

# Pathology and Astrocytes in Autism

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**Abstract:** A distinct pathology for autism spectrum disorder (ASD) remains elusive. Human and animal studies have focused on investigating the role of neurons in ASD. However, recent studies have hinted that glial cell pathology could be a characteristic of ASD. Astrocytes are the most abundant glial cell in the brain and play an important role in neuronal function, both during development and in adult. They regulate neuronal migration, dendritic and spine development, and control the concentration of neurotransmitters at the synaptic cleft. They are also responsible for synaptogenesis, synaptic development, and synaptic function. Therefore, any change in astrocyte number and/or function could contribute to the impairment of connectivity that has been reported in ASD. Data available to date is scarce but indicates that while the number of astrocytes is reduced, their state of activation and their GFAP expression is increased in ASD. Disruption of astrocyte function in ASD may affect proper neurotransmitter metabolism, synaptogenesis, and the state of brain inflammation. Astrocytes alterations are common to ASD and other neurodevelopmental disorders. Future studies about the role of astrocytes in ASD are required to better understand this disorder.

**Keywords:** autism, astrocyte, postmortem, GFAP

## Introduction

Autism spectrum disorder (ASD) is as a neurodevelopmental disorder that presents with disturbances in social communication and repetitive behaviors.<sup>1</sup> One in every 54 children suffers from ASD in the United States with a prevalence 4.3 times higher in males than in females.<sup>2</sup> Global prevalence around the world is approximately of 1/100 children varying based on geographic, ethnic, and socioeconomic factors.<sup>3</sup> The etiology of ASD is not well understood, however genetic, environmental, and immune factors have been reported to be the cause.<sup>4</sup> Many genes linked to ASD have also been associated to other neurodevelopmental disorders, indicating a etiological heterogeneity and genetic pleiotropy in ASD.<sup>5</sup> Candidate genes linked to ASD include *DISC1*, *DYX1C1*, *RELN*, *AVPR1a*, *ITGB3*, *RPL10*, and *SHANK3*, among many others.<sup>6</sup> These genes regulate development, metabolism, plasticity, synapsis, and other important functions.<sup>7,8</sup> Although numerous genes have been involved in ASD, a genetic diagnosis is not possible in most of the cases because the established genetic causes of ASD account for only a small portion of cases.<sup>9</sup> Environmental factors such as hypoxia or trauma at birth, heavy metal exposure, maternal obesity, vitamin D deficiency, and maternal diabetes, have been associated with ASD.<sup>10</sup> There is also a significant link between ASD with increase in reactive oxygen species (ROS) and a reduction in antioxidant capacity in the brain of ASD patients. ROS accumulation can directly enhance neuroinflammation and cytokine release.<sup>11</sup> Accordingly, immune system impairment with elevated expression of pro-inflammatory cytokines and chemokines and microglia activation have been reported in postmortem ASD brains.<sup>12,13</sup> Genetic, environmental, and immune factors are involved in the ASD phenotype, but how exactly is poorly understood.

The pathology of ASD is yet to be determined. However, the anatomy of several brain areas such as cerebellum, amygdala, hippocampus and cerebral cortex have been reported to be affected.<sup>14-16</sup> Increased brain size and disorganization of white and grey matter have been identified in patients with ASD.<sup>17,18</sup> MRI studies showed abnormalities in gyral cortical anatomy, especially in the sylvian fissure, superior temporal sulcus, intraparietal sulcus, and inferior frontal gyrus in ASD patients.<sup>19,20</sup> Multiregional dysplasia is present in 92% of ASD cases.<sup>21</sup> It has been hypothesized that focal

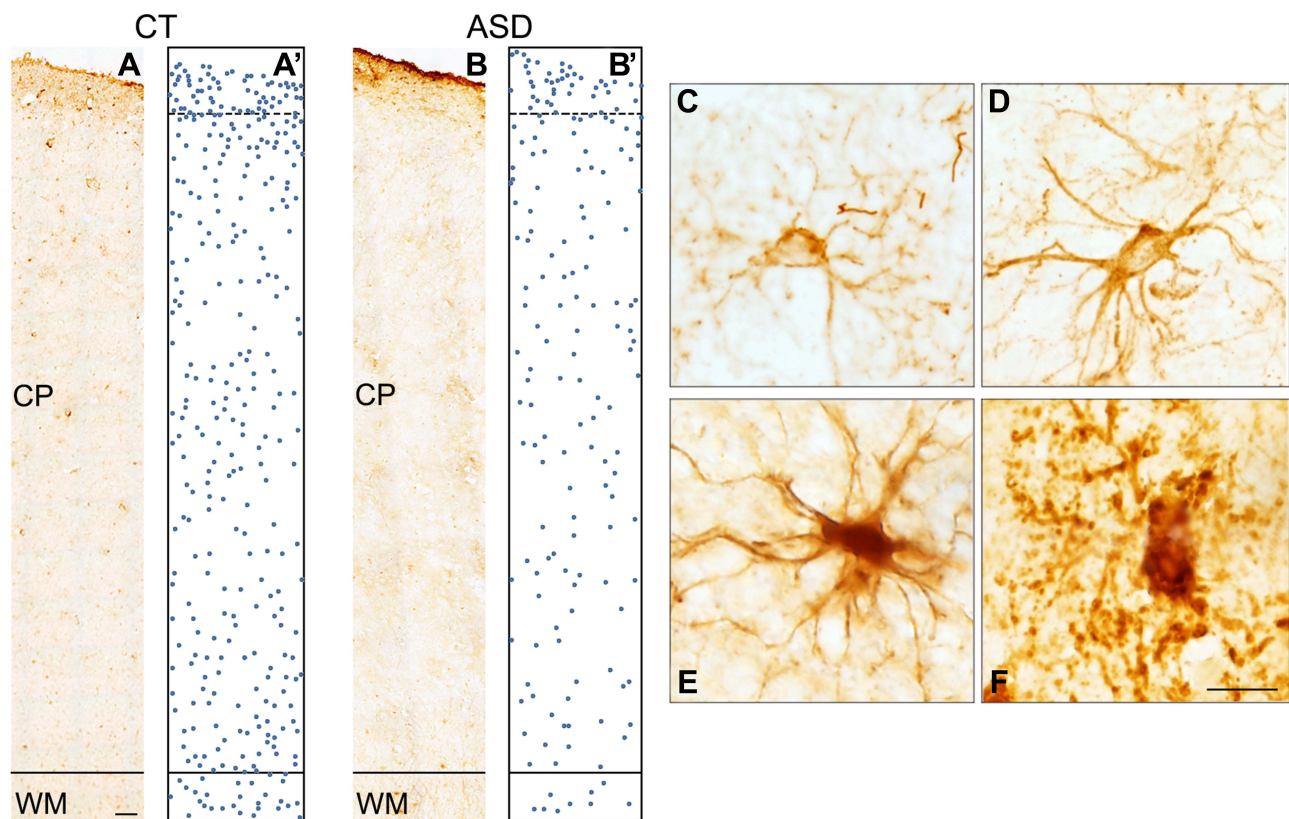
dysplasia in ASD may result from abnormalities in progenitor cell division, and/or migration and maturation of newly generated cells during prenatal brain development.<sup>21,22</sup> Cortical dysplasia in ASD could explain high seizure prevalence and sensory disturbance in ASD.<sup>23</sup> Mini-columnar abnormalities have also been reported in ASD.<sup>24,25</sup> Mini-columns contain oriented arrays of pyramidal cells and GABAergic interneurons that modulate pyramidal cells input and output. Mini-columns are considered the basic functional unit in the neocortex. In ASD, there are more mini-columns but they are smaller in size. There is also less neuropil space resulting in cells more compacted.<sup>24,25</sup> The increased number of mini-columns may result from additional division of progenitor cells during prenatal development, while the deficits in peripheral neuropil space may result from lack of inhibitory cells.<sup>26</sup> White matter is also affected in ASD. In particular, there is a reduction in the number of long axons that are connected to long distance areas, and an increase in thin axons that communicate neighboring areas. This indicates a disconnection between long distance pathways and short distance over-connection. This is the case for the white matter in the anterior cingulate cortex, an area associated with attention, social interaction and emotion, functions altered in ASD. Moreover, there is also a reduction in axonal myelin thickness in some areas such as the white matter of the orbitofrontal cortex.<sup>27</sup>

The ASD brain also presents with alterations in the number of specific cell types. However, most of the cell types and regions of the brain have not been studied, and some of the data collected do not agree. Alteration in cerebellar cortex including a decrease in size and number of Purkinje cells and abnormality in functional connectivity between the cerebellum and other areas of the brain was reported in postmortem ASD brains. Decrease in Purkinje cells number was more noticeable in posterior lobe (lobule VIIA) of the cerebellum. Accordingly, a reduction in grey matter volume and a smaller vermis lobules VI–VII were present in ASD children.<sup>28</sup> Children with ASD had a bigger amygdala than typically developing children.<sup>29</sup> A study on non-neuronal cell population numbers in the amygdala, reported no changes in number, however there was a strong microglial activation in two of eight ASD brains. In addition, there was a reduced number of oligodendrocytes in the amygdala of adult ASD cases aged 20 and older.<sup>30</sup> In the fusiform gyrus in seven postmortem ASD subjects, there was a decrease in number of neurons in layers III, V and VI, and in the mean perikaryal neuronal volumes in layers V and VI.<sup>31</sup> An increase in the pyramidal cell population<sup>32,33</sup> and a reduction in oligodendrocyte and astrocyte numbers (Figure 1A–B') have also been reported in the prefrontal cortex of ASD postmortem brains.<sup>33,34</sup> Also, a reduction in parvalbumin+ chandelier GABAergic interneurons was found in the dorsolateral and ventral prefrontal cortex.<sup>17,35,36</sup> Decreased dendrite numbers in the dorsolateral prefrontal cortex and reduced dendrite branching in the CA4 and CA1 have been reported in individuals with ASD.<sup>37</sup> Overall, abnormalities in different cell type populations and their morphology may lead to the disturbed neuronal function characteristic of ASD.

## Astrocytes in ASD

Astrocytes are key elements for neuronal metabolic and structural support in the brain. They control ion concentration, modulate neurotransmitter release, maintain the blood–brain barrier, and regulate blood flow in the nervous system, among many other functions.<sup>38</sup> They also have crucial roles in neurodevelopment including in neurogenesis, neuronal migration, and synaptic plasticity.<sup>39,40</sup> In addition, with pre- and postsynaptic neurons, perisynaptic astrocytes form tripartite synapses to modulate synaptic transmission.<sup>41</sup> Together with microglia, astrocytes are regulators of the inflammatory responses. Innate immune responses are mediated through activation of microglia and astrocytes that produce cytokines, chemokines, and other immune mediators.<sup>38,42,43</sup> Astrocyte activation could be either neurotoxic, by accelerating inflammatory responses and tissue damage, or neuroprotective by promoting neuronal survival and tissue repair, though this classification is not clear cut. Pro-inflammatory astrocytes secrete pro-inflammatory factors, such as tumor necrotic factor  $\alpha$  (TNF $\alpha$ ) and nitric oxide (NO), whereas neuroprotective astrocytes upregulate neurotrophic factors and thrombospondins to control neuroinflammation. Excessive neuroinflammation with increased reactive astrocytes and pro-inflammatory cytokines has been reported in ASD. Given the role of astrocytes in higher cognitive functions, any alteration in their number, distribution, morphology, and/or function, could lead to major neuronal dysfunction that could contribute to neurodevelopmental disorders such as ASD.<sup>44</sup>

Glial fibrillary acidic protein (GFAP) is a type III intermediate filament that is mainly expressed in astrocytes. It is also known as a marker for reactive astrocytes (Figure 1C–F).<sup>42,45</sup> GFAP is reported to be elevated in the cerebrospinal fluid of ASD subjects.<sup>46,47</sup> Increased GFAP is correlated with astrogliosis and reactive damage that might result in



**Figure 1** (A and B) GFAP+ astrocytes in prefrontal cortical plate (CP) and the white matter (WM) (A) control (CT) and (B) ASD. (A' and B') Reconstruction of an average case depicting GFAP+ astrocyte location in the CP and WM. (A') control (CT) and (B'). (C–F) Astrocytes activation state. (C) Resting astrocyte with few processes and small cell body, (D) mild reactive astrocyte with slightly enhanced staining of glial processes and minor enlargement of cell body, (E) moderate reactive astrocyte with significant increase of cell body size and glial cell ramifications with dark stained processes and (F) severe reactive astrocyte with gemistocytic cell body and degraded processes that present as dark stained puncta.<sup>105</sup> Scale bar in A, A', B, B': 500  $\mu$ m; C, D, E, F: 20  $\mu$ m.

immune response and further cytokines release.<sup>13,48</sup> Data regarding *GFAP* gene expression in different regions of the ASD brain is controversial. Some studies reported upregulation of *GFAP* gene expression in the prefrontal cortex and cerebellum,<sup>49,50</sup> whereas others reported no significant changes in *GFAP* gene expression in anterior cingulate cortex and anterior prefrontal cortex in ASD brains.<sup>51,52</sup> Rats treated with propionic acid showed increased *GFAP* gene expression in the hippocampus, and presented ASD-like behaviors including aggressive behavior during adjacent interactions.<sup>53</sup> At the protein level, several studies reported an increase in GFAP protein in superior frontal cortex, parietal cortex, cerebellum, and anterior cingulate cortex white matter.<sup>13,48,51</sup> There was also an increase in GFAP protein in the cerebellum of postmortem brains whereas vimentin was decreased in both cerebellum and prefrontal cortex.<sup>54</sup> In a valproic acid (VPA) animal model of ASD, there was an increase in the number of astrocytes and GFAP in medial prefrontal cortex and primary somatosensory cortex on postnatal day 30.<sup>55</sup> In contrast, some other studies showed no change in GFAP protein in anterior cingulate grey matter, amygdala, and anterior and dorsolateral prefrontal white matter of postmortem ASD brains.<sup>30,51,56</sup> Other proteins expressed by astrocytes are also changed in ASD. There was decreased amount of aquaporin 4 (AQP4), a water channel protein located in astrocytes, in the medial prefrontal cortex, but an elevation in the primary somatosensory area in the VPA animal model of ASD. AQP4 is mainly responsible for eliminating water from the cerebral parenchyma as well as supporting potassium buffering.<sup>55,55</sup> In addition, there was a reduction in AQP4 protein in the cerebellum and an increase of connexin (cnx) 43, a gap junction protein located in astrocytes, in BA9 of postmortem ASD brains.<sup>57</sup> Beside buffering ions and neurotransmitters concentration, cnx43 is responsible for regulating cellular growth and cell-cell adhesion. Increased cnx43 expression in ASD subjects could signify enhancement of glial-neuronal communication in frontal lobe that is in charge of executive functions.<sup>57</sup>

Data regarding the number of astrocytes in the brain with ASD are scarce (Table 1). We previously reported a decrease in the number of astrocytes, labeled with GFAP and S100β, and a mild activation in GFAP+ astrocytes in the prefrontal areas BA9, BA46, and BA47 of postmortem ASD brains compared to control individuals.<sup>34</sup> Figure 1 depicts representative images of astrocytes labeled with GFAP antibody and their location in control and ASD prefrontal cortex and astrocytes in different stages of activation. In another study from our laboratory, using Nissl staining, we showed a generalized reduction in astrocytes number with an increase in the neuronal population in layer II in the same areas.<sup>33</sup> A reduced number of astrocytes could result from a reduced production and/or increased cell death. Increased overall glial cell densities, including astrocytes, oligodendrocytes and microglial cells, in layer II of olfactory cortex was reported, that may correlate with sensory deficits including damaged olfactory identification observed in patients with ASD. This increased glial cell density was correlated positively with the scores for restricted and repetitive behavior domain in the autism diagnostic interview – revised (ADI-R) questionnaire.<sup>58</sup> Using clustering nuclear profiles, genetic studies showed upregulated protoplasmic astrocyte gene expression in the prefrontal cortex and anterior cingulate cortex of postmortem ASD brains.<sup>59</sup> In addition, upregulation of a gene set that was enriched in astrocytes and microglia was observed in frontal and temporal cortex of 251 postmortem samples from 48 ASD cases and 49 control subjects.<sup>60</sup> These data contrast with anatomical studies demonstrating a decreased number of astrocytes in the prefrontal cortex. This may be because anatomical landmarks were not taking into account and the number of astrocytes was quantified using homogenated tissue.

**Table 1** Summarizing Astrocyte Abnormalities in ASD Human Studies

Astrocyte Markers and Functions	Alteration	Regions	References
GFAP	Increased	CSF, PFC, cerebellum, Superior frontal cortex, parietal Cortex, anterior cingulate cortex white white matter	[13,46–51]
	No change	Anterior cingulate grey matter, amygdala, anterior and dorsolateral prefrontal white matter	[51,52]
Vimentin	Decreased	Cerebellum and the PFC	[54]
Aquaporin4	Decreased	Cerebellum	[57]
Connexin43	Increased	BA9 of the PFC	[57]
Astrocytes population	Decreased	BA9, BA46, BA47 of the PFC	[33,34]
Astrocytes activation state	Increased	BA40, BA9, BA46, BA47, cerebellum, anterior cingulate cortex white matter	[13,34,48,51]
Neurotransmitter release	Elevated glutamine synthase level	Plasma	[64]
	Increased mRNA level of EAAT1	Cerebellum	[50]
	Decreased AMPA receptor density	Cerebellum	[50]
Neuroinflammation	Releasing MCP-I and IL-6	Cortical and subcortical white matter	[13]
	Increased gene expression of TSPO	Frontal cortex and cerebellum	[73]
	Elevated MCP-I/CCL2 Chemokine	Brain and blood	[13,74]
Synaptogenesis	Disrupted RAC1 signaling	Brain	[82,83]
	TGF-β1 dysfunction		[87]
	Mutations in Hevin, Neurexins and Neuroligins		[89]

## Astrocytes and Neurotransmitters

Astrocytes play a critical role in neurotransmitter homeostasis, and in regulating the excitation/inhibition balance that is disturbed in the ASD cortex. Disturbance in astrocyte calcium signaling through inositol 1,4,5-trisphosphate 6 receptor 2 (IP3R2), that regulates neurotransmitter release, leads to ASD-like behaviors including repetitive behaviors and abnormal social interaction in mice.<sup>61–63</sup> Also, elevated level of glutamine synthetase (GS), an adenosine triphosphate-dependent enzyme that maintains glutamate levels located in astrocytes, was reported in the plasma of ASD patients.<sup>64</sup> Increased mRNA expression of excitatory amino acid transporter 1 (EAAT1), located in astrocytes and responsible for glutamate uptake, and glutamate receptor AMPA 1, were found in the cerebellum of postmortem ASD brains. However, the density of AMPA glutamate receptor protein was decreased in the cerebellum. These findings reveal abnormalities in glutamatergic system in ASD.<sup>50</sup> Some other studies reported a correlation between the glutamate transporter single gene polymorphism and the severity of anxiety and repetitive behaviors in ASD children.<sup>65</sup> Furthermore, excessive electrical activity resulting from an abnormal glutamatergic function has been reported in ASD patients that can lead to pathologic behaviors.<sup>66</sup> In VPA animal model of ASD, there was a decrease of 40% in glutamate transporter 1 (GLT1) at P15, but an increase of 92% in GLT1 with an increase of 160% in glutamate uptake at P120. The amount of glutathione (GSH) was also increased 27% at P120 suggesting a disturbance in astrocytic glutamate clearance from the synaptic cleft in an animal model of ASD.<sup>67</sup>

Some report ASD as a hypo-glutamatergic disorder because of the symptoms produced by glutamate antagonists in ASD.<sup>68</sup> Accordingly, a hypo-glutamatergic animal model displayed behavioral phenotypes that overlapped with the features observed in ASD<sup>69</sup>, indicating an alteration in the glutamatergic function in ASD.

Astrocytes also participate in gamma-aminobutyric acid (GABA) clearance. Some studies have shown a relationship between astrocyte abnormalities and the GABAergic system dysfunction in ASD. Wang et al showed a reduction in astrocyte-derived ATP that impaired GABAergic system and lead to ASD-like behaviors in the PFC of the IP3R2 mutant mice. ATP can modulate GABAergic synaptic transmission via P2X2 receptors located at the GABAergic interneuron terminals.<sup>63</sup> In an in vitro study, cultured astrocytes exposed to VPA showed impairment in GABAergic inhibitory synapses but the excitatory synapses remained unchanged. This indicates that VPA can alter E/I balance in neural network by affecting the astrocyte-neuron interaction, highlighting the impact of astrocyte dysfunction in ASD pathology.<sup>70</sup> Overall, there is evidence that astrocyte regulating of both glutamate and GABA neurotransmitters is altered in the ASD brain.

## Astrocytes and Neuroinflammation

Neuroinflammation plays a main role in ASD pathology and many studies reported activation of astrocytes in postmortem ASD brains.<sup>13,71,72</sup> Reactive astrocytes are the major source of releasing cytokines. The macrophage chemoattractant protein (MCP-1), that is in charge of monocyte/macrophage recruitment to the areas of inflammation, and pro-inflammatory cytokine interleukin-6 (IL-6), are altered in cortical and subcortical white matter in ASD.<sup>13</sup> The expression of the translocator protein 18 kDa (TSPO), that is a marker for brain inflammation, and the amount of activated microglia in the frontal cortex and cerebellum are increased in reactive astrocytes in ASD.<sup>73</sup> Monocyte chemoattractant protein-1 (MCP-1/CCL2) is a chemokine that has been reported to be elevated in the brain and blood of ASD cases.<sup>13,74</sup> CCL2 is produced by astrocytes and microglia in the brain and is necessary for proliferation, migration and activation of microglia and astrocytes.<sup>75,76</sup> Elevated level of CCL2 could also increase blood–brain barrier (BBB) permeability and allow more T-lymphocytes to enter the brain during neuroinflammation.<sup>77</sup> Multifocal perivascular lymphocytic cuffs are associated with astrocytes blebs that represents a cytotoxic reaction to lymphocyte attack, suggesting a dysregulation in cellular immunity that could damage astrocytes in ASD brains.<sup>78</sup> Although many studies reported immune system dysfunction in ASD, it is not clear whether it is a cause or a consequence of the pathology.<sup>72</sup>

## Astrocytes and Synaptogenesis

Astrocytes perform a critical role in synaptic formation, maturation, function, and elimination. An alteration in astrocyte structure and function alters neuronal activity.<sup>79</sup> Astrocytes secrete platelet responsive protein (TSP) that works through

its neuronal receptor calcium channel subunit  $\alpha 2\delta$ -1, to control excitatory synaptogenesis.<sup>80</sup> The synaptic signaling protein Rho GTPase Ras-related C3 Botulinum toxin substrate 1 (RAC1), is downstream of the TSP- $\alpha 2\delta$ -1 pathway and has an important role in regulating synaptic and spinal growth.<sup>81</sup> Disturbed RAC1 signaling is strongly associated with ASD and epilepsy pathology.<sup>82,83</sup> The fact that astrocytes control the TSP- $\alpha 2\delta$ -1-RAC1 pathway, is an example of the role of astrocytes on synaptic formation in ASD.<sup>84</sup> Astrocytes secrete cytokines, such as transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) to regulate synaptogenesis. TGF- $\beta$ 1 enhances phosphorylation of calcium/calmodulin dependent protein kinase II (CaMK II), downstream of NMDA receptors, to induce the formation of inhibitory synapses.<sup>85</sup> TGF- $\beta$ 1, with the NMDA coactivator D-serine, encourages the formation of excitatory synapses through NMDA receptor-dependent mechanisms.<sup>86</sup> Supporting a role of TGF- $\beta$ 1 in the formation of inhibitory synapses suggest that a relationship between the TGF- $\beta$ 1 dysfunction and inhibitory synapse disturbance in ASD.<sup>87</sup> Hevin is another protein secreted by astrocytes that is essential for maintaining synaptogenesis. Hevin bridges the presynaptic protein Neurexin-1 $\alpha$  (*NRX1 $\alpha$* ) and postsynaptic Neuroligin-1B (NL1B) to assemble excitatory synapses.<sup>88</sup> Mutations in Hevin, Neurexins and Neuroligins are strongly related to ASD pathology suggesting a critical role of these proteins in normal brain development.<sup>89</sup>

## Astrocytes in Other Neurodevelopmental Disorders

Astrocyte abnormalities have also been reported in other neurodevelopmental disorders, such as schizophrenia (SZ), bipolar disorder (BD) and major depressive disorder (MDD). A reduction in astrocyte densities was present in some brain areas of postmortem brains with SZ including cingulate and motor cortex, medial and ventrolateral regions of the nucleus accumbens, basal nuclei and substantia nigra.<sup>90</sup> In an electron microscopic morphometric study of astrocytes in hippocampal CA3 region of 19 SZ cases, mitochondrial volume fraction and area density was negatively correlated with the duration of disease. However, the volume fraction of lipofuscin granules was positively associated with the duration of illness suggesting progressive astrocyte dysfunction due to the mitochondrial deficit.<sup>91</sup> An increased expression of *GFAP* mRNA with astrogliosis was also observed in SZ patients with neuroinflammation.<sup>92</sup> Furthermore, in animal studies of SZ, transgenic mice that expressed a mutant form of the disrupted in schizophrenia 1 (*DISC1*) gene in astrocytes, showed behavioral abnormalities related to SZ supporting the role of astrocytes in SZ pathology.<sup>93,94</sup>

In BD, astrocytic density was also reduced supporting astrocyte dysfunction in regulating glutamate homeostasis, calcium signaling, circadian rhythms and metabolism. Beneficial therapeutical effects of many BD drugs such as lithium, valproic acid (VPA) and carbamazepine (CBZ) are partly due to their positive actions on astrocytes by affecting the gene expression in astrocytes and regulating astroglia homeostatic pathways.<sup>95,96</sup> There is also an elevation reported in the expression profile of cortical astrocytes in the postmortem BD subjects generated from eight different cohorts of subjects.<sup>97</sup> In an in vitro study, astrocytes derived from induced pluripotent stem cells (iPSCs) generated from BD individuals showed alteration in transcriptome and a decrease in neuronal activity when they were co-cultured with neuronal cells. BD astrocytes also increased IL-6 secretion in the blood of BD patients highlighting the role of astrocytes in inflammatory signaling in BD pathology.<sup>98</sup>

A reduction in the astrocyte density in various regions of the brain including the prefrontal cortex, cingulate cortex and amygdala is an important feature in MDD pathology.<sup>99–101</sup> Golgi staining showed astrocytic hypertrophy in cell bodies and processes in the white matter of cingulate cortex of depressed patients that died by suicide. The presence of hypertrophic astrocytes could reflect local inflammation supporting the neuro-inflammatory hypothesis in depressed patients.<sup>102</sup> In addition, the protein and mRNA level of pro-inflammatory cytokines secreted by reactive astrocytes were increased in the prefrontal cortex of suicide victims.<sup>103</sup> However, other astrocytic proteins and markers such as *GFAP*, AQP4, *cnx43*, *cnx30*, glutamate transporters, and glutamine synthetase were reduced in MDD.<sup>104</sup>

## Conclusion

Astrocytes play an important role in neurodevelopment and neuronal function in the brain, including higher cognitive functions. Available data indicates that astrocyte number is decreased in the cerebral cortex, while their state of activation and GFAP expression is increased in the ASD brain. This dysfunction and other astrocytic alterations may contribute to

the ASD pathology. More research is needed to help our understanding of the mechanisms involved in astrocytic-related pathophysiology in ASD, and to introduce astrocytes as one of the promising targets for ASD treatment. Future research should answer questions as if the decreased in astrocyte number found in cortex occurs in other brain areas, if there are areas where astrocytic activation is more pronounced than others, what is the role of astrocytes on development, plasticity, and inflammation, and what other astrocytic functions are altered in ASD.

## Disclosure

The authors report no conflicts of interest in this work.

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