Star power: the emerging role of astrocytes as neuronal partners during cortical plasticity
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Plasticity is a fundamental property of neuronal circuits, allowing them to adapt to alterations in activation. Generally speaking, plasticity has been viewed from a ‘neuron-centric’ perspective, with changes in circuit function attributed to alterations in neuronal excitability, synaptic strength or neuronal connectivity. However, it is now clear that glial cells, in particular astrocytes, are key regulators of neuronal plasticity. This article reviews recent progress made in understanding astrocyte function and attempts to summarize these functions into a coherent framework that positions astrocytes as central players in the plasticity process.

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Introduction
Astrocytes, characterized by their unique star-shaped morphology, are one of the most numerous and important cell types in the mammalian central nervous system (CNS) [1]. However, the contribution of astrocytes to CNS plasticity has often been overlooked, despite early work clearly indicating that astrocytes play a key role in plasticity following sensory deprivation [2**] (Figure 1a). Instead, the majority of work has concentrated on the structural and functional alterations seen during plasticity from a neuronal perspective.

Historically, this can be explained by the relative lack of tools for astrocyte-specific manipulation, which meant that it was impossible to unequivocally dissect out the role(s) played by astrocytes in plasticity. However, the last twenty years have seen an upsurge of interest in astrocyte biology. This has largely been driven by the introduction of new technologies [3] that have allowed us to obtain detailed mechanistic insights into their functions. The result is that astrocytes have been shown to play critical roles in initial synapse formation and function during early post-natal (cortical) development, including the so-called ‘critical periods’, when circuits are highly plastic and refined based on experience-dependent inputs [4**].

Such circuit remodeling remains possible in adult animals, albeit reduced in strength, with astrocyte-specific activation recently shown to enhance deprivation-induced plasticity in visual cortex [5**] (Figure 1b). Furthermore, it appears that, just like neurons, astrocytes recapitulate functions from early post-natal development to drive this process, as transplantation of young post-natal astrocytes into adult animals reinstates high levels of plasticity in the sensory cortex [2**] (Figure 1a). Hence, we think this is an opportune moment to summarize our current knowledge on astrocyte function into a coherent step-by-step framework, providing a plausible mechanistic explanation of adult plasticity, as seen following sensory deprivation (vision loss) and subsequent cortical reorganization. This general framework places astrocytes as central players in the plasticity response (Figure 2) and is described in detail below.

Step 1) Triggering plasticity: Astrocytes possess thousands of individual processes, which extend out into the neuropil, interacting with neurons at synapses, an arrangement often referred to as the ‘tripartite’ synapse [6]. This structural interaction is common: one astrocyte can contact many individual synapses [1], with reports of up to 90% of such structures being tripartite [7]. This places astrocytes in an ideal position to sense ongoing changes in neuronal activity. Both glutamatergic synaptic transmission [8] and neuronal release of sonic hedgehog (Shh) [9] have been shown to play roles in the induction and maintenance of the mature astrocyte transcriptome in vivo, with a reduction in signaling appearing sufficient to induce transcriptome deregulation. At present, it is unclear whether this form of transcriptional regulation is restricted to neuronally released glutamate and Shh, or whether other factors play a role [10]. However, given the large body of evidence indicating a central role for
Astrocyte enhancement of neuronal plasticity responses in visual deprivation paradigms.

(a) Developmental ocular dominance (OD) plasticity can be reinstated in the adult visual cortex after transplantation of immature astrocytes. Visual inputs from the contralateral (purple) and ipsilateral (orange) eyes converge onto the binocular lateral third of the mouse primary visual cortex. Seven distinct OD-classes, ranging from exclusively contralateral (1) to exclusively ipsilateral (7), can be defined, based on the responsiveness of V1 neurons to eye-specific inputs. In normal sighted mice, many V1 neurons are responsive to visual stimuli from both eyes, but favor contralateral inputs. Short-term monocular deprivation, by lid suture during the critical period, induces a redistribution of the OD classes towards the non-deprived, ipsilateral eye, whereas the deprived-eye responses weaken (adapted from Ref. [58]). In the adult brain, neuronal plasticity is constrained and lid suture no longer induces an OD shift similar to that seen in young animals. OD plasticity can, however, be reintroduced in adult (cat) visual cortex after transplantation of immature astrocytes (based on Ref. [59]).

(b) Control vector + CNO

G_i DREADD + CNO

P120

0 weeks

7 weeks

7 weeks

Zif268 neuronal activity marker

Enhanced cortical reorganization

Current Opinion in Neurobiology
reduced inhibition in triggering adult cortical plasticity [11], the role of neuronal GABA signaling in maintaining the mature astrocyte transcriptome seems an obvious candidate for further investigation.

Therefore, based on the immediate drop in (inhibitory) neuronal activity caused by vision loss and subsequent changes in cortical E/I balance (Figure 1), we hypothesize that adult astrocytes undergo a rapid transcriptome changes, effectively reverting to an immature state, recapitulating aspects of early development which facilitates circuit rewiring. Such a concept is entirely consistent with work performed following CNS injury [12,13], which shows astrocytes adopt an immature phenotype [12,14], concomitant to circuit rewiring [12].

Step 2) Remodeling the extracellular matrix (ECM): Adult CNS cells are embedded in a complex ECM, which limits structural changes during periods of low plasticity [15]. Major components of the neural ECM are thought to include proteoglycans (e.g. brevican and neurocan), which interact with collagen, glycoproteins (e.g. tenascins) and hyaluronic acid. It is thought that ECM remodeling is achieved, at least in part, through enzymatic degradation by members of the MMP (matrix metalloproteinase) and ADAMTS (A Disintegrin and metalloprotease with thrombospondin motifs) superfamilies [16]. Multiple CNS cell types synthesize ECM components and proteases to varying degrees — making the precise contributions of individual cell types to ECM formation and modification difficult to assess in vivo. However, MMP9, ADAMTS-5 and ADAMTS-8 have all been detected in astrocytes, while increased MMP9 activity is associated with plasticity induced by environmental enrichment (summarized in Ref. [17]). This is consistent with live imaging studies demonstrating that brain ECM is highly plastic during development and remodeled in response to local cellular activity [18]. It is also noteworthy that injury (cortical lesion) reverts astrocytes to a developmentally immature state, with cells expressing ECM components typically associated with neural stem cells/progenitors, suggesting injury response parallels development with ECM modification facilitating circuit rewiring [14]. This may also be associated with the release of astrocyte-derived factors, such as pentraxin 3, which not only play a role in ECM remodeling but co-operate with proteins, such as thrombospondin, to promote synaptogenesis [19] (and see Step 4).

Astrocytes may also contribute to ECM remodeling indirectly. The cytokine interleukin-33 (IL-33) activates CNS microglia. Recent work demonstrated that neuron-derived IL-33 leads to microglial engulfment of ECM, enhancing structural plasticity of neurons during hippocampal memory formation [20]. However, (adult) astrocytes also express IL-33 [21,22]. Although definitive evidence for astrocytic IL-33 release enhancing local ECM remodeling during plasticity is currently missing, such a role is plausible, as it promotes microglial synapse engulfment during post-natal circuit development [23] (and see Step 3).

Step 3) Removal of redundant synaptic connections: Reactivation of a cortical area likely involves elimination of non-functional synaptic connections, allowing reutilization of cortical space (Figure 1). ECM modification presumably allows synapses to be removed from circuits by freeing them from a physically constraining matrix and allowing relevant cell–cell interactions.

Astrocytes directly eliminate CNS synapses in both the developing and adult brain through the MERTK and MEGF10 phagocytic pathways [24], which both depend on the lipid phosphatidylinerine (PS). Under normal conditions, PS is present in the inner cytoplasmic leaflet of the synaptic plasma membrane, but when exposed on the cell surface it acts as an ‘eat me’ signal [25]. MERTK is an engulfment receptor that binds opsonins, such as growth arrest-specific protein 6 (GAS6), which have labeled exposed PS on neurons [26]. In contrast, MEGF10 appears to act through complement C1q binding to PS [27] (and also see below). The precise mechanisms by which neurons externalize PS to trigger opsonization and removal of redundant connections are unclear at present [25]. However, the process appears linked to neuronal activity levels, with ‘weak’ or ‘inactive’ synapses being preferentially eliminated [24].

Astrocytes are also indirectly involved in synapse removal. Microglia effectively eliminate ‘weak’ synapses marked by deposition of complement C3 in an activity-dependent fashion [28]. In this system, astrocyte-derived transforming growth factor (TGF)-β induces expression of complement protein C1q in neurons [29], which then triggers a proteolytic cascade of downstream complement factors, resulting in neuronal opsonization by complement C3 and phagocytosis by microglia expressing C3.

(b) In a monocular enucleation model of adult visual cortex plasticity, neuronal reactivation can be enhanced via Gq GPCR-based astrocyte activation. Unilateral eye removal leads to an immediate drop in neuronal activity (grey) in the monocular regions of the contralateral visual cortex in adult mice aged post-natal (P) day 120, visualized as decreased expression of the neuronal activity marker zif268 using in situ hybridization. Within 7 weeks, plasticity-induced cortical reorganization leads to functional reactivation (yellow) of the deprived visual cortex, in mice injected with a control vector expressing mCherry and administered clozapine N-oxide (CNO). This increased neuronal activity is initially driven by open-eye responses, followed by a later phase of cross-modal plasticity driven by whisker-inputs. This neuronal reactivation can be enhanced (orange) by CNO-based activation of astrocytes in the sensory deprived cortex, following vector-based delivery of a Gq-coupled Designer Receptor Exclusively Activated by a Designer Drug (DREADD) [57].
Proposed mechanistic framework for sensory loss–induced adult plasticity, incorporating a key role for astrocytes based on established functions. The central panel shows a highly branched astrocyte (blue), with processes enwrapping pre-synaptic and post-synaptic elements (grey), forming a tripartite synapse (expanded view in box). Given this close physical association with synapses, and the ability of astrocytes to release a wide variety of soluble molecules (orange dots) capable of influencing plasticity, we propose tripartite synapses as core units of the plasticity response in (adult) brain.

**Step 1:** An initial decrease, or complete loss, of (inhibitory) neuronal activity (yellow), leads to an astrocyte response, which either initiates or enhances plasticity (orange).

**Step 2:** Extracellular matrix (ECM) remodeling, via changes in ECM protein production, enzymatic degradation of pre-existing ECM proteins (orange dots), or a combination of both processes, is necessary for synaptic remodeling in adulthood.

**Step 3:** After sensory loss, the reutilization of deprived cortical space likely depends on removal (pruning) of non-functional synaptic connections. Tagging inactive synapses with an ‘eat-me-signal’ leads to their phagocytosis by glial cells (orange pac man). Externalized phosphatidylserine (orange border) leads to phagocytosis of synapses by astrocytes. Astrocyte-secreted C1q (yellow border) tags the synapse, inducing microglial phagocytosis. Synapses can also be protected from elimination by expression of CD47 (magenta border), which functions as a ‘don’t-eat-me’ signal.
receptors. The exact mechanism(s) by which TGF-β release is triggered remains unclear. However, astrocyte processes encode differences in activity at individual synapses as Ca^{2+} transients with differing properties [30], while evidence also suggests astrocytes can summate responses to neuronal activity [31]. Such a system would allow astrocytes to sense and compare relative activity levels over time, being a plausible mechanism to target ‘weak’ synapses. Microglial phagocytosis may be enhanced by the interaction between astrocyte-driven C1q deposition and exposure of PS on neurons, which needs to be further explored [32].

Recent work suggests synapses are protected from inappropriate removal during development by the presence of ‘don’t eat me’ markers, which can even override the presence of pro-phagocytic signals. To date, the best characterized of these markers is CD47 [33]. CD47 remains highly expressed throughout the neuropil into adulthood, consistent with a role as a ubiquitous protective signal for established neuronal circuits [33]. How CD47 levels are modulated during plasticity, specifically in relation to PS exposure or C1q deposition, is unclear, but undoubtedly has consequences for the removal of redundant synapses.

**Step 4 Synapse formation:** Neuronal reactivation is dependent on the formation of new synapses. Following late-onset vision loss (Figure 1), major structural rearrangements in neuronal circuits do not occur, and it is likely new synapses are formed by local sprouting of synaptic boutons from pre-existing axons, which then establish new dendritic contacts [34,35]. At present, the role of local (astrocyte) guidance cues in establishing precise patterns of connectivity in adult animals is unclear, despite it being well established that such cues play key roles during development [36].

Tripartite synapse assembly can be considered a multi-step process. Astrocyte-neuron interactions are mediated by cell adhesion molecules (CAMs) present in opposing membranes. Many CAMs that were once thought to be exclusively expressed in neurons have recently been shown to be important in astrocytes. These include homophilic trans-synaptic interactions between γ-protocadherins [37] and heterophilic trans-synaptic interactions between astrocyte neuroligins and neuronal neurexins [38]. In addition to contact-mediated interactions, astrocytes also secrete many soluble factors (including ECM components) that are essential for synaptogenesis and synapse maturation. Thrombospondins are the classic astrocyte-secreted factors, which regulate structural synapse formation during development [39] and during injury-induced circuit remodeling [40]. Astrocyte-secreted factors, including (but not limited to) cholesterol and glypicans 4/6, are then necessary to enhance pre-synaptic function [41] and post-synaptic responses [42], respectively. Interestingly, astrocyte-derived chordin-like 1 (Chrdl1) is thought necessary for synapse maturation during ongoing development, which occurs concomitant to a reduction in plasticity [4**]. To date, the majority of astrocyte-secreted factors identified (including glypicans and Chrdl1) are linked with excitatory synapses. While astrocyte-secreted factors also strongly induce inhibitory synapse formation and function, the identity of the signals involved remains largely unknown and an area of ongoing research [1]. However, recent work has begun to untangle this issue, with expression of neuronal cell adhesion molecule (NRCAM) in cortical astrocytes demonstrated to interact transcellularly with neuronal NRCAM, which is coupled to gephyrin, mediating inhibitory synapse formation and function [43].

**Step 5 Synapse function:** Once synapses are physically established, astrocytes play well documented roles in their maintenance (extensively reviewed in Ref. [44]). Astrocytes provide ongoing support to neurons through the release of trophic factors, for example brain-derived neurotrophic factor (BDNF). Astrocytes are also involved in maintaining local environmental homeostasis, regulating extracellular K^+ levels, pH and neurotransmitter levels; these can all impact on local neuronal activity, contributing to functional plasticity, including in the context of vision loss. Finally, astrocytes are key suppliers of energy to neurons through the production and export of lactate.

As astrocytes enwrap synapses and sense local activity, they are also in a prime position to actively modulate synaptic transmission through the release of neuroactive substances (glio-transmitters) [45]. Known glio-transmitters include glutamate, GABA, t-serine and ATP [46]. Secreted glio-transmitters can act on both pre-synaptic and
post-synaptic elements, actively depressing or potentiat-
ing synaptic transmission through a variety of mecha-
nisms [46]. Additional complexity results from the fact
that single astrocytes apparently decode different pat-
terns of neuronal activity, and respond by releasing dis-
tinct gliotransmitters that regulate local synaptic trans-
mission [47*]. Astrocytes also exist in gap junction
coupled networks [48]. Given that they respond to neu-onal stimulation with transient Ca\(^{2+}\) elevations, which
can spread from individual processes into the cell body
[30], it appears these cells may also serve as bridges,
allowing crosstalk between synapses with no direct neu-
ronal connectivity — a process known as lateral regulation
[49]. In addition, gliotransmitter release may be triggered
by microglial activation [50], raising the tantalizing pos-
sibility that astrocyte-microglia cross-talk is a hallmark
of plasticity, occurring at several stages of the process (for
example, see Steps 2 and 3). Finally, astrocytes possess
receptors for neuromodulators, such as acetylcholine
and endocannabinoids, activation of which leads to gliotran-
mitter release [51,52], suggesting that changes in global
brain state, linked to behavior, may also affect plasticity
via astrocytes, possibly explaining the positive effects of
environmental enrichment [53,54] and exercise [55].

Further questions and concluding remarks
There are an increasing number of studies documenting
that astrocytes play key roles in all aspects of circuit
remodeling across plasticity paradigms involving vision loss
[2*,5**]. The introduction of powerful genetic tools [3] has
permitted detailed mechanistic studies of the roles played
by astrocytes in CNS development and response to injury,
which largely parallel those needed during adult plasticity.
Our own data, unambiguously demonstrating that astro-
cytes are essential for visual cortex reorganization in adults
[5**], has led us to develop a conceptual framework for the
role of astrocytes in plasticity, which can be experimentally
tested in the coming years. No doubt, as we learn more
about how these cells function, new questions concerning
their role(s) in plasticity will arise. Amongst these, central
issues we consider of importance are:

i) The influence of cellular heterogeneity: Astrocytes show
considerable differences in morphology, molecular com-
position and function, both between and within brain
regions [21,22,56], with consequences for neuronal mat-
uration and synapse function [57]. What astrocyte factors
specify the formation and function of excitatory or inhibi-
tory synapses [1]? Are excitatory and inhibitory synapses
formed and maintained by specific astrocyte subtypes
[21]? How does this influence plasticity, which is thought
to be driven by loss of neuronal GABAergic signaling and
changes in E/I balance producing an environment per-
missive for circuit remodeling ([11,58])?

Given the central role of GABAergic transmission in
plasticity, it is interesting to note that interneurons appear
stabilized in a specialized form of ECM, commonly
referred to as a perineuronal net, enveloping the cell body,
proximal dendrites and axon initial segment [17]. It will
be critical to determine the degree to which astrocytes (or
specific astrocyte subtypes) are involved in the modifica-
tion of perineural nets linked to ongoing circuit modifi-
cation [54].

ii) The effects of aging: Aging astrocytes downregulate
the expression of genes involved in synapse formation (e.g.
cholesterol) and upregulate genes involved in synapse
elimination (e.g. complement C3) [59]. Does an aging
astrocyte transcriptome explain why the adult brain shows
limited plasticity [58]? As the brain ages, does it become
progressively harder for astrocytes to revert to a more
‘immature’ state, as present during early development
when circuits undergo extensive modification?

iii) Response to injury: Circuit rewiring following injury,
such as stroke, can be considered an extreme form of
plasticity [12,13]. To what degree do mechanisms of
plasticity in the healthy brain and responses to injury/
disease overlap? What is their relationship to normal
developmental processes, particularly given that astrocyte
responses to injury/disease appear heterogeneous, being
specific to the triggering insult [60]? How is the injury
response affected by aging? How does chemogenetic
activation of astrocytes boost plasticity [5**,61]? Can these
insights be harnessed for therapeutic purposes?

In summary, astrocytes are key regulators of (adult)
plasticity and should be considered ‘equal partners’ in
the process. Only by considering plasticity as an inte-
grated response across cell types (also including oligoden-
drocytes and microglia) will it be possible to obtain a step-
by-step understanding of this fascinating process. Many
surprises lie in wait: What is certain is that astrocytes will
play a ‘starring role’ in the process.

Conflict of interest statement
Nothing declared.

Acknowledgements
JW is supported by a post-doctoral fellowship from the Fund for Scientific
Research Flanders (FWO 12V7519N). This work was further supported
by an FWO grant to LA (G061216N), and FWO grants to MGH (1S20134N
and 1S273515N), a KU Leuven Research Council grant to LA (C14/16/048),
KU Leuven Research Council Grants jointly held by LA and MGH (C14/
20071 and CELISA/19036), as well as a European Research Council
Starting Grant (AstroFunc: 281961) and VIB Institutional Funding to MGH.
Figures were created with BioRender.

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have been highlighted as
• of special interest
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Astrocytes: a starring role in plasticity Wahis et al. 181

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