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Translational potential of astrocytes in brain disorders

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Abstract

Fundamentally, all brain disorders can be broadly defined as the homeostatic failure of this organ. As the brain is composed of many different cells types, including but not limited to neurons and glia, it is only logical that all the cell types/constituents could play a role in health and disease. Yet, for a long time the sole conceptualization of brain pathology was focused on the well-being of neurons. Here, we challenge this neuron-centric view and present neuroglia as a key element in neuropathology, a process that has a toll on astrocytes, which undergo complex morpho-functional changes that can in turn affect the course of the disorder. Such changes can be grossly identified as reactivity, atrophy with loss of function and pathological remodeling. We outline the pathogenic potential of astrocytes in variety of disorders, ranging from neurotrauma, infection, toxic damage, stroke, epilepsy, neurodevelopmental, neurodegenerative and psychiatric disorders, Alexander disease to neoplastic changes seen in gliomas. We hope that in near future we would witness glial-based translational medicine with generation of deliverables for the containment and cure of disorders. We point out that such as a task will require a holistic and multi-disciplinary approach that will take in consideration the concerted operation of all the cell types in the brain.

Keywords

astrocytes; morpho-functional changes; pathology; potential therapeutic targets

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1. Astrogliopathology: Reactivity, atrophy with loss of function and pathological remodeling

Fundamentally, all diseases, including neurological disorders can be broadly defined as homeostatic failures within tissue, organ or a system. For a long time neuropathology was dominated by the neuron-centric views with all conceptualization of brain pathology being focused on neurons, on their survival or death. The neuron-centricity is now being challenged and neuroglia begins to be regarded as a central element of neuropathology (Burda and Sofroniew, 2014; Giaume *et al.*, 2007; Nedergaard *et al.*, 2010; Parpura *et al.*, 2012; Sofroniew, 2009).

Astroglia is the name for a highly heterogeneous population of neural cells, populating the grey and white matter of the central nervous system (CNS), which are chiefly responsible for the homeostasis of the neural tissue and contribute to its defense in pathology (Kettenmann and Ransom, 2013; Verkhratsky and Butt, 2013). Astroglial expression of a wide array of receptors for neurotransmitters and neurohormones is regulated by the neurochemical environment and, as a rule, astrocytes possess receptors allowing them to sense neighboring neuronal transmission (Parpura and Verkhratsky, 2012a). Activation of these receptors triggers dynamic changes of concentration of ions (mainly Ca^{2+} and Na^{+}) in the astroglial cytoplasm, which regulate astroglial functions and serve as a substrate for astroglial excitability (Agulhon *et al.*, 2008; Kirischuk *et al.*, 2012; Parpura and Verkhratsky, 2012b, 2013; Rose and Karus, 2013; Verkhratsky *et al.*, 2014c; Zorec *et al.*, 2012). The functions of astrocytes are highly diverse and are regionally specialized (Anderson *et al.*, 2014; Chaboub and Deneen, 2012; Matyash and Kettenmann, 2010; Oberheim *et al.*, 2012; Parpura *et al.*, 2012; Schitine *et al.*, 2015). In the gray matter astrocytes divide (through the process known as tiling that starts in the late embryogenesis) the parenchyma into relatively independent units, traditionally known as neurovascular units and recently often called astroglio-vascular units, that integrate, within an individual astroglial territorial domain, neural and vascular elements (Bushong *et al.*, 2002; Iadecola and Nedergaard, 2007; Nedergaard *et al.*, 2003). By employing a variety of molecular mechanisms (exocytosis, membrane transporters or diffusion through plasmalemmal channels) astrocytes secrete numerous neurotransmitters, neurohormones and trophic factors (Malarkey and Parpura, 2008; Parpura *et al.*, 2011) that regulate synapse formation and maintenance, modulate synaptic transmission and synchronization of neuronal networks and signal to other (in addition to neurons) cellular elements (e.g., microglia, oligodendroglia, pericytes, and endothelial cells). At the level of the whole brain, astrocytes form the glia limitans (i.e., a thin barrier surrounding the brain and spinal cord and containing astrocytic end-feet associated with the parenchymal basal lamina) and regulate emergence and function of brain-blood and brain-cerebro-spinal fluid barriers and contribute to overall brain metabolism being the sole producers and repository of glycogen (Kettenmann and Ransom, 2013; Verkhratsky and Butt, 2013).

Cellular pathophysiology of the CNS involves all cells that constitute brain tissue, with each cell type playing its defined function (Burda and Sofroniew, 2014). Astrocytes contribute to virtually all neuropathological conditions. First and foremost, astrocytes maintain CNS

homeostasis; the homeostatic function of astroglia is linked to their neuroprotective capabilities. Insults to the CNS regardless of their etiology put the strain on the organ homeostasis and it is astrocytes that through dedicated molecular cascades protect neurons against glutamate excitotoxicity, extracellular K^+ overload, and reactive oxygen species (ROS). Astrocytes also supply stressed neurons with energy substrates. The loss of these critical astroglial functions permits and exacerbates progression of various diseases, from which amyotrophic lateral sclerosis, toxic encephalopathies and neurodegeneration are prominent examples (Verkhratsky *et al.*, 2014a). In addition, astrocytes are capable of mounting a specific defensive response, generally known as reactive astrogliosis (Fig. 1), a multicomponent and complex remodeling of astroglia triggered by lesions to the CNS (Burda and Sofroniew, 2014; Pekny *et al.*, 2014; Sofroniew, 2009; Verkhratsky *et al.*, 2014b). Astrogliotic phenotypes are yet to be investigated in detail, although the context specificity becomes increasingly clear. Transciptomes of reactive astrocytes activated by two distinct stimuli, the ischemic stroke and injection of bacterial lipopolysaccharide showed remarkable difference, indicating that the stress signal defines characteristic of astrogliotic program (Zamanian *et al.*, 2012). Astrogliosis is an important component of cellular pathophysiology and its suppression generally aggravates neuropathology.

Besides reactivity, however, numerous neurological diseases are associated with astroglial degeneration, astroglial atrophy and functional asthenia (Fig. 1). Astroglial atrophy and loss of function has been documented in many neurological diseases, including psychiatric disorders and neurodegeneration (Hazell, 2009; Rajkowska and Stockmeier, 2013; Rossi *et al.*, 2008; Verkhratsky *et al.*, 2014a; Verkhratsky *et al.*, 2014d). Atrophy of astrocytes leads to a decrease in synaptic coverage by astrocytic perisynaptic membranes, decrease in astroglial homeostatic support (which is often manifested through compromised uptake of glutamate, that in turn affects neurotransmission and promotes excitotoxicity) and decrease in astroglia-dependent neuroprotection. In pathological conditions, astroglial asthenia may result in failed astrogliotic reaction, which in turn exacerbates the evolution of neuropathology (Verkhratsky *et al.*, 2014b). Finally, astrocytes in various neurological contexts may undergo pathological remodeling (Fig. 1). For example, in Alexander disease the expression of mutated glial fibrillary acidic protein (GFAP) causes severe leukomalacia (Messing *et al.*, 2012) and profound remodeling of astroglial homeostatic cascades is seen in hyperammonemia (Kelly *et al.*, 2009; Montana *et al.*, 2014).

2. Neurotrauma

Traumatic lesions to both the brain and spinal cord vary substantially in their form (i.e. penetrating wounds or concussions; the later when occurring in the cervical spinal cord is known medically as cervical cord neurapraxia), volume (focal or diffuse), severity and anatomical localization. These mechanistic differences define cellular pathology by affecting different types of cells in the nervous tissue, by damaging the blood-brain barrier, inflicting hemorrhages, inducing secondary infections, etc. Astroglial reactivity dominates the response of neural tissue to all forms of neurotrauma, although the resulting activated gliotic phenotypes are highly heterogeneous depending on pathological context (Burda *et al.*, 2015); furthermore, astrogliotic response is graded by the severity of the insult and proximity to the lesion. Initiation of astroglial gliotic program is likely to involve a massive

release of adenosine triphosphate (ATP) from cells within the damaged areas with subsequent activation of astroglial Ca^{2+} signaling mediated by inositol 1,4,5 trisphosphate ($InsP_3$)-induced Ca^{2+} release from the endoplasmic reticulum (Huang *et al.*, 2012; Roth *et al.*, 2014). Genetic deletion of $InsP_3$ receptors type 2 (which are predominantly expressed in astrocytes) suppresses astrogliotic response (Kanemaru *et al.*, 2013). Extracellular ATP signaling is also instrumental for activation of microglia (Kettenmann *et al.*, 2011), with the microgliosis representing the second arm of the gliotic response to traumatic lesions of the brain.

Reactive astrocytes serve numerous functions in protecting the CNS against neurotrauma. In focal traumatic injuries reactive astrocytes limit the lesion by forming the glial scar barrier around the areas of damage (Fig. 1); inhibition of astrogliosis and suppression of scar formation substantially exacerbates pathology and increases the ensuing neurological deficit (Sofroniew, 2005). Reactive astroglial phenotypes, however, are multiple and they depend on the distance from the lesion core. In the very vicinity of the wound astroglial cells proliferate, undergo anisomorphic gliosis and form the scar; astrocytes proximal to the traumatic injury react with hypertrophy and biochemical remodeling without changing their territorial organization, i.e. undergo isomorphic gliosis (Fig. 1). The multitude of reactive phenotypes reflects multiple functional outcomes of reactivity. In the context of neurotrauma astrocytes not only isolate the damage with a scar but also regulate inflammatory response, provide for homeostatic protection of the nervous tissue (through removing glutamate, buffering K^+, releasing ROS scavengers, etc.) and regulate post-traumatic remodeling of synaptic networks. Furthermore, astrocytes can secrete molecules that reduce the blood-brain barrier permeability and facilitate its reparation, Finally, reactive astrocytes are instrumental for post-traumatic regeneration of the nervous tissue (see (Burda *et al.*, 2015) and references therein). In some conditions, however, traumatic injury may impair upon astroglial protective functions; lesions to the brain are reported to reduce expression of astrocytic glutamate transporters, hence aggravating glutamate excitotoxicity (Beschorner *et al.*, 2007; Rao *et al.*, 1998).

3. Infectious diseases of the CNS

Infections/infestation of the nervous tissue caused by bacteria, viruses, fungi and parasites are classified into meningitis, encephalitis or brain abscess. The reaction of neuroglia is fundamental to infectious pathology with activated microglia and reactive astrocytes being often indispensable for limiting the extent of damage. Astroglial responses to pathology depend on the nature of an infectious agent. Infection with the gram-positive *Pneumococcus* or *Staphylococcus* rapidly induces an astrogliotic program manifested by hypertrophy and up-regulation of GFAP expression (Iovino *et al.*, 2013), and secretion of pro-inflammatory factors including tumor necrosis factor α (TNF-α), interleukins (ILs) and macrophage inflammatory protein 1α (Liu *et al.*, 2010). Activation of microglia in a context of the gram-positive bacterial infection involves NOD2 (nucleotide-binding oligomerization domain containing 2) signaling (Liu *et al.*, 2010) and activation of neurokinin-1 receptors stimulated by substance P receptors (Chauhan *et al.*, 2011). Astroglial reactivity is also linked to activation of toll-like TLR2 type receptors (Esen *et al.*, 2004). Bacterial infection is also reported to down-regulate expression of connexins that form intercellular gap junctional and

hence astroglial syncytia, which is regarded as a neuroprotective mechanism, limiting the spread of inflammation (Esen *et al.*, 2007). Astrogliotic response in the context of bacterial infection has clear defensive capacity: the neurological damage was exacerbated when *S. aureus* were injected in the brains of mice with the genetic deletion of GFAP (Stenzel *et al.*, 2004).

The gram-negative bacteria similarly cause early astrogliosis, augmented with astroglial proliferation; expression of GFAP decreased following an antibiotic treatment (Chauhan *et al.*, 2008; Dotevall *et al.*, 1996). Direct incubation of astrocytes with the gram-negative *Borrelia burgdorferi* up-regulated synthesis and release of the matrix metalloprotease 9, that could contribute to the disruption of the blood-brain barrier (Perides *et al.*, 1999). In addition, an exposure to *B. burgdorferi* caused an increase in the production of IL-6, TNF-α, IL-8, chemokine (C-X-C motif) ligand 1 (CXCL-1), and CXCL-10 in human cultured astrocytes (Brissette *et al.*, 2013).

Astroglial responses to viral infections of the CNS are more complex. First, astrocytes can be directly infected. For example, up to 19% of astroglial cells in post-mortem specimens obtained from HIV-1 patients contain viral genetic material and hence act as an infectious reservoir (Gray *et al.*, 2014; Joseph *et al.*, 2015; Narasipura *et al.*, 2014). Astrocytes have been found to accumulate HIV-1 within Cluster of Differentiation 81(CD81)-lined vesicles; as long as the virus remained in these vesicles it had protected from degradation. Furthermore, the same vesicles were instrumental for the secondary *trans*-infection of T-cells (Gray *et al.*, 2014). In the HIV dementia both astrogliosis as well astroglial degeneration and death have been documented; the loss of astroglial function can contribute to cognitive decline through an overall decrease in homeostatic support (Churchill *et al.*, 2009). Similarly to gram-positive bacteria, HIV-1 infection down-regulated expression of connexins, thus limiting astroglial coupling (Orellana *et al.*, 2014). The herpes simplex virus 1 (HSV1) also infects astrocytes and triggers their activation, which manifests in the form of inflammatory response with an increase of TNF-α and IL-6 production. Astroglial activation in the context of HSV infection was mediated through TLR3, and contributed to neuroprotection; the deficiency in TLR3 exacerbated HSV pathology in mice (Reinert *et al.*, 2012) and in humans (Herman *et al.*, 2012). Astroglial functional asthenia was also shown to contribute to the human cytomegalovirus (CMV) brain damage; in this context astrocytic deficiencies included a decrease in release of thrombospondins, otherwise required for normal synaptogenesis, and compromised glutamate uptake that participated in increased excitotoxicity (Zhang *et al.*, 2013; Zhang *et al.*, 2014). In addition, CMV infected astrocytes secreted a viral IL-10 homologue, which affected the microglial production of CXCL10, which in turn decreased an overall immune response to the infection (Cheeran *et al.*, 2003).

Finally, astroglia are the primary cellular target for *Toxoplasma gondii*. Infected astrocytes undergo biochemical remodeling which leads to an increased production and secretion of kynurenic acid that acts on neuronal glutamate and acetylcholine receptors, being implicated in pathogenesis of some forms of schizophrenia, which will be discussed in details below.

4. Toxic damage to the brain

4.1. Heavy metal toxic encephalopathies

Astroglia are the main target of encephalopathies following exposures to the toxic concentrations of heavy metals, such as manganese, lead, aluminum or methylmercury. Accumulation of heavy metals in astrocytes (mediated through various types of plasmalemmal transporters) results in the down-regulation of EAAT1/2 glutamate transporters and hence in compromised glutamate uptake (Struys-Ponsar *et al.*, 2000; Suarez-Fernandez *et al.*, 1999; Verkhratsky *et al.*, 2013; Yin *et al.*, 2007). This in turn leads to excitotoxicity and neuronal death as well as to the imbalance of neurotransmission, which all could contribute to psychotic and cognitive symptoms of heavy metal poisoning.

4.2. Hyperammonemia and hepatic encephalopathy

Increased concentration of blood ammonium occurs in several diseases, of which the most prominent is the hepatic failure; elevation of ammonium in the brain causes numerous mental and behavioral symptoms including confusion, forgetfulness, irritability, alterations of consciousness, such as lethargy and somnolence. In terminal stages, hyperammonemia is associated with brain edema that causes death (Brusilow *et al.*, 2010; Butterworth, 2011; Felipo, 2013). For a long time the primary target of hyperammonemia was associated with astroglia-specific glutamine synthetase that “metabolizes” ammonium owing to its fixation to glutamate, hence forming glutamine (Albrecht *et al.*, 2010; Norenberg, 1987; Rose *et al.*, 2013). Occlusion of the normal metabolism of glutamate (i.e., its conversion into glutamine catalyzed by glutamine synthetase) in the context of ammonium overload (as glutamine synthetase gets inhibited by ammonium) was believed to result in neurotransmission disbalance causatively linked to mental and cognitive symptomatology (Brusilow *et al.*, 2010; Butterworth, 2011). Pathological potential of astroglia, however, turns out to me more complex. Recent observations demonstrated that in conditions of increased ammonium astrocytes rapidly undergo functional remodeling which severely compromises their homeostatic capabilities. This is represented by: (i) failure in K^+ buffering due to (at least in part) decreased expression of astroglial $K_{ir}4.1$ mediated through N-methyl D-aspartate (NMDA) type of glutamate receptors (Obara-Michlewska *et al.*, 2014; Rangroo Thrane *et al.*, 2013); (ii) aberrant astroglial Ca^{2+} signaling and Ca^{2+} homoeostasis due to an increase in expression of voltage-gated Ca^{2+} channels and Ca^{2+} -permeable transient receptor potential (TRP) channels as well as in abnormal Ca^{2+} release from intracellular stores (Haack *et al.*, 2014; Liang *et al.*, 2014; Wang *et al.*, 2015); (iii) aberrant Ca^{2+} signals trigger exocytotic astroglial glutamate release which may add to excitotoxic damage of the brain (Gorg *et al.*, 2010; Montana *et al.*, 2014); and (iv) massive pathological elevations in cytosolic Na^+ concentration and compromised H^+ transport which leads to abnormalities in pH regulation (Kelly *et al.*, 2009; Kelly and Rose, 2010). This astroglial remodeling may fundamentally contribute to the hyperammonemia damage.

5. Astrogliopathology in stroke

Astroglial contribution to pathophysiology of stroke is multifaceted and dichotomous (Gleichman and Carmichael, 2014; Zhao and Rempe, 2010). The main modes of astrocytic

reaction to focal ischemia are represented by homeostatic/neuroprotective response and reactive astrogliosis. In conditions of stroke, local interruption of the blood flow triggers pan-necrosis at the infarction core, the site and volume of which being determined by anatomical location and duration of the ischemic attack. Often, the conditions of focal ischemia are transient, as the blood flow can be restored when the vessel blockage is removed. In this case, restored blood flow results in reperfusion of the damaged area, which itself is potentially damaging because of the production of ROS and secondary ion disbalances. Primarily pathogenesis of ischemia is associated with the limitation of oxygen supply (hypoxia or anoxia), as well as with restrictions in supply of metabolic substrates. In the infarction core all cells rapidly die; the core is surrounded by the ischemic penumbra, which contains viable cells, although with compromised metabolism and function. The infarction core is formed very rapidly, within minutes to hours after initiation of the stroke. This is followed by a much slower process of expansion of the infarction zone through the penumbra, which develops over many hours and days.

After the onset of stoke and formation of ischemic core and penumbra astrocytes become critical elements that define the infarction size and lasting neurological deficit. The penumbra is regularly invaded with the waves of spreading depolarization that are initiated at the necrotic border and are instrumental for spreading the infarction volume (Lauritzen *et al.*, 2011; Nedergaard, 1996). Astrocytes are the main neuroprotective elements in the penumbra that limit neuronal death through controlling ions and glutamate and supporting neurons with energy substrates; stressing astrocytes by, for example, debilitating their mitochondria exacerbates neuronal death (Sayre *et al.*, 2014). Astrocytes are central for containing glutamate excitotoxicity, which is the major cause of neuronal death in the ischemic penumbra; importantly, astroglial plasmalemmal glutamate transporters are controlled by transmembrane Na^+ gradient, and loss of Na^+ homeostasis inhibits glutamate clearance (Kirischuk *et al.*, 2012). Levels of expression of EAAT2/GLT-1 astroglial transporter are critical for neuroprotection; down-regulation of GLT-1 expression with siRNA increases the infarct size (Rao *et al.*, 2001), whereas over-expression of GLT-1 reduces the infarction volume and limits neurological deficit (Harvey *et al.*, 2011). Pharmacological boost of GLT-1 expression/function with tamoxifen or riluzole similarly reduced infarction in animal models (Weng and Kriz, 2007; Zhang *et al.*, 2005). Another important component of astroglia-provided neuroprotection in the post-stroke tissue is associated with antioxidant defense; astrocytes maintain glutathione and ascorbic acid systems and thus buffer ROS (Dringen *et al.*, 2000; Dringen and Hirrlinger, 2003; Makar *et al.*, 1994)

Stroke and ischemia rapidly trigger astrogliotic activation, the degree of which depends on the distance to the ischemic core (Burda and Sofroniew, 2014). The main outcome of astrogliosis in the immediate vicinity of the necrotic area is formation of an astroglial scar, whereas more peripheral reactive astrocytes are important for post-lesion regeneration (Gleichman and Carmichael, 2014). At the same time reactive astrocytes may acquire a neurotoxic phenotype and be detrimental to neuronal survival (Gleichman and Carmichael, 2014).

6. Epilepsy

There is increasing evidence that astrocytes undergo profound pathological remodeling in the context of epilepsy; emerging pathological phenotype is characterized by changes in ion channels, receptors, transporters which all in all lead to a generalized failure of astroglial-dependent homeostasis in affected brain areas (Bedner *et al.*, 2015; Steinhauser *et al.*, 2015). In human astrocytes studied in tissue obtained from patients with mesial temporal lobe epilepsy and associated sclerosis, astrocytes displayed abnormal electrophysiological properties and were completely devoid of intercellular gap junction coupling. Similar properties were found in astroglial cells in hippocampi of the intracortical kainate injection mouse epilepsy model (Bedner *et al.*, 2015). Sclerotic tissue also demonstrated an increased expression of GFAP suggesting some form of reactivity. Pathophysiological contribution of astrocytes seems to be linked with an impaired K^+ buffering, as indeed increased concentration of K^+ in the extracellular space is associated with epilepsy (Lothman and Somjen, 1976; Moody *et al.*, 1974), and experimental increase in K^+ content in the neural tissue triggers epileptiform activity (Traynelis and Dingledine, 1988). On the molecular level, the K^+ buffering pathway, which seems to suffer the most in epilepsy, is associated with an expression level of inward rectifier $K_{ir}4.1$ channels. Both, the density of $K_{ir}4.1$-mediated currents and presence of $K_{ir}4.1$ protein were substantially reduced in astrocytes in the human sclerotic CA1 hippocampal area (Bordey and Sontheimer, 1998; Heuser *et al.*, 2010; Hinterkeuser *et al.*, 2000); see also (Steinhauser *et al.*, 2015) for details and extended reference list. Pan-deletion of $K_{ir}4.1$ encoding gene *KCNJ10* triggered motor impairments and death at postnatal day 8. However, animals with astroglia-specific *KCNJ10* knockout demonstrated ataxia, seizures and died around postnatal day 30; astrocytes in these animals were depolarized, and K^+ buffering as well as glutamate uptake were profoundly hampered (Djukic *et al.*, 2007). Several other studies have confirmed these findings and clearly demonstrated that deletion of astroglial $K_{ir}4.1$ channels induces epilepsy in laboratory animals (Steinhauser *et al.*, 2015). In humans, mutations of *KCNJ10* gene are associated with epilepsy – ataxia - sensorineural deafness - salt-wasting renal tubulopathy (EAST)/ seizures - sensorineural deafness – ataxia - mental retardation - electrolyte imbalance (SeSAME) syndrome, an autosomal recessive disorder (Bockenhauer *et al.*, 2009; Scholl *et al.*, 2009). In addition to loss of Kir4.1 function astrocytes in epileptic brain lose their connexin-mediated coupling, which hinders spatial K^+ buffering (Steinhauser *et al.*, 2015).

Another pathologically relevant result of astroglial remodeling in epilepsy is associated with the impairment of glutamate uptake (Coulter and Eid, 2012). Genetic deletion of astroglial-specific EAAT2 (known in rodents as GLT-1) glutamate transporter results in an epileptiform phenotype with lethal spontaneous seizures, increased susceptibility to acute cortical injury and seizures after administration of sub-convulsive doses of pentylenetetrazole (Tanaka *et al.*, 1997). Pharmacological blockade of EAATs by intracerebroventricular injections of DL-threo-beta-benzyloxyaspartate triggered seizures, further corroborating the role of glutamate uptake (Demarque *et al.*, 2004). Decreased expression of glutamine synthetase (GS; critical for supplying neurons with glutamine and hence for maintenance of normal glutamatergic and GABA transmissions) was also linked to epilepsy pathogenesis, i.e., a decrease in GABA-ergic transmission following reactive

astrogliosis-induced down-regulation of glutamine synthetase caused neuronal hyperexcitability similar to that seen in animal models of temporal lobe epilepsy (Ortinski *et al.*, 2010).

Long-lasting pharmacological inhibition of GS reduced glutamate levels in astrocytes and decreased synthesis of neuronal GABA, and developed seizures (Benedetti *et al.*, 2011; Wang *et al.*, 2009). The evidence that GS levels are significantly decreased in the human hippocampus and amygdala in temporal lobe epilepsy further corroborated critical role of this enzyme in epileptogenesis (Eid *et al.*, 2013). Such assumption was aslo supported by the observation that reduced GS expression induced by gene mutations resulted in severe seizures (Haberle *et al.*, 2011).

In epilepsy astrocytes can also influence neuronal excitability through aberrant adenosine homeostasis, because of changes in the expression of the astroglia-specific adenosine kinase (ADK), which is the central enzyme for adenosine turnover in the CNS (Aronica *et al.*, 2013; Boison and Aronica, 2015). Increased expression of ADK was detected in tissue specimens of subjects with pharmacologically refractory temporal lobe epilepsy (Aronica *et al.*, 2013; Aronica *et al.*, 2011; Masino *et al.*, 2011). Increased ADK expression reduces availability of adenosine, which, in turn, leads to an increased neuronal network excitability, thus being potentially responsible for the enhanced susceptibility to seizures (Li *et al.*, 2008; Li *et al.*, 2012; Li *et al.*, 2007).

7. Neurodevelopmental disorders

7.1. Autism spectrum disorders (ASD)

Autism or as more recently defined as autistic spectrum disorders (ASD) is a hypernym that covers widely heterogeneous conditions that are broadly manifested by aberrant social interaction, restrictive patterns of behaviors and sometimes cognitive deficiency (Quaak *et al.*, 2013). These are generally believed to represent neurodevelopmental abnormalities, although the pathological mechanisms are many, and they also can be widely different. The failure in synaptic wiring of the brain as well as aberrant neurotransmission are likely to be responsible for many types of autistic developments (Cellot and Cherubini, 2014; Giovedi *et al.*, 2014; Rojas, 2014); in addition, autistic pathology is often connected to oxidative stress (McGinnis, 2004; Smaga *et al.*, 2015). Astroglial function is critical for synaptogenesis, synaptic maturation and maintenance (Verkhratsky and Nedergaard, 2014); likewise, astroglial cells are the main source of ROS scavengers and anti-oxidants, such as glutathione and ascorbic acid, respectively (Bridges *et al.*, 2012; Wilson *et al.*, 2000). Similarly, as described above, astrocytes are the main target for various toxic factors, such as heavy metals, which are also implicated in ASD etiology (Zeidan-Chulia *et al.*, 2014). Pathological changes in astroglia in the ASD context are far from being described in detail; there are indications of increased glial reactivity (Zeidan-Chulia *et al.*, 2014), and in post-mortem human brains up-regulation of connexin 43 expression and down-regulation of aquaporin 4 expression (both molecules being specifically associated with astrocytes) were reported (Fatemi *et al.*, 2008).

7.2. Down syndrome

Down syndrome (DS), associated with the trisomy of chromosome 21, is characterized by mental retardation, and has certain neuropathological semblance of Alzheimer's disease; in DS both neuritic plaques and interneuronal tangles are present (Wisniewski *et al.*, 1985). ASD is frequently diagnosed in children with DS. Astrocytes are reported to be significantly depleted in the cortex of DS sufferers (Karlsen and Pakkenberg, 2011). There are also indications of functional deficits in DS astrocytes that are unable to properly support synaptogenesis and neuronal maturation (Chen *et al.*, 2014).

7.3. Fragile X syndrome

Fragile X syndrome is a neurodevelopmental disorder associated with the expression of Fragile X mental retardation protein. It is also known as Martin–Bell syndrome or Escalante's syndrome, and is one of the frequent causes of ASD and mental disability (Kidd *et al.*, 2014). The Fragile X mental retardation protein expression in astrocytes decreases their capability of supporting and protecting neurons in the *in vitro* conditions, which may contribute to delayed neuronal maturation and development (Jacobs and Doering, 2010; Jacobs *et al.*, 2010).

7.4. Costello syndrome

Primary role for astroglia in Costello syndrome, that belongs to a family of neurodevelopmental disorders caused by aberrant Ras (a name abbreviated from rat sarcoma) signaling and hence termed RASopathies (Tidyman and Rauen, 2009), has been revealed very recently (Krencik *et al.*, 2015). It appears that astrocytes expressing mutated *HRA*S (Harvey rat sarcoma viral oncogene homolog) gene, resulting in hyperactivation of Ras signaling, which accelerates differentiation and maturation of astrocytes, and leads to astroglial hypertrophy. This in turn is claimed to promote early neuronal maturation and aberrant experience-dependent formation of neuronal ensembles, which in turn may be responsible for cognitive and behavioral abnormalities.

8. Astroglia in major neuropsychiatric diseases

8.1. Mood disorders

There is an increasing understanding that astroglial pathology, especially in the fronto-limbic areas of the brain may substantially contribute to pathophysiology of mood disorders (Popoli *et al.*, 2012; Rajkowska and Stockmeier, 2013; Sanacora and Banasr, 2013; Verkhratsky *et al.*, 2014d). First and foremost, the morphometric analysis revealed much more pronounced changes in the number of glial cells (astrocytes and oligodendrocytes) than in the number of neurons in the context of mood disorders, including major depressive disorder and bipolar disorder. Decrease in astroglial numbers and packing density was observed throughout the fronto-limbic areas of the brain, including the orbito-frontal area, and anterior cingulate, prefrontal, entorhinal and subgenual cortices, as well as the amygdala (Bowley *et al.*, 2002; Cotter *et al.*, 2002; Cotter *et al.*, 2001; Ongur *et al.*, 1998; Rajkowska *et al.*, 1999). Decreased number of astroglial GFAP-positive profiles and overall GFAP immunoreactivity were detected in the animal models of chronic stress (Braun *et al.*, 2009;

Czeh *et al.*, 2006). In parallel, several other astroglial markers, such as aquaporin 4, astroglial connexins, astroglial plasmalemmal glutamate transporters and glutamine synthetase were all reduced in the context of attention deficit disorder and chronic stress (Barley *et al.*, 2009; Bernard *et al.*, 2011; Rajkowska and Stockmeier, 2013; Sequeira *et al.*, 2009).

Direct ablation of astrocytes in the medial-prefrontal cortex of mice with the specific toxin L-alpha-aminoadipic acid (L-AAA) resulted in a depressive behavior similar to that induced by chronic stress (Banasr and Duman, 2008). Chronic stress also reduced astroglial expression of connexin 43 as well as dye coupling between astroglial cells in the prefrontal cortex. Moreover, pharmacological inhibition of gap junctional conductance in the prefrontal cortex induced anhedonia that is one of the main symptoms of depression (Sun *et al.*, 2012). Likewise, inhibition of astroglial plasmalemmal glutamate transporters also induced anhedonia (Bechtholt-Gompf *et al.*, 2010). Chronic treatment with antidepressants directly affected astroglia, by increasing expression of receptors and transporters responsible for CNS homeostasis and limiting glutamate release (Czeh and Di Benedetto, 2013; Dong *et al.*, 2015; Liu *et al.*, 2015; Ren *et al.*, 2015). In conclusion, mood disorders are associated with astrodegeneration and astroglial asthenia, which in turn affect brain homeostatic reserve and arguably synaptic transmission.

8.1.2. Schizophrenia—Pathologically changed astrocytes are the common feature of morphology of the schizophrenia-affected human brain. Decrease in astroglial numbers/densities, as well as pathological (dystrophic or swollen) astroglial profiles have been observed in various brain regions, including cortical and hippocampal structures (Falkai and Bogerts, 1986; Rajkowska *et al.*, 2002; Schmitt *et al.*, 2009; Webster *et al.*, 2001). Astroglial reactivity in schizophrenia remains a debatable matter, as it might be tainted by age, medication and other associated factors (Schnieder and Dwork, 2011). In addition, a significant decrease in expression of astroglia-specific molecules fundamental for CNS homeostasis, including deiodinase type II, aquaporin-4, S100β, glutamine synthetase, plasmalemmal glutamate transporters, and thrombospondin, was found in the deep layers of the anterior cingulate gyrus, suggesting that a subset of astrocytes localized to specific cortical layers can be affected in schizophrenia (Xia *et al.*, 2014). Decreased expression of EAAT1/2 plasmalemmal glutamate transporters is documented for the prefrontal cortex (Bauer *et al.*, 2008; Bauer *et al.*, 2010) and hippocampus (Ohnuma *et al.*, 2000; Shan *et al.*, 2013). Of note, genetic deletion of EAAT1 resulted in endophenotypes reflective of schizophrenia, including locomotor hyperactivity and abnormal social behavior (Karlsson *et al.*, 2008; Karlsson *et al.*, 2009). In addition, expression of hexokinase 1 (which contributes to regulation of glutamate-glutamine shuttle) was decreased in the post mortem tissue from schizophrenia sufferers (Shan *et al.*, 2014a). Incidentally, astroglial expression of plasmalemmal cystine-glutamate exchanger Sxc-, which by continuous release of glutamate controls extrasynaptic concentration of the latter (Bridges *et al.*, 2012), was increased in the rodent phencyclidine model of schizophrenia (Baker *et al.*, 2008). Metabolism of the endogenous positive modulator of NMDA receptors, D-serine, which at least in part, is associated with astrocytes, is also affected in schizophrenia; levels of D-serine appear to be lower in the diseased brain (Bendikov *et al.*, 2007). Expression of mutant *Disrupted-In-*

Schizophrenia-1 (DISC1) gene in astrocytes affects cell-specific D-serine racemase (Ma *et al.*, 2013), which leads to D-serine depletion in the brain, which in turn is linked to higher risk of schizophrenia (Labrie *et al.*, 2009). Astrocytes also produce kynurenic acid, a metabolite of tryptophan produced mainly by astrocytes, which can act as an endogenous inhibitor of NMDA (as an antagonist to the glycine site) and acetylcholine receptors. Higher levels of kynurenic acid were detected in the post-mortem brains of psychotics (Holtze *et al.*, 2012). The astroglial production of kynurenic acid increases after the brain infection with *Toxoplasma gondii*; this increases the risk of schizophrenia (Schwarcz and Hunter, 2007). Abnormal astroglial capability to control glutamate homeostasis may result in profound synaptic remodeling and increase in glutamate spillover, which in turn may substantially affect spatial specificity of synaptic transmission and contribute to overall confused information processing characteristics of schizophrenia (Shan *et al.*, 2014b)

All in all, these data indicate a functional impairment of astroglial control over glutamatergic transmission. Considering that aberrant glutamatergic transmission is currently regarded as one of the leading mechanisms in pathophysiology of schizophrenia (Laruelle, 2014; Meador-Woodruff *et al.*, 2003), astrocytes may certainly hold the key in this devastating disorder.

8.1.3. Addictive disorders—Astroglial reactivity as well as the decrease in the astroglial number and atrophy were reported in post-mortem human material from different forms of addictions (Armstrong *et al.*, 2004; Büttner and Weis, 2006; Fattore *et al.*, 2002; Miguel-Hidalgo, 2009; Oehmichen *et al.*, 1996; Suarez *et al.*, 2000; Weber *et al.*, 2013). Treatment of animals with several drugs of abuse, including cocaine (Bowers and Kalivas, 2003; Fattore *et al.*, 2002), methamphetamine (Friend and Keefe, 2013; Guilarte *et al.*, 2003) and morphine (Song and Zhao, 2001), resulted in up-regulation of GFAP expression and reactive astrogliosis. At the same time, a prolonged exposure to ethyl alcohol led to a decrease in GFAP expression and morphological atrophy of astrocytes (Franke, 1995; Rintala *et al.*, 2001). In post-mortem human tissue obtained from alcoholics, hypertrophic astrocytes were observed along with areas depleted from GFAP positive astroglial profiles (Cullen and Halliday, 1994; Miguel-Hidalgo, 2005).

The above controversial findings may be associated with distinct stages of addiction: in the brains of patients with short-lasting alcoholic dependence the density of astrocytes diminished and astrocytic profiles were atrophic, whereas in subjects with a longer history of addiction the number of astrocytes increased and GFAP expression was up-regulated (Miguel-Hidalgo *et al.*, 2006; Miguel-Hidalgo *et al.*, 2002; Skuja *et al.*, 2012). In alcoholism, the number of astrocytes was decreased in the prefrontal cortex (Miguel-Hidalgo *et al.*, 2006). Likewise, GFAP expression and astrocytic numbers were remarkably decreased in the prelimbic cortex of ethanol-preferring rats (Miguel-Hidalgo, 2005), whereas binge-like ethanol administration in adolescence reduced astrocytic density (without affecting neuronal density) in the adult rat medial prefrontal cortex of males but not females (Koss *et al.*, 2012). Injecting glial toxin L-AAA to ablate astroglia as well as injection of connexin inhibitor 8-alpha-glycyrrhetinic acid into the prelimbic area of the prefrontal cortex of rats significantly increased alcohol preference (Miguel-Hidalgo *et al.*, 2009).

Aberrant glutamate clearance and metabolism are likely to be the leading functional change in astrocytes in the context of addiction: expression of both EAAT2 and Sxc^- glutamate transporters were decreased, although overall extracellular glutamate concentration increases probably because of imbalance between glutamate uptake (EAAT2) and release (Sxc^-) (Moussawi *et al.*, 2011; Reissner and Kalivas, 2010; Reissner and Kalivas, 2014). Down-regulation of astrocytic EAAT2 transporter has been observed in several animal models of addiction to, for example, cocaine (Knackstedt *et al.*, 2010), nicotine (Gipson *et al.*, 2013) or alcohol; incidentally treating alcohol-preferring rats with the β-lactam antibiotic ceftriaxone (that increases EAT expression) decreased alcohol seeking and increased expression of astroglial glutamate transporters (Qrunfleh *et al.*, 2013; Sari *et al.*, 2013). Another component of glutamatergic transmission impaired by addiction is D-serine, levels of which are reported to be decreased by cocaine (Curcio *et al.*, 2013), while intraperitoneal injections of D-serine reduced cocaine seeking/addictive behavior (Kelamangalath and Wagner, 2010; Yang *et al.*, 2013).

Recent astrocyte-specific expression of designer receptor exclusively activated by a designer drug (DREADD) responding to clozapine N-oxide (CNO) pointed out to astroglial contribution to the extracellular level of glutamate in the nucleus accumbens core (NAcore) (Scofield *et al.*, 2015). Namely, long-term cocaine-induced reductions in extracellular glutamate in the NAcore affect synaptic plasticity (mediated via neuronal autoreceptors, i.e., group II metabotropic glutamate receptor (mGluR) repossible for relapse vulnerability (consult references within (Scofield *et al.*, 2015)). In the DREADD-expressing astrocytes, CNO increased NAcore extracellular glutamate levels in vivo, which was mediated by soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE)/exocytotic pathway. At behavioural level, cue-induced reinstatement of cocaine seeking, but not sucrose self-administration, in rats extinguished from cocaine was inhibited by CNO, an action mediated via the group II mGluRs.

9. Neurodegenerative diseases

9.1. Alzheimer's Disease

Alzheimer's disease (AD; named so by Emil Kraepelin (Kraepelin, 1910) to praise the description of the disease made by Alois Alzheimer in 1907 (Alzheimer, 1907)) is a chronic progressive neurodegenerative disease that starts long before clinical manifestations. Etiology of idiopathic or sporadic AD remains unknown, reflecting most likely a combination of genetic, lifestyle and environmental factors. The rare (with less than 1–5% incidence) form of familial, or early onset AD, FAD (http://www.nia.nih.gov/alzheimers) is associated with expression of mutated genes for amyloid precursor protein (APP), presenilins (PS1 and PS2) and tau (Bertram *et al.*, 2010). The clinical progression of AD is characterized by a progressive cognitive and functional deficiency that ultimately leads to death. The mean life expectancy following diagnosis is approximately six years, although the disease advancement shows individual variability (Molsa *et al.*, 1986).

Histopathologically, the disease is characterized by the emergence of extracellular β-amyloid containing senile plaques and the formation of intraneuronal neurofibrillary tangles from misphosphorylated tau protein (Selkoe, 2001). Senile plaques may affect synaptic

contacts and disturb the proper blood supply by interfering with astrocytic endfeet (otherwise plastering blood vessels), hence contributing to cell death and brain atrophy.

Transformations of astrocytes begin at the early phases of the AD and are mainly characterized by atrophy (Beauquis *et al.*, 2013; Beauquis *et al.*, 2014; Kulijewicz-Nawrot *et al.*, 2012; Olabarria *et al.*, 2010; Verkhratsky *et al.*, 2010; Yeh *et al.*, 2011). In triple transgenic AD mice, expressing human mutated APP (Swedish mutation; K670N/M671L), PS1 (M146V) and tau protein (P301L) (Oddo *et al.*, 2003), astrocytes from several brain regions were characterized, analyzed and quantified by surface area and volume occupied by GFAP-positive profiles. All of the parameters analyzed were decreased suggesting atrophic changes of astroglia, while the number of astrocytes remained unaltered (Kulijewicz-Nawrot *et al.*, 2012; Olabarria *et al.*, 2010; Yeh *et al.*, 2011). These changes were observed as early as 1 month of age in the entorhinal cortex, at ~ 6 months in the prefrontal cortex and at ~ 9 – 12 months in the hippocampus, before β-amyloid aggregation and senile plaques formation started (Kulijewicz-Nawrot *et al.*, 2012; Olabarria *et al.*, 2010; Yeh *et al.*, 2011). Similar astroglial atrophy was observed in another AD model, the transgenic mutant APP (PDAPP-J20) mice carrying the Swedish and Indiana (V717F) APP human mutations (Beauquis *et al.*, 2013; Beauquis *et al.*, 2014). Additionally, the decrease in GFAP content was accompanied with reduced immunoreactivity for glutamine synthetase in the prefrontal cortex but not in the entorhinal cortex (Olabarria *et al.*, 2011; Yeh *et al.*, 2013) suggesting functional deficiency. Atrophic astrocytes lose the ability to perform their essential homeostatic functions, hence instigating a profound and irreversible chain of pathological changes in the brain, resulting, over time, in weakening of synaptic contacts and in early cognitive impairment. Astrocytes have a crucial role in synaptogenesis and maintenance of synapses (Eroglu and Barres, 2010; Verkhratsky and Nedergaard, 2014). Therefore, deficient homeostatic support of neuronal networks may result in a decrease of synaptic activity and synaptic loss, which represent an early event in AD progression (Terry, 2000; Verkhratsky *et al.*, 2014a; Verkhratsky *et al.*, 2010). Furthermore, functional astroglial atrophy may affect their ability to clear β-amyloid; this was connected with aberrant interactions between dynein-dynactin complexes which resulted in abnormal endocytosis, which was identified in the brains of aged monkeys and may represent the mechanism for deficient clearance of β-amyloid (Kimura *et al.*, 2014).

The early stage of the AD is also characterized with metabolic changes, e.g., progressive reduction in glucose metabolism, detected in functional brain imaging in AD patients, which may restrain energy metabolism in both astrocytes and neurons (Mosconi *et al.*, 2008). Since glycolytic pathways are more active in astrocytes (as compared to neurons), these glial cells are more likely to be affected with the above glucose metabolism impairment. Experimental work on primary cultured astrocytes *in vitro* showed both, albeit in separate studies, a decrease (Parpura-Gill *et al.*, 1997; Soucek *et al.*, 2003) and an increase (Allaman *et al.*, 2010) in glucose consumption after treatment with β-amyloid. Post-mortem analysis of AD brain tissue also yielded conflicting results; both an increase (Bigl *et al.*, 1999; Soucek *et al.*, 2003) and a decrease (Blass *et al.*, 2000; Liang *et al.*, 2008) in activity of glycolytic enzymes were described. Metabolic supply is tightly connected with the blood flow, which is significantly reduced in patients with AD, especially in the early phase of the disease (Bell and Zlokovic, 2009; Zlokovic, 2008). Astrocytes together with neurons secrete a number of

signaling molecules to control microcirculation (Attwell *et al.*, 2010; Iadecola and Nedergaard, 2007; Zonta *et al.*, 2003). Therefore, changes in astroglial morphology, both atrophic in an early stage, and hypertrophic in a late stage of the disease, can have a significant impact on remodeling of vascularization in the diseased brains (Farkas and Luiten, 2001).

Reactive astrocytes as a marker of profound changes in the AD brain morphology were observed already by Alois Alzheimer (Alzheimer, 1910), who found hypertrophic glial cells surrounding degenerating neurons and senile plaques. More recent studies of AD brains from deceased patients found up-regulation of the main astrogliotic markers, GFAP and S100β proteins (Beach and McGeer, 1988; Griffin *et al.*, 1989; Meda *et al.*, 2001; Mrak and Griffin, 2005; Rodriguez *et al.*, 2009; Verkhratsky *et al.*, 2010). While astrogliosis is mostly associated with senile plaques, some reactive astrocytes were found in gray matter areas with no apparent plaque load (Simpson *et al.*, 2010). Furthermore, even though some studies reported on a certain degree of correlation between increased GFAP expression with the Braak stage of AD, there was no evidence of correlation between reactive astrogliosis and the amount of β-amyloid deposits (Simpson *et al.*, 2010). Astrogliosis around senile plaques and β-amyloid deposits were also detected in AD transgenic mice, suggesting that the animal models recapitulate this aspect of pathological progression (Olabarria *et al.*, 2010; Rodriguez-Arellano *et al.*, 2015; Verkhratsky *et al.*, 2010). In the gray matter of the transgenic mice over-expressing the London (V717I) APP mutant, reactive astrocytes emerged prior to the formation of plaques. These reactive astrocytes were grouped together, were secreting pro-inflammatory factors and demonstrated increased expression of inducible nitric oxide synthetase (iNOS); it has been suggested that these groups of reactive astroglia marked locations for future formation of senile plaques (Heneka *et al.*, 2005). It is important to emphasize that in the above context astrogliosis is protective and its inhibition exacerbates β-amyloid load (Kraft *et al.*, 2013). Furthermore, astrogliosis in animal models is region-specific; its absence in entorhinal and prefrontal cortices may underlie vulnerability of these areas in AD affected brains (Kulijewicz-Nawrot *et al.*, 2012; Yeh *et al.*, 2011).

Experiments *in vitro* documented reactive changes in cultured astrocytes after exposure to soluble β-amyloid (DeWitt *et al.*, 1998); this reactivity was also associated with an abnormal Ca^{2+} oscillations (Abramov *et al.*, 2003, 2004). Exposure of cultured astrocytes to pathologically relevant concentrations of β-amyloid affected expression of proteins related to Ca^{2+} signaling and homeostasis in brain region-dependent manner (Grolla *et al.*, 2013; Lim *et al.*, 2014), and down-regulated expression of glutamate transporters (Matos *et al.*, 2008). Reactive astrocytes associated with senile plaques in APP/PS1 AD animal model were shown to generate spontaneous Ca^{2+} oscillations and abnormal Ca^{2+} waves (Kuchibhotla *et al.*, 2009). These limited reports in functional changes of astrocytes in AD imply that they are β-amyloid initiated. However very little is known about precise molecular mechanisms of these events.

Existing therapies for AD are limited and ineffective. There are only four drugs approved by The Food and Drug Administration (FDA) for use in the USA. They mainly deal with delaying and slowing symptoms for a limited time rather than resolving underlying causes. Therefore, there is an urge to pursue new approaches for more effective therapies. Only

recently, astrocytes emerged as a potential drug targets; as described above, astrocytic changes throughout all phases of the disease are evident. Astroglial atrophy can be reversed with environmental stimulation including exposure to increased physical activity or enriched environment; these astroglial changes coincide with decrease in β-amyloid load (Beauquis *et al.*, 2013; Rodriguez *et al.*, 2013). Viral transfection of astrocytes in APP/PS1 AD model with a peptide that interferes with the immune/inflammatory calcineurin/nuclear factor of activated T-cells (NFAT) signaling cascades, improved cognitive shortfalls and decreased β-amyloid load (Furman *et al.*, 2012). As AD is a complex disease which seeks multiple approaches to treatments and perhaps multiple treatments of its symptoms, the emerging potential of astroglia-specific therapy may yield novel healing tactics designed to prevent and delay the disease progression.

9.2. Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS), or Lou Gehrig disease, is a chronic, progressive and incurable neurodegenerative disease of mostly unknown etiology characterized by the impairment of the motor function due to progressive neuromuscular weakening, inflexible muscles, and spasticity. The disease develops usually at age of 40 – 60 with symptoms appearing and progressing fast; in most cases patients pass away within 3 – 5 years after diagnosis due to respiratory failure. Currently, only one FDA approved drug, i.e. riluzole, is employed for ALS therapy, and it is of very limited effectiveness, mainly treating symptoms of the disease (Hardiman, 2011). ALS appears in two different forms: sporadic ALS and familial ALS (fALS). Sporadic ALS is more common representing approximately 90–95% cases, appearing as a consequence of accumulated exposure to risk factors, which include aging and environmental agents. The remaining up to ~ 5% of cases are classified as fALS and they appear as an autosomal dominant trait linked to mutations in various genes, including human *Superoxide dismutase 1* (h*SOD1*) (Rosen *et al.*, 1993), *TAR DNA binding protein 43* (*TARDBP*) (Kabashi *et al.*, 2008; Sreedharan *et al.*, 2008), *Fused in sarcoma* (*FUS*) (Kwiatkowski *et al.*, 2009; Vance *et al.*, 2009), *Alsin* (Yang *et al.*, 2001), *Optineurin* (Maruyama *et al.*, 2010), *C9orf72* (DeJesus-Hernandez *et al.*, 2011; Deng *et al.*, 2011; Renton *et al.*, 2011), *Ubiquilin 2* (Deng *et al.*, 2011), and *Profilin 1* (Wu *et al.*, 2012).

Astroglia contribute to several pathways responsible for ALS-associated neuronal damage. Conceptually, astrocytes can contribute to neuronal death either directly (by releasing neurotoxic substances) or indirectly (through the loss of homeostatic/protective functions). Selective expression of *hSOD1*-mutant gene in astrocytes employed the *Cre*/loxP recombination system and reduced expression of the hSOD1-mutant caused delay in ALS development (Yamanaka *et al.*, 2008), while animals lacking hSOD1-mutant in astrocytes exhibited a later onset of the disease and a longer lifespan (Wang *et al.*, 2011). Transplantation of wild-type healthy astroglial precursors into the spinal cord of ALS transgenic animals, delayed the progression of the disease and prolonged the lifetime (Lepore *et al.*, 2008). Inversely, implantation of hSOD1 mutant expressing astrocyte precursors into the spinal cord of wild type rodents was sufficient to initiate the motor neuron degeneration and ALS symptoms *in vivo* (Papadeas *et al.*, 2011). Experiments *in vitro* also corroborated pathological role for astroglia. Mixed astrocyte and motor neuron co-cultures showed that astrocytes are responsible for elevation of factors causing neuronal

damage (Bilsland *et al.*, 2008; Di Giorgio *et al.*, 2008; Di Giorgio *et al.*, 2007; Ferraiuolo *et al.*, 2011; Haidet-Phillips *et al.*, 2011; Marchetto *et al.*, 2008; Nagai *et al.*, 2007; Phatnani *et al.*, 2013). Those factors include, but are not limited to: (i) the excess of extracellular glutamate due to down-regulation of plasmalemmal EAAT2; (ii) an increase in the extracellular level of D-serine, a positive modulator of NMDA receptors, which may aggravate glutamate excitotoxicity; (iii) an increased secretion of prostaglandin E2, inflammatory mediator contributing to inflammatory response and motor neuron deficiency; (iv) excessive release of interferon γ, detected in astrocytes expressing mutant SOD1; (v) secretion of Transforming Growth Factor β from astrocytes accompanied with an up-regulation of its type II receptor in neurons, which coincides with an onset of the disease; (vi) release of Pro-Nerve Growth Factor, which may trigger apoptosis in the motor neurons; and (vii) release of lipocalin 2, a transporter for lipids and lipophilic molecules, which is able to induce apoptotic cascade leading to neuronal death (reviewed in (Valori *et al.*, 2014)). In addition it was also found that immunoglobulin G isolated from ALS patients increased vesicular mobility in astrocytes which may indicate increased secretion of various factors possibly associated with the pathology (Stenovec *et al.*, 2011).

Consequences of expression of dysfunctional mutant hSOD1 gene are detrimental for both motor neurons and astrocytes because over-production/accumulation of ROS. As astrocytes are responsible for maintaining homeostasis of ROS (Dringen *et al.*, 2000; Dringen and Hirrlinger, 2003), their incapability to adequately control ROS levels, would promote the neuronal damage; this was attested by various genetic and pharmacological approaches (Cassina *et al.*, 2008; Vargas *et al.*, 2008). Similar combinations of genetic and pharmacological tactics are employed in an effort to directly modulate expression of EAAT2. Antibiotic ceftriaxone, that stimulates glutamate uptake, has already passed Phase I and II of clinical trials suggesting good tolerance of therapeutic doses (Berry *et al.*, 2013). Furthermore, there are positive results in preclinical trials with a compound harmine, a beta-carboline alkaloid that increases EAAT2 expression *in vivo* (Li *et al.*, 2011).

9.3. Huntington's disease

Huntington's disease (HD) is an autosomal dominant inherited disease caused by the nucleotide triplet, cytosine-adenosine-guanine (CAG) encoding glutamine, repeat in the exon 1 of the widely expressed huntingtin gene (Roze *et al.*, 2008). This gene is encoding the huntingtin protein, which is expressed in the nervous system and is involved in various cellular functions including intracellular transport, regulation of transcription, development and control of apoptosis (Zheng and Diamond, 2012). Gene mutation results in the synthesis of mutant huntingtin protein (mhtt) containing an expanded polyglutamine section in its N-terminal portion. The neurodegeneration in HD mainly occurs in striatal medium spiny neurons and in cortical pyramidal neurons (Hedreen *et al.*, 1991; Vonsattel *et al.*, 1985).

Mutant huntingtin protein has been found not only in neurons but also in astroglia in brain tissue from human patients (Singhrao *et al.*, 1998) and in mouse HD models (Faideau *et al.*, 2010; Shin *et al.*, 2005). In human HD tissues a prominent astrogliosis, which correlated with disease severity, has been well documented (Faideau *et al.*, 2010; Vonsattel *et al.*, 1985). Importantly, astroglial reactivity represents an early histopathological feature of HD,

being detectable already at the lowest (grade 0) stage of the disease (Faideau *et al.*, 2010). Astrogliosis has been also observed in animal HD models; for example, in the RosaHD/Nestin-Cre model (in which mhtt is expressed in all neural cells), reactive astrocytes are present in the cortex and striatum (Gu *et al.*, 2005). In another mouse model, where mhtt was targeted to astrocytes by lentiviral expression, astrogliosis increased with animal age (Faideau *et al.*, 2010).

Astrocytes also contribute to HD through compromised glutamate and potassium uptake. Excitotoxicity is generally acknowledged as an important feature of HD responsible for neuronal death (Gray, 2014). Expression of EAAT2 is significantly decreased in human HD tissues at mRNA and protein levels (Arzberger *et al.*, 1997; Cross *et al.*, 1986); incidentally decrease in EAAT2 expression correlated with the severity of the disease (Faideau *et al.*, 2010). Reduction in the expression level of GLT-1 was also found in R6/2 HD mice in the cortex and striatum, and this decrease progresses with age (Behrens *et al.*, 2002; Shin *et al.*, 2005). Expression of an mhtt fragment containing 82 glutamine repeats and virally targeted to astrocytes similarly reduced expression of GLT-1 (Faideau *et al.*, 2010). Experimental increase in GLT-1 expression in astrocytes expressing mhtt by a lentiviral vector decreased astroglial reactivity (Faideau *et al.*, 2010), while treatment of R6/2 mice with ceftriaxone increased GLT-1 expression and improved motor symptoms (Faideau *et al.*, 2010). Astrocytes may also contribute to excitotoxicity in HD context through increased glutamate release, which indeed was found in astroglial cells isolated from the cortex of the BACHD mouse model (Lee *et al.*, 2013); this enhancement of glutamate release was linked to an increased expression of pyruvate carboxylate and hence an increased *de novo* production of glutamate. Besides compromised regulation of extracellular glutamate, astrocytes also display compromised potassium buffering, as recently demonstrated in HD mouse R6/2 and Q175 models (Tong et al., 2014). Indeed, HD mice had an increase in striatal extracellular K^+levels *in vivo*. Astrocytes with mhtt nuclear inclusions had decreased expression of $K_{ir}4.1$ K^+ channels (representing the main molecular entity responsible for potassium siphoning/buffering) resulting in an increase of medium spiny neurons excitability *in vitro*. Thus, it appears that the deregulation of glutamate and potassium extracellular levels in astrocytes contributes to pathology seen in HD. Consequently, the identified molecular entities, i.e., EAAT2, pyruvate carboxylate and $K_{ir}4.1$ channels, may represent targets for novel therapeutic interventions in HD.

Astrocytes from HD mice and patients display higher levels of vascular endothelial growth factor-A, which promotes endothelial cell proliferation and may contribute to the augmented vascular density, observed in HD brains. Reactive astrogliosis may contribute to pericyte demise, causing a reduced pericyte overlay of cerebral blood vessels and worsened vascular reactivity. This, in turn, may modify the normal cerebral circulation and thus contribute to the disease progression (Hsiao *et al.*, 2015).

9.4. Parkinson disease

Astroglial contribution to pathogenesis of Parkinson's disease (PD) has never been studied in great detail, and existing data are rather fragmentary (McGeer and McGeer, 2008). There is a general consensus that both environmental factors and genetic predisposition are

ethologically relevant, with particular role played by various toxic agents, which may involve astroglia (Rappold and Tieu, 2010). Probably the best example of such astroglia-mediated toxicity is PD induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a lipophilic substance, which after crossing the blood-brain barrier is accumulated in astrocytes, where it is converted, by monoamine-oxidase B (MAO-B), into the toxic metabolite, MPP+. This latter is released from astrocytes and is transported into dopaminergic neurons by the plasmalemmal dopamine transporter. Subsequently, MPP+ acts as a potent inhibitor of neuronal mitochondrial Complex I hence compromising ATP synthesis, increasing production of ROS and leading to cell death (Meredith *et al.*, 2008). Additionally, MAO-B associated toxicity may be linked to excessive generation of ROS that are by-products of dopamine degradation (e.g., dopamine quinones) (Rappold and Tieu, 2010). Indeed, MAO-B is a central enzyme for catabolism of catecholamines, including dopamine, which in the CNS, is expressed almost exclusively in astrocytes (Ekblom *et al.*, 1993). Potential importance of MAO-B for PD development has been shown in experiments with transgenic mice, in which inducible over-expression of the enzyme triggered Parkinsonian symptoms (Mallajosyula *et al.*, 2008; Siddiqui *et al.*, 2011). The levels of MAO-B increase in aging, which is a proven risk factor for PD, and moreover the expression levels of MAO-B correlate with neuronal death in the substantia nigra (Mahy *et al.*, 2000; Fowler *et al.*, 1980; Mandel *et al.*, 2003). Incidentally, the lower risk of PD development in smokers is associated with a significantly decreased MAO-B activity (Fowler *et al.*, 1996).

The astrogliosis in PD is generally quite mild, if at all existing, although some increase in GFAP expression has been observed in dopaminergic areas in idiopathic PD patients (Forno *et al.*, 1992; Mirza *et al.*, 2000) as well as in MPTP animal model (Sriram *et al.*, 2004). There are indices of astroglia-related neuroprotection in the PD context; for example, selective activation of the transcription factor Nrf2 in astrocytes protects mice from MPTP-induced PD through boosting anti-oxidant response (Chen *et al.*, 2009). The overall glutathione levels (which again is manly produced by astrocytes) were found to be greatly reduced (by ~40%) in PD, which may indicate the failure of astroglial protection against antioxidative stress (Rappold and Tieu, 2010). In a rare PD form linked to mutated orphan nuclear receptor Nurr1 expression death of dopaminergic neurons is mediated through astrocytes and microglia which both produce neurotoxic factors (Saijo *et al.*, 2009). Astrocytes also contain PD related proteins such as α-synuclein, parkin and phosho-tau; in the in vitro conditions astrocytes were found to accumulate α-synuclein and form large astrocytic Lewy bodies (Lee *et al.*, 2010). In transgenic mice over-expressing α-synuclein in neurons α-synuclein immunoreactivity was present not only in neurons but also in astrocytes (Lee *et al.*, 2010).

The α-synuclein (AS)-positive cytoplasmic aggregates were found in astroglial cells of synucleinophaties others than PD, such as dementia with Lewy bodies and multiple system atrophy (MSA). These glial AS-aggrgates are hypothesized to provide a reduced trophic support contributing to the neuronal damage. In the PD only protoplasmic astroglia has an elevated cytoplasmic AS accumulation, whereas no evident changes were observed in fibrous astrocytes (Song *et al.*, 2009). The protoplasmic astrocytes in PD apparently internalize AS without becoming reactive. This absence of reactive response against a substantial neurodegeneration was also seen in MSA, although here, the oligodendroglial

inclusions triggered an evident response, which was also observed in the fibrous astrocytes. Since astrocytic accumulation of AS enhances their vulnerability to oxidative stress and leads to apoptosis, degeneration of protoplasmic astrocytes may occur in all synucleinophaties (Song *et al.*, 2009). There is increasing evidence that astroglial protein S100β can operate as a cytokine or damage-associated molecular pattern protein not only in inflammatory but also in neurodegenerative diseases (Iuvone *et al.*, 2007). Enhanced levels of S100β were detected in the substantia nigra of PD subjects, as well as in the ventral midbrain of MPTP-treated mice (Sathe *et al.*, 2012). Increased S100β mRNA was also seen in the same region, supporting the notion that astrocytes, the main source of S100β, may be implicated into PD pathobiology. Incidentally, ablation of S100B resulted in neuroprotection in a rodent model of PD (Sathe *et al.*, 2012).

Finally, recently it has been found that transplantation of astrocytes generated from glial precursors exerts beneficial effect of experimental PD, probably through secretion of multiple trophic factors such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, neurturin and insulin-like growth factor 1; in addition these astrocytes have high levels of antoxidants, including glutathione (Proschel *et al.*, 2014).

10. Alexander disease

Alexander disease (AxD) is a rare, chronic and usually fatal neurodegenerative disorder, which may be defined as a primary genetic astrogliopathology. The AxD results from the expression of mutant GFAP, which leads to astroglial malfunction that, in turn, triggers severe deficits to the developing white matter. About 95% of diagnosed cases of AxD are caused by dominant gain-of-function mutations on the gene encoding GFAP. The histopathological sign of AxD is an accumulation of protein aggregates, known as Rosenthal fibers (Messing *et al.*, 2012). The AxD is, in essence, a leukodystrophy, and according to the newest classification AxD is divided in two categories: (i) Type I characterized with an early onset and severe mental and physical disabilities, megalencephaly, seizures, spasticity, difficulty speaking and swallowing, and (ii) Type II with a later onset and somewhat different and milder clinical manifestations with normal development and head size, seldom presenting seizures, ataxia, visual and autonomic abnormalities, troubles in sleeping patterns, hyperreflexia, difficulty speaking and swallowing (Prust *et al.*, 2011).

Astrocytes in AxD show signs of reactivity and simultaneous pathological remodeling; they secrete various factors, such are TNF-α and IL-1β. Experimental over-expression and accumulation of GFAP in astrocytes to toxic levels induce functional abnormalities. These alterations include reduction in EAAT2/GLT-1 on the plasma membrane, and thereby reduced glutamate clearance, decrease in activity of proteasomes, increase in autophagy, and up-regulation of the stress-activated protein kinase/c-Jun N-terminal kinase (JNK) pathway (see (Messing *et al.*, 2012) for details and references). Several mechanisms by which mutated GFAP acts on cellular functions have been suggested: (i) mutated GFAP through positive feedback loop inhibits proteasome function which activates JNK, and activated JNK directly further inhibits proteasome (Tang *et al.*, 2006); (ii) mutated GFAP inactivates one or more proteins by degradation in the Rosenthal fibers where fragments of the small stress

proteins, HSP27, αB crystalline, the 20S proteasome subunit, p-JNK, p62 and plectin, are detected (Messing *et al.*, 2012).

Therapeutic strategies developed by several groups are based on proposed mechanisms and morphological manifestations and directed towards reduction of GFAP levels either by hindering synthesis or enhancing degradation, averting formation of Rosenthal fibers with addition of αB crystalline, or preventing stress pathways activation and increasing glutamate transporter's expression on the plasma membrane. Some progress has been made on all fronts, although efforts have not yielded a successful treatment yet. More importantly, studies centered on GFAP and mechanisms of reactive astrocytes in AxD provide significant insight for many other neurological disorders (Sosunov *et al.*, 2013) that share similar astrogliotic appearances.

11. Glioma

Gliomas are neoplasms initiated in the brain, comprising about 60% of all diagnosed primary brain tumors. According to histopathological features and aggressiveness, the World Health Organization distinguishes four glioma grades, with the Grade IV or glioblastoma multiforme (GBM) being the most aggressive and commonly diagnosed. Despite robust approaches in the treatment of GBM, namely surgical intervention, radiation and chemotherapy, the prognosis for survival longer than average 12–14 months is very grim. As a general rule, gliomas with a more astrocyte-like phenotype are associated with a worse prognosis (Cohen and Colman, 2015; Jovcevska *et al.*, 2013). One of the obstacles for the successful treatment of GBM is the infiltrative nature of their growth and close interactions with healthy brain cells, including astrocytes, oligodendrocytes, neurons, microglia and blood vessels.

Gliomas originate either from astrocytes and other glial cells or from their precursors. Many gliomas show some degree of similarity to various glial cell types and their progenitors. Tumors originated from astrocytes are clinically categorized as either low-grade or high-grade astrocytomas based on their specific histological features (Furnari *et al.*, 2007). Due to a profound heterogeneity within the tumor tissue, gliomas often show a complex mixed phenotype, which makes it more difficult to define their origin. Conceivably, they could evolve from various types of healthy cells turned rogue, or from one cell type which during uncontrollable growth accumulates (under influences from local environment) more mutations to form a complex polymorphic population of cancerous cells. Full understanding of the tumor progression, including defining the cell(s) of origin, is necessary for successful therapies.

One of the current hypotheses on the glioma origin suggests a cancer stem cell (CSC) to be the tumor initiator. The idea is appealing, since this renewable and multipotent CSC has been shown to exist in various gliomas and uphold proliferative tumor growth and progression (Park and Rich, 2009; Stiles and Rowitch, 2008). However, it still does not address the identity of healthy cells from which glioma originates. Speculatively, it is possible that astrocytes dedifferentiate into malignant cells directly of via an intermediate cell type, be that a SCS or a cell with a phenotype resembling astrocytic progenitors;

malignant transformation in astrocytes induced by specific DNA mutations and controlling gene expression by DNA binding proteins has been demonstrated (Moon *et al.*, 2011). Another possibility is that gliomas can develop directly from neural stem cells (i.e., nestin positive stem cells which typically develop into astrocytes) or via a SCS as an intermediary. From therapeutic standpoint defining the cell(s) giving rise to gliomas would allow early and effective interventions by either specifically destroying cells of origin without harming other healthy brain cells or interrupting signaling pathways that allow neoplastic transformation.

Frequent symptom and a side effect that seriously decreases quality of life in about 60–80% of glioma patients is tumor-associated epilepsy (Hildebrand *et al.*, 2005; Kurzwelly *et al.*, 2010; Lynam *et al.*, 2007; Oberndorfer *et al.*, 2002). As already discussed, there are several alterations observed in astrocytes associated with seizure/epilepsy affected brain regions. One of them is aberrant glutamate homeostasis due to the activity of Sxc^{-} which represents an underlying cause of epileptic seizures in some glioma-bearing animals and patients (Buckingham *et al.*, 2011). Increased levels of glutamate released from glioma were demonstrated in cultures (Ye and Sontheimer, 1999), in animal models (Buckingham *et al.*, 2011) and in high grade astrocytoma patients (Roslin *et al.*, 2003). In addition to release of glutamate via Sxc^{-}, it seems that a decrease in expression of EAAT1/2 on reactive astrocytes in the peritumoral tissue contributes to glutamate overload in the extracellular space (de Groot *et al.*, 2005; Takano *et al.*, 2001). Increased expression of astrogliotic marker GFAP in the surrounding tissue, i.e., tumor-induced astrogliosis, was found to positively correlate with the tumor size both in mouse models of glioma (Lee *et al.*, 2011), and in glioma patients (Burel-Vandenbos *et al.*, 2011; Raore *et al.*, 2011). The tumor cells, however, especially those of high-grade astrocytomas, frequently lose most of their GFAP expression, likely indicating the undifferentiated state of these cells, rather than the contribution to tumor development and progression (Wilhelmsson *et al.*, 2003).

In addition to astroglia contributions to maintaining extracellular CNS homeostasis already highlighted throughout this review, astrocytes also serve as the metabolic hub. At physiological conditions, astrocytes show a high glycolytic rate resulting in production of lactate, while maintaining active tricarboxylic acid cycle to synthesize *de novo* glutamate as they express pyruvate carboxylase (Bouzier-Sore and Pellerin, 2013); besides glycolytic utilization of glucose astrocytes can store it in the form of glycogen. Gliomas are well equipped to use these pathways to generate non-physiologically high concentrations of lactate and glutamate, as assessed from patients *in vivo* using microdialysis (Marcus *et al.*, 2010). It turned out that gliomas (similar to neurons), are needy of glutamine, otherwise provided to the brain parenchyma by astrocyte via the glutamate-glutamine cycle(Wise and Thompson, 2010). Preferential interference with mentioned (or other yet undisclosed) glioma metabolic pathways may provide a target for novel adjuvant therapies for these neoplasms.

12. Concluding remarks

The brain is a complex adaptive matter. Thus, it should come as no surprise that the neuron-centric pathological doctrine has limited success in producing the major new breakthroughs in the prevention and therapy of the brain disorders. In part this is due to the lack of attention

to other cells in this organ. Namely, it is abundantly clear that astrocytes, in their primary role of maintaining the overall homeostasis of the nervous system, are key elements of most if not all the brain disorders. Insult to the brain, be that mechanical, chemical or otherwise, has its toll on astrocytes, which undergo complex morpho-functional changes that can be good, bad or ugly for the course of the disorder. A display of these astrocytic changes can be grossly identified as reactivity, which comes in two flavors pending on the (dis)organization of the astrocytic territorial domains, atrophy with loss of function and pathological remodeling. Although at present we mainly grapple with defining the pathophysiology of astrocytes and demystifying their responses as merely secondary detrimental processes, one can see light at the end of the tunnel in the discoveries of the primary causes of some disorders as the astrocyte-autonomous blemishes. For instance, the genetic primary neuropathology known as Alexander disease stems from the expression of mutant GFAP that affects astroglial function and results in severe damage to the white matter. By identifying and cataloguing such molecular entities clearly defining the pathogenic potential of astrocytes, we could allow for future translational medicine, i.e., generation of deliverables for the containment and cure of disorders. Certainly, any organ disorder can come from dysfunction(s) of any and the entire cellular constitutes, and the brain is not an exception. Although we here entertained the astrocyte-centric view of the brain pathology, by no means we support the notion that this prodigy alone would achieve the curation of the brain disorders. Rather, such noble task will surely require a holistic and multi-disciplinary approach that will take in contemplation the concerted operation of all the cell types in the brain.

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Abbreviation list

AD	Alzheimer Disease
ALS	Amyothophic Lateral Sclerosis

APP	amyloid precursor protein
AS	α-synuclein
ASD	Autism spectrum disorder
ADK	adenosine kinase
ATP	adenosine triphosphate
AxD	Alexander disease
CD81	Cluster of Differentiation 81
CMV	cytomegalovirus
CNO	clozapine N-oxide
CNS	central nervous system
CSC	cancer stem cell
CXCL-1	chemokine (C-X-C motif) ligand 1
DISC1	Disrupted-In-Schizophrenia-1
DREADD	designer receptor exclusively activated by a designer drug
DS	Down syndrome
EAST	epilepsy -ataxia - sensorineural deafness - salt-wasting renal tubulopathy
fALS	familial ALS
FDA	The Food and Drug Administration
FTD	fronto-temporal dementia
FUS	Fused in sarcoma
GABA	γ-amino butyric acid
GBM	glioblastoma multiforme
GFAP	glial fibrillary acidic protein
GS	glutamine synthetase
HD	Huntington’s Disease
HRAS	Harvey rat sarcoma viral oncogene homolog
hSOD1	human Superoxide dismutase
HSV1	herpes simplex virus 1
$InsP_3$	inositol 1,4,5 trisphosphate

IL	interleukin
iNOS	inducible nitric oxide synthetase
JNK	c-Jun N-terminal kinase
L-AAA	L- alpha-aminoadipic acid
mGluR	metabotropic glutamate receptor
mhtt	mutant huntingtin protein
MAO-B	monoamine-oxidase B
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MSA	multiple system atrophy
NFAT	immune/inflammatory calcineurin/nuclear factor of activated T-cells
NAcore	the nucleus accumbens core
NMDA	N-methyl D-aspartate
NOD2	nucleotide-binding oligomerization domain containing 2
PD	Parkinson’s Disease
PS	presenilin
Ras	rat sarcoma
ROS	reactive oxygen species
SeSAME	seizures - sensorineural deafness–ataxia - mental retardation - electrolyte imbalance
SNARE	soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor
TARDBP	TAR DNA binding protein
TNF-α	including tumor necrosis factor α
TRP	transient receptor potential

Article highlights

- Brain pathology results from the homeostatic failure
- Brain homeostasis is mainly maintained by astroglia
- Astrocyte are key elements of most if not all the brain disorders

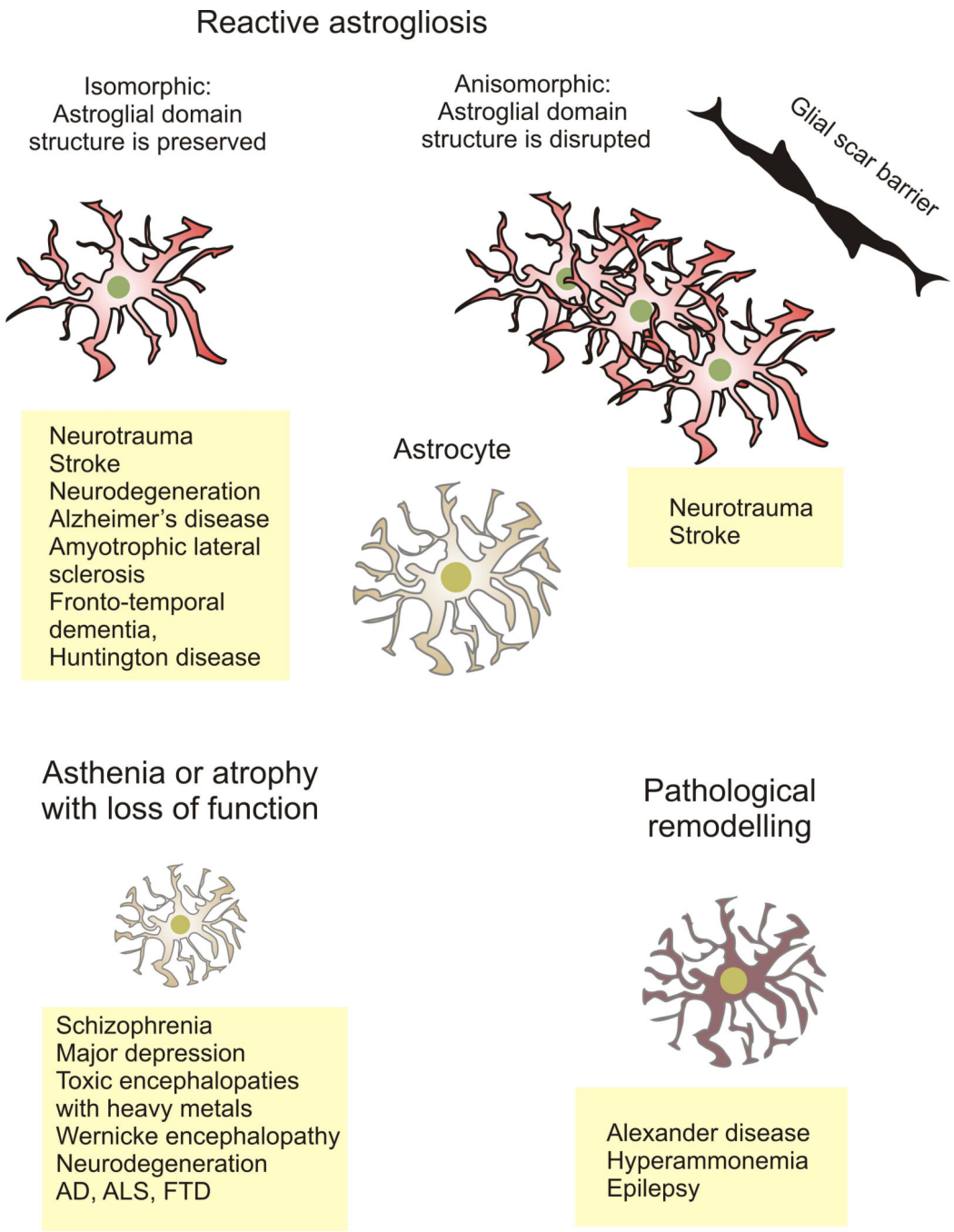

Figure 1. Astrogliopathology

Astrocytes undergo morpho-functional changes in the brain pathology (see text for details). AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; FTD, fronto-temporal dementia