


MINI-SYMPOSIUM: Astroglia in Neurodegenerative Diseases

Stratification of astrocytes in healthy and diseased brainAlexei Verkhratsky ^{1,2,3}; Robert Zorec^{4,5}; Vladimir Parpura⁶¹ Division of Neuroscience & Experimental Psychology, The University of Manchester, Manchester, United Kingdom.² Achúcarro Basque Center for Neuroscience, IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain.³ Department of Neuroscience, University of the Basque Country UPV/EHU and CIBERNED, 48940 Leioa, Spain.⁴ Laboratory of Cell Engineering, Celica BIOMEDICAL, Tehnološki park 24, Ljubljana 1000 Slovenia, Europe.⁵ Laboratory of Neuroendocrinology-Molecular Cell Physiology, Institute of Pathophysiology, Faculty of Medicine, University of Ljubljana, Zaloška 4, Ljubljana 1000, Slovenia, Europe.⁶ Department of Neurobiology, Civitan International Research Center and Center for Glial Biology in Medicine, Evelyn F. McKnight Brain Institute, Atomic Force Microscopy & Nanotechnology Laboratories, 1719 6th Avenue South, CIRC 429, University of Alabama at Birmingham, Birmingham, AL 35294-0021.**Keywords**

astroglia, brain, homeostasis, pathology.

Corresponding author:

Prof. Alexei Verkhratsky MD, PhD, DSc, Faculty of Life Sciences, The University of Manchester, Manchester, UK

(E-mail: Alexej.Verkhatsky@manchester.ac.uk)

Received 15 May 2017

Accepted 6 June 2017

doi:10.1111/bpa.12537

Abstract

Astrocytes, a subtype of glial cells, come in variety of forms and functions. However, overarching role of these cell is in the homeostasis of the brain, be that regulation of ions, neurotransmitters, metabolism or neuronal synaptic networks. Loss of homeostasis represents the underlying cause of all brain disorders. Thus, astrocytes are likely involved in most if not all of the brain pathologies. We tabulate astroglial homeostatic functions along with pathological condition that arise from dysfunction of these glial cells. Classification of astrocytes is presented with the emphasis on evolutionary trails, morphological appearance and numerical preponderance. We note that, even though astrocytes from a variety of mammalian species share some common features, human astrocytes appear to be the largest and most complex of all astrocytes studied thus far. It is then an imperative to develop humanized models to study the role of astrocytes in brain pathologies, which is perhaps most abundantly clear in the case of glioblastoma multiforme.

INTRODUCTION: THE CONCEPT OF HOMEOSTATIC NEUROGLIA

The complexity of human brain is remarkable: more than 200 billions (ie, 2×10^{11}) of neural cells (neurones and neuroglia) are packed within a limited volume (average human brain occupies 1200–1400 cm³). These neural cells form complex networks, connected with 15–20 trillions of chemical and electrical synapses that provide for this organ computing power. Assuming the memory capacity of a single chemical synapse of ~ 5 bits, the total memory capacity of the human brain exceeds 1 petabyte (21). The logistics support underlying this highly complex analytical machine (which uses multiple information processing algorithms being thus fundamentally different from binary-oriented artificial computing) is provided by a specific class of cells known as neuroglia.

Neuroglia, which comprise cells of neural (astrocytes, oligodendrocytes and NG2 glia and all peripheral glia) and non-neural (microglia) origins, represent the homeostatic and defensive arm of the nervous system (110, 260). Glial cells provide homeostatic control on all levels of organization of the CNS (Table 1) from molecular (eg, regulation of ion and neurotransmitter turnover) to network (eg, regulation, of synaptic connectivity and axonal myelination) and systemic (chemosensing and regulation of energy balance).

Astrocytes, which are distributed in both white and gray matters of the brain and the spinal cord, are main homeostatic cells (174, 263); oligodendrocytes are responsible for axonal myelination and axonal homeostatic support throughout the brain, being thus central elements of the brain connectome (73); NG-2 glia contribute to CNS homeostasis, and provide a pool of oligodendroglial progenitor cells involved in adult (re)myelination (158, 208). All these macroglial cells are responsible for CNS protection and defence through a complex and evolutionary conserved programme of reactive astrogliosis, Wallerian degeneration and activation of NG2 glia (178, 203, 260, 266). Microglial cells [which enter the brain as foetal macrophages—(80)] acquire a specific morphological phenotype (small cell bodies with highly motile processes) and express an extended complement of receptors characteristic for both neural and immune cells. Combination of motile processes and multiple receptors are instrumental for constant surveillance of the nervous tissue for the signs of damage (108). Microglial cells shape neuronal networks through synaptic stripping and phagocytosis of redundant and apoptotic neurones during development (109, 252). Insults to the brain trigger microglial activation, which produces multiple and often disease-specific phenotypes, while overactivation of microglia may assume neurotoxic proportion and exacerbate neuropathology (92, 108).

Table 1. Physiological functions of astroglia.

Function	Molecular pathways	Reference
<i>Ion homeostasis</i>		
K ⁺ buffering and homeostasis	Na ⁺ -K ⁺ pump, NKA Na ⁺ -K ⁺ -Cl ⁻ co-transporter 1 NKCC1/SLC12A2 (operational at high K ⁺ loads) Inward rectifier K ⁺ channels K _{ir} 4.1 Connexins Cx43, Cx30	(41, 51, 115, 122, 132, 164, 171, 172, 192, 225, 254)
Cl ⁻ homeostasis	GABA _A receptors Anion channels, ClC-2, Volume-regulated anion channels VRAC/SWELL1 Best1 Cl ⁻ channels Na ⁺ -K ⁺ -Cl ⁻ co-transporter 1 NKCC1/SLC12A2	(24, 65, 107, 173, 230)
H ⁺ homeostasis and control of extracellular pH	Na ⁺ -H ⁺ exchanger NHE1/SLC9A1 Na ⁺ -HCO ₃ ⁻ transporter NBCe1/SLC4A4 Plasmalemmal V-type H ⁺ pump	(40, 54, 84, 89)
Na ⁺ , Ca ²⁺ homeostasis	Plasmalemmal Ca ²⁺ pump PMCA Na ⁺ -Ca ²⁺ exchanger NCX1/SLC8A1, NCX2/SLC8A2 and NCX3/SLC8A3	(112, 114, 206, 265, 268)
<i>Neurotransmitter homeostasis</i>		
Glutamate	Na ⁺ -dependent glutamate transporters EAAT1/ SLC1A6 and EAAT2/SLC1A2 Cystine/glutamate antiporter Sxc ⁻ composed of xCT/SCL7A11 and 4F2hc/SLC3A2 proteins	(113, 257, 293) (6, 151)
GABA	Na ⁺ -dependent GABA transporter GAT3/SLC6A11	(148, 223)
Glutamate/GABA-glutamine shuttle	Glutamine synthetase GS Na ⁺ -dependent glutamine transporters	(96, 163, 205)
Glycine	Na ⁺ -dependent glycine transporters GlyT1/SLC6A9	(69, 100, 288)
Monoamines	Norepinephrine transporter NET/SLC6A2 (which transports both noradrenaline and dopamine) Monoamine oxidase B MAO-B	(221, 247) (95, 212)
Adenosine	Na ⁺ -dependent concentrative nucleoside transport- ers CNT2/SLC28A2 and CNT3/SLC28A3 Adenosine kinase ADK	(127, 183) (27, 242)
<i>Metabolic support</i>		
Uptake of glucose, synthesis of glycogen	Glucose transporter	(5)
Aerobic glycolysis, shuttling of lactate to neurones	Monocarboxylate transporters 1 and 4 (MCT1/ SLC16A1, MCT4/SLC16A3)	(87, 180, 181)
<i>Network homeostasis and synaptic transmission</i>		
Synaptogenesis	Cholesterol, thrombospondins, hevin, secreted pro- tein acidic and rich in cysteine SPARC	(67, 119, 139, 187)
Synaptic maturation	Activity-dependent neurotrophic factor, tumor necrosis factor α (TNF α), cholesterol, astroglia- derived glypicans 4 and 6	(7, 67, 187)
Synaptic extinction	Complement factor C1q	(42, 214)
<i>Organ homeostasis</i>		
Regulation of the formation and permeability of blood-brain and CSF-brain barriers		(1, 2)
Formation of glial-vascular interface and regulation of microcirculation	Epoxyeicosatrienoic acids EETs, 20-hydroxyeicosatetraenoic acid 20-HETE, prosta- glandin E ₂ PGE ₂ , Ca ²⁺ -dependent K channels K _{Ca} 3.1	(18, 74, 101, 144, 153, 246, 294)
Functional operation of the glymphatic system	Water channel aquaporin-4 AQP4	(102, 103, 154, 156)
Gliocrine system, astrocytes act as secretory cells of the brain	Neurotransmitters, neuromodulators, neurohor- mones, cytokines, neurotrophic factors	(259, 262, 296)
<i>Systemic homeostasis</i>		
Central chemoception of plasma Na ⁺ concentration	Na ⁺ -activated Na _x channels	(159, 160, 229, 277)

Table 1. *Continued.*

Function	Molecular pathways	Reference
Central chemoreception of oxygen, pH and CO ²	Oxygen sensor associated with mitochondria in cortical astrocytes pH sensor in brain stem astrocytes Na ⁺ -Ca ²⁺ exchanger. K _{ir} 4.1 K ⁺ channels	(12, 83, 253, 279)
Regulation of sleep	Astrocytes are linked to the sleep homeostat through an elevation of brain adenosine content in the wake state. Astrocytes may also regulate sleep through dynamic control over ion composition of the interstitium	(60, 86, 188, 248)

EVOLUTION OF GLIA ACCOMPANIES INCREASING COMPLEXITY OF THE BRAIN

Evolutionary emergence of the supportive neural cells coincided with the centralization of the nervous system and appearance of neuronal conglomerates in the form of ganglia or neuronal rings. The ancient forms of neuroglia, defined as cells covering neuronal elements have been characterized in round worms and in the Acoela worms. The nervous system of the round worm *C. elegans* comprises 302 neurones and 50 supportive cells of the ectodermal origin (which can be classified as neuroglia) and six GLR cells originating from mesoderm, these later being interconnected (through gap junctions) to both neurones and muscle cells (168). The majority (46) of glial cell of *C. elegans* are forming (together with neuronal terminals) the sensory organs of the worm, known as sensilla. Four ensheathing glial cells localized in the head of the *C. elegans* extend velate processes covering neurones in the neural ring of the animal, and thus can be defined as proto-astrocytes (185, 240). The supportive cells extending multiple processes into the neuropil were also identified in the Acoela worms (25); in platyhelminthes (polyclads and triclads) supportive cells have been found in the nerve cord (82).

Further evolution brought up a substantial diversification of glia. The ganglionic nervous system of the medicinal leech contains several types of specialized glia, represented by giant glial cells responsible for homeostatic control over the neuropil, by packet glial cells which enwrap neuronal cell bodies and by connective glial cells that cover and support axons (55). The giant glial cells express multiple ionotropic and metabotropic neurotransmitter receptors and ion channels (55, 152). Neuronal activity and behavioral patterns trigger glial depolarization and cytosolic Ca²⁺ signaling (58, 130). Packet glia regulate K⁺ homeostasis around neuronal somata (211), whereas giant glial cells control ion homeostasis in the neuropil, being particularly important for regulation of pH (by plasmalemmal Na⁺-HCO₃⁻ co-transporter, Na⁺-H⁺ and Cl⁻-HCO₃⁻ exchangers). Furthermore giant glial cells remove extracellular glutamate and choline through dedicated Na⁺-dependent plasmalemmal transporters (56, 57, 98, 283).

Even higher level of diversification characterizes neuroglia in the arthropods, and particularly in the insects. In *Drosophila*, glial cells account for ~10% of all cells in the CNS and are represented by several major classes. These include: (i) wrapping glia of the peripheral nervous system; (ii) surface glia (comprising perineural and subperineural cells), which make the brain-hemolymph barrier;

(iii) cortex glia that cover neuronal cells bodies in the CNS; (iv) neuropil glia (ensheathing and astrocyte-like glia) that cover CNS axons and synapses; and (v) tract glial cells, which cover axonal tracts connecting different neuropils in the CNS (8, 64, 76, 90, 117). The major types of glial cells are further subdivided on a basis of their morphology and function; for example, the glia of the lamina (neuropil) of the optic lobe is classified into fenestrated glia, pseudocartridge glia, distal and proximal satellite glia, epithelial glia and marginal glia (38, 64, 250). Glial cells in insects are responsible for homeostatic functions, such as regulation of ionic balance in the CNS fluids and regulating clearance, recycling and metabolism of neurotransmitters (29, 140). In particular neuropil glial cells in *Drosophila* express glutamate receptors (133), excitatory amino acid transporters dEAAT1 and dEAAT2, as well as glutamine synthetase generating glutamine the glutamate-glutamine cycle, the latter responsible for transport and recycling of glutamate between neurones and glia (53, 106).

In early vertebrates, the CNS parenchymal glia is replaced by the radial glia, which is associated with an emergence of layer organization of the brain. In the early chordates and in the low vertebrates (eg. in sea cucumber, star fishes, chondrichthian fishes and teleosts) the radial glia is the only type of parenchymal glia responsible for both neurogenesis and homeostatic control over the nervous tissue (16, 32, 136, 137). Increase in the thickness of the brain is accompanied with the emergence of the parenchymal astrocytes, which cover an increased homeostatic demand associated with the brain size (196, 280). In higher vertebrates radial glia generally disappears after birth, with some types of radial astroglial remaining in the cerebellum (Bergmann glia), in the retina (Müller glia) and in the hypothalamus (tanycytes).

ASTROGLIA: DEFINITION AND APPEARANCE

The name of astrocyte was invented by Michael (Mihály) von Lenhossék (125) to define a subclass of parenchymal glia; Lenhossék also proposed to call all neuroglial cells of the gray matter spongocytes. Astroglia are defined as a highly heterogeneous class of neural cells of ectodermal, neuroepithelial origin that sustain homeostasis and provides for defence of the central nervous system (260). Astroglia are further sub-classified into protoplasmic astrocytes of the gray matter, fibrous astrocytes of the white matter, velate astrocytes of the cerebellum, radial astrocytes (represented by Müller retinal glial cells, cerebellar Bergmann glial cells and

tanycytes of the hypothalamus and parts of the spinal cord), pituitary cells in the neuro-hypophysis, perivascular and marginal astrocytes, Gomori-positive astrocytes (rich in iron and identified in the arcuate nucleus of the hypothalamus and in the hippocampus) and surface-associated astrocytes. In addition, astroglia include several types of cells that line the ventricles or the subretinal space represented by ependymocytes, choroid plexus cells and retinal pigment epithelial cells. The brains of the high primates contain specific interlamellar, polarized and varicose projection astrocytes (260).

Identification and visualization of astrocytes in the nervous tissue relies on the morphological criteria and expression of specific markers. The latter include glial fibrillary acidic protein (GFAP), vimentin, protein S100, plasmalemmal glutamate transporters EAAT-1 and EAAT-2 (known in rodents as GLAST and GLT-1, respectively), glutamate synthetase, inward rectifying $K_{v}4.1$ channels, water channels aquaporin 4 (AQP4), connexins Cx30 and Cx43, aldehyde dehydrogenase 1 family member L1 (ALDH1L1) foliate metabolism enzyme, fructose-1, 6-bisphosphate aldolase (or aldolase C), and transcription factor SOX9 (13, 14, 35, 36, 154, 161, 167, 176, 213, 218, 244, 275). None of these markers, however, labels all astrocytes throughout the brain.

The most commonly used immunostaining with antibodies against GFAP visualizes only a sub-population of astrocytes with a substantial regional and developmental heterogeneity. In the juvenile hippocampus anti-GFAP staining reveals ~ 80% of all astroglia (35, 167), whereas in other regions of the healthy brain only a minority (10–20%) of astrocytes are GFAP-positive (111, 213, 276). In addition GFAP staining reveals only the main processes of astrocytes, with no labeling of perisynaptic and peripheral processes or small endfeet, thus labeling only ~15% of an individual astrocyte (195, 231). Immunostaining with antibodies against protein S100B labels, as a rule, 2–3 times more astroglial compartments compared with GFAP labeling (167, 213). At the same time immunoreactivity for S100B is detected in other CNS cells including oligodendrocytes, ependymal cells, choroid plexus epithelium, vascular endothelial cells, and even in some neurones (199, 237). The antibodies against EAAT-1 (the most widespread astroglial glutamate transporter) stain radial glia, fibrous and protoplasmic astrocytes, cerebellar Bergmann glia, retinal Müller glia, radial stem glia in the dentate gyrus and subventricular zone in developing and adult CNS (20, 228, 281). Some splice variants of EAAT-1, however, were found in some neurones, oligodendrocytes and ependymal cells (217). Of note, EAATs expression show substantial inter-species differences (281). Immunoreactivity for glutamine synthetase (GS) was detected in fibrous and protoplasmic astrocytes, in radial glia, Bergmann glia, retinal Müller glia, tanycytes and ependymal cells; furthermore this staining labels many GFAP-negative astrocytes. For example, in the mouse entorhinal cortex, 78% of all labeled glial cells were GS-positive, 12% GFAP-positive and only 10% were positive for both GS and GFAP (286). Similarly, in the hippocampus double staining showed that only 60% of cells immunoreactive for GS were positive for GFAP (276). In addition, staining with antibodies against GS, which is present in the astrocyte cytoplasm, visualizes the complete cellular profile.

Immunolabeling with the water channel AQP4 antibody reveals mainly astroglial endfeet where these channels are concentrated (154), although in human astrocytes this polarization may not be as strict as in mice (66, 189). Antibodies against connexin Cx30

selectively visualize gray matter astrocytes (155), whereas staining against Cx43 does not discriminate between fibrous and protoplasmic astroglia. Polyclonal antibodies against ALDH1L1 stain both GFAP positive and GFAP negative astroglial cells in the cortex; at the cellular level ALDH1L1 - staining allows visualization of fine processes (36). ALDH1L1 is, however, developmentally regulated and it is also expressed in some oligodendrocytes (285). Astrocytes in mouse and human brain are enriched with SOX9, a transcription factor. Immunostaining with specific antibodies against SOX9 exclusively stain astroglial nuclei, and hence are used for *fluorescence activated cell sorting* of astrocytes and for isotopic fractionation (244). Distal and perisynaptic astroglial processes can also be labeled with antibodies against MLC1 protein (28).

For labeling astroglia in the *in vivo* brain, the gliophilic fluorescent probe sulforhodamine 101 and its analogues sulforhodamine B or G are frequently used (157). This positively charged molecule is selectively taken up by astrocytes and could be delivered either by injection into the brain tissue (157) or even by intravenous injection (15). There is some regional selectivity in rhodamine probes accumulation; it is readily taken up by hippocampal astroglial but does not stain astrocytes in the ventrolateral medulla (220). Rhodamine deployment, however, has some adverse effects on neuronal excitability; rhodamine injections induce seizures *in situ* and *in vivo* (105, 193).

ASTROGLIA: THE NUMBERS

There is still a degree of confusion about the total numbers of neurones and glia, and numerical distributions of different glial cell types in the CNS of mammals. The glia to neurones ratio (GNR) varies considerably between species. The nervous system of invertebrates contains relatively few neuroglial cells, with the GNR in leech, for example, being ~ 0.025; and in *Drosophila* ~0.1. At the same time the buccal ganglia of the great ramshorn snail *Planorbis corneus* contains 298 neurones and 391 glial cells [GNR ~ 1.3 (184)].

In vertebrates the GNR roughly increases proportionally to an increase in the size of the brain; for example, in the cortex the glia to neurone ratio is about 0.3–0.4 in rodents and rabbit, ~ 1.1 in cat; ~1.2 in horse, 0.5–1.0 in rhesus monkey, 2.2 in Göttingen minipig, ~1.5–1.7 in humans, and as high as 4–8 in elephants and the fin whale. Technique of isotopic fractionation developed in recent decade shows that total numbers of neurones and glia in the human brain are similar, although with substantial variations between different brain regions (19, 93). The ratio between non-neuronal cells and neurones varied between 11:1 for the brain stem, 3.7:1 in cortical regions including the corpus callosum and 0.2:1 in the cerebellum (19, 93, 126, 274). The glia to neurone ratio (excluding microglia) in the gray matter of the human cortex was estimated at 1.65 (227). The total number of astrocytes in rodents does not exceed 10–20% of total cells in the brain (244). Based on morphological criteria, in the human neocortex astrocytes accounted for ~ 20%–40%, oligodendrocytes for 50%–75% and microglia for 5%–10% of the total glial population (26, 182). Stereological studies on the cortex of the rhesus monkey, however, demonstrated both developmental and regional differences in numerical distribution of glial cells. In area 17 of young monkeys, for example, astrocytes accounted for 40% of total glia, oligodendrocytes for 53% and

microglia for ~7%. In cortical layers 1–3 astrocytes were at 57%, oligodendrocytes at 36% and microglia at 7%, whereas in the layer 4 (which has higher degree of myelination) 30% of glia belong to astrocytes, 62% to oligodendroglia and remaining 8% for microglia (186).

IDIOSYNCRATIC HUMAN ASTROGLIA

Astrocytes in humans and higher primates differ very much from other mammals (studied so far) in their size and morphological complexity; furthermore, several types of astroglia exist only in the brains of hominids. The protoplasmic astrocytes in the human gray matter occupy ~ 16 times more volume and have ~ 10 times more primary processes compared to the same cells in the rat brain (166). It has been estimated that on average human protoplasmic astrocytes contact and integrate around 2 million of synapses residing in their territorial domains, whereas rodent astrocytes cover ~20 000–120 000 synaptic contacts (35, 166). Human fibrous astrocytes are similarly much larger than rodent ones [the average area of human fibrous astrocyte domain is 180 μm^2 vs. 85 μm^2 in mouse (166)].

The brains of higher primates (old world monkeys and apes) and humans contain several specific types of astrocytes. One of the most abundant types of these cells is represented by interlaminar astrocytes [named so by Jorge Colombo (46)]. These cells were originally described at the end of the 19th century (11, 134, 198). In the human brain, interlaminar astrocytes are characterized by a small (~10 μm) spheroid cell body localized in the cortical layer I; these cells have several short and one or two very long (up to 1 mm) processes, which penetrate through the thickness of the cortex to end in the layers II to IV; terminal portions of these processes appear as bouton- or club-like structures known as terminal masses or end bulbs (43, 166). Incidentally *in vivo* injections of high KCl concentrations increased the number of these terminal masses suggesting association with K^+ homeostasis (44). Often the processes of interlaminar astrocytes contact blood vessels (236). Interlaminar astrocytes appear in first postnatal months and they originate from astroglial precursors and not from radial glia (45). Interlaminar astroglia in the human tissues were reported to be labeled with antibodies against CD44, a receptor for extracellular matrix molecules (3, 236). In addition interlaminar astrocytes show high immunoreactivity for GFAP and S100B, whereas expression of plasmalemmal glutamate transporters and glutamine synthetase seem to be rather low (236). Electrophysiological examination of these astrocytes revealed passive K^+ conductance similar to other types of astroglia; only half of interlaminar astrocytes, however, showed coupling with other astroglial cells (236). Processes of interlaminar astrocytes have been found to be disrupted in Down syndrome and in Alzheimer's disease; furthermore, the size of terminal masses was found to be significantly increased in the latter (43).

Another type of astroglia specific for the brains of high primates and humans is represented by polarized astrocytes. Somata of these cells are located in the deep cortical layers close to the white matter; polarized astrocytes have two exceptionally long (up to 1 mm in length) processes that penetrate into superficial cortical layers (166)

The deep cortical layers also contain a population of cells displaying general properties of protoplasmic astrocytes, but having also several (1–5) very long (up to 1 mm) unbranched processes with evenly spaced varicosities; these processes extend in all

directions through the cortex, with many of them contacting blood vessels (166, 236). These cells were identified as “stellate independent cells” by Cajal (37), as varicose projection astrocytes by Oberheim *et al* (166) and as astrocytes with long processes by Sosunov *et al* (236). Similarly to interlaminar astrocytes, these cells can be labeled with antibodies against CD44 (236). The number of these atypical astrocytes with long processes varied very substantially between individual specimens, and they were never observed in neonatal brains, arguably reflecting individual life-long adaptive changes (236).

HUMAN ASTROCYTES AND COGNITIVE CAPACITY—IS THERE A DIRECT LINK?

Highly idiosyncratic properties of human astrocytes (absent in a less intellectually developed mammals) suggest their possible role in information processing and intelligence. Astrocytes can be considered as integrators of neural networks, which may simultaneously influence millions of synaptic contacts. Direct implantation of human foetal glial progenitors into the brains of young immunosuppressed mice resulted in expansion of human cells which eventually populated large portion of the mouse brain largely replacing the host astrocytes (88). Further experiments demonstrated that embryonic human glial progenitors, or glial precursors derived from induced stem cells exhibit a growth advantage and replace the host glia after grafting (81, 282). Animals carrying human astrocytes had improved memory and outperform the wild type animals in several cognitive tests including novel object recognition or auditory fear conditioning (88). Electrophysiological investigations also found a reduced threshold for generation of long-term potentiation in mice living with human astroglia (88). The mechanisms for increased cognitive performance, however, remain unknown; they may reflect higher homeostatic capacity of human astrocytes, different coverage of synapses by astrocytic processes (295) or else increased plasticity stimulated by the release of various factors from human glia.

HUMAN GLIOMA GROWN IN MICE

There are ~ 25 000 new glioma cases recorded annually in the United States (<http://www.abta.org/>). The most aggressive glioma type is glioblastoma multiforme (GBM; WHO grade IV). The main obstacle to the successful treatment of GBM is its reappearance following surgical removal/radiation therapy in the near vicinity (1–2 cm) of the original locus or, less commonly, by the formation of satellite loci in distant parts of the brain. Both events indicate the invasive nature of this neoplasm (200, 289). Since 1928, it has been recognized that glioma cells have spread throughout the brain by the time patients are symptomatic (52). Yet, GBM extracranial metastases are very rare (0.44%) (200) and multifocal gliomas represent only 0.5%–20% of clinical cases (175). It is the infiltration of GBM cells from a single solid tumor mass into adjacent brain tissue that fits the most common (80%–99.5%) clinical presentation of GBM (216). This migration/invasion needs to be studied as it may represent a fertile ground for novel therapeutic approaches. The most relevant model one can use to study gliomas has been introduced as human patient-derived xenograft (PDX) tumors (78). Here, patient biopsy samples of GBMs are propagated in the brains

Table 2. Astrocytopathology.

Nosological forms	Astrocytopathy	References
<i>Leucodystrophies</i>		
Alexander disease	Sporadic mutations of glial fibrillary acidic protein (GFAP) with pathological remodeling of astrocytes and severe white matter lesions. Decrease in astroglial glutamate uptake	(30, 143, 271)
Megalencephalic leukoencephalopathy with subcortical cysts (MLC)	The disease is caused by mutations in the MLC1 gene often in combination with mutations in the hepatic and glial cell adhesion molecule gene (Hepacam/Glialcam). The MLC1 protein is predominantly expressed in astrocytic end-feet. MLC1 is a part of membrane signaling complex which includes Na ⁺ -K ⁺ - pump, inward rectifier K _v 4.1 channels, aquaporin4 (AQP4), caveolin-1 and TRPV4 channels. The mechanism possibly involves a loss of astroglial control over fluid homeostasis and cell volume.	(28, 63, 120, 121, 124, 131)
Vanishing white matter syndrome (VWM) or childhood ataxia with central nervous system hypomyelination (CACH)	Mutations in the eukaryotic translation initiation factor 2 (EIF-2B) gene. The disease is associated with atrophic (dysmorphic) astrocytes, altered GFAP filaments, deficient astroglial reactivity and impaired astrocytic differentiation. Pathologically remodeled astrocytes secrete factors inhibiting oligodendroglial maturation.	(31, 59, 61, 256)
<i>Demyelinating diseases</i>		
Neuromyelitis Optica (NMO)	Autoantibodies-induced loss of AQP4 and GFAP, astroglial atrophy and demise.	(97, 194)
Baló's disease	Down-regulation of expression of Cx43 and AQP4, mislocalization of MLC1, astroglial hypertrophy. Loss of astroglial function is considered to be a primary cause for oligodendroglial lesions and demyelination.	(135, 138)
<i>Neurotoxic encephalopathies</i>		
Hepatic encephalopathy	Pathological remodeling of astrocytes; failure of K ⁺ and glutamate homeostasis with ensuing excitotoxicity, pathological Ca ²⁺ signaling and aberrant glutamate release, deficient operation of glutamate-glutamine shuttle because of excessive ammonium obliterating the GS pathway.	(4, 85, 150, 162, 165)
Heavy metal (lead, manganese mercury, aluminum)-induced encephalopathies	Astroglial loss of function: accumulation of heavy metal into astrocytes instigated significant down regulation of plasmalemmal glutamate transporters with ensuing excitotoxicity.	(241, 243, 269, 287)
Wilson disease	Pathological remodeling of astrocytes; failure of astroglial regulation of copper homeostasis.	(62, 215, 249)
<i>Psychiatric diseases</i>		
Wernicke-Korsakoff encephalopathy	Loss of astroglial function: substantial (up to 80%) down-regulation of astroglial plasmalemmal glutamate transporters with ensuing glutamate excitotoxicity.	(91)
Major depressive disorder	Reduction in astroglial densities in cortex and amygdala, reduced expression of GFAP, decrease in expression of plasmalemmal glutamate transporters, connexins Cx43 and Cx30, glutamine synthetase and AQP4. Impaired astroglial homeostatic capabilities may underlie aberrant neurotransmission responsible for depressive symptoms.	(47–50, 191, 209, 210)
Schizophrenia	Astrodegeneration and astroglial atrophy, down-regulation of homeostatic molecular pathways, including plasmalemmal glutamate transporters, AQP4, GS, thrombospondins. Up-regulation of plasmalemmal cystine-glutamate exchanger and increased production of kynurenic acid may further deregulate glutamatergic transmission and underlie psychotic symptoms.	(71, 190, 219, 222, 270)

Table 2. Continued.

Nosological forms	Astrocytopathy	References
Addictive disorders	Combination of astrodegeneration and astroglial reactivity, impaired astroglial glutamate homeostasis. Ablation of astrocytes from the prelimbic area of the prefrontal cortex, as well as inhibition of astroglial gap junctions increased alcohol seeking behavior. Atrophic astrocytes were observed in nucleus accumbens of cocaine-addicted rats.	(17, 145–147, 197, 224, 278)
<i>Neurodegenerative diseases</i>		
Alzheimer's disease	Astroglial atrophy at the early stages, reactive remodeling of senile plaque associated astrocytes, reduced astrogliosis at the terminal stages, decreased astroglial synaptic coverage, loss of astroglial homeostatic support, impairment of water transport, glutamate uptake and glutamate-glutamine shuttle. Astrocytes associated with senile plaques display Ca ²⁺ hyperexcitability and generate abnormal propagating intercellular Ca ²⁺ waves.	(104, 118, 129, 170, 201, 202, 204, 261, 264, 267, 273)
Ageing-related tau astroglipathy	Exclusive expression of pathological tau in astrocytes is the sole histological symptom of several age-dependent dementias.	(116)
Amyotrophic lateral sclerosis (ALS)	Early astrodegeneration, astroglial death (through apoptosis) and loss glutamate clearance function underlie subsequent excitotoxicity and neuronal demise. Selective silencing of human SOD1 mutated gene in astrocytes delays ALS progression. Neuronal death, occurring at later stages of ALS triggers astrogliotic response.	(207, 255, 284)
Parkinson's disease	Astrocytes provide protection of dopaminergic neurones; and astrocytes reportedly may accumulate α -synuclein. There are some evidence for suppressed astroglial reactivity, which may indicate decrease in neuroprotection.	(75, 141, 142, 235)
Huntington's disease (HD)	Progressive astroglial reactivity, although no signs of astrogliosis in HD mouse model. Decrease in glutamate uptake, deficient K ⁺ buffering, pathologically increased release of glutamate.	(68, 70, 99, 123, 251)
<i>Other diseases</i>		
Glioblastoma	Cancer developed from astrocytes or their precursor's	(149)
Traumatic brain injury	Reactive astrogliosis prevails with a gradient of phenotypes from the lesion to the healthy tissue. Astrocytes move toward the lesion site (anisomorphic astrogliosis) and form the scar. Reactive astrocytes control post-lesion regeneration.	(9, 33, 232)
Ischemia and stroke	Reactive astrocytes surround the area of the infarction core and define survival or demise of neurones in the penumbra. Astrocytes may also convey death signals.	(9, 245, 292)
Epilepsy	Reactive astrogliosis and pathological remodeling of astroglia. Down-regulation of expression of K _v 4.1 channels, changes in astroglial morphology and disappearance of gap junction coupling were found in astrocytes from hippocampal specimens obtained from patients with mesial temporal lobe epilepsy.	(22, 23, 226, 238)
Migraine	Loss of function mutation of astroglia-specific α 2 subunit of Na ⁺ -K ⁺ pump. Decrease of expression of astroglial plasmalemmal glutamate transporters.	(39)
Autistic spectrum disorders (ASD)	Pathological remodeling of astrocytes is observed in different forms of ASD.	(291)

of immunocompromised mice. These tumors have been genomically, transcriptomically and kinomically profiled, extensively characterized and found virtually identical to human gliomas growing in patients' brains, unlike mouse gliomas that are significantly different (78).

CLASSIFICATION AND COMPLEXITY OF ASTROGLIOPATHIES

The neurocentric paradigm of neuropathology has been challenged recently; the leading role for neuroglia in shaping the evolution and outcome of neurological disorders begins to be appreciated (34, 79, 174, 178, 233, 271, 272, 291). The modifications of astroglia in neuropathology are multifaceted, often disease-specific and may undergo metamorphoses during the course of pathological evolution (Table 2). Astroglial pathological changes are broadly classified into: (i) astrodegeneration with astroglial atrophy and loss of function; (ii) pathological remodeling of astrocytes and (iii) reactive astrogliosis (178, 261, 266). The first two groups of non-reactive pathological transformation of astrocytes can be summarily identified as astrocytopathies to distinguish from reactive astrogliosis (72).

Astrodegeneration manifests by morphological atrophy, a decrease in astroglial density (through increased cell death) and/or a loss of function; it occurs in many types of neurological disorders. In psychiatric diseases, such as schizophrenia, major depressive disorder or Wernicke-Korsakoff encephalopathy, the number of astrocytes is reduced, and their homeostatic pathways, such as, for example, those associated with glutamate homeostasis, are suppressed (48, 49, 146, 190, 191, 209, 270). These homeostatic failures instigate aberrant neurotransmission or excitotoxic cell death that underlies psychotic symptoms. Morphological atrophy of astrocytes and down-regulation of glutamate uptake are observed in the nucleus accumbens of cocaine-addicted rats (224). Astrodegeneration and astroglial death are contributing to early stages of neurodegenerative diseases such as amyotrophic lateral sclerosis or Alzheimer's disease; in the former, the impairment of astroglial glutamate uptake causes excitotoxic death of motor neurones (207, 255), whereas in the latter, reduced astroglial coverage may explain early synaptic deficiency and early cognitive failures (261, 264, 273). Astroglial atrophy in Alzheimer's disease may also involve changes in secretory vesicles trafficking (239).

Pathological remodeling represents acquisition of abnormal properties by astroglia which drive pathology. This remodeling is evident in several types of leukodystrophies, such as Alexander disease, megalencephalic leukoencephalopathy with subcortical cysts or vanishing white matter syndrome, in which astrocytopathy results in lesions to the white matter (120). In particular, in Alexander disease astroglial expression of mutant GFAP leads to severe leukomalacia (143). Another example of pathological remodeling in astroglia is evident in mesial temporal lobe epilepsy, where astrocytes change their morphology, substantially reduce intercellular coupling and down-regulate expression of $K_{ir}4.1$ channels; these changes lead to a failure in K^+ homeostasis which relates to seizure initiation (22). Pathological remodeling of astroglial function is also observed in specific forms of schizophrenia associated with *Toxoplasma gondii* infection. The parasite targets predominantly astroglia, which causes the aberrant increase in

production and secretion of kynurenic acid; this latter being an endogenous inhibitor of NMDA and acetylcholine receptors causes imbalanced neurotransmission to underlie psychotic developments (222).

Reactive astrogliosis is triggered in many neurological disorders. Morphologically reactive astrogliosis is characterized by up-regulation of intermediate filaments such as GFAP and vimentin associated with astroglial hypertrophy (177). Reactive astrogliosis is an evolutionary conserved defensive reprogramming of astroglia aimed at: (i) increased neuroprotection and trophic support of nervous tissue; (ii) isolation of the lesioned area; (iii) reconstruction of the damaged blood-brain barrier; and (iv) providing for post-lesion regeneration of brain circuits (10, 177, 178, 232). Activation of astrocytes is a complex process which arguably produces multiple "reactive" phenotypes, which can be distinct in different diseases. Gene expression profiling of reactive astrocytes demonstrated significant context-dependent (ischemia vs. endotoxin activation) differences (290). All in all, initiation of astroglial programme proceeds through a controlled continuum of changes in cellular biochemistry and function that are tuned to the nature and strength of the insult. It seems also that astrocytes within the same lesioned area are heterogeneous in their expression of transcription factors, inflammatory agents and signaling molecules (77, 94). Distinct responses of astrocytes may be due to different densities of receptors, such as β -adrenergic receptors, which, when activated, reduce cytotoxic oedema by inducing astrocytic shrinkage (258).

Conceptually, reactive astrogliosis is a survivalist programme that increases the resilience of the nervous tissue to the environmental insults, while experimental inhibition of astroglial reactivity often exacerbates neuropathology (178). For example, suppression of astroglial reactivity increased both the size of the traumatic lesions and neurological deficit (169). Genetic ablation of GFAP and vimentin reduced astroglial response which augmented post-traumatic synaptic loss (176) and resulted in larger ischemic infarcts (128). In the context of neurodegeneration, inhibition of astroglial reactivity increased the β -amyloid load in the animal model of the Alzheimer's disease (179). At the same time, excessive or chronic activation of astrocytes may be maladaptive and may increase the damage of the nervous tissue (177). Astroglial reactivity dominates in acute neurological conditions, such as neurotrauma, ischemic or hemorrhagic stroke or CNS infection. The severity of the insult defines the degree of astroglial response, which often results in the formation of glial scar (33, 178, 234). In neurodegeneration astroglial reactivity arises following the appearance of specific lesions, such as senile plaques or Lewy bodies, or is triggered by neuronal death, as, for example, occurs in amyotrophic lateral sclerosis or in Huntington disease (178).

CONCLUDING REMARKS

Astroglia are the homeostatic arm of the CNS, which make possible the functional activity of nervous tissue. Astrocytes of humans and higher primates differ fundamentally from the same cells in other mammals in their complexity, size and specific subtypes. These differences arguably reflect on an increased complexity of neuronal networks which require extensive support. Grafting of human astrocytes into rodent brains increase (by yet unknown mechanism) the functional performance of the brain. Astrocytes

contribute to all neurological diseases. Astroglial pathological responses are complex and may occur either as a primary pathogenic events which instigate the neuropathology (such as Alexander disease) or secondary responses, which nonetheless contribute to evolution of neuropathology (such as astroglial reactivity in neurotrauma or ischemia). Astroglial pathological changes are multifaceted and can range from degeneration and atrophy to reactivity and pathological remodeling. These different forms of astroglipathology may occur simultaneously or sequentially following different stages of neuropathology. Regrettably, studies of neurological diseases performed on animal models, most likely do not reveal pathology of human astroglia, and hence urgent need exists in developing “humanized” experimental preparations that may recapitulate astroglipathology of the human brain.

ACKNOWLEDGMENTS

V.P.'s work is supported by the National Institutes of Health (HD078678). R.Z.'s work is supported by grants P3 310, J3 6790, J3 6789 and J3 7605 from the Slovenian Research Agency (ARRS), CipKeBip, COST Action BM1002 and EU COST Action CM1207—GLISTEN.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ (2010) Structure and function of the blood-brain barrier. *Neurobiol Dis* **37**:13–25.
- Abbott NJ, Ronnback L, Hansson E (2006) Astrocyte-endothelial interactions at the blood-brain barrier. *Nat Rev Neurosci* **7**:41–53.
- Akiyama H, Tooyama I, Kawamata T, Ikeda K, McGeer PL (1993) Morphological diversities of CD44 positive astrocytes in the cerebral cortex of normal subjects and patients with Alzheimer's disease. *Brain Res* **632**:249–259.
- Albrecht J, Zielinska M, Norenberg MD (2010) Glutamine as a mediator of ammonia neurotoxicity: a critical appraisal. *Biochem Pharmacol* **80**:1303–1308.
- Allen A, Messier C (2013) Plastic changes in the astrocyte GLUT1 glucose transporter and beta-tubulin microtubule protein following voluntary exercise in mice. *Behav Brain Res* **240**:95–102.
- Allen JW, Shanker G, Aschner M (2001) Methylmercury inhibits the in vitro uptake of the glutathione precursor, cystine, in astrocytes, but not in neurons. *Brain Res* **894**:131–140.
- Allen NJ, Bennett ML, Foo LC, Wang GX, Chakraborty C, Smith SJ, Barres BA (2012) Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors. *Nature* **486**:410–414.
- Altenhein B, Cattenoz PB, Giangrande A (2016) The early life of a fly glial cell. *Wiley Interdiscip Rev Dev Biol* **5**:67–84.
- Anderson MA, Ao Y, Sofroniew MV (2014) Heterogeneity of reactive astrocytes. *Neurosci Lett* **565**:23–29.
- Anderson MA, Burda JE, Ren Y, Ao Y, O'Shea TM, Kawaguchi R *et al* (2016) Astrocyte scar formation aids central nervous system axon regeneration. *Nature* **532**:195–200.
- Andriezen WL (1893) The neuroglia elements of the brain. *Br Med J* **2**:227–230.
- Angelova PR, Kasymov V, Christie I, Sheikhbaehi S, Turovsky E, Marina N *et al* (2015) Functional oxygen sensitivity of astrocytes. *J Neurosci* **35**:10460–10473.
- Ango F, Wu C, Van der Want JJ, Wu P, Schachner M, Huang ZJ (2008) Bergmann glia and the recognition molecule CHL1 organize GABAergic axons and direct innervation of Purkinje cell dendrites. *PLoS Biol* **6**:e103.
- Anlauf E, Derouiche A (2013) Glutamine synthetase as an astrocytic marker: its cell type and vesicle localization. *Front Endocrinol (Lausanne)* **4**:144.
- Appaix F, Girod S, Boisseau S, Romer J, Vial JC, Albrieux M *et al* (2012) Specific *in vivo* staining of astrocytes in the whole brain after intravenous injection of sulforhodamine dyes. *PLoS One* **7**:e35169.
- Ari C, Kalman M (2008) Evolutionary changes of astroglia in Elasmobranchii comparing to amniotes: a study based on three immunohistochemical markers (GFAP, S-100, and glutamine synthetase). *Brain Behav Evol* **71**:305–324.
- Armstrong V, Reichel CM, Doti JF, Crawford CA, McDougall SA (2004) Repeated amphetamine treatment causes a persistent elevation of glial fibrillary acidic protein in the caudate-putamen. *Eur J Pharmacol* **488**:111–115.
- Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA (2010) Glial and neuronal control of brain blood flow. *Nature* **468**:232–243.
- Azevedo FA, Carvalho LR, Grinberg LT, Farfel JM, Ferretti RE, Leite RE *et al* (2009) Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *J Comp Neurol* **513**:532–541.
- Bary D, McDermott K (2005) Differentiation of radial glia from radial precursor cells and transformation into astrocytes in the developing rat spinal cord. *Glia* **50**:187–197.
- Bartol TM, Bromer C, Kinney J, Chirillo MA, Bourne JN, Harris KM, Sejnowski TJ (2015) Nanoconnectomic upper bound on the variability of synaptic plasticity. *Elife* **4**:e10778.
- Bedner P, Dupper A, Huttmann K, Muller J, Herde MK, Dublin P *et al* (2015) Astrocyte uncoupling as a cause of human temporal lobe epilepsy. *Brain* **138**:1208–1222.
- Bedner P, Steinhauser C (2013) Altered K_{ir} and gap junction channels in temporal lobe epilepsy. *Neurochem Int* **63**:682–687.
- Benfenati V, Nicchia GP, Svelto M, Rapisarda C, Frigeri A, Ferroni S (2007) Functional down-regulation of volume-regulated anion channels in AQP4 knockdown cultured rat cortical astrocytes. *J Neurochem* **100**:87–104.
- Bery A, Cardona A, Martinez P, Hartenstein V (2010) Structure of the central nervous system of a juvenile acoeel, *Syngasteria roscoffensis*. *Dev Genes Evol* **220**:61–76.
- Blinkow S, Glezer I (1968) The neuroglia. In: *The Human Brain in Figures and Tables; A Quantitative Handbook*. SM Blinkow, II Glezer, (eds), pp. 237–253. New York: Plenum Press.
- Boison D (2008) Adenosine as a neuromodulator in neurological diseases. *Curr Opin Pharmacol* **8**:2–7.
- Boor PK, de Groot K, Waisfisz Q, Kamphorst W, Oudejans CB, Powers JM *et al* (2005) MLC1: a novel protein in distal astroglial processes. *J Neuropathol Exp Neurol* **64**:412–419.
- Borycz J, Borycz JA, Loubani M, Meinertzhagen IA (2002) tan and ebony genes regulate a novel pathway for transmitter metabolism at fly photoreceptor terminals. *J Neurosci* **22**:10549–10557.
- Brenner M, Messing A (2015) A new mutation in GFAP widens the spectrum of Alexander disease. *Eur J Hum Genet* **23**:1–2.
- Bugiani M, Boor I, van Kollenburg B, Postma N, Polder E, van Berkel C *et al* (2011) Defective glial maturation in vanishing white matter disease. *J Neuropathol Exp Neurol* **70**:69–82.
- Bundgaard M, Cserr H (1981) A glial blood-brain barrier in elasmobranchs. *Brain Res* **226**:61–73.

33. Burda JE, Bernstein AM, Sofroniew MV (2016) Astrocyte roles in traumatic brain injury. *Exp Neurol* **275**(Pt 3):305–315.
34. Burda JE, Sofroniew MV (2014) Reactive gliosis and the multicellular response to CNS damage and disease. *Neuron* **81**: 229–248.
35. Bushong EA, Martone ME, Jones YZ, Ellisman MH (2002) Protoplasmic astrocytes in CA1 stratum radiatum occupy separate anatomical domains. *J Neurosci* **22**:183–192.
36. Cahoy JD, Emery B, Kaushal A, Foo LC, Zamanian JL, Christopherson KS *et al* (2008) A transcriptome database for astrocytes, neurons, and oligodendrocytes: a new resource for understanding brain development and function. *J Neurosci* **28**: 264–278.
37. Cajal S (1937) Neuroglia. In: *The Neuron and the Glial Cell Translation of Textura Del Sistema Nervioso Del Hombre y De Los Ertebrados De La*. J Torre, WC Gibson (eds), pp. 263–290, C.C. Thomas: Springfield, IL.
38. Cantera R, Trujillo-Cenoz O (1996) Glial cells in insect ganglia. *Microsc Res Tech* **35**:285–293.
39. Capuani C, Melone M, Tottene A, Bragina L, Crivellaro G, Santello M *et al* (2016) Defective glutamate and K⁺ clearance by cortical astrocytes in familial hemiplegic migraine type 2. *EMBO Mol Med* **8**: 967–986.
40. Chesler M (2003) Regulation and modulation of pH in the brain. *Physiol Rev* **83**:1183–1221.
41. Chever O, Djukic B, McCarthy KD, Amzica F (2010) Implication of Kir4.1 channel in excess potassium clearance: an in vivo study on anesthetized glial-conditional Kir4.1 knock-out mice. *J Neurosci* **30**: 15769–15777.
42. Chung WS, Clarke LE, Wang GX, Stafford BK, Sher A, Chakraborty C *et al* (2013) Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. *Nature* **504**:394–400.
43. Colombo JA (2016) The interlaminar glia: from serendipity to hypothesis. *Brain Struct Funct* **222**: 1109–1129.
44. Colombo JA, Gayol S, Yanez A, Marco P (1997) Immunocytochemical and electron microscope observations on astroglial interlaminar processes in the primate neocortex. *J Neurosci Res* **48**:352–357.
45. Colombo JA, Reisin HD (2004) Interlaminar astroglia of the cerebral cortex: a marker of the primate brain. *Brain Res* **1006**:126–131.
46. Colombo JA, Yanez A, Puissant V, Lipina S (1995) Long, interlaminar astroglial cell processes in the cortex of adult monkeys. *J Neurosci Res* **40**:551–556.
47. Cotter D, Mackay D, Chana G, Beasley C, Landau S, Everall IP (2002) Reduced neuronal size and glial cell density in area 9 of the dorsolateral prefrontal cortex in subjects with major depressive disorder. *Cereb Cortex* **12**:386–394.
48. Cotter D, Mackay D, Landau S, Kerwin R, Everall I (2001) Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry* **58**:545–553.
49. Czeh B, Di Benedetto B (2013) Antidepressants act directly on astrocytes: evidences and functional consequences. *Eur Neuropsychopharmacol* **23**:171–185.
50. Czeh B, Simon M, Schmelting B, Hiemke C, Fuchs E (2006) Astroglial plasticity in the hippocampus is affected by chronic psychosocial stress and concomitant fluoxetine treatment. *Neuropsychopharmacology* **31**:1616–1626.
51. D'Ambrosio R, Gordon DS, Winn HR (2002) Differential role of K_{IR} channel and Na⁺/K⁺-pump in the regulation of extracellular K⁺ in rat hippocampus. *J Neurophysiol* **87**:87–102.
52. Dandy WE (1928) Hemisphere for certain tumors with hemiplegia: preliminary report. *JAMA* **90**:823–825.
53. De Pinto V, Caggese C, Prezioso G, Ritossa F (1987) Purification of the glutamine synthetase II isozyme of *Drosophila melanogaster* and structural and functional comparison of glutamine synthetases I and II. *Biochem Genet* **25**:821–836.
54. Deitmer JW, Rose CR (1996) pH regulation and proton signalling by glial cells. *Prog Neurobiol* **48**:73–103.
55. Deitmer JW, Rose CR, Munsch T, Schmidt J, Nett W, Schneider HP, Lohr C (1999) Leech giant glial cell: functional role in a simple nervous system. *Glia* **28**:175–182.
56. Deitmer JW, Schlue WR (1987) The regulation of intracellular pH by identified glial cells and neurones in the central nervous system of the leech. *J Physiol* **388**:261–283.
57. Deitmer JW, Schlue WR (1989) An inwardly directed electrogenic sodium-bicarbonate co-transport in leech glial cells. *J Physiol* **411**: 179–194.
58. Deitmer JW, Verkhatsky AJ, Lohr C (1998) Calcium signalling in glial cells. *Cell Calcium* **24**:405–416.
59. Dietrich J, Lacagnina M, Gass D, Richfield E, Mayer-Proschel M, Noble M *et al* (2005) EIF2B5 mutations compromise GFAP⁺ astrocyte generation in vanishing white matter leukodystrophy. *Nat Med* **11**:277–283.
60. Ding F, O'Donnell J, Xu Q, Kang N, Goldman N, Nedergaard M (2016) Changes in the composition of brain interstitial ions control the sleep-wake cycle. *Science* **352**:550–555.
61. Dooves S, Bugiani M, Postma NL, Polder E, Land N, Horan ST *et al* (2016) Astrocytes are central in the pathomechanisms of vanishing white matter. *J Clin Invest* **126**:1512–1524.
62. Dringen R, Scheiber I, Bulcke F (2015) Copper metabolism of astrocytes. *Springerplus* **4**:L3.
63. Duarri A, Lopez de Heredia M, Capdevila-Nortes X, Ridder MC, Montolio M, Lopez-Hernandez T *et al* (2011) Knockdown of MLC1 in primary astrocytes causes cell vacuolation: a MLC disease cell model. *Neurobiol Dis* **43**:228–238.
64. Edwards TN, Meinertzhagen IA (2010) The functional organisation of glia in the adult brain of *Drosophila* and other insects. *Prog Neurobiol* **90**:471–497.
65. Egawa K, Yamada J, Furukawa T, Yanagawa Y, Fukuda A (2013) Cl⁻ homeodynamics in gap junction-coupled astrocytic networks on activation of GABAergic synapses. *J Physiol* **591**:3901–3917.
66. Eidsvaag VA, Enger R, Hansson HA, Eide PK, Nagelhus EA (2017) Human and mouse cortical astrocytes differ in aquaporin-4 polarization toward microvessels. *Glia* **65**:964–973.
67. Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Park CY, Ozkan E *et al* (2009) Gabapentin receptor $\alpha 2\delta$ -1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. *Cell* **139**: 380–392.
68. Estrada-Sánchez AM, Rebec GV (2012) Corticostriatal dysfunction and glutamate transporter 1 (GLT1) in Huntington's disease: interactions between neurons and astrocytes. *Basal Ganglia* **2**:57–66.
69. Eulenburg V, Armsen W, Betz H, Gomez J (2005) Glycine transporters: essential regulators of neurotransmission. *Trends Biochem Sci* **30**:325–333.
70. Faideau M, Kim J, Cormier K, Gilmore R, Welch M, Auregan G *et al* (2010) *In vivo* expression of polyglutamine-expanded huntingtin by mouse striatal astrocytes impairs glutamate transport: a correlation with Huntington's disease subjects. *Hum Mol Genet* **19**:3053–3067.
71. Falkai P, Bogerts B (1986) Cell loss in the hippocampus of schizophrenics. *Eur Arch Psychiatry Neurol Sci* **236**:154–161.
72. Ferrer I (2017) Diversity of astroglial responses across human neurodegenerative disorders and brain aging. *Brain Pathol* (in press).
73. Filley CM, Fields RD (2016) White matter and cognition: making the connection. *J Neurophysiol* **116**:2093–2104.
74. Filosa JA, Bonev AD, Straub SV, Meredith AL, Wilkerson MK, Aldrich RW, Nelson MT (2006) Local potassium signaling couples neuronal activity to vasodilation in the brain. *Nat Neurosci* **9**:1397–1403.

75. Fitzmaurice J, Duffy G, Kilbride B, Sheridan JJ, Carroll C, Maher M (2004) Comparison of a membrane surface adhesion recovery method with an IMS method for use in a polymerase chain reaction method to detect *Escherichia coli* O157:H7 in minced beef. *J Microbiol Methods* **59**:243–252.
76. Freeman MR, Doherty J (2006) Glial cell biology in *Drosophila* and vertebrates. *Trends Neurosci* **29**:82–90.
77. Garcia AD, Petrova R, Eng L, Joyner AL (2010) Sonic hedgehog regulates discrete populations of astrocytes in the adult mouse forebrain. *J Neurosci* **30**:13597–13608.
78. Giannini C, Sarkaria JN, Saito A, Uhm JH, Galanis E, Carlson BL *et al* (2005) Patient tumor EGFR and PDGFRA gene amplifications retained in an invasive intracranial xenograft model of glioblastoma multiforme. *Neuro Oncol* **7**:164–176.
79. Giaume C, Kirchhoff F, Matute C, Reichenbach A, Verkhratsky A (2007) Glia: the fulcrum of brain diseases. *Cell Death Differ* **14**:1324–1335.
80. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S *et al* (2010) Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* **330**:841–845.
81. Goldman SA, Nedergaard M, Windrem MS (2012) Glial progenitor cell-based treatment and modeling of neurological disease. *Science* **338**:491–495.
82. Golubev AI (1988) Glia and neuroglia relationships in the cerebral nervous system of the *Turbellaria* (electron microscopic data). *Fortschr Zool* **36**:31–37.
83. Gourine AV, Kasymov V, Marina N, Tang F, Figueiredo MF, Lane S *et al* (2010) Astrocytes control breathing through pH-dependent release of ATP. *Science* **329**:571–575.
84. Grichtchenko II, Chesler M (1994) Depolarization-induced alkalization of astrocytes in gliotic hippocampal slices. *Neuroscience* **62**:1071–1078.
85. Haack N, Dublin P, Rose CR (2014) Dysbalance of astrocyte calcium under hyperammonemic conditions. *PLoS One* **9**:e105832.
86. Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T *et al* (2009) Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. *Neuron* **61**:213–219.
87. Halestrap AP (2012) The monocarboxylate transporter family - Structure and functional characterization. *IUBMB Life* **64**:1–9.
88. Han X, Chen M, Wang F, Windrem M, Wang S, Shanz S *et al* (2013) Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. *Cell Stem Cell* **12**:342–353.
89. Hansen DB, Garrido-Comas N, Salter M, Fern R (2015) HCO₃⁻ - independent pH regulation in astrocytes *in situ* is dominated by V-ATPase. *J Biol Chem* **290**:8039–8047.
90. Hartenstein V (2011) Morphological diversity and development of glia in *Drosophila*. *Glia* **59**:1237–1252.
91. Hazell AS (2009) Astrocytes are a major target in thiamine deficiency and Wernicke's encephalopathy. *Neurochem Int* **55**:129–135.
92. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL *et al* (2015) Neuroinflammation in Alzheimer's disease. *Lancet Neurol* **14**:388–405.
93. Herculano-Houzel S (2014) The glia/neuron ratio: how it varies uniformly across brain structures and species and what that means for brain physiology and evolution. *Glia* **62**:1377–1391.
94. Herrmann JE, Imura T, Song B, Qi J, Ao Y, Nguyen TK *et al* (2008) STAT3 is a critical regulator of astrogliosis and scar formation after spinal cord injury. *J Neurosci* **28**:7231–7243.
95. Hertz L, Chen Y, Gibbs ME, Zang P, Peng L (2004) Astrocytic adrenoceptors: a major drug target in neurological and psychiatric disorders? *Curr Drug Targets CNS Neurol Disord* **3**:239–267.
96. Hertz L, Dringen R, Schousboe A, Robinson SR (1999) Astrocytes: glutamate producers for neurons. *J Neurosci Res* **57**:417–428.
97. Hinson SR, McKeon A, Lennon VA (2010) Neurological autoimmunity targeting aquaporin-4. *Neuroscience* **168**:1009–1018.
98. Hirth IC, Deitmer JW (2006) 5-Hydroxytryptamine-mediated increase in glutamate uptake by the leech giant glial cell. *Glia* **54**:786–794.
99. Hsiao HY, Chen YC, Huang CH, Chen CC, Hsu YH, Chen HM *et al* (2015) Aberrant astrocytes impair vascular reactivity in Huntington disease. *Ann Neurol* **78**:178–192.
100. Huang H, Barakat L, Wang D, Bordey A (2004) Bergmann glial GlyT1 mediates glycine uptake and release in mouse cerebellar slices. *J Physiol* **560**:721–736.
101. Iadecola C, Nedergaard M (2007) Glial regulation of the cerebral microvasculature. *Nat Neurosci* **10**:1369–1376.
102. Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, Benveniste H (2013) Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J Clin Invest* **123**:1299–1309.
103. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA *et al* (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med* **4**:147ra111.
104. Jones VC, Atkinson-Dell R, Verkhratsky A, Mohamet L (2017) Aberrant iPSC-derived human astrocytes in Alzheimer's disease. *Cell Death Dis* **8**:e2696.
105. Kang J, Kang N, Yu Y, Zhang J, Petersen N, Tian GF, Nedergaard M (2010) Sulforhodamine 101 induces long-term potentiation of intrinsic excitability and synaptic efficacy in hippocampal CA1 pyramidal neurons. *Neuroscience* **169**:1601–1609.
106. Kawano T, Takuwa K, Kuniyoshi H, Juni N, Nakajima T, Yamamoto D, Kimura Y (1999) Cloning and characterization of a *Drosophila melanogaster* cDNA encoding a glutamate transporter. *Biosci Biotechnol Biochem* **63**:2042–2044.
107. Kettenmann H, Backus KH, Schachner M (1987) Aminobutyric acid opens Cl⁻ channels in cultured astrocytes. *Brain Res* **404**:1–9.
108. Kettenmann H, Hanisch UK, Noda M, Verkhratsky A (2011) Physiology of microglia. *Physiol Rev* **91**:461–553.
109. Kettenmann H, Kirchhoff F, Verkhratsky A (2013) Microglia: new roles for the synaptic stripper. *Neuron* **77**:10–18.
110. Kettenmann H, Ransom BR (2013) *Neuroglia*. p. 864. Oxford University Press: Oxford.
111. Kimelberg HK (2004) The problem of astrocyte identity. *Neurochem Int* **45**:191–202.
112. Kirischuk S, Kettenmann H, Verkhratsky A (1997) Na⁺/Ca²⁺ exchanger modulates kainate-triggered Ca²⁺ signaling in Bergmann glial cells *in situ*. *FASEB J* **11**:566–572.
113. Kirischuk S, Kettenmann H, Verkhratsky A (2007) Membrane currents and cytoplasmic sodium transients generated by glutamate transport in Bergmann glial cells. *Pflugers Arch* **454**:245–252.
114. Kirischuk S, Parpura V, Verkhratsky A (2012) Sodium dynamics: another key to astroglial excitability? *Trends Neurosci* **35**:497–506.
115. Kofuji P, Newman EA (2004) Potassium buffering in the central nervous system. *Neuroscience* **129**:1045–1056.
116. Kovacs GG, Ferrer I, Grinberg LT, Alafuzoff I, Attems J, Budka H *et al* (2016) Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy. *Acta Neuropathol* **131**:87–102.
117. Kremer MC, Jung C, Batelli S, Rubin GM, Gaul U (2017) The glia of the adult *Drosophila* nervous system. *Glia* **65**:606–638.
118. Kuchibhotla KV, Lattarulo CR, Hyman BT, Bacskai BJ (2009) Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. *Science* **323**:1211–1215.
119. Kucukdereli H, Allen NJ, Lee AT, Feng A, Ozlu MI, Conatser LM *et al* (2011) Control of excitatory CNS synaptogenesis by astrocyte-secreted proteins Hevin and SPARC. *Proc Natl Acad Sci USA* **108**:E440–E449.

120. Lanciotti A, Brignone MS, Bertini E, Petrucci TC, Aloisi F, Ambrosini E (2013) Astrocytes: Emerging stars in leukodystrophy pathogenesis. *Transl Neurosci* **4**: doi: 10.2478/s13380-013-0118-1.
121. Lanciotti A, Brignone MS, Camerini S, Serafini B, Macchia G, Raggi C *et al* (2010) MLC1 trafficking and membrane expression in astrocytes: role of caveolin-1 and phosphorylation. *Neurobiol Dis* **37**: 581–595.
122. Larsen BR, Assentoft M, Cotrina ML, Hua SZ, Nedergaard M, Kaila K *et al* (2014) Contributions of the Na⁺/K⁺-ATPase, NKCC1, and K_i4.1 to hippocampal K⁺ clearance and volume responses. *Glia* **62**: 608–622.
123. Lee W, Reyes RC, Gottipati MK, Lewis K, Lesort M, Parpura V, Gray M (2013) Enhanced Ca²⁺-dependent glutamate release from astrocytes of the BACHD Huntington's disease mouse model. *Neurobiol Dis* **58**:192–199.
124. Leegwater PA, Yuan BQ, van der Steen J, Mulders J, Konst AA, Boor PK *et al* (2001) Mutations of MLC1 (KIAA0027), encoding a putative membrane protein, cause megalencephalic leukoencephalopathy with subcortical cysts. *Am J Hum Genet* **68**:831–838.
125. Lenhossék M (1895) *Der Feinere Bau Des Nervensystems Im Lichte Neuester Forschung*, 2nd edn. Fischer's Medicinische Buchhandlung H. Kornfeld: Berlin.
126. Lent R, Azevedo FA, Andrade-Moraes CH, Pinto AV (2012) How many neurons do you have? Some dogmas of quantitative neuroscience under revision. *Eur J Neurosci* **35**:1–9.
127. Li B, Gu L, Hertz L, Peng L (2013) Expression of nucleoside transporter in freshly isolated neurons and astrocytes from mouse brain. *Neurochem Res* **38**:2351–2358.
128. Li L, Lundkvist A, Andersson D, Wilhelmsson U, Nagai N, Pardo AC *et al* (2008) Protective role of reactive astrocytes in brain ischemia. *J Cereb Blood Flow Metab* **28**:468–481.
129. Lim D, Ronco V, Grolla AA, Verkhatsky A, Genazzani AA (2014) Glial calcium signalling in Alzheimer's disease. *Rev Physiol Biochem Pharmacol* **167**:45–65.
130. Lohr C, Deitmer JW (2006) Calcium signaling in invertebrate glial cells. *Glia* **54**:642–649.
131. Lopez-Hernandez T, Ridder MC, Montolio M, Capdevila-Nortes X, Polder E, Sirisi S *et al* (2011) Mutant GlialCAM causes megalencephalic leukoencephalopathy with subcortical cysts, benign familial macrocephaly, and macrocephaly with retardation and autism. *Am J Hum Genet* **88**:422–432.
132. Macaulay N, Zeuthen T (2012) Glial K⁺ clearance and cell swelling: key roles for cotransporters and pumps. *Neurochem Res* **37**:2299–2309.
133. Martin CA, Krantz DE (2014) *Drosophila melanogaster* as a genetic model system to study neurotransmitter transporters. *Neurochem Int* **73**:71–88.
134. Martinotti C (1889) Contributo allo studio della corteccia cerebrale, ed all'origine centrale dei nervi. *Ann Fren Sci Affin* **1**:314–332.
135. Masaki K, Suzuki SO, Matsushita T, Yonekawa T, Matsuoka T, Isobe N *et al* (2012) Extensive loss of connexins in Balo's disease: evidence for an auto-antibody-independent astrocytopathy via impaired astrocyte-oligodendrocyte/myelin interaction. *Acta Neuropathol* **123**:887–900.
136. Mashanov VS, Zueva OR, Garcia-Arraras JE (2010) Organization of glial cells in the adult sea cucumber central nervous system. *Glia* **58**: 1581–1593.
137. Mashanov VS, Zueva OR, Heinzeller T, Aschauer B, Naumann WW, Grondona JM *et al* (2009) The central nervous system of sea cucumbers (Echinodermata: Holothuroidea) shows positive immunostaining for a chordate glial secretion. *Front Zool* **6**:11.
138. Matsuoka T, Suzuki SO, Iwaki T, Tabira T, Ordinario AT, Kira J (2010) Aquaporin-4 astrocytopathy in Balo's disease. *Acta Neuropathol* **120**:651–660.
139. Mauch DH, Nagler K, Schumacher S, Goritz C, Muller EC, Otto A, Pfrieger FW (2001) CNS synaptogenesis promoted by glia-derived cholesterol. *Science* **294**:1354–1357.
140. Meinertzhagen IA, O'Neil SD (1991) Synaptic organization of columnar elements in the lamina of the wild type in *Drosophila melanogaster*. *J Comp Neurol* **305**:232–263.
141. Mena MA, de Bernardo S, Casarejos MJ, Canals S, Rodriguez ME (2002) The role of astroglia on the survival of dopamine neurons. *Mol Neurobiol* **25**:245–263.
142. Mena MA, Garcia de Yébenes J (2008) Glial cells as players in parkinsonism: the “good,” the “bad,” and the “mysterious” glia. *Neuroscientist* **14**:544–560.
143. Messing A, Brenner M, Feany MB, Nedergaard M, Goldman JE (2012) Alexander disease. *J Neurosci* **32**:5017–5023.
144. Metea MR, Newman EA (2006) Glial cells dilate and constrict blood vessels: a mechanism of neurovascular coupling. *J Neurosci* **26**: 2862–2870.
145. Miguel-Hidalgo JJ (2005) Lower packing density of glial fibrillary acidic protein-immunoreactive astrocytes in the prefrontal cortex of alcohol-naïve and alcohol-drinking alcohol-preferring rats as compared with alcohol-nonpreferring and Wistar rats. *Alcohol Clin Exp Res* **29**:766–772.
146. Miguel-Hidalgo JJ (2009) The role of glial cells in drug abuse. *Curr Drug Abuse Rev* **2**:76–82.
147. Miguel-Hidalgo JJ, Overholser JC, Meltzer HY, Stockmeier CA, Rajkowska G (2006) Reduced glial and neuronal packing density in the orbitofrontal cortex in alcohol dependence and its relationship with suicide and duration of alcohol dependence. *Alcohol Clin Exp Res* **30**:1845–1855.
148. Minelli A, DeBiasi S, Brecha NC, Zuccarello LV, Conti F (1996) GAT-3, a high-affinity GABA plasma membrane transporter, is localized to astrocytic processes, and it is not confined to the vicinity of GABAergic synapses in the cerebral cortex. *J Neurosci* **16**:6255–6264.
149. Montana V (2016) Glioma: the mechanisms of infiltrative growth. *Opera Med Physiol* **1**:83–90.
150. Montana V, Verkhatsky A, Parpura V (2014) Pathological role for exocytotic glutamate release from astrocytes in hepatic encephalopathy. *Curr Neuropharmacol* **12**:324–333.
151. Moussawi K, Riegel A, Nair S, Kalivas PW (2011) Extracellular glutamate: functional compartments operate in different concentration ranges. *Front Syst Neurosci* **5**:94.
152. Muller M, Henrich A, Klockenhoff J, Dierkes PW, Schlue WR (2000) Effects of ATP and derivatives on neuropeptide glial cells of the leech central nervous system. *Glia* **29**:191–201.
153. Mulligan SJ, MacVicar BA (2004) Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. *Nature* **431**:195–199.
154. Nagelhus EA, Ottersen OP (2013) Physiological roles of aquaporin-4 in brain. *Physiol Rev* **93**:1543–1562.
155. Nagy JI, Patel D, Ochalski PA, Stelmack GL (1999) Connexin30 in rodent, cat and human brain: selective expression in gray matter astrocytes, co-localization with connexin43 at gap junctions and late developmental appearance. *Neuroscience* **88**:447–468.
156. Nedergaard M (2013) Neuroscience. Garbage truck of the brain. *Science* **340**:1529–1530.
157. Nimmerjahn A, Kirchhoff F, Kerr JN, Helmchen F (2004) Sulforhodamine 101 as a specific marker of astroglia in the neocortex *in vivo*. *Nat Methods* **1**:31–37.
158. Nishiyama A, Boshans L, Goncalves CM, Wegrzyn J, Patel KD (2016) Lineage, fate, and fate potential of NG2-glia. *Brain Res* **1638**: 116–128.
159. Noda M, Hiyama TY (2015) The Na_x channel: What it is and what it does. *Neuroscientist* **21**:399–412.
160. Noda M, Sakuta H (2013) Central regulation of body-fluid homeostasis. *Trends Neurosci* **36**:661–673.

161. Nolte C, Matyash M, Pivneva T, Schipke CG, Ohlemeyer C, Hanisch UK *et al* (2001) GFAP promoter-controlled EGFP-expressing transgenic mice: a tool to visualize astrocytes and astrogliosis in living brain tissue. *Glia* **33**:72–86.
162. Norenberg MD (1987) The role of astrocytes in hepatic encephalopathy. *Neurochem Pathol* **6**:13–33.
163. Norenberg MD, Martinez-Hernandez A (1979) Fine structural localization of glutamine synthetase in astrocytes of rat brain. *Brain Res* **161**:303–310.
164. Nwaobi SE, Cuddapah VA, Patterson KC, Randolph AC, Olsen ML (2016) The role of glial-specific $K_{ir}4.1$ in normal and pathological states of the CNS. *Acta Neuropathol* **132**:1–21.
165. Obara-Michlewska M, Ruszkiewicz J, Zielinska M, Verkhratsky A, Albrecht J (2014) Astroglial NMDA receptors inhibit expression of $K_{ir}4.1$ channels in glutamate-overexposed astrocytes in vitro and in the brain of rats with acute liver failure. *Neurochem Int* **88**:20–25.
166. Oberheim NA, Takano T, Han X, He W, Lin JH, Wang F *et al* (2009) Uniquely hominid features of adult human astrocytes. *J Neurosci* **29**:3276–3287.
167. Ogata K, Kosaka T (2002) Structural and quantitative analysis of astrocytes in the mouse hippocampus. *Neuroscience* **113**:221–233.
168. Oikonomou G, Shaham S (2011) The glia of *Caenorhabditis elegans*. *Glia* **59**:1253–1263.
169. Okada S, Nakamura M, Katoh H, Miyao T, Shimazaki T, Ishii K *et al* (2006) Conditional ablation of Stat3 or Socs3 discloses a dual role for reactive astrocytes after spinal cord injury. *Nat Med* **12**:829–834.
170. Olabarria M, Noristani HN, Verkhratsky A, Rodriguez JJ (2010) Concomitant astroglial atrophy and astrogliosis in a triple transgenic animal model of Alzheimer's disease. *Glia* **58**:831–838.
171. Olsen ML, Higashimori H, Campbell SL, Hablitz JJ, Sontheimer H (2006) Functional expression of $K_{ir}4.1$ channels in spinal cord astrocytes. *Glia* **53**:516–528.
172. Olsen ML, Sontheimer H (2008) Functional implications for $K_{ir}4.1$ channels in glial biology: from K^+ buffering to cell differentiation. *J Neurochem* **107**:589–601.
173. Park H, Oh SJ, Han KS, Woo DH, Park H, Mannaioni G *et al* (2009) Bestrophin-1 encodes for the Ca^{2+} -activated anion channel in hippocampal astrocytes. *J Neurosci* **29**:13063–13073.
174. Parpura V, Heneka MT, Montana V, Oliet SH, Schousboe A, Haydon PG *et al* (2012) Glial cells in (patho)physiology. *J Neurochem* **121**:4–27.
175. Patil CG, Eboli P, Hu J (2012) Management of multifocal and multicentric gliomas. *Neurosurg Clin N Am* **23**:343–350.
176. Pekny M, Johansson CB, Eliasson C, Stakeberg J, Wallen A, Perlmann T *et al* (1999) Abnormal reaction to central nervous system injury in mice lacking glial fibrillary acidic protein and vimentin. *J Cell Biol* **145**:503–514.
177. Pekny M, Pekna M (2014) Astrocyte reactivity and reactive astrogliosis: costs and benefits. *Physiol Rev* **94**:1077–1098.
178. Pekny M, Pekna M, Messing A, Steinhäuser C, Lee JM, Parpura V *et al* (2016) Astrocytes: a central element in neurological diseases. *Acta Neuropathol* **131**:323–345.
179. Pekny M, Wilhelmsson U, Pekna M (2014) The dual role of astrocyte activation and reactive gliosis. *Neurosci Lett* **565**:30–38.
180. Pellerin L, Bergersen LH, Halestrap AP, Pierre K (2005) Cellular and subcellular distribution of monocarboxylate transporters in cultured brain cells and in the adult brain. *J Neurosci Res* **79**:55–64.
181. Pellerin L, Magistretti PJ (2012) Sweet sixteen for ANLS. *J Cereb Blood Flow Metab* **32**:1152–1166.
182. Pelvig DP, Pakkenberg H, Stark AK, Pakkenberg B (2008) Neocortical glial cell numbers in human brains. *Neurobiol Aging* **29**:1754–1762.
183. Peng L, Huang R, Yu AC, Fung KY, Rathbone MP, Hertz L (2005) Nucleoside transporter expression and function in cultured mouse astrocytes. *Glia* **52**:25–35.
184. Pentreath VW, Radojic T, Seal LH, Winstanley EK (1985) The glial cells and glia-neuron relations in the buccal ganglia of Planorbis corneus (L.): cytological, qualitative and quantitative changes during growth and ageing. *Philos Trans R Soc Lond B Biol Sci* **307**:399–455.
185. Perens EA, Shaham S (2005) *C. elegans* daf-6 encodes a patched-related protein required for lumen formation. *Dev Cell* **8**:893–906.
186. Peters A, Verderosa A, Sethares C (2008) The neuroglial population in the primary visual cortex of the aging rhesus monkey. *Glia* **56**:1151–1161.
187. Pfrieger FW (2010) Role of glial cells in the formation and maintenance of synapses. *Brain Res Rev* **63**:39–46.
188. Porkka-Heiskanen T, Strecker RE, McCarley RW (2000) Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: an in vivo microdialysis study. *Neuroscience* **99**:507–517.
189. Potokar M, Jorgacevski J, Zorec R (2016) Astrocyte aquaporin dynamics in health and disease. *Int J Mol Sci* **17**:
190. Rajkowska G, Miguel-Hidalgo JJ, Makkos Z, Meltzer H, Overholser J, Stockmeier C (2002) Layer-specific reductions in GFAP-reactive astroglia in the dorsolateral prefrontal cortex in schizophrenia. *Schizophr Res* **57**:127–138.
191. Rajkowska G, Stockmeier CA (2013) Astrocyte pathology in major depressive disorder: insights from human postmortem brain tissue. *Curr Drug Targets* **14**:1225–1236.
192. Ransom CB, Ransom BR, Sontheimer H (2000) Activity-dependent extracellular K^+ accumulation in rat optic nerve: the role of glial and axonal Na^+ pumps. *J Physiol* **522**(Pt 3):427–442.
193. Rasmussen R, Nedergaard M, Petersen NC (2016) Sulforhodamine 101, a widely used astrocyte marker, can induce cortical seizure-like activity at concentrations commonly used. *Sci Rep* **6**:30433.
194. Ratelade J, Verkman AS (2012) Neuromyelitis optica: aquaporin-4 based pathogenesis mechanisms and new therapies. *Int J Biochem Cell Biol* **44**:1519–1530.
195. Reichenbach A, Derouiche A, Kirchhoff F (2010) Morphology and dynamics of perisynaptic glia. *Brain Res Rev* **63**:11–25.
196. Reichenbach A, Neumann M, Bruckner G (1987) Cell length to diameter relation of rat fetal radial glia—does impaired K^+ transport capacity of long thin cells cause their perinatal transformation into multipolar astrocytes? *Neurosci Lett* **73**:95–100.
197. Reissner KJ, Kalivas PW (2014) Emerging roles for glial pathology in addiction. In: *Pathological Potential of Neuroglia: Possible New Targets for Medical Intervention*, V Parpura, A Verkhratsky (eds), pp. 397–418, Springer: New York Heidelberg Dordrecht London.
198. Retzius G (1894) *Biologiske Undersøgelser. Neue Folge, Vol VI. Mit 32 Tafeln*. Von Gustav Fischer: Jena - Stockholm.
199. Rickmann M, Wolff JR (1995) S100 protein expression in subpopulations of neurons of rat brain. *Neuroscience* **67**:977–991.
200. Robert M, Wastie M (2008) Glioblastoma multiforme: a rare manifestation of extensive liver and bone metastases. *Biomed Imaging Interv J* **4**:e3.
201. Rodriguez-Arellano JJ, Parpura V, Zorec R, Verkhratsky A (2016) Astrocytes in physiological aging and Alzheimer's disease. *Neuroscience* **323**:170–182.
202. Rodriguez-Vieitez E, Saint-Aubert L, Carter SF, Almkvist O, Farid K, Scholl M *et al* (2016) Diverging longitudinal changes in astrocytosis and amyloid PET in autosomal dominant Alzheimer's disease. *Brain* **139**:922–936.
203. Rodriguez JJ, Butt AM, Gardenal E, Parpura V, Verkhratsky A (2016) Complex and differential glial responses in Alzheimer's disease and ageing. *Curr Alzheimer Res* **13**:343–358.
204. Rodriguez JJ, Terzieva S, Olabarria M, Lanza RG, Verkhratsky A (2013) Enriched environment and physical activity reverse astrogliodegeneration in the hippocampus of AD transgenic mice. *Cell Death Dis* **4**:e678.

205. Rose CF, Verkhatsky A, Papura V (2013) Astrocyte glutamine synthetase: pivotal in health and disease. *Biochem Soc Trans* **41**: 1518–1524.
206. Rose CR, Verkhatsky A (2016) Principles of sodium homeostasis and sodium signalling in astroglia. *Glia* **64**:1611–1627.
207. Rossi D, Brambilla L, Valori CF, Roncoroni C, Crugnola A, Yokota T et al (2008) Focal degeneration of astrocytes in amyotrophic lateral sclerosis. *Cell Death Differ* **15**:1691–1700.
208. Sakry D, Trotter J (2016) The role of the NG2 proteoglycan in OPC and CNS network function. *Brain Res* **1638**:161–166.
209. Sanacora G, Banasr M (2013) From pathophysiology to novel antidepressant drugs: glial contributions to the pathology and treatment of mood disorders. *Biol Psychiatry* **73**:1172–1179.
210. Sanacora G, Treccani G, Popoli M (2012) Towards a glutamate hypothesis of depression: an emerging frontier of neuropsychopharmacology for mood disorders. *Neuropharmacology* **62**:63–77.
211. Saubermann AJ, Castiglia CM, Foster MC (1992) Preferential uptake of rubidium from extracellular space by glial cells compared to neurons in leech ganglia. *Brain Res* **577**:64–72.
212. Saura J, Kettler R, Da Prada M, Richards JG (1992) Quantitative enzyme radioautography with 3H-Ro 41–1049 and 3H-Ro 19–6327 in vitro: localization and abundance of MAO-A and MAO-B in rat CNS, peripheral organs, and human brain. *J Neurosci* **12**:1977–1999.
213. Savchenko VL, McKanna JA, Nikonenko IR, Skibo GG (2000) Microglia and astrocytes in the adult rat brain: comparative immunocytochemical analysis demonstrates the efficacy of lipocortin 1 immunoreactivity. *Neuroscience* **96**:195–203.
214. Schafer DP, Stevens B (2013) Phagocytic glial cells: sculpting synaptic circuits in the developing nervous system. *Curr Opin Neurobiol* **23**:1034–1040.
215. Scheiber IF, Dringen R (2013) Astrocyte functions in the copper homeostasis of the brain. *Neurochem Int* **62**:556–565.
216. Scherer HJ (1938) Structural development in gliomas. *Am J Cancer* **34**:333–351.
217. Schmitt A, Asan E, Lesch KP, Kugler P (2002) A splice variant of glutamate transporter GLT1/EAAT2 expressed in neurons: cloning and localization in rat nervous system. *Neuroscience* **109**:45–61.
218. Schmitt A, Asan E, Puschel B, Kugler P (1997) Cellular and regional distribution of the glutamate transporter GLAST in the CNS of rats: nonradioactive in situ hybridization and comparative immunocytochemistry. *J Neurosci* **17**:1–10.
219. Schmitt A, Steyskal C, Bernstein HG, Schneider-Axmann T, Parlapani E, Schaeffer EL et al (2009) Stereologic investigation of the posterior part of the hippocampus in schizophrenia. *Acta Neuropathol* **117**:395–407.
220. Schnell C, Hagos Y, Hulsmann S (2012) Active sulforhodamine 101 uptake into hippocampal astrocytes. *PLoS One* **7**:e49398.
221. Schroeter S, Apparundaram S, Wiley RG, Miner LH, Sesack SR, Blakely RD (2000) Immunolocalization of the cocaine- and antidepressant-sensitive l-norepinephrine transporter. *J Comp Neurol* **420**:211–232.
222. Schwarcz R, Hunter CA (2007) *Toxoplasma gondii* and schizophrenia: linkage through astrocyte-derived kynurenic acid? *Schizophr Bull* **33**:652–653.
223. Scimemi A (2014) Structure, function, and plasticity of GABA transporters. *Front Cell Neurosci* **8**:161.
224. Scofield MD, Li H, Siemsen BM, Healey KL, Tran PK, Woronoff N et al (2016) Cocaine self-administration and extinction leads to reduced glial fibrillary acidic protein expression and morphometric features of astrocytes in the nucleus accumbens core. *Biol Psychiatry* **80**:207–215.
225. Seifert G, Huttmann K, Binder DK, Hartmann C, Wyczynski A, Neusch C, Steinhauser C (2009) Analysis of astroglial K⁺ channel expression in the developing hippocampus reveals a predominant role of the K_i4.1 subunit. *J Neurosci* **29**:7474–7488.
226. Seifert G, Steinhauser C (2013) Neuron-astrocyte signaling and epilepsy. *Exp Neurol* **244**:4–10.
227. Sherwood CC, Stimpson CD, Raghanti MA, Wildman DE, Uddin M, Grossman LI et al (2006) Evolution of increased glia-neuron ratios in the human frontal cortex. *Proc Natl Acad Sci U S A* **103**: 13606–13611.
228. Shibata T, Yamada K, Watanabe M, Ikenaka K, Wada K, Tanaka K, Inoue Y (1997) Glutamate transporter GLAST is expressed in the radial glia-astrocyte lineage of developing mouse spinal cord. *J Neurosci* **17**:9212–9219.
229. Shimizu H, Watanabe E, Hiyama TY, Nagakura A, Fujikawa A, Okado H et al (2007) Glial Na_x channels control lactate signaling to neurons for brain [Na⁺] sensing. *Neuron* **54**:59–72.
230. Sik A, Smith RL, Freund TF (2000) Distribution of chloride channel-2-immunoreactive neuronal and astrocytic processes in the hippocampus. *Neuroscience* **101**:51–65.
231. Simard M, Arcuino G, Takano T, Liu QS, Nedergaard M (2003) Signaling at the gliovascular interface. *J Neurosci* **23**:9254–9262.
232. Sofroniew MV (2014) Astrogliosis. *Cold Spring Harb Perspect Biol* **7**:a020420.
233. Sofroniew MV (2014) Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. *Neuroscientist* **20**:160–172.
234. Sofroniew MV (2015) Astrocyte barriers to neurotoxic inflammation. *Nat Rev Neurosci* **16**:249–263.
235. Song YJ, Halliday GM, Holton JL, Lashley T, O'Sullivan SS, McCann H et al (2009) Degeneration in different parkinsonian syndromes relates to astrocyte type and astrocyte protein expression. *J Neuropathol Exp Neurol* **68**:1073–1083.
236. Sosunov AA, Wu X, Tsankova NM, Guilfoyle E, McKhann GM, 2nd, Goldman JE (2014) Phenotypic heterogeneity and plasticity of isocortical and hippocampal astrocytes in the human brain. *J Neurosci* **34**:2285–2298.
237. Steiner J, Bernstein HG, Bielow H, Berndt A, Brisch R, Mawrin C et al (2007) Evidence for a wide extra-astrocytic distribution of S100B in human brain. *BMC Neurosci* **8**:2.
238. Steinhauser C, Seifert G, Bedner P (2012) Astrocyte dysfunction in temporal lobe epilepsy: K⁺ channels and gap junction coupling. *Glia* **60**:1192–1202.
239. Stenovec M, Trkov S, Lasic E, Terzieva S, Kreft M, Rodriguez Arellano JJ et al (2016) Expression of familial Alzheimer disease presenilin 1 gene attenuates vesicle traffic and reduces peptide secretion in cultured astrocytes devoid of pathologic tissue environment. *Glia* **64**:317–329.
240. Stout RF, Jr., Verkhatsky A, Papura V (2014) *Caenorhabditis elegans* glia modulate neuronal activity and behavior. *Front Cell Neurosci* **8**:67.
241. Struys-Ponsar C, Guillard O, van den Bosch de Aguilar P (2000) Effects of aluminum exposure on glutamate metabolism: a possible explanation for its toxicity. *Exp Neurol* **163**:157–164.
242. Studer FE, Fedele DE, Marowsky A, Schwerdel C, Wernli K, Vogt K et al (2006) Shift of adenosine kinase expression from neurons to astrocytes during postnatal development suggests dual functionality of the enzyme. *Neuroscience* **142**:125–137.
243. Suarez-Fernandez MB, Soldado AB, Sanz-Medel A, Vega JA, Novelli A, Fernandez-Sanchez MT (1999) Aluminum-induced degeneration of astrocytes occurs via apoptosis and results in neuronal death. *Brain Res* **835**:125–136.
244. Sun W, Cornwell A, Li J, Peng S, Osorio J, Aalling N et al (2017) SOX9 is an astrocyte-specific nuclear marker in the adult brain outside the neurogenic regions. *J Neurosci* (in press).
245. Takano T, Oberheim N, Cotrina ML, Nedergaard M (2009) Astrocytes and ischemic injury. *Stroke* **40**:S8–12.

246. Takano T, Tian GF, Peng W, Lou N, Libionka W, Han X, Nedergaard M (2006) Astrocyte-mediated control of cerebral blood flow. *Nat Neurosci* **9**:260–267.
247. Takeda H, Inazu M, Matsumiya T (2002) Astroglial dopamine transport is mediated by norepinephrine transporter. *Naunyn Schmiedebergs Arch Pharmacol* **366**:620–623.
248. Thakkar MM, Winston S, McCarley RW (2003) A₁ receptor and adenosinergic homeostatic regulation of sleep-wakefulness: effects of antisense to the A₁ receptor in the cholinergic basal forebrain. *J Neurosci* **23**:4278–4287.
249. Tiffany-Castiglioni E, Hong S, Qian Y (2011) Copper handling by astrocytes: insights into neurodegenerative diseases. *Int J Dev Neurosci* **29**:811–818.
250. Tix S, Eule E, Fischbach KF, Benzer S (1997) Glia in the chiasm and medulla of the *Drosophila melanogaster* optic lobes. *Cell Tissue Res* **289**:397–409.
251. Tong X, Ao Y, Faas GC, Nwaobi SE, Xu J, Hausteine MD *et al* (2014) Astrocyte K_{ir}4.1 ion channel deficits contribute to neuronal dysfunction in Huntington's disease model mice. *Nat Neurosci* **17**:694–703.
252. Tremblay ME, Stevens B, Sierra A, Wake H, Bessis A, Nimmerjahn A (2011) The role of microglia in the healthy brain. *J Neurosci* **31**:16064–16069.
253. Turovsky E, Theparambil SM, Kasymov V, Deitmer JW, Del Arroyo AG, Ackland GL *et al* (2016) Mechanisms of CO₂/H⁺ sensitivity of astrocytes. *J Neurosci* **36**:10750–10758.
254. Untiet V, Kovermann P, Gerkau NJ, Gensch T, Rose CR, Fahlke C (2017) Glutamate transporter-associated anion channels adjust intracellular chloride concentrations during glial maturation. *Glia* **65**:388–400.
255. Valori CF, Brambilla L, Martorana F, Rossi D (2014) The multifaceted role of glial cells in amyotrophic lateral sclerosis. *Cell Mol Life Sci* **71**:287–297.
256. van der Knaap MS, Leegwater PA, Konst AA, Visser A, Naidu S, Oudejans CB *et al* (2002) Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. *Ann Neurol* **51**:264–270.
257. Vandenberg RJ, Ryan RM (2013) Mechanisms of glutamate transport. *Physiol Rev* **93**:1621–1657.
258. Vardjan N, Horvat A, Anderson JE, Yu D, Croom D, Zeng X *et al* (2016) Adrenergic activation attenuates astrocyte swelling induced by hypotonicity and neurotrauma. *Glia* **64**:1034–1049.
259. Vardjan N, Zorec R (2015) Excitable astrocytes: Ca²⁺- and cAMP-regulated exocytosis. *Neurochem Res* **40**:2414–2424.
260. Verkhratsky A, Butt AM (2013) *Glial Physiology and Pathophysiology*. Wiley-Blackwell: Chichester.
261. Verkhratsky A, Marutle A, Rodriguez-Arellano JJ, Nordberg A (2015) Glial asthenia and functional paralysis: A new perspective on neurodegeneration and Alzheimer's disease. *Neuroscientist* **21**:552–568.
262. Verkhratsky A, Matteoli M, Parpura V, Mothet JP, Zorec R (2016) Astrocytes as secretory cells of the central nervous system: idiosyncrasies of vesicular secretion. *EMBO J* **35**:239–257.
263. Verkhratsky A, Nedergaard M (2017) Physiology of astroglia. *Physiol Rev* (in press).
264. Verkhratsky A, Olabarria M, Noristani HN, Yeh CY, Rodriguez JJ (2010) Astrocytes in Alzheimer's disease. *Neurotherapeutics* **7**:399–412.
265. Verkhratsky A, Orkand RK, Kettenmann H (1998) Glial calcium: homeostasis and signaling function. *Physiol Rev* **78**:99–141.
266. Verkhratsky A, Parpura V (2016) Astroglipathology in neurological, neurodevelopmental and psychiatric disorders. *Neurobiol Dis* **85**:254–261.
267. Verkhratsky A, Rodriguez-Arellano JJ, Parpura V, Zorec R (2017) Astroglial calcium signalling in Alzheimer's disease. *Biochem Biophys Res Commun* **483**:1005–1012.
268. Verkhratsky A, Rodriguez JJ, Parpura V (2012) Calcium signalling in astroglia. *Mol Cell Endocrinol* **353**:45–56.
269. Verkhratsky A, Rodriguez JJ, Parpura V (2013) Astroglia in neurological diseases. *Future Neurol* **8**:149–158.
270. Verkhratsky A, Rodriguez JJ, Steardo L (2014) Astroglipathology: a central element of neuropsychiatric diseases? *Neuroscientist* **20**:576–588.
271. Verkhratsky A, Sofroniew MV, Messing A, deLanerolle NC, Rempel D, Rodriguez JJ, Nedergaard M (2012) Neurological diseases as primary gliopathies: a reassessment of neurocentrism. *ASN Neuro* **4**:pii:e00082.
272. Verkhratsky A, Steardo L, Parpura V, Montana V (2016) Translational potential of astrocytes in brain disorders. *Prog Neurobiol* **144**:188–205.
273. Verkhratsky A, Zorec R, Rodriguez JJ, Parpura V (2016) Astroglia dynamics in ageing and Alzheimer's disease. *Curr Opin Pharmacol* **26**:74–79.
274. von Bartheld CS, Bahney J, Herculano-Houzel S (2016) The search for true numbers of neurons and glial cells in the human brain: A review of 150 years of cell counting. *J Comp Neurol* **524**:3865–3895.
275. Walther EU, Dichgans M, Maricich SM, Romito RR, Yang F, Dziennis S *et al* (1998) Genomic sequences of aldolase C (Zebirin II) direct lacZ expression exclusively in non-neuronal cells of transgenic mice. *Proc Natl Acad Sci USA* **95**:2615–2620.
276. Walz W, Lang MK (1998) Immunocytochemical evidence for a distinct GFAP-negative subpopulation of astrocytes in the adult rat hippocampus. *Neurosci Lett* **257**:127–130.
277. Watanabe E, Hiyama TY, Shimizu H, Kodama R, Hayashi N, Miyata S, Yanagawa Y, Obata K, Noda M (2006) Sodium-level-sensitive sodium channel Na_x is expressed in glial lamina processes in the sensory circumventricular organs. *Am J Physiol Regul Integr Comp Physiol* **290**:R568–R576.
278. Weber M, Scherf N, Kahl T, Braumann UD, Scheibe P, Kuska JP *et al* (2013) Quantitative analysis of astrogliosis in drug-dependent humans. *Brain Res* **1500**:72–87.
279. Wenker IC, Kreneisz O, Nishiyama A, Mulkey DK (2010) Astrocytes in the retrotrapezoid nucleus sense H⁺ by inhibition of a K_{ir}4.1-K_{ir}5.1-like current and may contribute to chemoreception by a purinergic mechanism. *J Neurophysiol* **104**:3042–3052.
280. Wicht H, Derouiche A, Korf HW (1994) An immunocytochemical investigation of glial morphology in the Pacific hagfish: radial and astrocyte-like glia have the same phylogenetic age. *J Neurocytol* **23**:565–576.
281. Williams SM, Sullivan RK, Scott HL, Finkelstein DI, Colditz PB, Lingwood BE *et al* (2005) Glial glutamate transporter expression patterns in brains from multiple mammalian species. *Glia* **49**:520–541.
282. Windrem MS, Schanz SJ, Morrow C, Munir J, Chandler-Militello D, Wang S, Goldman SA (2014) A competitive advantage by neonatally engrafted human glial progenitors yields mice whose brains are chimeric for human glia. *J Neurosci* **34**:16153–16161.
283. Wuttke WA, Pentreath VW (1990) Evidence for the uptake of neuronally derived choline by glial cells in the leech central nervous system. *J Physiol* **420**:387–408.
284. Yamanaka K, Chun SJ, Boillee S, Fujimori-Tonou N, Yamashita H, Gutmann DH *et al* (2008) Astrocytes as determinants of disease progression in inherited amyotrophic lateral sclerosis. *Nat Neurosci* **11**:251–253.
285. Yang Y, Vidensky S, Jin L, Jie C, Lorenzini I, Frankl M, Rothstein JD (2011) Molecular comparison of GLT1+ and ALDH1L1+ astrocytes in vivo in astroglial reporter mice. *Glia* **59**:200–207.
286. Yeh CY, Verkhratsky A, Terzieva S, Rodriguez JJ (2013) Glutamine synthetase in astrocytes from entorhinal cortex of the triple transgenic animal model of Alzheimer's disease is not affected by pathological progression. *Biogerontology* **14**:777–787.

287. Yin Z, Milatovic D, Aschner JL, Syversen T, Rocha JB, Souza DO *et al* (2007) Methylmercury induces oxidative injury, alterations in permeability and glutamine transport in cultured astrocytes. *Brain Res* **1131**:1–10.
288. Zafra F, Aragon C, Olivares L, Danbolt NC, Gimenez C, Storm-Mathisen J (1995) Glycine transporters are differentially expressed among CNS cells. *J Neurosci* **15**:3952–3969.
289. Zagzag D, Esencay M, Mendez O, Yee H, Smirnova I, Huang Y *et al* (2008) Hypoxia- and vascular endothelial growth factor-induced stromal cell-derived factor-1alpha/CXCR4 expression in glioblastomas: one plausible explanation of Scherer's structures. *Am J Pathol* **173**:545–560.
290. Zamanian JL, Xu L, Foo LC, Nouri N, Zhou L, Giffard RG, Barres BA (2012) Genomic analysis of reactive astrogliosis. *J Neurosci* **32**: 6391–6410.
291. Zeidan-Chulia F, Salmina AB, Malinovskaya NA, Noda M, Verkhatsky A, Moreira JC (2014) The glial perspective of autism spectrum disorders. *Neurosci Biobehav Rev* **38**:160–172.
292. Zhao Y, Rempe DA (2010) Targeting astrocytes for stroke therapy. *Neurotherapeutics* **7**:439–451.
293. Zhou Y, Danbolt NC (2013) GABA and glutamate transporters in brain. *Front Endocrinol (Lausanne)* **4**:165.
294. Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, Carmignoto G (2003) Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat Neurosci* **6**:43–50.
295. Zorec R, Horvat A, Vardjan N, Verkhatsky A (2015) Memory formation shaped by astroglia. *Front Integr Neurosci* **9**:56.
296. Zorec R, Verkhatsky A, Rodriguez JJ, Parpura V (2016) Astrocytic vesicles and gliotransmitters: slowness of vesicular release and synaptobrevin2-laden vesicle nanoarchitecture. *Neuroscience* **323**:67–75.