Chapter 12
Neurodegeneration and Neuroglia: Emphasis on Astroglia in Alzheimer's Disease

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Abstract Neurodegenerative diseases, which affect almost exclusively humans, are chronic disorders that ultimately result in atrophy of the brain and profound cognitive deficit. Neurodegenerative process reflects a profound failure of brain homeostasis. Neuroglial cells, being primarily the cells responsible for brain homeostasis and defense, naturally contribute to an overall homeostatic failure underlying neurodegeneration. In this chapter we shall deliver a brief on astroglial contribution to common neurodegenerative disorders and then continue with a detailed account on the pathological potential of astroglia in Alzheimer's disease. Astrocytes undergo complex alterations in Alzheimer's disease, which are represented by region-specific atrophy and asthenia at the early stages and reactivity at the late stages of the disease. These complex changes can be considered as pathologically relevant because they may define the early cognitive deficits and the later neurotoxicity in Alzheimer's disease. Targeting astroglia in neurodegeneration may result in new therapeutic strategies aimed at preventing and delaying the progression of Alzheimer's disease.

Keywords Astrocytes · Astrogliosis · Alzheimer's disease · Homeostatic failure neurodegeneration

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V. Parpura, A. Verkhratsky (eds.), *Pathological Potential of Neuroglia,*
DOI 10.1007/978-1-4939-0974-2_12,

12.1 Neurodegeneration and Neuroglia

Neurodegenerative diseases, which affect almost exclusively humans, are chronic disorders that result in a progressive loss of function, structure and number of neural cells, ultimately resulting in atrophy of the brain and profound cognitive deficit. Etiology of neurodegeneration is multifaceted including trauma (caused by physical, chemical or infectious attack), genetic predisposition, metabolic insufficiency or the combination of the above likely with some other, yet unidentified factors. Similarly, cellular and molecular mechanisms of neurodegeneration are many and because of their complexity it is often almost impossible to identify the single leading cause. At the cellular level neurodegenerative processes are often associated with aberrant handling of various proteins leading to the accumulation (both intra- and extracellular) of abnormal proteins such as β-amyloid, tau or α-synuclein (Jellinger 2008). All in all, however, neurodegenerative process reflects a profound failure of brain homeostasis, which results in a functional and structural decline in the connectivity of neural networks, which ultimately destroys information processing. Neurodegeneration begins with a functional weakening of synapses and a neurotransmission disbalance, the combination of which affects the flow of information through the neural networks. As a neurodegenerative disease progresses, the functional abnormalities worsen leading to the disappearance of synaptic contacts, alterations of cellular integrity and ultimately to death of subpopulation of the brain cells. These structural-functional changes are reflected by a generalized atrophy of the brain accompanied with profound cognitive deficiency (Terry 2000; Selkoe 2001; Knight and Verkhratsky 2010; Palop and Mucke 2010).

The common and prevailing point of view considers neurons as the main substrates of pathological progression of neurodegeneration, and it is generally assumed that failures in neuronal protein synthesis and/or direct neuronal damage caused by various factors assume the leading role in the pathogenesis of neurodegenerative disorders. These neuron-centric doctrine has been challenged only recently (Rodriguez et al. 2009; Rossi and Volterra 2009; Salmina 2009; Heneka et al. 2010; Verkhratsky et al. 2010; Rodriguez and Verkhratsky 2011; Verkhratsky et al. 2012, 2013; Brambilla et al. 2013;), when data begun to accumulate indicating a pathogenic potential of neuroglia. Neuroglial cells, being the primary cells responsible for brain homeostasis and defense, naturally contribute to an overall homeostatic failure underlying neurodegeneration.

We shall start this chapter with a brief narration on astroglial contribution to common neurodegenerative disorders and continue with a detailed account on the pathological potential of astroglia in Alzheimer's disease (AD)

12.2 Astroglial Atrophy and Astrogliosis in Neurodegenerative Diseases

Pathological changes in astroglia that occur in the course of neurodegeneration include astroglial atrophy, both morphological and functional, and astrogliosis. These pathological reactions are differentially observed at different stages

of neuropathological progression; often astroglial loss of function is observed at the early stages of the disease, whereas at the advanced stages a development of disease-specific lesions (such as, for example, senile plaques) and neuronal death trigger astrogliotic response. Pathological remodeling of astroglia is accompanied by changes in microglia similarly represented by either microglial loss of function with subsequent fading of neuroprotective capacity, or with the activation of microglia that contributes to neuroinflammation. Neurodegeneration also affects oligodendroglia and NG2 cells leading to a failure of myelination, which further exacerbates the alteration of connectivity in the central nervous system. These complex changes in neuroglia are documented for all major types of neurodegenerative disorders.

12.2.1 Neurodegeneration Associated with Toxic Encephalopathies

Astroglial dysfunction lies at the core of acute and chronic neurodegeneration associated with brain poisoning by various toxic agents. The primary mechanism of astroglial-dependent neurotoxicity that results in a profound neuronal death is associated with a failure of astroglial glutamate uptake. Astrocytes selectively express two types of glutamate transporters, the excitatory amino acid transporters 1 and 2 (EAAT1 and 2); with the aid of these transporters astroglial cells remove about 80% of glutamate released during synaptic transmission. The same mechanism is critical for astroglial protection against glutamate excitotoxicity; silencing of astroglial glutamate uptake greatly increases neuronal damage following exposure to glutamate (Danbolt 2001). Deficient astroglial glutamate transport is almost invariably present in neurodegeneration and can be considered as one of the common mechanism of this process (Kim et al. 2011).

Toxic poisoning of the brain with metals triggers neuronal death, which causes psychotic symptoms and deteriorates cognition. Astrocytes that express a complement of specific transporters are primary targets of heavy metals. Astrocytes, for example, accumulate methylmercury, which inhibits glutamate, glutamine and cystine transporters, thus severely compromising glutamate homoeostasis (Yin et al. 2007; Ni et al. 2012). These changes are primary pathogenetic elements of methylmercury-induced encephalopathy (or Minamata disease (McAlpine and Araki 1958)) manifested by cognitive decline, impaired vision and hearing, as well as motor symptoms. Astrocytes, which express high capacity manganese transport system, also appear as a main target for manganese toxicity; accumulation of manganese inhibits astroglial glutamate uptake with subsequent excitotoxic neuronal damage (Sidoryk-Wegrzynowicz and Aschner 2013). Astrocytes are primary targets for other heavy metals, such as arsenic, lead and cadmium, which all reduce the expression of glial fibrillary acidic protein (GFAP) and trigger astroglial apoptosis (Rai et al. 2013). Aluminum toxic encephalopathy (which proceeds with cognitive deficits and speech alterations) is mediated through astrocytes, which accumulate aluminum; this metal impairs glutamate transporters and gap junctions and causes astrocytic

death (Suarez-Fernandez et al. 1999). Astroglial demise through apoptosis plays a leading role in the encephalotoxic damage caused by cypermethrin, a class II pyrethroid insecticide (Maurya et al. 2012).

12.2.2 Wernicke Encephalopathy

Wernicke encephalopathy, which represents the pathological substrate for Korsakoff syndrome (ante- and retrograde amnesia, apathy and confabulation (Wernicke 1881–1883; Korsakoff 1889)) is a rapidly progressing thalamo-cortical neurodegeneration. Failure of astroglial glutamate uptake (resulting from ~60–70% decrease in the expression of EAAT1 and EAAT2) is the key pathogenetic element of Wernicke encephalopathy. A decrease in glutamate transporters expression was identified in postmortem samples, as well as in the rat thiamine deficiency model of the disease (Hazell 2009; Hazell et al., 2009); in this model astrocytes showed several atrophic signs including decrease in GFAP profiles, the expression of glutamine synthetase (GS) and GAT-3 γ-aminobutyric acid (GABA) transporter.

12.2.3 Post-infectious Neurodegeneration: Human Immunodeficiency Virus-1 (HIV-1) Associated Dementia

The HIV-associated dementia (HAD) is a primary neuroglial pathology; the HIV-1 infects microglial cells, which sustain virus propagation and through the release of neurotoxic factors precipitate neuronal death (Mattson et al. 2005; Kaul and Lipton 2006). In recent years, despite the overall success in containing HIV infection, the incidence of HAD is on the increase (Kaul 2009). In HAD, astrocytes show signs of both astrodegeneration and reactive astrogliosis. Substantial depletion of astroglial population has been recorded in the basal ganglia, with a correlation between the speed of cognitive impairments and the degree of astroglial death (Thompson et al. 2001). Astrogliotic reactions are most prominent in the entorhinal cortex and in the hippocampus (Vanzani et al. 2006).

12.2.4 Non-AD Dementiae

Astroglial pathology is documented for various forms of non-AD dementiae, such as fronto-temporal lobar degeneration and Pick's disease. These pathological remodeling include both astroglial atrophy with apoptotic death (Broe et al. 2004) and astrogliosis, the latter being, for example, prominent in the frontal and temporal cortices of patients with fronto-temporal dementia (Kersaitis et al. 2004). In thalamic dementia, profound astrogliosis was suggested to represent a key pathogenetic factor (Potts and Leech 2005).

12.2.5 Amyotrophic Lateral Sclerosis (ALS)

Astrodegeneration seems to be a key factor defining the early stages of experimental ALS; atrophic changes in astroglia and astroglial death in the human superoxide dismutase 1 (hSOD1) G93A mutation transgenic ALS model mice precede neuronal death and clinical symptoms (Rossi et al. 2008; Rossi and Volterra 2009). Furthermore, selective silencing of hSOD1 gene in astrocytes delays ALS progression (Yamanaka et al. 2008). Neuronal death, occurring at the later stages of ALS triggers astrogliotic response (Rossi and Volterra 2009).

12.2.6 Parkinson's Disease

Little is known about the contribution of neuroglia to the pathogenesis of Parkinson's disease (PD). In recent years, neuroinflammatory component begun to be considered in the context of PD and there are indications of specific role for activated microglia in causing the death of dopaminergic neurons (Depboylu et al. 2012), although there are also data showing that the activation of microglia follows the death of neurons, rather than causing it (Henry et al. 2009). Pharmacological inhibition of microglial activation was found to be neuroprotective against 6-hydroxydopamine (6-OHDA) neurotoxicity (Lazzarini et al. 2013), the treatment with 6-OHDA being employed to generate one of the most common animal model of PD. Astrocytes may also contribute to PD development, being generally protective of dopaminergic neurons at least in vitro (Mena et al. 2002; Mena and Garcia de Yebenes 2008). Similarly, astrocytes in neuronal-glial co-cultures convert L-DOPA, the immediate precursor of dopamine, from neurotoxic to neurotrophic substance, and hence astroglia can be important for L-DOPA substitute therapy (Mena et al. 1996).

12.3 Astrocytes in Alzheimer's Disease

Alzheimer's disease (Alzheimer 1907), characterized by specific histopathological lesions represented by senile plaques (extracellular depositions of β-amyloid) and interneuronal tangles resulted from abnormal phosphorylation of tau protein (Braak et al. 1998; Armstrong 2009), is a frequent cause of dementia in aging world population. The ultimate endpoint of the disease is an atrophic shrinkage of the brain accompanied with severe cognitive decline. The main current hypothesis of AD pathogenesis puts main emphasis on β-amyloid (Gerlai 2001; Hardy and Selkoe 2002; Korczyn 2008; Karran et al. 2011); criticism of which is, however, mounting (Hardy 2006, 2009; Biochemical Society 2011; Reitz 2012). The progression of the disease (according to the spread of β-amyloid load and damage to the grey matter)

begins in the transentorhinal cortex and then senile plaques spread to the entorhinal cortex, hippocampus and the temporal, frontal, and parietal lobes (Thompson et al. 2001, 2003).

12.3.1 Note on Astroglia in Aging

Aging is the major risk factor for AD; with the exception of family forms of the disease, which account for an exceedingly small number of cases (<1%), the incidence of sporadic AD correlates with age. Our knowledge of age-dependent changes in astroglia is rudimentary. There is a general consensus that aging is associated with profuse astrogliosis (Schipper 1996; Unger 1998; Lynch et al. 2010), although this notion is not based on systematic studies of either humans or animals. Majority of histological reports are based on counting GFAP positive astrocytes or on morphometry of GFAP positive profiles. Thus, the findings might be misleading given that in many brain regions healthy astrocytes do not show GFAP immunoreactivity. Consequently, an increase in the number of GFAP positive cells may not reflect actual changes in the quantity of astrocytes. Nonetheless, an increase in the number of astroglial cells was reported for the hippocampus of female C57BL mice (Mouton et al. 2002), for the CA1 area of the hippocampi of old Sprague-Dawley rats (Amenta et al. 1998), and for the parietal cortex and dentate gyrus of Wistar rats (Pilegaard and Ladefoged 1996; Peinado et al. 1998). At the same time age-dependent changes in the number of astrocytes were observed neither in the primary visual cortex of rhesus monkeys (Peters et al. 2008) nor the number of astrocytes changed in the aged human cortex (Pakkenberg et al. 2003). Increase in GFAP expression, however, was identified in the white matter of old monkeys which may signify axonal damage (Hinman and Abraham 2007). In male SV129/C57BL6 aged mice, systematic study with three astroglial markers GFAP, S100β and GS revealed rather heterogeneous changes in various brain regions (Figs. 12.1, 12.2, 12.3). In the hippocampus, for example, a prominent increase in the surface and volume of GFAP positive profiles in old (24 month) mice was not paralleled with substantial increases in the morphology of GS and or S100β positive profiles; in the entorhinal cortex, aging resulted in a significant reduction of the surface and volume of GFAP-positive profiles with an increase in the expression of S100β-positive astrocytes (Figs. 12.4, 12.5, 12.6) (Rodriguez et al. 2013b).

12.3.2 Astrocytes and β-Amyloid

There are several sporadic reports implicating astrocytes in the accumulation of β-amyloid through either compromised β-amyloid clearance or increased β-amyloid production. Reactive astrocytes, surrounding senile plaques, were suggested to accumulate and degrade β-amyloid (see (Guenette 2003; Nicoll and Weller 2003) for

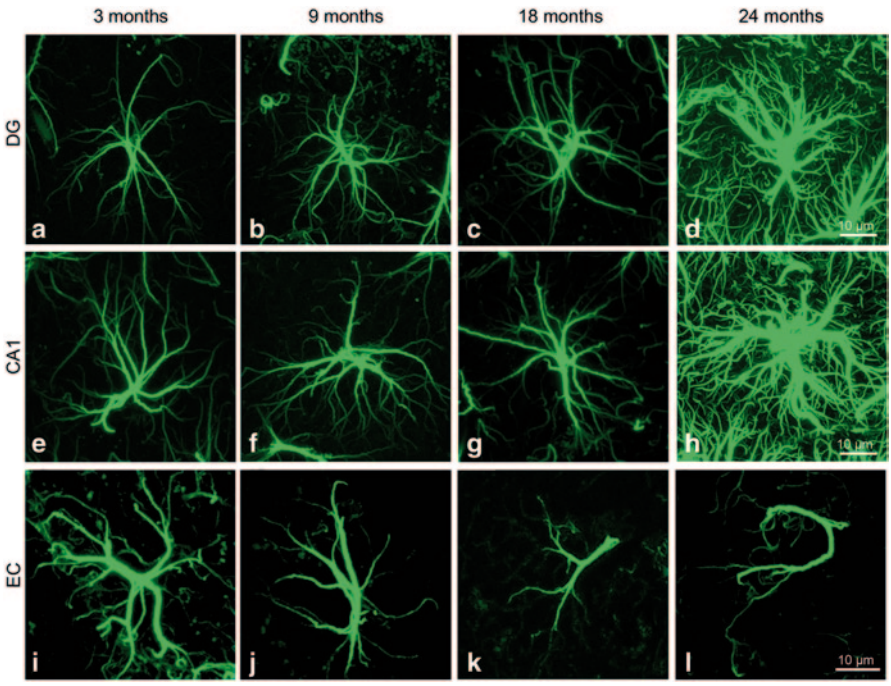

Fig. 12.1 Representative confocal 3-dimensional reconstructed images showing GFAP-immunoreactivity (IR) astrocytes in the dentate gyrus (DG), cornus ammonis 1 (CA1) and entorhinal cortex (EC) of animals at 3 months (**a**, **e** and **i**), 9 months (**b**, **f** and **j**), 18 months (**c**, **g** and **k**) and 24 months of age (**d**, **h** and **l**), respectively. (Reproduced from Rodriguez et al. (2013b) with permission.)

details and references). These reactive astrocytes, at least in the transgenic mice expressing mutant amyloid precursor protein (APP), were found to express the amyloid degrading enzyme neprilysin, a zinc metallopeptidase (Apelt et al. 2003). Cultured primary astrocytes, isolated from healthy mice brains, were able to actively accumulate β-amyloid; at the same time, astrocytes obtained from transgenic mice bearing a mutant APP were not capable of taking β-amyloid up (Wyss-Coray et al. 2003), this being another example of functional astroglial asthenia in the context of AD. Accumulation of β-amyloid was detected in astroglial cells from the entorhinal cortex of AD patients (Nagele et al. 2003) although β-amyloid was rarely found in astrocytes from the triple transgenic-AD (3xTg-AD) mice (Olabarria et al. 2010), harboring mutated presenilin 1 M146V, APP Swedish mutation (K670N/M671L) and mutated tau P301L transgenes (Oddo et al. 2003).

Healthy astrocytes do not express the main component of β-amyloidogenic pathway, the β-site APP-cleaving enzyme 1 (BACE 1; generally known as β-secretase), which seems to be exclusively expressed by neurons. Exposure of astrocytes to chronic stress, however, was reported to induce BACE1 expression, thus, potentially enabling astrocytes with β-amyloid producing capability; this was, for example, reported for astrocytes activated following immune lesion of cholinergic

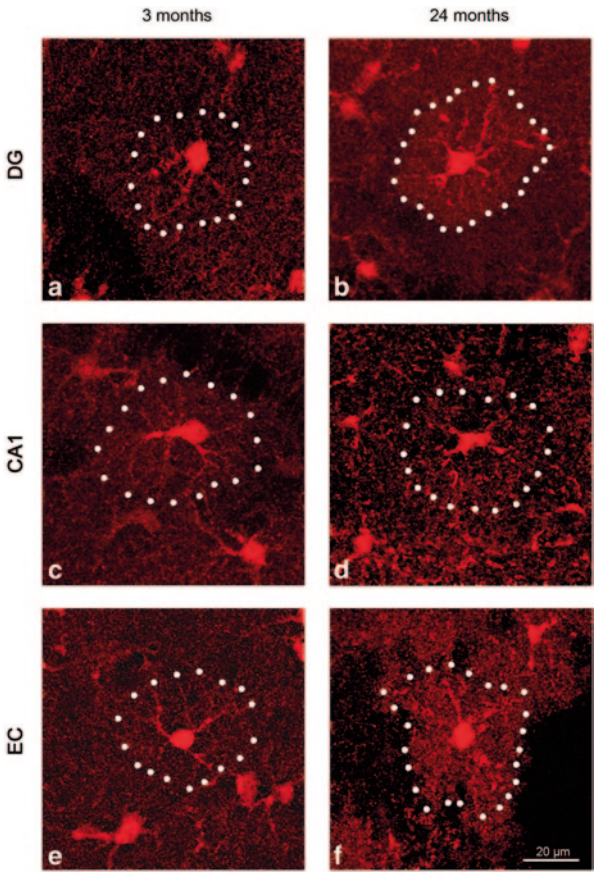

Fig. 12.2 Representative confocal 3-dimensional reconstructed images showing S100β-IR astrocytes in the DG, CA1 and EC of animals at 3 months (**a**, **c** and **e**) and 24 months of age (**b**, **d** and **f**), respectively. (Reproduced from Rodriguez et al. (2013b) with permission.)

septohippocampal afferents or occlusion of middle cerebral artery (Rossner et al. 2005). Expression of BACE1 was identified in reactive astrocytes in AD mice models (Tg2576, K670N/M671L APP or APP V717I) expressing mutated human amyloid precursor protein (Rossner et al. 2001; Hartlage-Rubsamen et al. 2003; Heneka et al. 2005). Incidentally, increase in APP production was described in a rat model of chronic neocortical astrogliosis, induced by grafting fetal cortical tissue in the midbrain of neonatal animals; these chronically activated astrocytes were immunopositive for APP, as well as for another AD-related marker apolipoprotein E (Martins et al. 2001). Nonetheless, the role of astroglia in β-amyloid turnover needs further confirmation and investigation.

12.3.3 Astrogliosis in AD

Reactive astrogliosis is generally considered to be a feature of the AD brains, and, indeed, Alois Alzheimer had found association of glia with damaged neurons; he

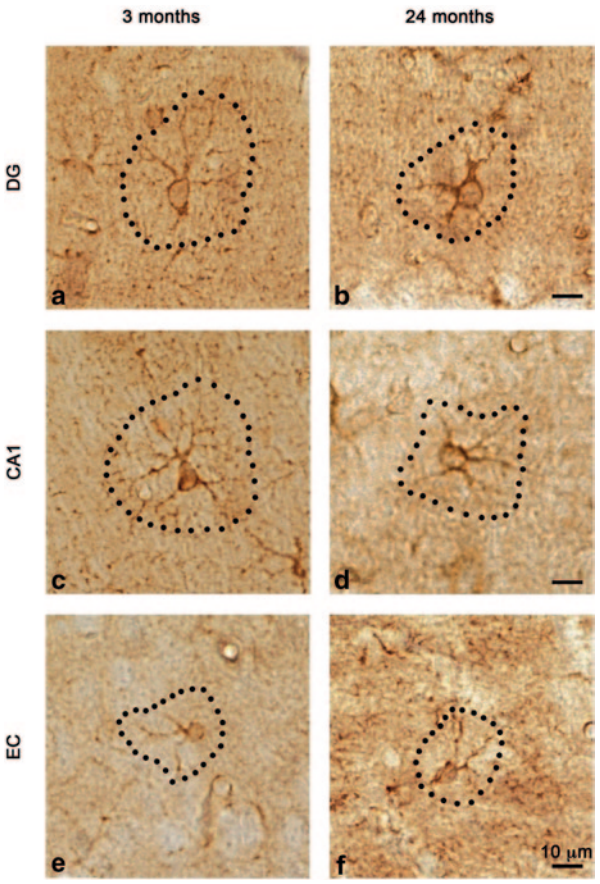

Fig. 12.3 Light micrographs showing the morphology and cell area of GS positive astrocytes in the DG, CA1 and EC of 3-month-old mice (**a**, **c** and **e**, respectively) and 24-month-old (**b**, **d** and **e**, respectively). (Reproduced from Rodriguez et al. (2013b) with permission.)

also observed glial cells abundantly populating senile plaques (Alzheimer 1910). Astrogliotic changes, mainly documented by an increase in the expression of GFAP and astroglial S100 β protein, have been observed in post-mortem tissues from AD patients (Beach and McGeer 1988; Griffin et al. 1989; Meda et al. 2001; Mrak and Griffin 2005; Rodriguez et al. 2009). Some reports claimed a degree of correlation between the astrogliosis (defined as increase in GFAP expression) and the Braak stage of AD, although there was no correlation between astrogliotic changes and β-amyloid load (Simpson et al. 2010). Reactive astrocytes were found to be associated with some senile plaques, but they were also identified in plaque free regions of the grey matter (Simpson et al. 2010). At the same time, no differences in GFAP expression was found between demented and non-demented brains (Wharton et al. 2009). Reactive, hypertrophic astrocytes, associated with senile plaques and perivascular β-amyloid deposits, were also observed in the brains of AD-models mice (Rodriguez et al. 2009; Olabarria et al. 2010; Verkhratsky et al. 2010) (Figs. 12.7 and 12.8).

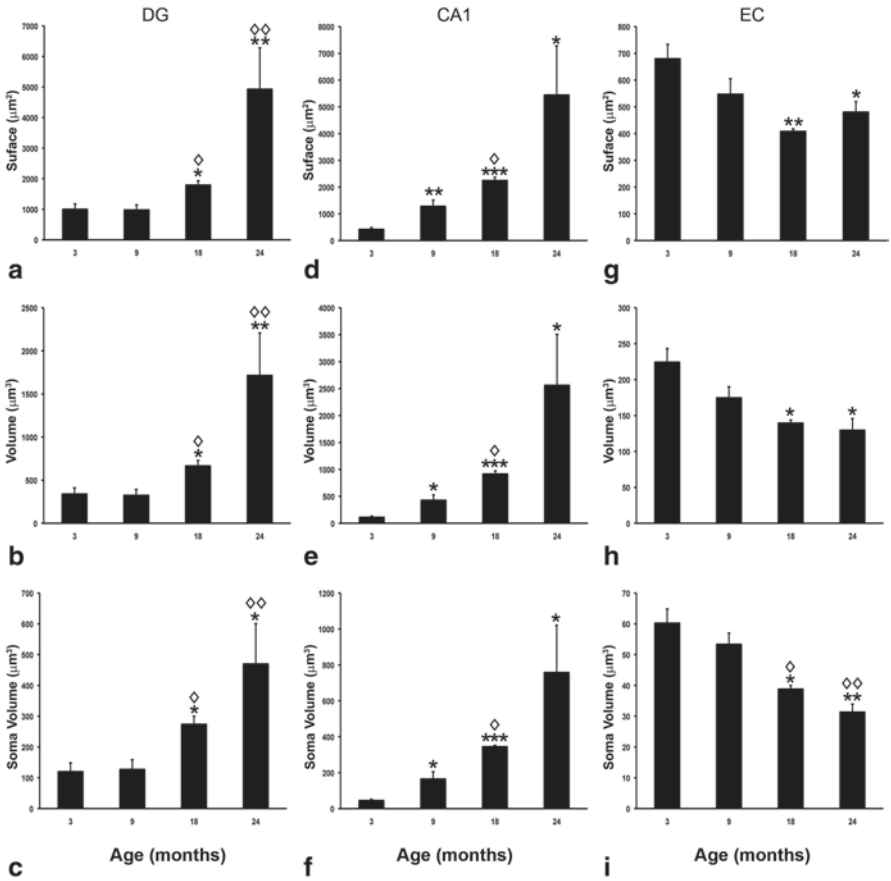

Fig. 12.4 Bar graphs showing the regional comparisons of GFAP surface, volume, and soma volume in the DG (**a**–**c**), CA1 (**d**–**f**) and EC (**g**–**i**) across ages. *Bars* represent mean± SEM (*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.0001$ compared with 3 months of age; ◊ $p \leq 0.05$; ◊◊ $p \leq 0.01$ compared with 9 months of age; in DG, $n = 6$, 7, 3 and 4 for 3, 9, 12 and 18 months, respectively; in CA1, $n = 4$, 3, 3, 4 for 3, 9, 12 and 18 months, respectively; in EC, $n = 4{,}5$, 3, 3 for 3, 9, 12 and 18 months, respectively). (Reproduced from Rodriguez et al. (2013b) with permission.)

Changes in GFAP expression reported in the AD tissue may, however, not only reflect the disease-specific changes but also the age-dependent remodeling of astrocytes, which, as narrated above, remains incompletely characterized. Furthermore, it has to be emphasized that reactive astrogliosis in AD is of a rather mild variety; astrocytes in the grey matter preserve their domain organization and there is no indication of anisomorphic gliosis and the formation of glial scars. Reactive astrocytes in AD animal models show aberrant physiology. These astrocytes, associated with senile plaques, were reported to generate spontaneous Ca^{2+} oscillations and abnormal Ca^{2+} waves (Kuchibhotla et al. 2009).

Molecular cues initiating astroglial reactivity in AD are multiple and may include extracellular β-amyloid as well as factors released by damaged cells. Soluble

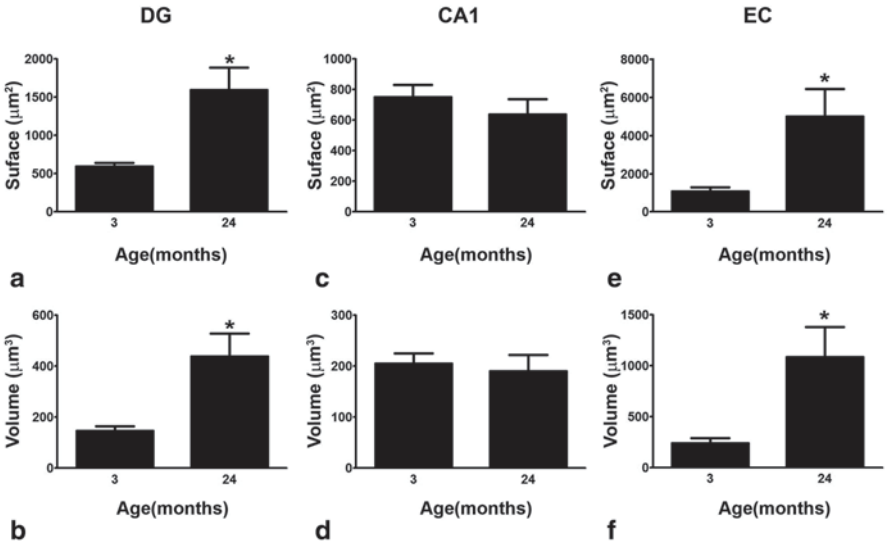

Fig. 12.5 Bar graphs showing the regional comparisons of S100β-IR surface area and volume in the DG (**a** and **b**), CA1 (**c** and **d**) and EC (**e** and **f**) at 2 and 24 months of age. *Bars* represent mean ± SEM (*$p \leq 0.05$ compared with 3 months of age; in DG, $n = 3$ and 4 for 3 and 24 months, respectively; in CA1, $n = 3$ for both 3 and 12 months; in EC, $n = 4$ and 3 for 3 and 12 months, respectively). (Reproduced from Rodriguez et al. (2013b) with permission.)

β-amyloid is reported to trigger reactive changes in astrocytes in vitro (DeWitt et al. 1998). Exposure of cultured astrocytes to β-amyloid also modifies signaling cascades. For example, extracellular β-amyloid triggers abnormal oscillatory Ca^{2+} fluctuations in cultured primary astrocytes (Abramov et al. 2003, 2004). Incubating primary astrocytes with pathologically relevant concentrations of soluble β-amyloid affects the expression of Ca^{2+} toolkit components; importantly, this remodeling differs for astrocytes derived from different brain regions (Grolla et al. 2013). Similarly, exposure to β-amyloid was claimed to down-regulate glutamate uptake in astroglial cells in vitro (Matos et al. 2008). All in all, however, the precise mechanisms of astroglial activation and remodeling of astroglial physiological signaling cascades in AD remains virtually unknown.

12.3.4 Astrodegeneration in AD: Reduction in Astroglial Profiles

Effects of AD pathology on astroglia, however, are not limited with astrogliotic response, to the contrary, astrogliosis most likely occurs in later stages of the disease, and reactive astrocytes are mainly associated with senile plaques (Olabarria et al. 2010). Recent studies of transgenic AD mice models revealed a profound astrodegeneration that occurs at the early stages of AD progression (Olabarria et al. 2010; Yeh et al. 2011; Kulijewicz-Nawrot et al. 2012; Beauquis et al. 2013).

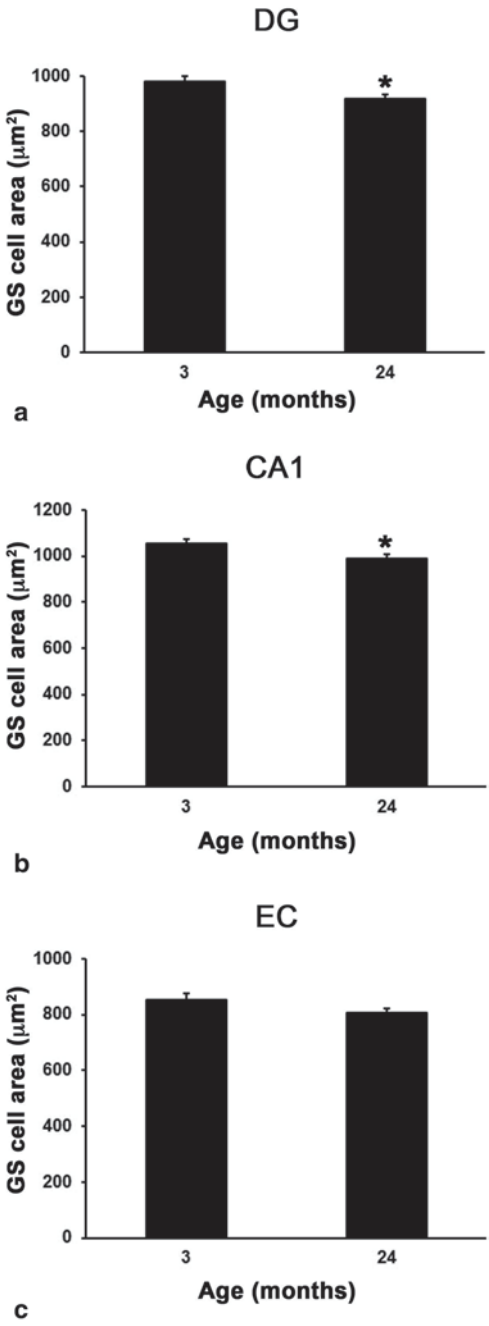

Fig. 12.6 Bar graph showing regional comparison of GS-positive cell area in the DG (**a**), CA1 (**b**) and EC (**c**) at 3 and 24 months of age (*$p \leq 0.05$ compared with 3 months of age; in DG, $n=4$ for both 3 and 24 months; in CA1, $n=4$ and 5 for 3 and 12 months, respectively; in EC, $n=4$ for both 3 and 12 months). (Reproduced from Rodriguez et al. (2013b) with permission.)

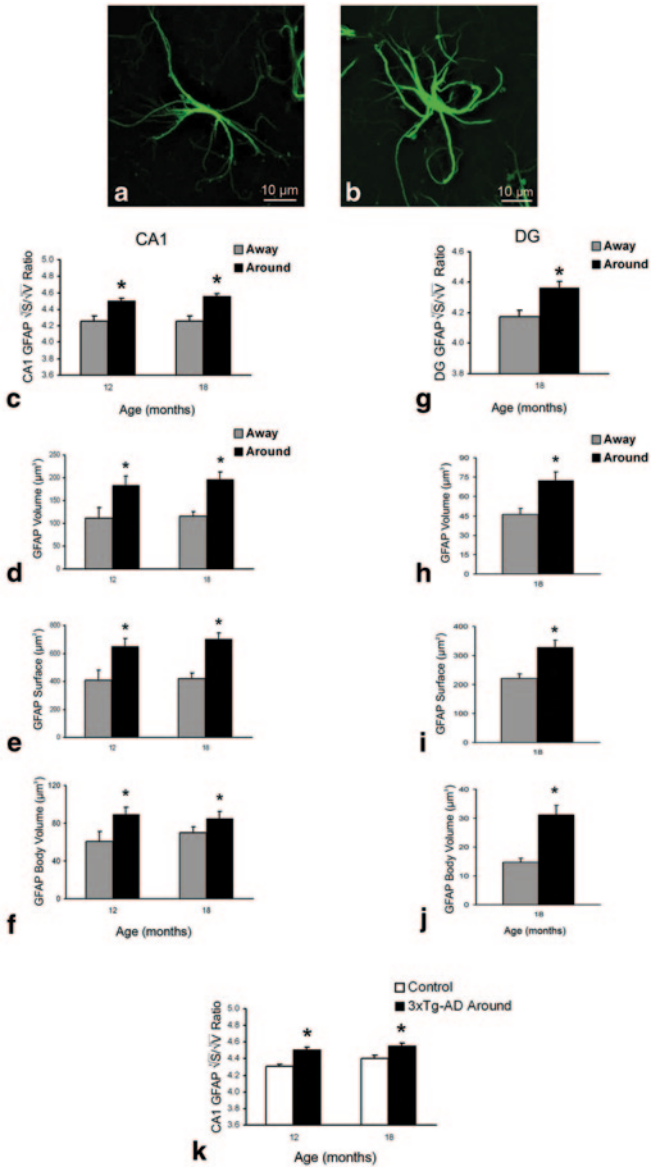

Fig. 12.7 Confocal single labeling micrographs of dual labeled immunohistochemistry illustrating the cytoskeleton alterations between astrocytes away (**a**) and around (**b**) plaques. Bar graphs showing GFAP positive astrocytic surface (**c**), volume (**d**), $^{2}\sqrt{S}/^{3}\sqrt{V}$ ratio (**e**) and body volume (**f**) differences between those astrocytes located around the amyloid plaques (Aβ) and those distant to the plaques in the CA1 of 3xTg-AD animals. $^{2}\sqrt{S}/^{3}\sqrt{V}$ ratio representation of astrocytic located around the amyloid plaques when compared to non-Tg control mice astrocytes at 12 and 18 months of age (**k**). Similar astrocytic surface (**g**), volume (**h**), $^{2}\sqrt{S}/^{3}\sqrt{V}$ ratio (**i**) and body volume (**j**) differences are observed in the DG at 18 months of age. Bars represent mean ± SEM.* = $p < 0.05$. (Modified from Olabarria et al. (2010) with permission.)

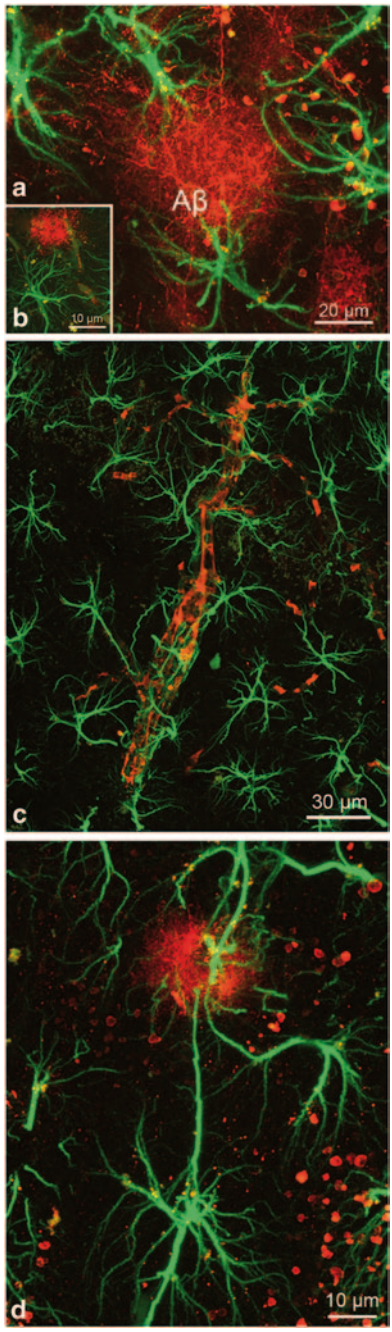

Fig. 12.8 Confocal dual labeling images (GFAP in *green* and Aβ in *red*) in 3xTg-AD mice showing the concentration of astrocytes around the Aβ accumulations (**a**–**d**). Astrocytes surround Aβ plaques (**a**, **b**) and Aβ loaded blood vessel (**c**), undergo astrogliosis including in some cases Aβ intracellular accumulation (**a**, **b**). Occasionally, some distant astrocytes send reactive processes towards a plaque (**d**). (Reproduced from Olabarria et al. (2010) with permission.)

In the above mentioned 3xTg-AD (Oddo et al. 2003), reduction in GFAP-positive profiles have been found in several brain regions (Olabarria et al. 2010; Yeh et al. 2011; Kulijewicz-Nawrot et al. 2012). These atrophic changes were quantified by decreased surface area and volume of GFAP-positive profiles, decreased volume of cell somata, decreased number of primary processes and reduction in the number of primary processes (Fig. 12.9). The total number of GFAP-positive astrocytes, however, remained stable in the hippocampus, entorhinal and prefrontal cortices of AD mice at all ages from birth to senescence (1–24 month of age) (Olabarria et al. 2010; Yeh et al. 2011; Kulijewicz-Nawrot et al. 2012). Similar atrophic changes were observed in hippocampal astrocytes from another AD animal model, the mutant APP (PDAPP-J20) mice carrying the Swedish and Indiana APP human mutations (Beauquis et al. 2013).

In the 3xTg-AD animals, reduced astroglial profiles appeared very early (at 1 months of age) in the entorhinal cortex, somewhat later in the prefronatal cortex (~6 months) and substantially later in the hippocampus (~9–12 months) (Figs. 12.10, 12.11) (Olabarria et al. 2010; Yeh et al. 2011; Kulijewicz-Nawrot et al. 2012). This atrophy of GFAP-positive profiles preceded β-amyloid deposition and formation of senile plaques. The reduction in GFAP profiles coincided with the reduced morphological presence of astroglial cells labeled with GS antibodies in the hippocampus and in the prefrontal cortex, but not in the entorhinal cortex (Olabarria et al. 2011; Yeh et al. 2013).

12.3.5 Astrodegeneration in AD: Loss of Homeostatic Support Defines Early Cognitive Impairments

Reduction in astroglial profiles, as evidenced by the morphometry of GFAP- and GS-positive cells, is indicative of a decrease in astroglial territories and hence in reduced astroglial coverage of the grey matter. This atrophy of astrocytes, which occurs early in the disease progression, may represent an important pathological stage in the disease progression. Atrophic astrocytes provide less synaptic coverage with deleterious consequences for synaptic transmission associated with compromised ion and neurotransmitter homeostasis and/or reduced local metabolic support (Verkhratsky et al. 2010; Rodriguez and Verkhratsky 2011). Astroglial degeneration, furthermore, affects the neuro-vascular unit and lessens neuroprotection. All these changes are likely to weaken synaptic transmission and affect synaptic plasticity, and thereby being responsible for initial cognitive deficiency observed during the early stages of AD.

These early cognitive deficits are the very first symptoms of AD, which start to develop years before the occurrence of specific histopathology (Terry 2000; Coleman et al. 2004). Weakening of cognitive abilities reflects in reduced synaptic connectivity due to decreased synaptic function and synaptic loss. Decrease in the number of synapses represents the earliest morphological changes in AD (Terry 2000), while the degree of synaptic loss correlates with the severity of dementia

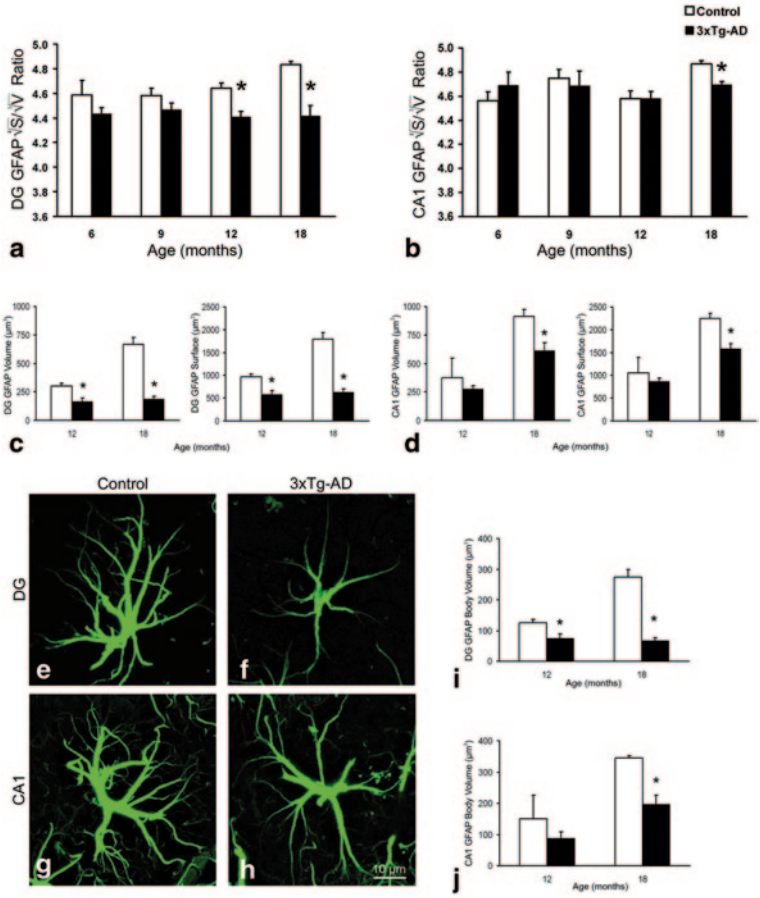

Fig. 12.9 Bar graphs showing a decreased GFAP surface, volume, $^{2}\sqrt{S}/^{3}\sqrt{V}$ ratio and body volume in both the DG (**a**, **c**, **i**) and the CA1 (**b, d, j**) of the hippocampus of the 3xTg-AD mice when compared to control animals. *Bars* represent mean ± SEM.* = $p < 0.05$. Confocal micrographs illustrating the astrocytic atrophy in 3xTg-AD mice in the DG (**f**) and CA1 (**h**) compared to control animals (**e** and **g**, respectively). (Modified from Olabarria et al. (2010) with permission.)

(DeKosky and Scheff 1990; Samuel et al. 1994). Early demise of synapses could be directly related to astrodegeneration and the resulting homeostatic failure. Astrocytes are critical for synaptogenesis and synaptic maintenance (Ullian et al. 2004; Eroglu and Barres 2010), whereas astroglial plasmalemmal transporters control local concentrations of ions and neurotransmitters, most notably glutamate, which, when not contained, causes local excitotoxicity. Astroglia also supports normal neuronal excitability and synaptic function through metabolic support accomplished by lactate shuttle (Magistretti 2006). Astrocytes are also critical for sustaining normal neurotransmission by supplying neurons with glutamine that is indispensable for

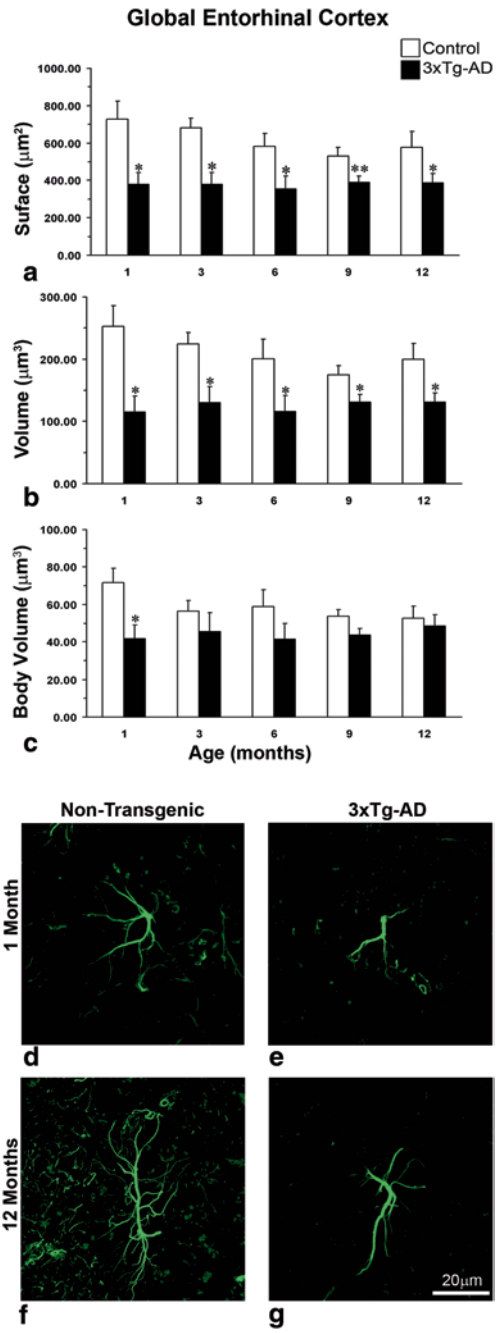

Fig. 12.10 Comparison of astrocytic GFAP surface and volume in the whole EC of non-Tg and 3xTg-AD animals across ages. Bar graphs showing comparison of GFAP (**a**) surface (**b**) volume and (**c**) body volume in global EC at the age of 1, 3, 6, 9 and 12 months between 3xTg-AD and non-transgenic animals. *Bars* represents mean ± SEM (*$p \leq 0.05$ compared with age matched non-transgenic control); Confocal micrograph showing astrocytic atrophy in 3xTg-AD at 1 month (**e**) and 12 months (**g**) compared with control animals (**d** and **f**). (Reproduced from Yeh et al. (2011) with permission.)

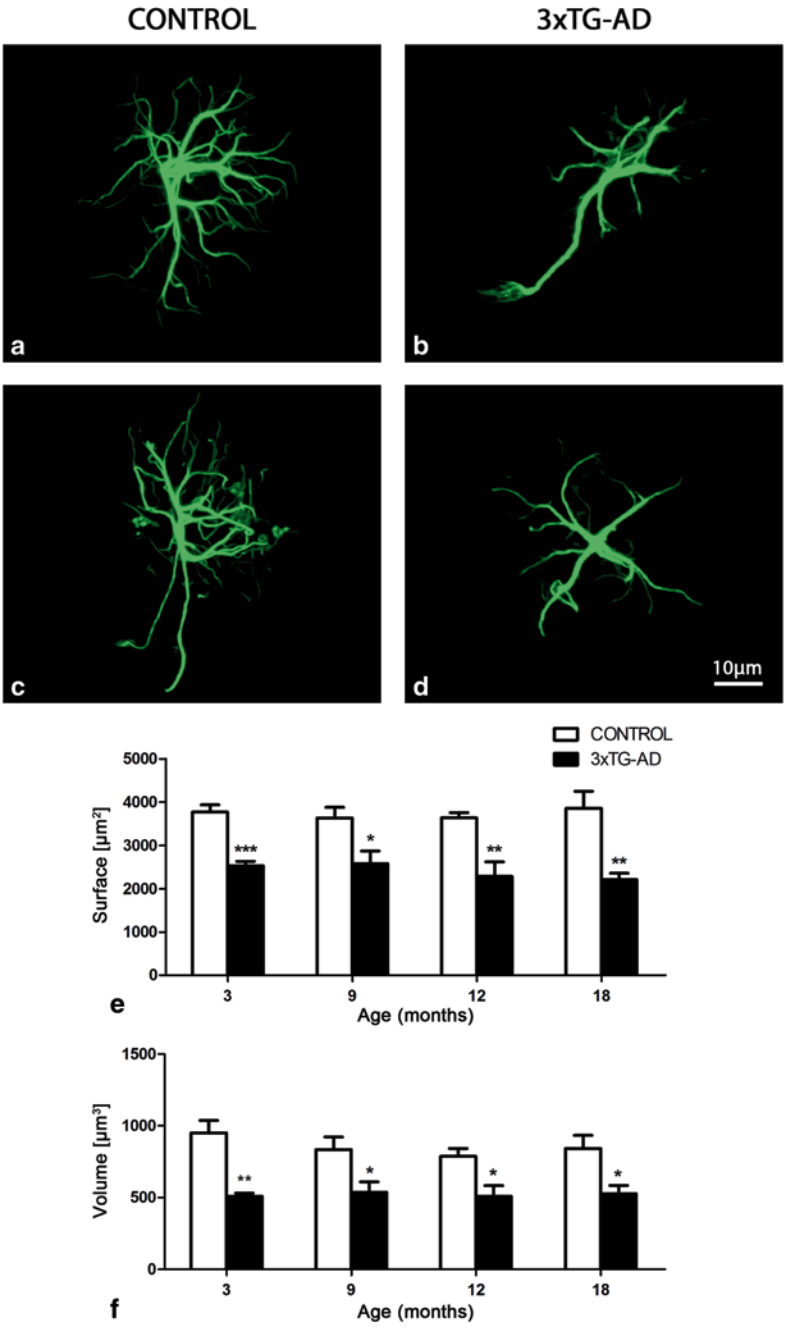

Fig. 12.11 Confocal images showing the classical morphology of GFAP-positive astrocytes in control non-Tg animals and astrocytic atrophy in the 3xTg-AD animals at 3 months (**a** and **b**, respectively) and 18 months (**c** and **d**, respectively) in the medial prefrontal cortex (mPFC). Bar graphs showing the decreases in the GFAP-positive surface area and volume throughout the whole extent of the mPFC (**e**–**f**) in 3xTg-AD mice when compared with control animals. *Bars* represent mean ± SEM. (Reproduced from Kulijewicz-Nawrot et al. (2012) with permission.)

glutamatergic and GABA-ergic pathways. Impairment of these critical functions associated with astrodegeneration can be a primary cause for distorted synaptic connectivity and early cognitive deficits in AD (Verkhratsky et al. 2010; Rodriguez and Verkhratsky 2011).

12.3.6 Astrodegeneration in AD: Dysfunctional Neuro-vascular Unit

AD pathology is often (if not always) associated with vascular deficiency. Blood flow is significantly reduced in the brains of patients with AD and especially in the early stages of the disease (see (Zlokovic 2008; Bell and Zlokovic 2009) for comprehensive review). These functional deficits reflect profound remodeling of vascularization in the diseased brains (Farkas and Luiten 2001). Brain microcirculation is controlled by both neuronal and astroglial inputs (Zonta et al. 2003; Iadecola and Nedergaard 2007; Attwell et al. 2010). Astrocytes are central elements of the neurovascular units that bridge neurons with local circulation. By releasing various factors, astrocytes target pericytes, vascular smooth muscle cells and endothelial cells, thus contributing to functional hyperemia and regulating blood-brain barrier (Zonta et al. 2003; Mulligan and MacVicar 2004; Takano et al. 2006). Astroglial atrophy, together with reactive rearrangement of neuro-vascular unit, may occur at both early and late stages of the disease and contribute to cognitive abnormalities and neuronal damage.

12.3.7 Astrodegeneration in AD: Deficits in Metabolic Support

Metabolic failure represents another common feature of AD. Progressive loss of glucose utilization has been observed in functional brain imaging in patients with different stages of AD; importantly, this metabolic stress is present in the early stages of the disease thus bearing a diagnostic significance (Mosconi et al. 2008). Experiments in vitro, in primary cultured astrocytes, demonstrated that treatment with β-amyloid affects cellular metabolism, although both decrease (Parpura-Gill et al. 1997; Soucek et al. 2003) and increase (Allaman et al. 2010) in glucose utilization were described. Similarly, both decrease (Blass et al. 2000; Liang et al. 2008) and increase (Bigl et al. 1999; Soucek et al. 2003) in the activity of glucose metabolism enzymes were reported in post-mortem AD brains.

12.3.8 *Astrodegeneration in AD: Paralysis of Astrogliotic Response Defines Susceptibility of Brain Tissue to AD Pathology*

Another important consequence of astroglial degeneration in AD is associated with the failure of their defensive function. In the 3xTg mice model, appearance of senile plaques as well as perivascular β-amyloid accumulation triggers astrogliotic response in hippocampal astrocytes, which become hypertrophic and upregulate GFAP expression (Olabarria et al. 2010, 2011). These hypertrophic astrocytes are specifically associated with β-amyloid deposits, whereas astrocytes distant to the plaques are generally atrophic (so in this sense, astroglial atrophy represents the early stage of AD progression and is complimented by astrogliosis at later stages, when specific lesions develop). In entorhinal and prefrontal cortices, however, astrocytic defense response appeared to be compromised because extracellular β-amyloid accumulation does not trigger astrogliotic response (Yeh et al. 2011; Kulijewicz-Nawrot et al. 2012). This protective failure may explain high vulnerability of entorhinal and prefrontal cortices to AD pathology.

12.4 Astrocytes as Therapeutic Targets in AD

Can astrocytes represent a new and potentially fundamentally important target for therapy in neurodegenerative disorders? Can astroglial atrophy and dysfunction be reversed or delayed, and can this affect the progression of AD or severity of cognitive deficits? These questions are of paramount importance for neurogliopathology. Only very recently astroglial cells begin to be considered as objects of treatment. Experiments on transgenic APP and 3xTg-AD mice have shown that chronic exposure of these animals to environmental stimulation (physical activity and/or enriched environment) reversed morphological atrophy of astrocytes, increased GFAP expression and normalized the appearance of GFAP-positive profiles (Fig. 12.12); these astroglia-specific changes were paralleled with a decrease in β-amyloid load (Beauquis et al. 2013; Rodriguez et al. 2013a). Chronic treatment of another AD model, the 5xFAD mice, which co-expresses the mutant forms of human APP (the Swedish mutation: K670N/M671L the Florida mutation: I716V; the London mutation: V717I) and presenilin-1 (M146L/L286V) transgenes (Oakley et al. 2006), with polyunsaturated fatty acid 2-hydroxy-docosahexaenoic acid, similarly reverted astroglial atrophy, restored adult neurogenesis and improved cognitive performance (Fiol-deRoque et al. 2013). Finally, genetic modification of astrocytes in APP/PS1 model of AD, in which astrocytes were virally transfected with a peptide that interferes with the immune/inflammatory calcineurin/nuclear factor of activated T-cells (NFAT) signaling cascades, ameliorated cognitive deficits and lowered β-amyloid burden (Furman et al. 2012). These all are of course very preliminary findings and yet they could signal new developments in astroglia-specific therapy of neurodegenerative diseases.

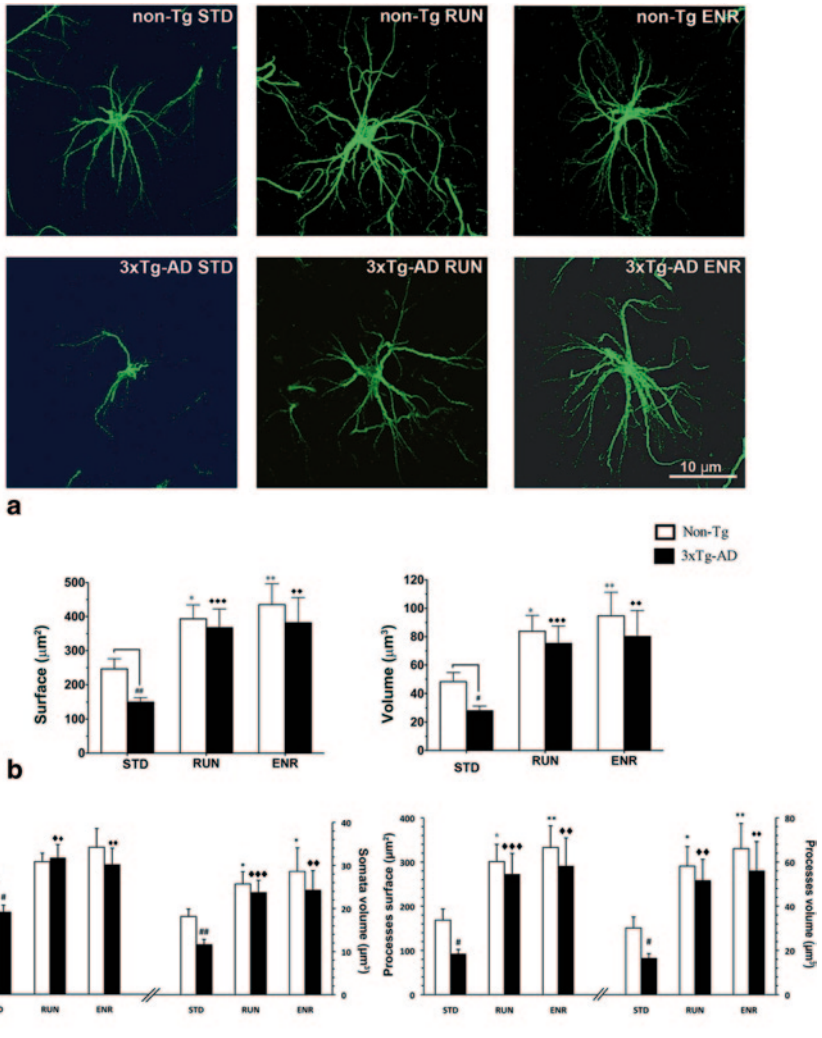

Fig. 12.12 GFAP-IR of astrocytes in the DG of non-Tg and 3xTg-AD animals housed in different conditions. **a** High magnification of representative confocal micrographs showing the astrocytic morphology in mice housed in standard conditions (STD;), RUN, and ENR. Scale bars, 10 µm. Note the morphological changes of the astrocytes from both genotypes induced by the different living conditions. **b** Histograms showing difference of surface area and volume of GFAP-positive astrocytes in the DG of non-Tg and 3xTg-AD mice housed under different housing conditions. **c** Histograms showing differences in surface area and volume of GFAP-IR astrocytic cell bodies and processes detected between non-Tg and 3xTg-AD mice housed under different housing conditions. *Bars* represent means ± S.E.M., #$p<0.05$, ##$p<0.01$ compared with non-Tg animals in same housing environment; *$p<0.05$, **$p<0.01$ compared with non-Tg mice housed under STD; $p<0.01$ and $p<0.001$ compared with 3xTg-AD mice housed under STD. (Reproduced from Rodriguez et al. (2013a) with permission.)

Conclusions

Astrocytes undergo complex alterations in AD, which are represented by atrophy and asthenia at the early stages and reactivity at the late stages of the disease, all these changes being region specific. These complex changes can be considered as pathologically relevant because they may define early cognitive deficits and later neurotoxicity. Targeting astroglia in neurodegeneration may result in new therapeutic strategies aimed at preventing and delaying the disease progression.

Acknowledgements We would like to thank Manoj K. Gottipati for comments on a previous version of the manuscript. Authors research was supported byAlzheimer's Research Trust (UK) Programme Grant (ART/PG2004A/1) to AV and JJR; by the National Institutes of Health (The Eunice Kennedy Shriver National Institute of Child Health and Human Development award HD078678) to V.P., by the Grant Agency of the Czech Republic (GACR 309/09/1696) to JJR and (GACR 305/08/1384) to AV.

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