavior. *Frontiers in Cellular Neuroscience*, 16. https://doi.org/10.3389/fncel.2022.1022431

Fuchsberger, T., & Paulsen, O. (2022). Modulation of hippocampal plasticity in learning and memory. *Current Opinion in Neurobiology*, 75. https://doi.org/10.1016/j.conb.2022.102558