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Experience-dependent control of synaptic remodeling and structural plasticity by glia

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The central nervous system (CNS) integrates intrinsic molecular cues with sensory experience to shape synaptic connectivity between neurons. Once established, these emergent neural circuits remain plastic into adulthood to facilitate behavioral adaptations to changes in the sensory landscape. While sensory experience has been recognized as a major contributor to synaptic wiring since the foundational work of Hubel and Wiesel in the mid-1900s, the field has only recently begun to uncover the roles of nonneuronal cells, or glia, in experience-dependent aspects of synaptic refinement and remodeling. Herein, we review recent work demonstrating that many glial cell types—including invertebrate glia, astrocytes, microglia, and oligodendrocyte-lineage cells—participate in the experience-dependent remodeling of neural circuits across the lifespan.

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Introduction

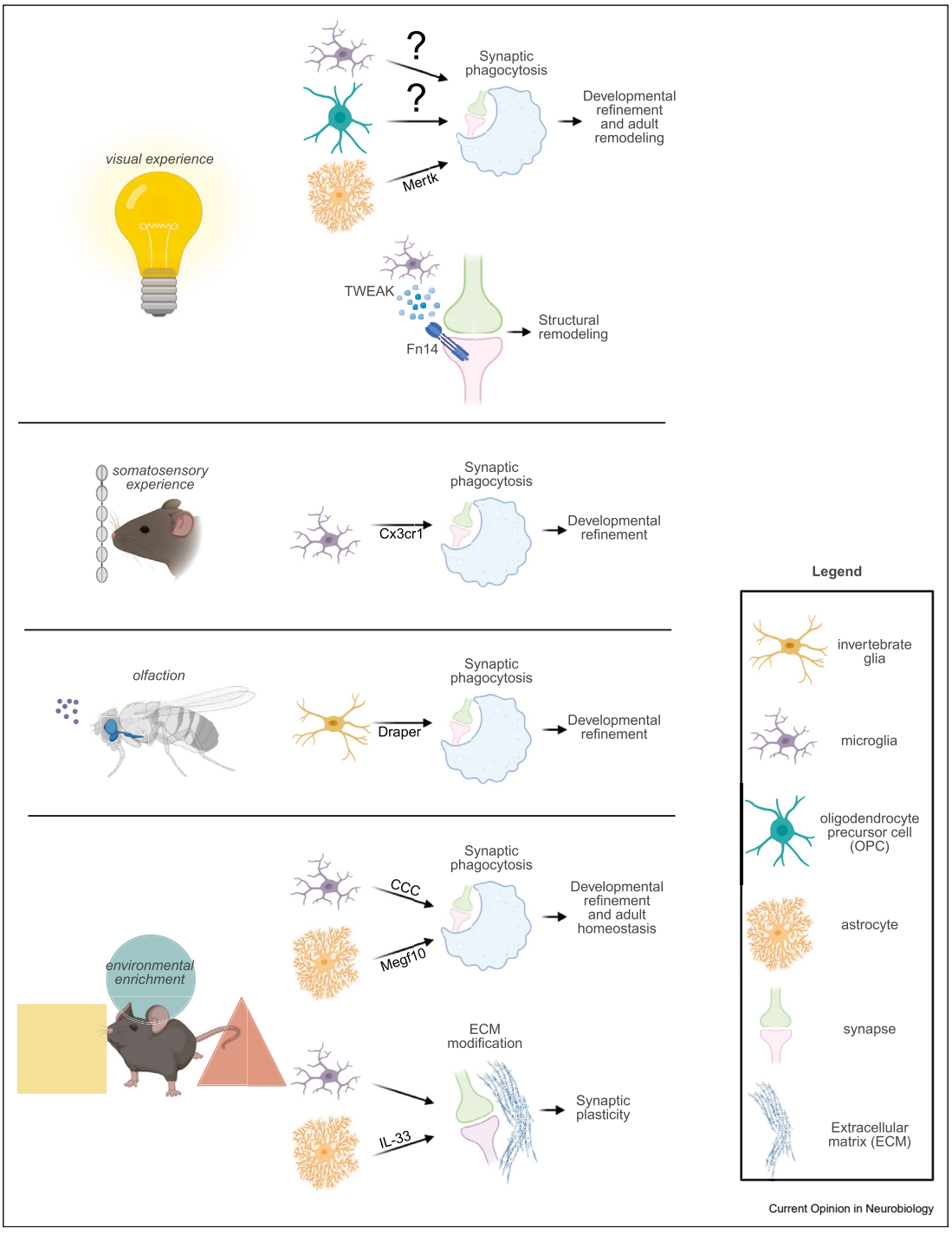
Neural circuits emerge developmentally through interactions between patterning cues intrinsic to the brain and sensory experiences originating from the external environment. Initially, intrinsic factors, such as Hebbian plasticity driven by intrinsically generated neural activity [1,2], axon guidance molecules [3], and evolving transcriptional programs [4] govern circuit formation by inducing synapse assembly. These newly assembled, immature circuits then undergo early postnatal phases of heightened plasticity (so-called *critical* or *sensitive periods*) in which they are further refined in response to sensory experience via the concurrent strengthening of some and elimination of other synapses [5,6]. Beyond circuit development, experience can also remodel synapses in the adult brain, for example during learning and memory [7,8]. Thus, sensory experience plays powerful roles in establishing, maintaining, and reorganizing synaptic connectivity during development and in the adult.

While several mechanisms through which neurons cell autonomously adapt their connectivity in response to experience have been described [9,10], emerging evidence suggests that nonneuronal brain cells, or glia, also contribute to experience-dependent adaptations in synaptic connectivity (Figure 1). In this review, we discuss the roles of glia in experience-dependent circuit plasticity, highlighting evidence that different types of glia can engage similar mechanisms to remodel synapses in response to experience, but that individual glial cell types are specialized to remodel distinct circuits in an age-, brain region-, and stimulus-dependent manner.

Overview of the diversity of glial cell types across organisms and systems

In combination with neurons, a diversity of glial cell types contribute to the organization of neural circuits in invertebrate and vertebrate systems [11–13]. For instance, the *Drosophila* (fruit fly) and *C. Elegans* (nematode worm) nervous systems include numerous types of glia which play overlapping roles in supporting neural circuits through neurotransmitter signaling [14,15], stabilizing dendritic arbors [16], and promoting synaptogenesis [17–19]. Additionally, invertebrate glia engulf neuronal material to remodel circuits in the nervous system. In *Drosophila*, for instance, astrocyte-like glia engulf axonal and synaptic material during metamorphosis [20]. Additionally, *Drosophila* ensheathing glia are implicated in the experience-dependent removal of axonal and synaptic material [21–24] (see below). Vertebrates similarly contain a variety of glial cell types that perform many of the same functions identified for invertebrate glia, including oligodendroglia, microglia, and astrocytes. Astrocytes are a critical component of the tripartite synapse [25] where they actively buffer neurotransmitter levels during synaptic transmission [26–28]. Oligodendrocyte-lineage cells, ranging from oligodendrocyte precursor cells (OPCs) to mature

Figure 1



Roles of glia in experience-dependent synaptic remodeling and plasticity. Microglia, astrocytes, oligodendrocyte precursor cells (OPCs), and invertebrate glia participate in the refinement and remodeling of synapses in response to sensory experience in the developing and adult brain. Glial-mediated synaptic remodeling occurs through synaptic phagocytosis, cytokine-dependent changes in synaptic structure, and extracellular matrix (ECM) modification.

oligodendrocytes, myelinate CNS axon fibers. In contrast to astrocytes and oligodendroglia, microglia are brain-resident macrophages derived from myeloid progenitors in the yolk sac. Long recognized as immune-competent protectors of the brain, microglia also play important roles in neural circuit development, plasticity, and function [29]. In summary, glia take diverse forms and possess a wide range of functions that facilitate

brain physiology, many of which are shared across glial cell types.

Mechanisms of glial-mediated experience-dependent synaptic refinement, remodeling, and plasticity

Part I: Synaptic phagocytosis

Phagocytosis of synapses during development

The phagocytic engulfment of synapses is a well-documented mechanism through which glia in both vertebrates [30–33] and invertebrates [34–37] modulate circuits. While most studies on this topic have focused on early developmental phases that precede the onset of sensory experience, more recent efforts have uncovered roles for glia in experience-dependent phases of synaptic refinement. For example, in *C. Elegans* (nematode worm), glia engulf the receptive endings of thermosensitive neurons in response to elevated temperatures in a phosphatidyl serine- and integrin-dependent manner, which is required for normal thermotaxis behavior (a form of taxis, which is the directional movement of an organism in response to a stimulus) [38]. Similarly, work on *Drosophila* (fruit fly) also suggests that glia are required for sensory experience-dependent synapse elimination during critical periods of development in larval and young adult flies [39,40]. Following emergence from the pupal case, flies experience a burst of sensory input that facilitates circuit refinement and plasticity [41,42]. Exposure of newly emerged flies to the odorant ethyl butyrate caused the loss of a subset of olfactory sensory neuron synapses in the adult antennal lobe [43]. Using a variety of genetic manipulations, biosensors, and electrophysiology, four independent studies collectively demonstrated that this process required the glial engulfment of synapses via the phagocytic receptor Draper (mammalian homolog MEGF10) in ensheathing glia [21–23,44]. Thus, glia mediate experience-dependent phases of circuit development in invertebrate systems through the phagocytic engulfment of synapses.

While studies in invertebrates have been informative, the majority of what is known about synaptic remodeling by glia has been garnered from studies in mammals, especially mice. The ability of astrocytes and microglia to refine developing neural circuits via synaptic phagocytosis was initially uncovered in the hippocampus and in the dorsal lateral geniculate nucleus (dLGN) of the thalamus, a retinorecipient region that undergoes circuit refinement during early life [30–32,45]. Initial work implicated first microglia and then astrocytes in the phagocytosis of retinal inputs to the dLGN in response to intrinsically generated activity prior to the onset of visual experience at eye-opening (around postnatal day [P]14) through distinct molecular pathways, with microglia relying upon the classical complement cascade (CCC) and astrocytes requiring Megf10 and Mertk [30,32]. In this context, both astrocyte- and microglia-mediated engulfment was dependent upon presynaptic retinal wave activity generated prior to the onset of visual experience. Strikingly, however, while microglia contain large amounts of synaptic material early on, they contained very little synaptic material during sensory-dependent refinement which occurs around the third week of postnatal life in the visual system of the mouse [46]. This result suggests that the engulfment of synapses by microglia, though important for the earliest postnatal stages of circuit maturation, may not be the primary mechanism through which experience shapes circuits in the mouse visual system (although microglia contribute to experience-dependent refinement in the dLGN through other mechanisms as described below).

Consistent with this early observation, functional studies suggest that microglia may be dispensable for a well-studied type of developmental visual experience-dependent synaptic remodeling termed ocular dominance plasticity (ODP). During ODP, animals are subjected to monocular deprivation (i.e. occlusion of visual input to a single eye) resulting in a robust restructuring of the circuitry in the visual cortex (V1) [47]. Global genetic loss of complement component 1q (C1q) or the fractalkine receptor (Cx3cr1), the two primary pathways through which microglia remodel synapses in other regions, did not impair ODP [48–50], nor did the depletion of microglia beginning at eye-opening [51]. However, in seeming contradiction to this, mice globally lacking the purinergic receptor P2ry12, which is highly enriched in microglia, exhibited reduced microglial synaptic engulfment and ODP in V1 [52]. Similarly, a study by Ma et al., 2020 revealed elevated neural activity, increased dendritic spine density, reduced spine elimination, and deficits in ODP in V1 following microglial depletion [53]. Though it is difficult to determine the reasons for this discrepancy, it should be noted that the degree to which microglia were depleted was different between these conflicting studies, with Brown et al., 2024 achieving near 100% depletion and Ma et al., 2020 depleting microglia by 78%. Why reduced vs complete ablation of microglia would result in different outcomes remains unclear; however, one idea is that the incomplete loss of microglia may lead to the surviving microglia becoming unhealthy and releasing inflammatory factors which may impact the function of nearby neurons, resulting in disrupted ODP. That said, partial loss of microglia in aging mice was shown to have beneficial effects on animal behavior while enhancing long-term potentiation in CA1 of the hippocampus, implying these cells reserve brain region-, age-, and/or stimulus-specific pathways for their functions [54]. In support of this hypothesis, early work investigating the role of visual experience on microglia–synapse interactions revealed that microglia increase the number of synaptic contacts and engulfment following light re-exposure after dark-rearing [55]. These studies imply that microglia may be

capable of responding to visual experience to shape experience-dependent plasticity in V1. Overall, the roles of microglia in experience-dependent circuit remodeling in the visual cortex remain controversial, and studies employing more precise manipulations of microglia beyond cellular depletion and global knockout (KO) mice will be necessary to address this discrepancy.

On the other hand, both astrocytes and oligodendrocyte precursor cells (OPCs) are promising candidates to regulate experience-dependent visual circuit plasticity via synapse engulfment. For example, astrocytes have been shown to engage c-Mer proto-oncogene tyrosine kinase (Mertk) signaling to engulf synapses in visual cortex during ODP [56]. In addition, recent work from the Cheadle lab showed that OPCs can also directly eliminate synapses in the visual cortex through phagocytosis, and that they elevate this function in response to experience during development in V1 [33]. Intriguingly, depletion of microglia dampened the ability of OPCs to engulf synapses, suggesting a role for glial−glial crosstalk in this process. Altogether, these results suggest that microglia are specialized to prune synapses during early development (P0-P5) in the mouse visual system prior to the onset of visual input, while astrocytes and OPCs may be more important for experience-dependent visual plasticity later on (P20-P30).

While their roles in the visual cortex are still under investigation, microglia are necessary for refining somatosensory circuits in response to tactile sensation. In particular, microglia enhance their engulfment of thalamocortical synapses in somatosensory cortex (S1) in response to sensory deprivation caused by the unilateral trimming or cauterization of whiskers around P4 — P5 [57]. This function of microglia required the ADAM10 metalloprotease-dependent cleavage of fractalkine (Cx3cl1), and signaling between the cleaved fractalkine fragment and the microglial cell-surface fractalkine receptor. Conversely, the classical complement cascade (CCC), which is required for the pruning of synapses by microglia in the dLGN , was dispensable for refinement in S1, confirming that microglia can engage different molecular machinery to prune synapses depending upon the brain region, circuit, or age analyzed [57]. This study demonstrated that microglia play a major role in mediating sensory-dependent synapse remodeling in the somatosensory system of the mouse.

Phagocytosis of synapses by glia promotes experience-dependent remodeling in adult circuits

Although considerable effort has been applied to investigate the roles of glial phagocytosis during development, studies on glial engulfment in the healthy adult are comparatively sparse. Recently, glial engulfment has been implicated in cue-mediated hippocampal learning and memory in adult mice. In a contextual fear conditioning (CFC) behavioral paradigm, Wang et al. [58] reported increased glial phagocytosis of pre- and postsynaptic material from CFC engram cells by microglia via the complement pathway in a process that was required for extinguishing fear responses to previously presented environmental triggers. In addition to microglia, astrocytes have also recently been proposed to promote experience-dependent changes in synaptic connectivity in the adult hippocampus downstream of environmental enrichment (EE), a multi-sensory stimulation paradigm. Exposure of adult mice to EE drove an increase in Megf10-dependent astrocytic engulfment of excitatory synapses compared to mice reared in standard housing [59]. In this context, astrocytic but not microglial engulfment was observed, again highlighting that different environmental stimuli can impact glial cell types differently. Altogether, these studies indicate that glia can respond to sensory experience via the phagocytic engulfment of synapses through cell-type-specific mechanisms.

Part II: Non-phagocytic induction of remodeling and plasticity by glia

Induction of structural plasticity via glial-mediated cytokine signaling

While glial cells can have profound effects on circuit organization through the direct phagocytic removal of synapses, they can also exert nonphagocytic control over synaptic connectivity [60,61]. Of particular relevance, the microglia-to-neuron tumor necrosis factor-like weak inducer of apoptosis (TWEAK)-fibroblast growth factor-inducible 14 (Fn14) cytokine signaling pathway plays an important role in sensory-dependent synaptic refinement in the developing visual system. Upon acute light stimulation, excitatory thalamocortical neurons in the developing mouse dLGN induce the expression of the pro-inflammatory cytokine receptor Fn14, a tumor necrosis factor (TNF) receptor superfamily member. Concurrently, microglia within the same brain region upregulate the expression of TWEAK, the cytokine ligand of Fn14, in response to visual stimulation. Loss-of-function experiments demonstrated that TWEAK-Fn14 signaling from microglia to neurons mediates the sensory experience-dependent refinement of the retinogeniculate circuit by driving the structural disassembly of synapses in the absence of phagocytosis [62,63]. While this seminal work was performed in the developing visual system, TWEAK-Fn14 signaling has since been shown to be a potent inducer of long-term depression (LTD) at adult hippocampal synapses [64], and the pathway has been shown to mediate memory and sleep in adult mice [65]. While TWEAK-Fn14 signaling is required for normal experience-dependent synaptic refinement and remodeling, other cytokines from both the tumor necrosis factor family and the interleukin family are also potent mediators of the strengthening, potentiation, and depression of synapses (recently reviewed elsewhere [66]).

Extracellular matrix remodeling to promote circuit plasticity

Apart from their influence on synapses through the release of signaling molecules like cytokines, glial cells can also influence the stability of circuits by modifying the ECM. ECM glycoproteins, such as chondroitin sulfate glycoproteins (CSPGs) which promote the formation of specialized extracellular matrix (ECM) structures called perineuronal nets (PNNs), are a major component of the tripartite synapse [67] and are thought to limit synaptic plasticity and to close critical periods [68–70]. While glia can contribute to the formation of PNNs [71], microglia have also been shown to clear PNNs and other ECM proteins via signaling between the neuronally expressed cytokine IL-33 and the IL-33r receptor in microglia [72,73] in response to EE in the hippocampus and neocortex [74,75]. In addition to phagocytosing ECM, microglia, along with astrocytes and OL lineage cells, express and release matrix metalloproteases (MMPs) which in turn act to degrade ECM components, providing another example by which glia can induce synaptic plasticity through mechanisms that are distinct from synapse engulfment [71,76].

As with microglia, we are also establishing a deeper understanding of how astrocytes can modify the development of the ECM to promote synaptic remodeling and plasticity. Unlike microglia, astrocytes are thought to promote ECM development in the visual cortex. In particular, astrocytic expression of the gap junction coupler Connexin-30 was required for MMP9 expression, and decreasing the expression of connexin-30 was sufficient to reduce maturation of the ECM and to dampen ODP plasticity [77,78]. Therefore, while it seems that microglia may promote plasticity through the engulfment of ECM material, astrocytes, rather, promote the formation and maintenance of ECM by downregulating MMPs and allowing the visual circuit to crystalize.

Closing thoughts

Although neuron-intrinsic mechanisms underlying experience-dependent synapse refinement, remodeling, and plasticity have been under investigation for decades, the roles of glia in these processes are only now becoming a major topic of study within the neuroscience field. Although the mechanisms through which glia detect and respond to cues from the external environment remain to be fully elucidated, these cells have been shown to mediate experience-dependent changes in synaptic connectivity by phagocytosing synapses and by eliciting changes in synaptic structure and dynamics via cytokine signaling and the modification of the ECM. An emerging theme is that different populations of glia can engage generally similar mechanisms to remodel synapses (such as phagocytosis or cytokine release), but that different cell classes are specialized to sculpt circuits in response to experience depending upon the age, brain region, and pattern of stimulation applied. One possible reason that different cell types mediate circuit remodeling dependent upon age is that glial cell types are established and mature at different rates, with yolk sac-derived microglia infiltrating the brain *in utero* then maturing during early postnatal ages, while astrocytes arise from radial glial cells and mature later [79,80]. On the other hand, OPCs are born in three successive waves that arise prenatally then postnatally, but the majority of OPCs that persist across the lifespan arise from the postnatally generated wave [81,82]. This idea is in line with the observation that microglia are active regulators of synapses in the visual and somatosensory systems around the first week of life but have not been consistently shown to mediate circuit refinement in adolescents or adults in either system. Similarly, glial cell types might be differentially sensitive to distinct types of neural activity based upon the spatiotemporal dynamics of their interactions with neurons. Finally, different types of glia engage distinct molecular pathways to remodel synapses, thus molecular complementarity with neurons in a given brain region could influence which glia are best poised to remodel their synapses. Over the next few years, defining the ways in which glia operate as intermediaries between environmental stimuli and neural physiology across timeframes, brain regions, and ages should lead to important new insights into how experience shapes the brain.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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