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Astrocytes as master modulators of neural networks: Synaptic functions and disease-associated dysfunction of astrocytes

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Abstract
Astrocytes are the most abundant glial cell type in the central nervous system and are essential to the development, plasticity, and maintenance of neural circuits. Astrocytes are heterogeneous, with their diversity rooted in developmental programs modulated by the local brain environment. Astrocytes play integral roles in regulating and coordinating neural activity extending far beyond their metabolic support of neurons and other brain cell phenotypes. Both gray and white matter astrocytes occupy critical functional niches capable of modulating brain physiology on time scales slower than synaptic activity but faster than those adaptive responses requiring a structural change or adaptive myelination. Given their many associations and functional roles, it is not surprising that astrocytic dysfunction has been causally implicated in a broad set of neurodegenerative and neuropsychiatric disorders. In this review, we focus on recent discoveries concerning the contributions of astrocytes to the function of neural networks, with a dual focus on the contribution of astrocytes to synaptic development and maturation, and on their role in supporting myelin integrity, and hence conduction and its regulation. We then address the emerging roles of astrocytic dysfunction in disease pathogenesis and on potential strategies for targeting these cells for therapeutic purposes.

KEYWORDS
astrocytes, astrocytic heterogeneity, glia, neurological disorders, synapse, white matter

INTRODUCTION

Astrocytes are the most abundant glial cell type in the central nervous system (CNS) and account for a substantial proportion of all cells in the human brain.1–6 These multifaceted cells are characterized by their highly arborized morphology and are suited to carry out diverse functions that include neurotransmitter cycling, ion homeostasis, synapse formation and maintenance, blood–brain barrier maintenance, and neuronal metabolic support.7 Astrocytes are principally divided into two groups, classified by location and distinguishing morphological features, including protoplasmic astrocytes found primarily in gray matter regions, and fibrous astrocytes, which are largely associated with myelinated axon bundles of the white matter.8 Protoplasmic astrocytes are typically larger with highly ramified processes, while fibrous astrocytes have smaller cell bodies and longer straight processes that typically align with myelinated fibers (Figure 1). Yet, within these major classes of astrocytes exist extensive molecular and presumably, functional heterogeneity, likely tracking the myriad of brain circuits that they support, through interactions with diverse neurons, cellular niches, and other glial cell types that utilize a broad array of synaptic...
The morphological distinction of gray versus white matter central nervous system astrocytes. Confocal, z-projection micrographs of eYFP-labeled astrocytes from the mouse cerebral cortex (A) and corpus callosum (B). Astrocytes were sparsely labeled via an adeno-associated virus (serotype PHP.eB) at postnatal day 0 and imaged at postnatal day 14. Protoplasmic astrocytes are highly arborized, with branches emanating from a central soma, ultimately occupying their cellular territories with fine perisynaptic astrocyte processes (PAPs) and endfeet. Fibrous astrocytes are also highly arborized, but with branches more aligned to the plane of the myelinated tracks of the white matter. Image credit: Carlos Benitez Villanueva and Aurelia Mapps.

However, astrocyte labeling studies of the mouse cortex via in utero or early postnatal electroporation approaches mark protoplasmic and layer I astrocytes, but very few white matter astrocytes. Similarly, a study combining single-cell sequencing, spatial transcriptomics, and clonal lineage tracing reported that hippocampal astrocytes consistent with either protoplasmic or fibrous molecular features derive from two distinct, fate-biased pools of progenitors. Together, these data suggest that while diverse macroglia may derive from a common early progenitor, upon diversification of the astrocytic lineage, further differentiation may be characterized by temporally restricted and regionally specified windows for the production of distinct subpopulations of phenotypically distinct astrocytes.

A similar segregation of fate-restricted progenitors appears to occur in the developing human cortex. Radial glia in the developing human neocortex can be classified as either CRYAB truncated radial glia, which lose their contact with the pial surface and remain in the ventricular zone (VZ), or HOPX+ outer radial glia, which lose their VZ contact to colonize the outer subventricular zone (OSVZ). The OSVZ is an expanded proliferative region found in humans and other primates, but not rodents. Ex vivo viral labeling of human VZ and OSVZ progenitors revealed distinct subpopulations of astrocytes, such that VZ progenitors yield gray matter astrocytes, while OSVZ progenitors produce astrocytes that largely infiltrate the presumptive white matter.

Hominid-specific astrocytic diversification may have augured cognitive evolution

Comparisons of human and rodent astrocytes have revealed key differences in their morphological and functional cellular features. The expansion of human astrocyte numbers and types is likely rooted in the increased complexity of the proliferative zones such as the OSVZ.
that give rise to them.\textsuperscript{27,28} Astrocytes in humans are larger in diameter with more arborized processes.\textsuperscript{27} Furthermore, several morphological types observed in humans and other hominids are not seen in rodents. These include varicose projection astrocytes that reside in layers 5 and 6 of the cortex (characterized by long fibers and prominent varicosities) and interlaminar astrocytes that reside in cortical layer 1 and extend processes throughout the cortical layers.\textsuperscript{27} This raises the intriguing possibility that human astrocyte subpopulations diverged and gained unique properties during evolution, thereby supporting hominin-specific network complexity and hence functional repertoires. While nuanced astrocyte diversification and functionality have arisen during evolution, a negative byproduct may be that their dysfunction is causally linked to the pathogenesis of complex human-specific neuropsychiatric and neurodegenerative disorders.\textsuperscript{29–33}

**Inter-regional diversity of astrocytes**

Extensive molecular heterogeneity is found within the major classes of astrocytes (protoplasmic and fibrous).\textsuperscript{34} Advances in tools and technologies, most notably single cell RNA sequencing (scRNA-seq), have begun to uncover the rich molecular diversity of both developing and mature astrocytes throughout the CNS.\textsuperscript{35–37} These tools permit an interrogation of the gene networks that distinguish astrocyte subgroups, as well as the identification of genetic markers for labeling and manipulating specific astrocyte subgroups.\textsuperscript{38–40} Recent work highlights the diversity of astrocytes across different brain regions (inter-regional heterogeneity) and within regions of the brain (intra-regional heterogeneity).\textsuperscript{9,41} These populations exhibit distinct molecular, morphological, and physiological features that likely reflect their region-specific functional roles. A comprehensive study assessed both the molecular heterogeneity and morphological features of astrocytes across 13 different CNS regions.\textsuperscript{42} The data from this study strongly suggest the existence of specialized region-specific, cellular and molecular functions of astrocytes, in addition to their pan-astrocytic functional roles. For instance, a comparison between hippocampal and striatal astrocytes found extensive differences in their cellular and molecular features, indicative of their specialized roles to these brain regions.\textsuperscript{43} Hippocampal astrocytes are characterized by increased expression of the glial fibrillary acidic protein (GFAP), while mu-crystallin expression is enriched in striatal astrocytes.

**Intra-regional diversity of astrocytes**

Even within a given region or compartment, astrocytic diversity may be profound. The mouse embryonic spinal cord provides a classic example where a subset of astrocytes (SEMA3A+) is derived from the ventral region.\textsuperscript{44} These specialized spinal cord astrocytes coordinate the formation of sensorimotor circuits by regulating the orientation of the axon initial segment, the function of excitatory and inhibitory synapses onto α-motor neurons, and the survival of these neurons. More recently, scRNA-seq studies have revealed intra-regional molecular heterogeneity of mature gray matter astrocytes of the cerebral cortex, which is a region organized into discrete layers composed of molecularly distinct neuron subtypes. These studies suggest that transcriptionally heterogeneous protoplasmic astrocytes roughly correspond to the organization of the neocortical layers.\textsuperscript{35,36} Cellular features of astrocytes located in upper, middle, and lower cortical layers display significant differences in astrocyte morphology, orientation, and even the extent of ensheathment of synaptic clefts.\textsuperscript{45} These data suggest that developmental programs specify the core identity of astrocytes on a broad regional basis, which is then amenable to local extrinsic cues from neurons and other glia that together instruct a terminal phenotype and hence regional heterogeneity,\textsuperscript{10} in a manner similar to that observed with microglia.\textsuperscript{46}

Indeed, in the developing cortex, neurons likely shape the molecular and functional features of laminated astrocytes, as the acquisition of layer-specific neuronal identities precedes astrocytic specification. This concept is supported by studies showing that the layer-specific transcriptional signatures of astrocytes are altered in mouse models with a disrupted organization of neuronal cortical layers.\textsuperscript{36,45} Sonic hedgehog (SHH), which is expressed by subsets of neurons in a broad variety of brain loci, likely participates in the regional, morphological, and molecular specification of astrocytes.\textsuperscript{36,45} In the cortex, SHH is expressed by a subset of deep-layer subcortical projection neurons, where it potentiates the astrocytic expression of synaptic-regulating genes that include Sparc, Sparc1, Kir4.1 (Kcnj10), and Il13.\textsuperscript{47–50} In parallel, cell-autonomous astrocyte-specific activation of SHH signaling appears sufficient to promote increased synapse formation.\textsuperscript{49} While the properties of SHH-expressing neurons in different regions of the brain vary widely, enough SHH target genes are conserved to suggest that a common network of genes are induced in astrocytes, regardless of their site of developmental origin. Uncovering the full complement of neuron-derived factors influencing subtype-specific astrocytic specification will have important implications for astrocyte-targeted interventions and may ultimately permit the modeling and induction of specific astrocytic phenotypes of therapeutic interest.

**ASTROCYTES AT THE SYNAPSE**

The synapse is a complex junction between neuronal cells that permits the flow of information. The neuronal elements of the synapse consist of a presynaptic active zone that releases neurotransmitters into the synaptic cleft, to be received by neurotransmitter receptors concentrated at the postsynaptic density of the postsynaptic neuron.\textsuperscript{51} In most brain regions, neuronal synapses include a third entity, an astrocyte process that surrounds, and to varying degrees, sequesters individual pairs of pre- and/or post-synaptic terminals (Figure 2A). In the gray matter, astrocytes are tiled into nonoverlapping territories where a single astrocytic domain may encompass tens of thousands of synapses in the mouse and hundreds of thousands in the human.\textsuperscript{27,52} Within these domains, astrocytes are critical regulators of the synapses they encompass—modulating and locally coordinating their intrasynaptic levels of neurotransmitters and neuroactive cations, while preventing...
Molecular mechanisms controlling synapse and white matter function. (A) Protoplasmic astrocytes of the gray matter regulate the formation and function of neuronal synapses, both excitatory and inhibitory. Astrocytic governance of synapses occurs via a wide variety of secreted factors and cell-adhesion molecules which are depicted alongside their neuronal receptors (see Table 1 for a full listing of factors, receptors, and their precise function). (B) Fibrous astrocytes interact with neuronal axons and myelinating oligodendrocytes of central nervous system white matter tracks. Calcium-dependent ATP release by white matter astrocytes controls the conduction velocity of axonal action potentials. White matter astrocytes also regulate the metabolic support and myelination potential of oligodendrocytes (see Table 2 for molecules from fibrous astrocytes that control myelination). Abbreviations: A2aR, adenosine A2a receptor; ATP, adenosine triphosphate; Bdnf, brain-derived neurotrophic factor; Bmp2/4, bone morphogenetic protein 2/4; cAMP, cyclic adenosine monophosphate; Chrdl1, chordin-like 1; Cntf, ciliary neurotrophic factor; Cxcl1, CXC motif chemokine ligand 1; Eph, ephrin; Hcn2, hyperpolarization-activated cyclic nucleotide-gated ion channel 2; Igf1, insulin-like growth factor 1; Il-33, interleukin-33; Nlgn, neuroligin; Nrg1, neuregulin 1; Nrxn, neurexin; Nrcam, neuronal cell adhesion molecule; Pdgf, platelet-derived growth factor α; Tgfβ1, transforming growth factor β1; Tgfβ1R, transforming growth factor β1 receptor; Thsp1/2, thrombospondin 1/2.

FIGURE 2 Molecular mechanisms controlling synapse and white matter function. (A) Protoplasmic astrocytes of the gray matter regulate the formation and function of neuronal synapses, both excitatory and inhibitory. Astrocytic governance of synapses occurs via a wide variety of secreted factors and cell-adhesion molecules which are depicted alongside their neuronal receptors (see Table 1 for a full listing of factors, receptors, and their precise function). (B) Fibrous astrocytes interact with neuronal axons and myelinating oligodendrocytes of central nervous system white matter tracks. Calcium-dependent ATP release by white matter astrocytes controls the conduction velocity of axonal action potentials. White matter astrocytes also regulate the metabolic support and myelination potential of oligodendrocytes (see Table 2 for molecules from fibrous astrocytes that control myelination). Abbreviations: A2aR, adenosine A2a receptor; ATP, adenosine triphosphate; Bdnf, brain-derived neurotrophic factor; Bmp2/4, bone morphogenetic protein 2/4; cAMP, cyclic adenosine monophosphate; Chrdl1, chordin-like 1; Cntf, ciliary neurotrophic factor; Cxcl1, CXC motif chemokine ligand 1; Eph, ephrin; Hcn2, hyperpolarization-activated cyclic nucleotide-gated ion channel 2; Igf1, insulin-like growth factor 1; Il-33, interleukin-33; Nlgn, neuroligin; Nrg1, neuregulin 1; Nrxn, neurexin; Nrcam, neuronal cell adhesion molecule; Pdgf, platelet-derived growth factor α; Tgfβ1, transforming growth factor β1; Tgfβ1R, transforming growth factor β1 receptor; Thsp1/2, thrombospondin 1/2.

the extrasynaptic spread of transmitters to surrounding synapses. As such, the astrocytic support of synaptic function demands their close proximity to the synaptic cleft. These perisynaptic astrocyte processes (PAPs) also sense neuronal activity through glial neurotransmitter receptors, whose activation may signal through the modulation of intracellular calcium (Ca^{2+}) levels. In an iterative feedback process, astrocytic Ca^{2+} responses to neurotransmitters can then regulate the release of “gliotransmitters,” such as purines and D-serine, which may in turn modulate the activity of neighboring glia and local neurons alike.53

Given the critical roles of astrocytes in modulating synaptic transmission, it is interesting to note that not all synapses are contacted by astrocyte processes. The proportion of synapses with associated astrocytic fiber coverage varies across and within brain regions.54 Electron microscopic studies revealed that astrocytic coverage of synapses ranges from 74% in the cerebellum, to roughly 50% in the cortex, with a wide disparity across cortical layers.45,55–57 Synaptic ensheathment by PAPs may be both plastic and activity-dependent,58,59 wherein inhibition of glutamatergic transmission or blocking the astrocytic response to synaptic glutamate may lead to reduced astrocytic domain volume and process growth.60 Furthermore, there is evidence of activity-dependent local RNA translation in PAPs following, for example, a fear conditioning paradigm.61 Together, these findings suggest that neural circuit plasticity may require coordinated, activity-dependent changes of both neuronal synapses and their associated astrocytes.

An expanding body of data demonstrates that astrocytes signal directly to neuronal synapses through both secreted and adhesion molecules (Figure 2A), which have profound effects on the development and maturation of synapses and neural circuits. Further research is needed to determine how the precise complement of these molecules is established in astrocytes, including whether they are directed by local neuron signals or are determined at the time of specification from heterogeneous progenitor cells. Nevertheless, here we review the most up-to-date findings of these crucial astrocytic signals influencing synapses.
Astrocyte-secreted factors influence synapses

The first evidence of astrocytic participation in the regulation of neuronal synapse formation was obtained in a classic series of experiments using retinal ganglion cell cultures. Retinal ganglion neurons exposed to astrocyte-conditioned media exhibited increases in both synaptic numbers and synaptic efficacy, suggesting the existence of soluble astrocyte-derived factors that function to promote synapse development. Subsequent studies led to the identification of a host of astrocyte-derived, synapse-modulating factors, including thrombospondins, cholesterol/ApoE, and glycans, among others.

Table 1 lists those secreted factors that have thus far been identified to regulate either excitatory or inhibitory synapse formation (see also Figure 2A). As a group, these synaptogenic cues may create gradients and permissive zones for synapse formation, capable of modulating synapse numbers without antecedent physical contact. Multiple recently characterized factors serve to illustrate the range of secreted molecule functions and their context-dependent roles during synaptic development.

Among these, hevin (SPARCL1) is a member of the secreted protein acidic and rich in cysteine (SPARC) family of proteins. Hevin promotes and stabilizes synapse formation of thalamocortical synapses via bridging two otherwise nonbinding forms of cell adhesion molecules (CAMs)—presynaptic neurexin-1α (NRXN1α) and postsynaptic neurellin1B (NLGN1B). By doing so, hevin simultaneously promotes the maturation of both pre- and post-synaptic specializations. Moreover, the synaptic bridging by hevin establishes a window of synaptic plasticity observed in the visual cortex of mice.

SPARC is another astrocyte-secreted factor shown to be involved in regulating synapse formation, though its exact functional role in astrocytes is potentially more complex. Initial studies of SPARC using null mutant mice suggested that it may have a role in antagonizing Hevin and repressing synapse formation, as SPARC-null mice displayed increased numbers of synapses. On the contrary, two recent studies provide evidence that astrocytic SPARC may be involved in promoting synapse formation. Moreover, SPARC is also highly expressed in microglia and may possess a differential involvement in the SPARC-mediated synapse changes observed in the null mutant. Collectively, these data argue that the functional role of secreted synaptogenic factors may differ based on context. For example, IL33 expressed by astrocytes in the developing spinal cord and thalamic neurons to microglia to promote phagocytic pruning of synapses, whereas IL33 expressed by hippocampal neurons regulates dendritic spine plasticity and memory formation by promoting the remodeling of the extracellular matrix. Further research is necessary to identify the critical contextual factors that elicit differential responses of microglia from the same IL33 signal stemming from different cell types.

Several astrocytic synapse-modulating factors also exhibit intraregional heterogeneity in their expression. Chordin-like 1 (CHRD1) is expressed in upper-layer astrocytes in the developing visual cortex where it promotes the insertion of GluA2 AMPA receptors at the synapse leading to increased synapse maturation and decreased plasticity. Norrin is a secreted factor expressed by cortical layer 5 astrocytes that regulates neuronal dendritic growth and spine formation by activating Wnt signaling. Norrin-null mice exhibit profound losses of dendritic spines in layer 5 neurons accompanied by behavioral hyperactivity. Interestingly, humans with loss-of-function Norrin mutations develop Norrie disease, a neurobehavioral disorder characterized by cognitive as well as behavioral abnormalities. These studies illustrate how perturbations of astrocytic secreted factors can impact synapse formation and the development of neurological disorders.

Astrocyte-neuron adhesion during synaptic development

Unlike secreted factors, CAMs require direct contact, thereby limiting their range of influence, while providing a more precise spatial regulation of synapses than achievable by secreted means. Adhesive interactions between astrocytes and neurons are mediated by several major classes of molecules, including protocadherins, ephrins, and several members of the immunoglobulin superfamily of CAMs. The list of candidate CAMs with enriched expression in astrocytes continues to grow (Figure 2A and Table 1). Below, we discuss select members of these gene families to highlight their various roles in astrocyte maturation and synaptic development.

The first CAM identified as regulators of astrocytic contact-dependent synapse formation were the protocadherins, a highly diverse set of homophilic CAMs expressed by both neurons and astrocytes. Culturing wild-type γ-protocadherin spinal cord interneurons with γ-protocadherin-null astrocytes led to a substantial decrease in inhibitory synaptic density; this could not be rescued by the addition of wild-type astrocyte conditioned media, suggesting the requirement for direct cell–cell contact. Additionally, it has been shown that astrocytic γ-protocadherins are necessary for dendritic complexity in developing mouse cortical neurons.

Another transcellular adhesion between astrocytes and neuronal synapses is the ephrin-A3/EPHA4 pair. The GPI-anchored Eph tyrosine kinase receptor ligand ephrin-A3 is expressed by astrocytes and found in PAPs, while its receptor, EPHA4, is localized to neuronal excitatory postsynaptic processes. This bidirectional communication regulates the density and morphology of dendritic spines in the hippocampus, while limiting the cell surface expression of glutamate aspartate transporters (Glast), a critical astrocyte regulator of synaptic glutamate levels. Loss of either ephrin-A3 from astrocytes or neuronal EPHA4 led to increased astrocytic Glast expression and deficits in hippocampal long-term potentiation and impaired contextual memory.

HepCAM (hepatocyte cell adhesion molecule, also known as Glial-CAM) is a homophilic CAM found to be highly expressed in glial cells and localized to astrocyte processes that are in close proximity to inhibitory synapses. Conditional deletion of Hepacam in astrocytes reduces inhibitory synaptic density and is associated with decreased synaptic inhibition and increased excitation. HepCAM is also an important regulator of astrocyte–astrocyte interactions, where it regulates astrocytic competition for territory during tiling. Whether
**TABLE 1** List of astrocyte-secreted and cell-adhesive molecules that regulate synapse formation and/or function.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Form</th>
<th>Cell type expression (ligand)</th>
<th>Receptor/interaction partner</th>
<th>Cell type expression (receptor)</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain-derived neurotrophic factor (BDNF)</td>
<td>Secreted</td>
<td>Various</td>
<td>Tropomyosin receptor kinase B (TrkB)</td>
<td>Neuron</td>
<td>Promote excitatory synapse formation</td>
<td>67</td>
</tr>
<tr>
<td>Cholesterol/ApoE</td>
<td>Secreted</td>
<td>Astrocyte</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Promote excitatory synapse formation</td>
<td>68</td>
</tr>
<tr>
<td>Chordin-like 1 (CHRD1L; a.k.a. Ventropin)</td>
<td>Secreted</td>
<td>Astrocyte</td>
<td>Bone morphogenic protein (BMP)—highest affinity to BMP4</td>
<td>Neuron</td>
<td>GluA2 receptor insertion at excitatory synapses</td>
<td>80, 81</td>
</tr>
<tr>
<td>D-Serine</td>
<td>Secreted</td>
<td>Astrocyte</td>
<td>NMDAR</td>
<td>Neuron</td>
<td>Promote synapse formation in adult born neurons</td>
<td>70</td>
</tr>
<tr>
<td>Ephrin-A3</td>
<td>Cell adhesion</td>
<td>Astrocyte/neuron</td>
<td>EPHA4</td>
<td>Neuron</td>
<td>Modulate long-term potentiation</td>
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</tr>
<tr>
<td>Ephrin-B1</td>
<td>Cell adhesion</td>
<td>Astrocyte/neuron</td>
<td>EPHB</td>
<td>Neuron</td>
<td>Balancing neuronal excitation and inhibition</td>
<td>79</td>
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<tr>
<td>γ-Protocadherin</td>
<td>Cell adhesion</td>
<td>Astrocyte/neuron</td>
<td>γ-Protocadherin, neuroligin2 (NLGN2)</td>
<td>Astrocyte/neuron</td>
<td>Dendritic complexity, excitatory and inhibitory synaptogenesis</td>
<td>83, 84</td>
</tr>
<tr>
<td>Glypican4/6</td>
<td>Secreted</td>
<td>Astrocyte/neuron</td>
<td>RPTPβ</td>
<td>Neuron</td>
<td>Excitatory synaptogenesis</td>
<td>74, 80, 81</td>
</tr>
<tr>
<td>Hepatocyte cell adhesion molecule</td>
<td>Cell adhesion</td>
<td>Astrocyte</td>
<td>HepaCAM</td>
<td>Astrocyte</td>
<td>Astrocyte gap junction coupling, balance neuronal excitation/inhibition</td>
<td>87</td>
</tr>
<tr>
<td>Hepatocyte cell adhesion molecule</td>
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<td>Astrocyte</td>
<td>HepaCAM</td>
<td>Astrocyte</td>
<td>Astrocyte gap junction coupling, balance neuronal excitation/inhibition</td>
<td>87</td>
</tr>
<tr>
<td>Hevin (SPARCl1)</td>
<td>Secreted</td>
<td>Astrocyte/neuron</td>
<td>Neurexin-1α, neuroligin1B (NLGN1B)</td>
<td>Neuron</td>
<td>Excitatory synaptogenesis and plasticity</td>
<td>75, 76</td>
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<tr>
<td>Interleukin-33 (IL33)</td>
<td>Secreted</td>
<td>Astrocyte/oligodendrocyte/neuron</td>
<td>ST2 (I1r1)</td>
<td>Microglia</td>
<td>Modulation of excitatory synapses</td>
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<tr>
<td>Neurexin-1-3 (NLGN1-3)</td>
<td>Cell adhesion</td>
<td>Astrocyte/neuron</td>
<td>Neurexins</td>
<td>Neuron</td>
<td>Astrocyte morphogenesis and excitatory synaptogenesis</td>
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</tr>
<tr>
<td>Norrin</td>
<td>Secreted</td>
<td>Astrocyte</td>
<td>Frizzled 4 (FZD4), leucine-rich repeat containing G protein-coupled receptor 4 (LGR4)</td>
<td>Neuron/endothelia</td>
<td>Dendrite complexity, blood–brain barrier integrity</td>
<td>82</td>
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<tr>
<td>Neuronal cell adhesion molecule (NRCAM)</td>
<td>Cell adhesion</td>
<td>Astrocyte/neuron</td>
<td>NRCAM</td>
<td>Neuron</td>
<td>Inhibitory synaptogenesis</td>
<td>91</td>
</tr>
<tr>
<td>Semaphorin 3a (SEMA3A)</td>
<td>Secreted</td>
<td>Astrocyte/neuron</td>
<td>Neuropilin1, plexinA1</td>
<td>Neuron</td>
<td>Establishment of motor neuron and sensory circuit formation</td>
<td>44</td>
</tr>
<tr>
<td>SPARC</td>
<td>Secreted</td>
<td>Astrocyte/microglia</td>
<td>Integrin-β3</td>
<td>Neuron</td>
<td>GluA1 excitatory synaptogenesis, inhibit synaptogenesis</td>
<td>76, 77</td>
</tr>
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</table>

(Continues)
hepaCAM interacts directly with neurons is unclear as hepaCAM also regulates the localization of the gap junction molecule connexin 43 (Cx43; also known as GJA1), which is involved in regulating astrocyte morphogenesis. In humans, hepaCAM mutations are linked to megalencephalic leukoencephalopathy with subcortical cysts, a syndrome of intellectual disability associated with disrupted gliovascular as well as glio-synaptic adhesion.88

Neuroligins are a group of CAMs with associations to human neurodevelopmental and neuropsychiatric disorders.89 Neuroligins (NLGN1-3, 4X, 4Y in primates; NLGN1-4 in rodents) were first characterized in neurons where each is differentially located in postsynaptic compartments (excitatory or inhibitory), while their heterophilic binding partners, the neurexins, are present on presynaptic specializations.90 Recent studies show that both neuroligins and neurexins are also expressed in astrocytes, expanding their role in the brain.23,30,91 For example, NLGN2 is highly expressed by cortical astrocytes. The specific loss of astrocytic NLGN2 in vivo led to a decrease in astrocyte arborization accompanied by reduced excitatory synapse density and function, and an imbalance of excitation and inhibition.23 This astrocytic NLGN2-null phenotype contrasts with the established role of neuronal NLGN2 in regulating inhibitory synapse formation92 and highlights how the cell compartment-specific expression of CAMs drastically influences their functional roles at synapses. It is important to note that neurulin-1 levels are decreased in the human glial cells from patients with schizophrenia.30 Thus, glial and neuronal neuroligin–neurexin interactions may play a significant role in the disease pathogenesis of neuropsychiatric disorders, such as schizophrenia, which demonstrate a shift in the ratio of excitation and inhibition.93,94

The neuronal cell adhesion molecule (NRCAM) was similarly characterized in neurons and then subsequently found to be expressed by astrocytes.91 Astrocytic NRCAM engages in homophilic binding with NRCAM-expressing neurons, in proximity to both excitatory and inhibitory synapses. Yet, the loss of either neuronal or astrocytic NRCAM function significantly reduced inhibitory synapse numbers, while excitatory synapses remained unaffected.91 Perhaps paradoxically, the loss of NRCAM was reported to increase astrocytic infiltration of the neuropil despite resulting in an increased distance between astrocytic processes and inhibitory synapses. These data, together with those defining the role of the neuroligins, indicate that specific adhesive interactions between astrocytes and neurons may regulate the formation of inhibitory versus excitatory synaptic connections. Overall, the rules by which specific synaptic phenotypes are instructed by astrocytic ligands, and the means by which astrocytes traffic adhesion molecules to those specific synaptic compartments, remain poorly understood and ripe for future investigation.

**FIBROUS ASTROCYTES IN THE WHITE MATTER**

The cellular and molecular functions of astrocytes in the white matter have been much less studied than those of their gray matter counterparts. The morphological distinction of white matter astrocytes was first documented in the drawings of Santiago Ramón y Cajal in the early 1900s. Nevertheless, new research is uncovering unique functions for these nonparenchymal glial cells. Fibrous astrocytes (Figure 1B), while derived from the same progenitors as protoplasmic astrocytes,95 reside specifically within the CNS white matter, including the major routes of the corpus callosum, anterior and posterior comissure tracts, the ascending/descending columns of the spinal cord, and axon bundles descending through subcortical structures, among others. By nature of their location, fibrous astrocytes do not interact with synaptic structures as do their gray matter counterparts. Instead, this specialized population of astroglia associates with, and transcellularly signals between myelinated neuronal axons, oligodendrocytes (and their precursors), microglia, and the vasculature (Figure 2B). As discussed below, new lines of research now reveal that fibrous astrocytes regulate network activity both directly, via interactions with axons, and indirectly, through the myelination of axons by oligodendrocytes. Increased interest in fibrous astrocytes in the context of neurological disorders and white matter pathologies is bringing their critical functions within the CNS to light. However, significant gaps remain in our knowledge of these astroglia, primarily due to the lack of tools to manipulate them without affecting gray matter protoplasmic astrocytes.
White matter astrocytes regulate network activity

In the crowded spaces of the white matter, neuronal axons are tightly ensheathed by myelin which is crucial for maintaining axon integrity and ensuring proper axon conduction velocities. Acting within the Nodes of Ranvier between myelin segments, fibrous astrocytes may play a critical role in regulating neural transmission by tuning the conduction speed along the axon (Figure 2B) (97). As intracellular Ca^{2+} levels rise within white matter astrocytes, likely in response to axonal action potentials, ATP release is triggered, which is quickly converted into adenosine by extracellular ATPases. The extracellular adenosine binds to its neuronal receptor A2B at the node, triggering hyperpolarization through the potassium/sodium hyperpolarization-activated cyclic nucleotide-gated ion channel 2 (HCN2), and dampening the speed of impulse propagation. As such, white matter astrocytes may serve as a brake on excessive long-range neural activity. This relatively new, and fundamentally intriguing, discovery highlights the direct role that astrocytes may play in adjusting the dynamics of neural transmission not only at the synaptic level but also along the axonal tracts that span distant brain regions.

These findings firmly interject a consideration of white matter astrocytes into the long-standing question of how neural activity is coordinated in time and space across the brain. Besides their well-documented role in metabolic and nutritive support of oligodendrocytes and axons alike, fibrous astrocytes ensure the coordinated activation of distant neural target centers. In line with this hypothesis, astrocyte-derived ATP has been identified to play an important role in regulating the transitions between sleep cycles by synchronizing network activity. Conversely, white matter astrocyte dysfunction could lead to disruptions of coordinated long-range network activity by producing deficits in motor or cognitive processing. For example, speech, which requires coordination between a variety of brain centers, is interrupted in human patients who stutter. A mutation in the gene GNPTAB was found in humans who stutter and whose functional expression appears to map back to fibrous astrocytes of the corpus collosum. The gene product of GNPTAB is essential for the appropriate trafficking of lysosomal enzymes, suggesting that the astrocytic clearance of material in the white matter might regulate efficient axonal signal propagation.

Recent work suggests that fibrous astrocytes may also modulate neural network dynamics and behavioral states by serving as short-term integrators of neural activity. Radial astrocytes of zebrafish accumulate intracellular Ca^{2+} levels with failed swim attempts and, upon reaching a threshold, shut off the network by activating inhibitory neurons to induce passivity. Collectively with other studies, the data demonstrate that astrocytes play a pivotal role in information processing within the brain. Moving forward, new tools to study fibrous astrocytes in real-time, their coordination with neuronal activity, and synchronization with functional and behavioral read-outs, will be needed to understand how these cells behave within higher-order networks.

Fibrous astrocytes coordinate oligodendrocyte differentiation and myelination

Oligodendrocytes are the myelinating cells of the CNS and are derived from oligodendrocyte progenitor cells (OPCs; also known as glial progenitor cells, since in humans, these cells are multilineage competent and may generate astrocytes as well as oligodendrocytes in vivo). OPCs are distributed throughout the developing and mature brain and undergo a stepwise maturational program to produce myelinating oligodendrocytes that ensheathe axons to permit the fast, efficient, and coordinated transmission of action potentials. Platelet-derived growth factor-alpha (PDGFA) is a potent and necessary factor that mediates both the survival and mitotic expansion of OPCs while suppressing their terminal differentiation; it is produced primarily by astrocytes, which thereby can regulate OPC and, hence, oligodendrocyte number. PDGFA may work in concert with the chemokine CXCL1 produced by white matter astrocytes, to limit when and where OPCs migrate and proliferate. The coordination of these astrocyte-derived signals with activity-dependent neuronal signals ultimately dictates the timing and extent of developmental myelination, as well as the fine-tuned process of adaptive myelination during learning.

Several cues that regulate oligodendrocytic myelogenesis have been identified, yet it remains unclear how these are coordinated and prioritized. Some cues are provided by neuronal properties, such as axon caliber, neural identity, and neural activity. In addition, astrocytes produce a multitude of secreted molecules implicated in developmental myelination. These include neuregulin, brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), insulin-like growth factor 1 (IGF1), and osteopontin, among others (Table 2A). Yet, fibrous astrocytes also secrete factors implicated in the inhibition of myelination; these include BMP2/4 and hyaluronan. Thus, it remains to be determined how astrocytes direct the balance between OPC differentiation and myelination, and how this process may differ in development and adulthood.

In addition to secreted factors, physical contact between astrocytes and oligodendrocytes may also regulate axonal myelination through the formation of gap junctions (Figure 2B). These interglial junctions are comprised predominantly by white matter astrocyte connexins (Cx) Cx30 (GJB6) or Cx43, juxtaposed to oligodendrocyte-expressed Cx32 (GJB1) and Cx47 (GJC2), respectively. While the expression pattern of these interglial connexins varies by brain region, Cx43 and Cx47 are the most widely expressed. In general terms, gap junctions between astrocytes and oligodendrocytes may permit the critical exchange of factors necessary for oligodendrocyte metabolic support, maintenance, and myelination (Table 2). Indeed, mutations in the gene encoding for Cx47 (GJC2), which thereby prevent the proper formation of Cx47-Cx43 gap junctions between oligodendrocytes and astrocytes, causes a severe hypomyelinating disorder that phenocopies Pelizaeus–Merzbacher disease, a fatal hereditary dysmyelinating leukodystrophy. Similarly, dual deletion of Cx47 and Cx30 in transgenic mice induces severe myelination defects, decreased...
As critical components of the synapse, astrocytes have numbers of oligodendrocytes, and motor impairments. Interestingly, these are a result of a disruption in heterotypic glial gap junction signaling since neither astrocyte–astrocyte nor oligodendrocyte–oligodendrocyte gap junction signaling were impaired in Cx47/Cx30 double knockouts. A host of questions thus remain regarding the role of gap junction signaling between astrocytes and oligodendrocytes; among them are the nature of the signals passed between these cells and how these influence the regulation of axonal conductance. Furthermore, it is unlikely that astrocyte–oligodendrocyte gap junction signaling is unidirectional; what functions might gap junction signaling provide to white matter astrocytes? In that regard, what are the precise roles of fibrous astrocytes in the white matter? Such fundamental questions are yet to be deeply explored.

### ASTROCYTIC DYSFUNCTION AS THE BASIS FOR NEUROBEHAVIORAL DISORDERS

Glia cells have been increasingly recognized in recent years for their roles in neurodevelopmental, neuropsychiatric, and neurodegenerative disorders. Because both gray and white matter astrocytes are integral to brain circuit function, it is no wonder that they play key roles in CNS diseases. Here, we summarize recent findings of the known and postulated roles of astrocytes in behavioral disorders.

#### Gray matter astrocytes in neuropsychiatric disease

In general, the complex neurobiology of the major psychiatric disorders, including schizophrenia, autism spectrum disorder (ASD), and the major depressive (MDD) and bipolar disorders, remains poorly understood. Each of these maladies demonstrates strong genetic components with an enriched representation of genes affecting synaptic function. As critical components of the synapse, astrocytes have been found to contribute to synaptic pathology, and indeed to causally contribute to disease phenotypes. As such, they may also play a pivotal role in the rescue of both synaptic deficits and disease phenotypes.

Recent studies combining RNA sequencing with histochemical characterization have reported a range of molecular and morphological alterations in gray matter astrocytes of neuropsychiatric patients. However, challenges remain in determining the causal contribution and necessity of astroglial pathology to these psychiatric disorders. Disrupted homeostasis of excitatory and inhibitory circuits in the brain has long been suspected of contributing to schizophrenia, bipolar, and major depressive disorders (MDDs). Glutamate is the most abundant excitatory neurotransmitter in the CNS, and astrocytes serve a prominent role in regulating its levels and synaptic availability. Glutamate is taken up by the glutamate transporter solute carrier family 1 member 2 (SLC1A2, also known as GLT1 or EAAT2), which is localized to PAPs and then shuttled back to neurons as glutamine.

#### TABLE 2

<table>
<thead>
<tr>
<th>Astrocyte factor</th>
<th>Receptor</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone morphogenic protein 2/4 (BMP2/4)</td>
<td>Bone morphogenic protein receptor (BMPR)</td>
<td>Inhibit OPC differentiation</td>
<td>128</td>
</tr>
<tr>
<td>Brain-derived neurotrophic factor (BDNF)</td>
<td>Tropomysin receptor kinase B (TRKB)</td>
<td>Potentiate developmental myelination</td>
<td>122</td>
</tr>
<tr>
<td>Ciliary neurotrophic factor (CNTF)</td>
<td>Ciliary neurotrophic factor receptor (CNTFR)</td>
<td>Enhance myelination</td>
<td>123</td>
</tr>
<tr>
<td>Connexin 30 (Cx30)</td>
<td>Cx32</td>
<td>Maintain oligodendrocyte support and myelination</td>
<td>131–133, 135</td>
</tr>
<tr>
<td>Cx43</td>
<td>Cx47</td>
<td>Maintain oligodendrocyte support and myelination</td>
<td>131, 133, 135</td>
</tr>
<tr>
<td>CXC motif chemokine ligand 1 (CXCL1)</td>
<td>Cxcr2</td>
<td>Counteract PDGFA to arrest OPC migration and proliferation</td>
<td>118</td>
</tr>
<tr>
<td>Hyaluronan</td>
<td>Cd44, Toll-like receptor 2 (TLR2)</td>
<td>Impairs remyelination after lysolecithin-induced demyelination</td>
<td>129, 130</td>
</tr>
<tr>
<td>Insulin-like growth factor 1 (IGF1)</td>
<td>Insulin-like growth factor 1 receptor (IGF1R)</td>
<td>Growth and differentiation of OPCs; stimulate remyelination in development and injury</td>
<td>124, 125</td>
</tr>
<tr>
<td>Neuregulin 1 (NRG1)</td>
<td>ErbB receptors</td>
<td>Enhance myelination</td>
<td>126</td>
</tr>
<tr>
<td>Osteopontin</td>
<td>Integrins (undetermined)</td>
<td>Promote myelination</td>
<td>127</td>
</tr>
<tr>
<td>Platelet-derived growth factor α (PDGFA)</td>
<td>Platelet-derived growth factor receptor α (PDGFRα)</td>
<td>Survival and migration of OPCs; inhibit differentiation into oligodendrocytes</td>
<td>114–117</td>
</tr>
</tbody>
</table>

Note: The molecules are alphabetically listed, indicating (1) the receptor expressed by the oligodendrocyte-lineage cell, and (2) the function of the factor in regulating the myelination process. Abbreviation: OPC, oligodendrocyte progenitor cell.
Astrocytes regulate the spatial and temporal dynamics of glutamatergic transmission. Reduced SLC1A2 is observed in the prefrontal cortex and nucleus accumbens in both rodent models of stress and in humans with MDD. Reduced expression of RNA and abundance of proteins relevant to glial glutamate homeostasis has also been observed in individuals with schizophrenia; these include SLC1A2, glutamine synthase (GUL), glutamate dehydrogenase (GLUD1), glutaminase (GLS), and serine racemase (SRR). These observations suggest important roles for astrocytes in neuropsychiatric disorders that arise from dysregulated excitatory transmission and suggest potential glial targets for therapeutic intervention.

Recent studies suggest that astrocytes also respond to neurodevelopmental factors known to impact emotional and affective states relevant to neuropsychiatric diseases. For instance, astrocytes in the central amygdala have been shown to express receptors for the neuropeptide oxytocin, where signaling is sufficient to mediate its anxiolytic effects. In addition to neurotransmitter uptake, astrocytes are heavily involved in the uptake of potassium (K\(^+\)) released into the extracellular space, predominantly through the inward rectifying potassium channel Kir4.1 (also known as KCNJ10). Astrocytic Kir4.1 expression was found to be dysregulated in the lateral habenula of a rat model of depression, in which it was associated with increased neuronal burst firing. Kir4.1 dysfunction in striatal astrocytes has also been linked to excitatory motor phenotypes in a mouse model of Huntington’s disease (HD), just as its expression—and that of a host of other potassium channels and transporters—is similarly deficient in pluripotent stem cell-derived glia derived from HD patients. Since high extracellular K\(^+\) levels potentiate neuronal firing—in neurons that may already be hyperexcitable due to increased synaptic glutamate—the combination of deficient synaptic K\(^+\) and glutamate clearance by diseased astrocytes may directly and strongly contribute to the neurological dysfunction of HD. Together, these studies illustrate both the role of astrocytic dysfunction in the pathogenesis of neuropsychiatric disorders, while also indicating the potential attractiveness of glia as targets for therapeutic manipulation and/or cellular replacement.

White matter astrocytes and neurological disorders

The CNS white matter tracts are particularly vulnerable to pathology on a variety of fronts, including genetic maladies, ischemic events, and autoimmune attacks. Historically, these pathologies have been attributed to impacted oligodendrocytes and neuronal axons of the white matter. However, fibrous astrocytes are now garnering increased attention as key regulators and possibly, therapeutic targets of white matter disorders.

White matter astrocyte contributions to psychiatric disorders

White matter tracts display profound deficits in psychiatric disorders in addition to the gray matter anomalies as discussed above. Magnetic resonance imaging studies in patients with schizophrenia and bipolar disorder identified significant increases in mean diffusion, volume ratio, and radial diffusivity (measures of microstructural changes in the organization and orientation of white matter tracks) compared to healthy controls. In fact, impaired white matter integrity is a hallmark of schizophrenia and other disorders displaying psychosis. On the surface, these alterations could be ascribed to a host of cellular and synaptic dysfunctions, not necessarily involving fibrous astrocytes. However, white matter astrocyte pathology that includes decreased fibrous astrocyte density paired with a reduction in the expression and translation of GFAP has been observed in patients with MDD. For more direct evidence of glial involvement in psychosis, a recent study engrailed human glial progenitor cells derived from induced pluripotent stem cells (iPSCs) from patients with schizophrenia into the mouse brain. Compared to controls, mice engrafted with patient-derived glial cells displayed impaired sensorimotor gating, increased anxiety-like behaviors, and reduced social approach behavior, accompanied by delayed astrocyte differentiation. A delay in the maturation of astrocytes could have profound effects on the development of the underlying neural circuitry. This idea is supported by recent findings that asynchronous neuronal maturation is associated with neural developmental disorders, such as autism. Moving forward, major efforts are required to tease apart the cellular contributions of white matter astrocytes to neurodevelopmental and neuropsychiatric disorders by using new tools and models that more accurately reflect human biology.

Neurodevelopmental and congenital dysmyelinating disorders

Leukodystrophies (leuko = white; dystrophy = imperfect growth) comprise a class of rare, genetically linked, white matter disorders characterized by the abnormal formation of myelin. Though myelin deposition is attributed directly to oligodendrocytes, white matter astrocytes play a key role in the underlying cause of several forms of leukodystrophies. The most notable example of an astrocyte-linked leukodystrophy is Alexander disease (AxD). Affecting roughly one in one million births, AxD manifests predominantly in early infancy to late childhood as a range of symptoms which can include seizures, spasticity, intellectual disability, and macrocephaly. AxD is a mono- genic gain-of-function disorder caused by dominant mutations in the gene encoding GFAP, a core component of intermediate filaments that make up the cytoskeleton of white matter astrocyte processes. The mutant GFAP proteins form inclusion aggregates known as Rosenthal fibers, which appear via hematoxylin and eosin staining and electron microscopy in the brain white matter, brainstem, and spinal cord. While it is not yet known whether these aggregates are themselves toxic, the genesis of dysfunction within astrocytes yields secondary effects to nearly all other cell types within the CNS.

A second astrocyte-implicated white matter disorder is mega- lencephalic leukoencephalopathy with subcortical cysts (MLC). This childhood-onset hereditary disease displays white matter vacuolation and macrocephaly, accompanied by ataxia, spasticity, and...
The symptoms of NMO can be varied, indicating a disruption to the development and organization of the gliovascular unit, including alterations to interstitial fluid clearance and neurovascular coupling. While most models rely on Mlc1 knockouts, the overexpression of Mlc1 induces more severe and early-onset MLC phenotypes. New lines of evidence indicate that hepaCAM homodimerizes in cis and trans to control astrocyte morphogenesis and astrocyte–astrocyte interactions and may present a secondary mechanism of disease progression. How these seemingly disparate functions controlling astrocyte morphogenesis, blood–brain barrier formation, and ion/water homeostasis directly affect white matter myelinization is still to be determined.

Vanishing white matter disease (VWMD) is another leukodystrophy whose pathogenesis is linked to astrocyte dysfunction. Recessive mutations in the genes encoding any of the five subunits of eukaryotic translation initiation factor 2B (eIF2B) lead to the vacuolization and cystic degeneration of white matter with disease severity correlated with age of onset. While astrocytes and oligodendrocytes both express eIF2B, it seems that astrocytes have increased susceptibility to eIF2B mutations with altered astrocyte proliferation and maturation rates coupled with metabolic stress signals in VWMD patients. Mouse lines harnessing mutant eIF2B subunit genes to model VWMD confirm that astrocytes are pivotal to the pathophysiological mechanisms of VWMD and demonstrate astrocyte dysfunction, including upregulated GFAP immunoreactivity, abnormal splicing of GFAP, increased endoplasmic reticulum stress, and inhibition of oligodendrocyte maturation. Additional research is needed to uncover the interplay between astrocytes and oligodendrocytes in the initiation and progression of VWMD and how astrocytes can be targeted for therapeutic interventions.

Astrocyte-targeted autoimmune and paraneoplastic states

Autoimmune and paraneoplastic disorders targeting glia comprise a broad class of disease stimulated by autoreactive immune cells. While the autoantibodies involved in these disorders vary widely and result either in direct antibody-mediated toxicity or indirect T-cell-mediated autoimmunity. The clinical outcomes of these disorders also vary widely and can include demyelination and white matter loss (as well as cortical pathology) with psychosis, movement abnormalities, and cognitive difficulties. While many autoimmune disorders directly target oligodendrocyte antigens—multiple sclerosis (MS) being prototypic—ample evidence now exists of both primary and paraneoplastic autoimmune disorders that directly target astrocytes.

Neuromyelitis optica (NMO), classically known as Devic’s disease, is the most well-known astrocyte-involved autoimmune syndrome. This syndrome of comorbid optic neuritis and myelitis is caused by the production of autoantibodies against aquaporin 4 (AQP4), a highly expressed glial water channel protein whose expression is largely restricted to perivascular astrocytic endfeet at the blood–brain barrier. AQP4-specific IgG1 antibodies can activate and thereby yield direct astrocytopathy, with both acute blood–brain barrier disruption and massive cytokine production in the setting of systemic inflammation. The symptoms of NMO can be varied, indicating that its effects may not be restricted to the optic nerves and spinal cord but rather may be more widespread. Yet, unlike autoimmune demyelinating disorders, such as MS, the lesions of NMO are only rarely present within the cortex, even though AQP4 is highly expressed by cortical astrocytes. While untested, perhaps autoantibodies targeting splice variants or alternative translation of AQP4 (e.g., AQP4x) expressed by astrocytes of the optic nerves and spinal cord may underlie the pathological region restriction of NMO.

In contrast, paraneoplastic syndromes are less-well studied than NMO. Anti-GFAP astrocytopathy is a novel autoimmune disorder, a large proportion of which are linked to the appearance of systemic cancers, most commonly ovarian teratomas. However, less than 30% of patients present with central demyelination with a larger proportion manifesting the cognitive and sensorimotor dysfunction of cortical and subcortical synaptic disruption. It seems likely that there are many more astrocyte-targeted autoimmune disorders, including the large syndromic category of autoimmune encephalitis for which target antigens have not yet been identified. As our understanding of these fascinating conditions improves, we may hope to use them as windows by which to study the role of astrocytes in modulating human cognition and behavior.

ASTROCYTE-TARGETED THERAPEUTIC STRATEGIES

As noted, astrocytic dysfunction is causally linked to the initiation and progression of a broad variety of neurodegenerative and neuropsychiatric disorders. As such, targeting these cells may be an effective strategy for modifying the course of these generally untreatable brain disorders, whether via traditional small molecules or via gene- and cell-based therapeutics. Preclinical models now demonstrate the efficacy of these approaches with human clinical trials getting underway for a variety of glia-involved conditions. Here, we highlight some of the recent efforts to treat CNS disorders by targeting astrocytes, whether by their repair or replacement.
Among the earliest glial-targeted approaches to proceed to clinical trials has been the use of antisense oligonucleotides (ASOs) to reduce the expression of toxic gain-of-function genes.195 This technology was developed in experimental models of AxD196,197 to suppress the mutant isof orm of GFAP that is causal in that disorder and is now in clinical trials (Clinical Trial Identifier NCT04849741). A similar ASO-based approach is under development for the treatment of some forms of Pelizaeus–Merzbacher disease.198 More broadly, with the advent of in vivo gene editing via CRISPR and/or base editors coupled with the cell-type specific delivery of those products, we may now consider altering the genome/epigenome of astrocytes for therapeutic purposes. In addition, astrocytes have been targeted for cellular reprogramming into neuronal subtypes to correct for diseased or lost neurons in neurodegenerative disorders, such as in Parkinson’s disease.199,200 While such glial–to-neuronal phenoconversion approaches are both controversial and at an early stage in development,201–203 they offer promise toward the treatment of a broad variety of neurological disorders.

Yet, these genetically based treatment strategies have been limited by the difficulty of achieving widespread and efficient transduction of targeted cells within the adult brain parenchyma. Both ASO and viral delivery may be dose-limited by toxicity, which may appear at levels insufficient to achieve therapeutic levels of transduction.204 As an alternative strategy, selected CNS disorders may be amenable to the replacement of diseased cells, via stem cell-based therapy. Human bipotential glial progenitor cells that give rise to oligodendrocytes and astrocytes can be derived in vitro from both embryonic stem cells and iPSCs.205–208 When transplanted at the glial progenitor stage, these cells readily engraft in rodent models where they retain both their differentiation potential and cell-autonomous hominid characteristics.209 In experimental rodents, glial transplantation has been noted to restore or frankly rescue function in a host of neurodegenerative disease models, including amyotrophic lateral sclerosis (ALS),210 leukodystrophies,211 HD,31 and childhood-onset schizophrenia30 among others. Clinical trials are now underway using astrocytes as a cell-based therapy for ALS (Clinical Trial Identifiers NCT02943850 and NCT03482050). Going forward, such cell engraftment strategies may permit the replacement of damaged or diseased glia with their healthy, younger counterparts as a means of restoring damaged or deficient neural circuits.212–214

CONCLUSION

The manner in which astrocytes influence brain circuits is as diverse and complex as their morphologies. Astrocytes modulate neural activity in both gray matter and white matter regions of the brain by adopting morphologies and functions suited to the needs of their local cellular environment. Whether through interactions with neurons in the gray matter, axons and their associated oligodendrocytes in the white matter, or through microglial intermediaries in both compartments, astrocytes can have profound impacts on brain development and function. Crosstalk between astrocytes, neurons, and other glia via both contact-dependent and secreted factors influence the maturation and morphological arborization of astrocytes and neurons alike, and more broadly, dictate their association in neural networks—whose synaptic activity and coordination is significantly regulated by the astrocytic syncytium. Going forward, understanding how astrocytes respond to and shape their environment, in terms of both its development and homeostatic maintenance, will be critical in unlocking their potential as therapeutic targets for the many diseases of the CNS in which they are involved.

AUTHOR CONTRIBUTIONS

J.A.S., C.C.H., and S.A.G. conceived and drafted the manuscript. J.A.S. prepared the figures. All authors approved the final version of the manuscript.

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