enigmatic biological phenomenon. In future studies, it will be interesting to identify the mechanism by which ARCP-1 mediates upregulation of *flp-19,* the cellular target(s) of FLP-19, and the downstream signaling components that mediate the effects of FLP-19. In addition, the present study demonstrates that *arcp-1* regulates not only CO_2 response but also salt-based associative learning, and, in future studies, it will be interesting to further investigate the extent to which *arcp-1* regulates other forms of behavioral plasticity. Finally, this study is foundational in its approach and paves the way for future mechanistic studies of inter-individual variability in complex behaviors. Applying a similar molecular genetic strategy to other wild isolates and flexible behaviors will undoubtedly enable the discovery of additional genetic mechanisms that contribute to inter-individual differences in behavioral flexibility.

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Glia: The Glue Holding Memories Together

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Adult oligodendrogenesis is regulated by neuronal activity and learning. Can it affect memory processes? In this issue of *Neuron*, Steadman et al. (2020) found that newly generated oligodendrocytes are crucial for memory acquisition and consolidation and required for the neuronal coupling between brain regions known to be involved in memory.

Long-distance information transfer between remote regions of the brain is carried by action potentials traveling along axons. While the size of the action potential is fixed, its conduction speed depends on the degree by which the axon is covered in myelin sheaths, formed by oligodendrocytes. As opposed to other cell types in the brain (neurons and astrocytes), new oligodendrocytes are continuously generated from oligodendrocyte precursor cells (OPCs) throughout the normal lifetime of an organism. Oligodendrogenesis is regulated by neuronal activity, as demonstrated by the findings that increasing neural activity *in vivo* induces preferential myelination of axons that belong to activated neurons (Gibson et al., 2014; Hines et al., 2015; Mensch et al., 2015). Even more remarkable, *de novo* myelination has been reported following motor learning (Gibson et al., 2014; McKenzie et al., 2014) or exposure to an enriched environment (Hughes et al., 2018), indicating that new oligodendrocytes may have an important role in shaping neuronal circuits in an experience-dependent manner. This may be especially relevant to multimodal cognitive processes that rely on the interaction between distant brain regions, like memory. In their elegant paper "Disruption of oligodendrogenesis impairs memory consolidation in adult mice," Steadman et al. (2020) show that the generation of new oligodendrocytes is crucial for the acquisition and consolidation of spatial and contextual memory. Moreover, this innovative study suggests that experience-dependent *de novo* myelination is required for coupling between different brain structures that are known to be involved in learning and memory processes (Figure 1).

Steadman et al. (2020) first show that memory formation induces oligodendrogenesis: they used a spatial memory task in which training occurs over multiple days, followed by tests 1 day (recent) and 1 month (remote) later. Similar to motor learning (Gibson et al., 2014; McKenzie et al., 2014) and sensory enrichment (Hughes et al., 2018), spatial memory acquisition was associated with increased oligodendrocyte generation, specifically in frontal cortical regions known to be involved in memory. Interestingly, newly born oligodendrocytes were also generated at the time of memory consolidation (between training and remote testing), not in the hippocampus itself, but rather in cortical areas associated with remote memory, like the anterior cingulate cortex (ACC), and in axonal pathways near them, like the anterior corpus callosum. This increase in oligodendrogenesis resulted in a larger number of myelinated axons in the anterior corpus callosum. Interestingly, spatial learning was also previously shown to induce microstructural changes in human white matter, measured by diffusion tensor imaging (DTI) (Hofstetter et al., 2013). These changes were positively correlated with spatial memory improvement (Hofstetter et al., 2013). Together, these findings, showing learning-induced changes in myelination across species, suggest that newly generated oligodendrocytes may have a functional role in spatial memory not only during learning but also during consolidation.

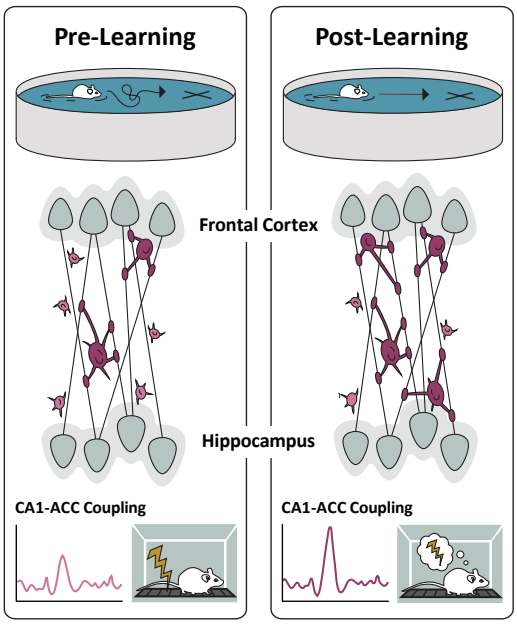

Figure 1. Learning Induces Adult Oligodendrogenesis, which Facilitates Coupling between Distant Brain Regions

De novo myelination was induced by the acquisition and consolidation of a spatial water maze task in frontal areas known to be involved in memory. Contextual fear conditioning increased coupling between the CA1 and the ACC, measured by local field potentials. Reducing adult oligodendrogenesis during learning or early consolidation resulted in spatial and contextual memory deficits and impaired the inter-region coordination. Figure credit: Aviya Benmelech-Chovav.

To determine the necessity of oligodendrogenesis for the different stages of spatial learning, the authors used transgenic mice in which OPCs were prevented from maturing into oligodendrocytes in a temporally controlled manner, starting either at acquisition or during consolidation of spatial memory. Reduced adult oligodendrogenesis during the training period resulted in impaired recent spatial memory. This finding is in line with previous reports showing that reduced oligodendrogenesis disrupts motor learning acquisition (McKenzie et al., 2014) and is associated with impaired object recognition (Geraghty et al., 2019). Moreover, mice in which oligodendrogenesis was prevented only after training (i.e., during consolidation) had remote memory deficits, indicating that new oligodendrocytes are required for acquisition and early consolidation of remote memory. Indeed, when oligodendrogenesis was blocked starting 3 days before remote recall, after the memory was already well established, no effect on memory retrieval was observed. Because intact remote memory is based on systems consolidation, a process involving modifications in hippocampal-frontal networks, the authors hypothesized that the memory deficits they observed after reducing oligodendrogenesis may result from impaired connectivity between these regions.

To test this hypothesis, Steadman et al. (2020) used a contextual fear learning paradigm, requiring only a single trial for acquisition and thus enabling measurement of neural activity immediately prior or following learning. Because remote memory consolidation is associated with increased synchronization between the hippocampus and frontal cortices, the authors hypothesized that reducing oligodendrogenesis before acquisition may result in decreased neuronal coupling between these regions. They placed electrodes in the dorsal CA1 region of the hippocampus and in the ACC (shown earlier in this work to have higher oligodendrogenesis during memory consolidation) to evaluate changes in coordinated neuronal activity between these regions before and after fear conditioning, when the generation of new oligodendrocytes is manipulated. Importantly, local neuronal activity in the dorsal hippocampus and the ACC was not affected by the reduction in oligodendrogenesis. However, the learning-induced coupling of these regions, observed in normal mice, was decreased when new oligodendrocytes could not be generated. This reduction in inter-region coupling was accompanied by impaired remote contextual fear memory retrieval, showing that new oligodendrocytes are required during remote memory consolidation to enable coordinated activity of distant brain regions.

The current paper (Steadman et al., 2020) reveals a novel role for adult oligodendrogenesis in memory consolidation and opens exciting research avenues that will examine a variety of questions. What are the mechanisms allowing oligodendrocytes to preferentially myelinate active axons during memory consolidation? Do adult-born oligodendrocytes have a role in other forms of memory (e.g., extinction) or in forgetting? Can decreased myelin coverage throughout the lifetime (Hill et al., 2018) cause memory deficits in aging? The path to answering such important questions will be vastly facilitated by the integration of chemogenetic or optogenetic tools, specifically targeting either OPCs or mature oligodendrocytes. Because these tools are reversible, they will allow a better

definition of the temporal window in which oligodendrocytes are involved in the different stages of memory and enable an understanding of the permanency of the observed effects. Moreover, the development of viral vectors instead of transgenic mice will allow a detailed topographical investigation of the importance of myelination in specific projections involved in memory.

By adopting a non-neurocentric research approach, Steadman et al. (2020) unveil a novel mechanism of inter-region plasticity modulation. Together with recent studies (e.g., Adamsky et al., 2018) looking at the involvement of other glia cells, like astrocytes, in memory acquisition and consolidation, it emphasizes the critical contribution of non-neuronal cells to high cognitive functions and exposes the subtlety and specificity in which glia cells can modulate neuronal circuits and, consequently, behavior.

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