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# Astrocytes in tauopathies

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## Abstract

Tauopathies are a group of neurodegenerative diseases characterised by the progressive accumulation across the brain of hyperphosphorylated aggregates of the microtubule-associated protein tau that vary in isoform composition, structural conformation and localisation. Tau aggregates are most commonly deposited within neurons but can show differential association with astrocytes, depending on the disease. Astrocytes, the most abundant neural cells in the brain, play a major role in synapse and neuronal function, and are a key component of the glymphatic system and blood brain barrier. However, their contribution to tauopathy progression is not fully understood. Here we present a brief overview of the association of tau with astrocytes in tauopathies. We discuss findings that support a role for astrocytes in the uptake and spread of pathological tau, and we describe how alterations to astrocyte phenotype in tauopathies may cause functional alterations that impedes their ability to support neurons and/or cause neurotoxicity. The research reviewed here further highlights the importance of considering non-neuronal cells in neurodegeneration and suggests that astrocyte-directed targets that may have utility for therapeutic intervention in tauopathies.

**Contribution to the field:** Several neurodegenerative diseases, including Alzheimer's disease are characterised by the presence of abnormal tau deposits in affected brain regions, that is closely associated with synapse loss and neurodegeneration. Astrocytes, the most abundant neural cell type are an intrinsic component of synapses and regulate neuronal circuits. Recent evidence has highlighted an important contribution of astrocytes to the prion-like propagation of abnormal tau in Alzheimer's disease and related tauopathies. We discuss the evidence linking astrocytes with tauopathies, including their newly described roles in tau uptake/spread, highlighting the importance of continued work in this area.

## 1 Introduction

Tauopathies are a heterogeneous group of neurodegenerative diseases in which the deposition of hyperphosphorylated tau aggregates in affected brain regions accompanies synapse and neuron loss (Guo et al., 2016). Primary tauopathies exhibit tau aggregates as the predominant pathological hallmark and include a diverse family of frontal-temporal lobar dementia (FTLD) subtypes referred to as FTLD-tau, and includes progressive supranuclear palsy (PSP) and Pick's disease (PiD).

## Astrocytes in Tauopathies

38 Alzheimer's disease (AD) is considered a secondary tauopathy owing to the presence of extracellular  
39 amyloid-beta (A $\beta$ ) plaques, and is the most common cause of dementia (Prince et al., 2014).

40 Tau proteins undergo several post-translational and other modifications in disease (Guo et al., 2016).  
41 Modified forms of tau spreads from the original site of deposition to anatomically connected regions  
42 by a "prion-like" mechanism, whereby tau proteopathic seeds passively recruit tau monomers (Jucker  
43 and Walker, 2018). The mechanisms underlying tau release, uptake and spread are not fully  
44 understood. It has long been acknowledged that in some tauopathies astrocytes accumulate tau  
45 leading to characteristic disease neuropathology. Accumulating evidence now suggests that  
46 astrocytes may actively participate in tau spread and/or clearance mechanisms by actively  
47 internalising tau. This review summarises the association of tau with astrocytes in tauopathies, and  
48 discusses the evidence implicating astrocytes in tau spread, as well as the impact of tauopathy brain  
49 environments on physiological astrocytic functions.

## 50 2 Tau protein

51 Human tau is encoded by the *MAPT* gene on chromosome 17 which comprises 16 exons. Exons 2, 3  
52 and 10 undergo alternative splicing to produce the six main tau isoforms present in the adult human  
53 central nervous system (CNS) (Andreadis, 2005). Alternative splicing of exon 10 gives rise to tau  
54 isoforms containing either three or four microtubule binding repeats (referred to as 3R or 4R tau) in  
55 the C-terminal region, and alternative splicing of exons 2 and 3 produces tau proteins with zero, one  
56 or two inserts in the N-terminal tail (0N, 1N or 2N tau, respectively). A conserved proline-rich  
57 domain is found between these two spliced regions and is known to be important for tau interactions  
58 with other proteins, including actin (He et al., 2009). Tau isoforms are developmentally regulated; the  
59 shortest 0N3R isoform is expressed in the fetal brain whereas in the adult human brain 3R and 4R  
60 isoforms are equally represented (Goedert and Jakes, 1990). Tau has a number of key functions, the  
61 most recognised of which is stabilising microtubules in the axons of neurons, however tau roles in  
62 other important physiological functions such as axonal transport, DNA protection, cell signalling at  
63 the membrane, and synaptic vesicle release, have been described (Wang and Mandelkow, 2016; Guo  
64 et al., 2017). Tau is primarily expressed in neurons (Binder, 1985), but is known to be expressed to a  
65 lesser extent in glial cells (Zhang et al., 2014; Darmanis et al., 2015; Seiberlich et al., 2015;  
66 McKenzie et al., 2018).

67 Monomeric tau is water soluble and resists aggregation (Wang and Mandelkow, 2016). In  
68 tauopathies, tau undergoes extensive post-translational and other modifications including, but not  
69 limited to, phosphorylation, acetylation, nitration, SUMOylation, glycosylation, ubiquitination,  
70 cleavage and aggregation (Guo et al., 2017). The best studied of these is phosphorylation. There are  
71 85 potential phosphorylation sites in 2N4R tau (Hanger et al., 2009) and increased phosphorylation  
72 of tau, alongside other tau modifications, can reduce tau affinity for microtubules, increase  
73 cytoplasmic tau concentrations and promote tau oligomerisation and aggregation (Guo et al., 2017).  
74 Differential extents of tau modifications lead to the accumulation of heterogeneous pools of modified  
75 tau between, and within, different tauopathies. Recently, Dujardin et al. (2020) found variations in  
76 relative abundance of soluble, oligomeric and seed-competent species of hyperphosphorylated tau in  
77 tauopathy brain. Specific post-translational modifications were found to influence tau seeding  
78 capacity, and tau seeding potential strongly correlated with the rate of clinical symptoms/disease  
79 progression.

80 The isoform composition of tau aggregates, as well as the structure of tau filaments, also differs  
81 between tauopathies. In AD, both paired helical and straight filaments contain identical protofilament

82 cores comprising residues 306-378 that define the aggregatory seed/core (Fitzpatrick et al., 2017).  
83 This structure differs from the folds of tau filaments observed in Pick's disease (Falcon et al., 2018)  
84 and tau filaments of chronic traumatic encephalopathy (CTE) have a unique hydrophobic core  
85 (Falcon et al., 2019). A novel fold in corticobasal degeneration (CBD) tau has now also been  
86 discovered (Zhang et al., 2020). These features may be important for the tau lesions that arise in  
87 different tauopathies (Table 1).

### 88 **3 Astrocytes in health and disease**

89 Astrocytes are organised into distinct domains, and each astrocyte can connect with thousands of  
90 neurons, allowing them to coordinate synaptic activity in the CNS (Parpura et al., 1994; Oberheim et  
91 al., 2006). Astrocytes were long considered as supporting cells in the brain, providing metabolic and  
92 nutritional support for neurons. However, astrocytes are critical for neuronal function due to their  
93 ability to sense changes in neuronal activity through their complement of cell surface receptors, and  
94 to modulate neuronal activity by releasing gliotransmitters and gliomodulators, as well as controlling  
95 the availability of glutamate, GABA and energy substrates (Parpura et al., 1994; Volterra and  
96 Meldolesi, 2005; Choi et al., 2014). Hence, astrocytes are now known to be actively involved in  
97 synaptic transmission (Santello et al., 2019), neural circuit maintenance (Mederos et al., 2018) and  
98 long-term potentiation (Lushnikova et al., 2009). In addition, astrocytic end-feet are a structural  
99 component of the blood-brain barrier (BBB), and together with endothelial cells and pericytes have a  
100 central role in the regulation of blood flow (Sofroniew and Vinters, 2010). Furthermore, astrocyte  
101 end-feet are crucial for the glymphatic system of the brain, a perivascular network that allows for  
102 exchange of interstitial and cerebrospinal fluid (CSF), providing a route for clearance of molecules  
103 and proteins including A $\beta$  (Iliff et al., 2012; Simon et al., 2018).

104 In the neurodegenerative brain, astrocytes undergo pathological changes **in responses to changes in**  
105 **the local brain environment** that precede neuronal loss (Kersaitis et al., 2004). These morphologically  
106 and functionally modified astrocytes are often termed 'reactive'. Reactive astrocytes show  
107 considerable heterogeneity related to their localisation in the brain and the severity and length of  
108 injury/insult to their local environment (Zamanian et al., 2012). Reactive astrocytes are traditionally  
109 characterised by increased levels of glial fibrillary acidic protein (GFAP), which allows cytoskeletal  
110 and morphological arrangements as astrocytes alter their function (Kamphuis et al., 2015; Acosta et  
111 al., 2017). The accumulation of GFAP-immunopositive astrocytes is common in neurodegenerative  
112 diseases. For example, reactive astrocytes are often found surrounding plaques in AD (Bouvier et al.,  
113 2016; Osborn et al., 2016). Indeed, levels of GFAP-reactive astrocytes are closely associated with  
114 dementia in AD (Perez-Nievas et al., 2013). While increased GFAP is also found in aged brain  
115 (Wruck and Adjaye, 2020), new evidence suggests that there are subgroups of astrocytes, with  
116 varying levels of GFAP expression, that distinguish aging from AD, at least in mice (Habib et al.,  
117 2020). Alterations in GFAP expression have also been noted in primary tauopathies including PSP,  
118 PiD and corticobasal degeneration (CBD) (Ferrer et al., 2014).

119 Functional changes in reactive astrocytes are well-documented and include impaired gliotransmitter  
120 release (Piacentini et al., 2017), alterations in calcium signalling (Shigetomi et al., 2019), deficient  
121 ability to regulate glutamate levels at neuronal synapses and aberrant GABA release (Acosta et al.,  
122 2017). In addition, astrocytes are now recognised to contribute to neuroinflammatory responses that  
123 accelerate the progression of neurodegenerative diseases (Phillips et al., 2014; Bouvier et al., 2016;  
124 Bright et al., 2019). For example, reactive astrocytes increase their production and release of pro-  
125 inflammatory cytokines, complement components, and reactive oxygen species, alongside  
126 downregulating anti-inflammatory and repair proteins to induce neurotoxicity in diseased

## Astrocytes in Tauopathies

127 environments (Lian et al., 2015; Bouvier et al., 2016; Leyns and Holtzman, 2017; Sadick and  
128 Liddelow, 2019). Recent seminal findings proposed that astrocytes respond to their local  
129 environment by adopting “A1-neurotoxic” or “A2-neuroprotective” phenotypes (Liddelow et al.,  
130 2017). Secretion of  $IL-1\alpha$ ,  $TNF\alpha$ , and C1q by microglia in response to damage, induces astrocytes to  
131 upregulate their expression of a specific cluster of “A1” genes, lose their trophic and synaptic support  
132 for neurons, and induce neuron death (Liddelow et al., 2017). Markers of A1 astrocytes are  
133 upregulated in AD and other neurodegenerative diseases (Liddelow et al., 2017), strongly implicating  
134 microglia-astrocyte communications in neurodegeneration. However, it is likely that there is a  
135 spectrum of reactive astrocyte states in different brain regions, throughout aging and disease  
136 progression (Boisvert et al., 2018; Habib et al., 2020), similar to dynamic microglial responses in  
137 disease (Vainchtein and Molofsky, 2020).

### 138 4 The association of astrocytes with tauopathy

139 Tau aggregates accumulate in both neurons and astrocytes in different tauopathies. In AD, tau  
140 aggregates containing both 3R and 4R tau deposit as intraneuronal neurofibrillary tangles and there is  
141 scant evidence of astrocytic tau inclusions (Garwood et al., 2017). In contrast, astrocytic tau  
142 pathology is the defining feature of several FTLD-tau subtypes (Table 1). In PSP, a  
143 neuropathological diagnosis criterion is ‘tufted’ astrocytes that show 4R tau aggregates in their  
144 proximal processes (Cairns et al., 2007; Kovacs and Budka, 2010). CBD has extensive clinical  
145 overlap with PSP. In CBD, astrocytic plaques containing 4R tau deposits that mark distal and end  
146 processes are an exclusive feature in most (Forrest et al., 2019), but not all (Ling et al., 2020) cases.  
147 Thread-like tau-positive astrocytic processes are also common in CBD (Dickson et al., 2011; Ling et  
148 al., 2016). Argyrophilic grain disease (AGD) is a rare tauopathy that is characterised by 4R tau-  
149 immunopositive astrocytes, described as thorn-shaped and fuzzy/bush-like, in the medial temporal  
150 lobe (Botez et al., 1999; Saito et al., 2004; Forrest et al., 2019). In contrast, PiD is typically  
151 characterised by neuronal 3R tau inclusions, predominantly in granular neurons in the hippocampus,  
152 frontal and temporal cortices (Dickson, 2001; Josephs et al., 2011). ‘Ramified’ astrocytes  
153 immunopositive for tau have also been reported in PiD, but they are not considered a major  
154 pathological hallmark of the disease (Dickson et al., 2011; Ferrer et al., 2014). Several rarer  
155 tauopathy subtypes that show 4R tau-immunopositive globular inclusions, **predominantly in**  
156 **oligodendrocytes, and more rarely** in the cytoplasm and proximal processes of astrocytes, are  
157 collectively termed globular glial tauopathy (GGT) (Ahmed et al., 2013).

158 **A spectrum of FTLD-tau subtypes that accumulate both 3R and 3R tau in neurofibrillary tangles**  
159 **(NFTs) typically occurring in cognitively normal aged individuals is referred as primary age-related**  
160 **tauopathy (PART) (Crary et al., 2014; Jellinger et al., 2015). Depending on the co-occurrence of A $\beta$**   
161 **pathology, PART can be histologically classified as “definite PART” in the absence of A $\beta$  deposits,**  
162 **or “possible PART” when a limited number of A $\beta$  deposits are present (Crary et al., 2014). Although**  
163 **the neuropathological characteristics of PART can overlap with other tauopathies, particularly AD,**  
164 **PART shows a lower threshold of amyloid load, and appears to have a more limited impact on**  
165 **cognition (Crary et al., 2014). Tau pathology in PART is predominantly neuronal and found in the**  
166 **CA2 hippocampal subfield, with little evidence of astrocytic tau deposits (Crary et al., 2014;**  
167 **Jellinger, 2018). In contrast, age-related tau astrogliaopathy (ARTAG) describes a spectrum of**  
168 **abnormal tau pathology, predominantly in the aged brain, that is characterised by thorn-shaped and**  
169 **granular or fuzzy astrocytes containing phosphorylated tau (Kovacs et al., 2016; Kovacs, 2018).**  
170 **ARTAG can present alongside more typical tau pathology in tauopathies such as CBD (Kovacs et**  
171 **al., 2018, 2020), but is not always linked with dementia (Lace et al., 2012). In a recent detailed**  
172 **review, Kovacs et al. (2020) describe two distinct distribution patterns of ARTAG. They describe**

173 ARTAG as a consequence of repeated mechanical damage (related to CTE), or chronic damage such  
174 as blood-brain barrier dysfunction. Furthermore, they propose that the location and type (white  
175 versus grey matter) of ARTAG pathology may result in decompensation of cognitive functions, the  
176 rate of which may be influenced by co-existing pathologies (Kovacs, 2020). It is important to note  
177 that the presence of astrocytic tau accumulations in the absence of dementia may suggest that tau-  
178 containing astrocytes are not damaging in tau-associated neurodegeneration, or at least in ARTAG,  
179 and may internalise tau aggregates as a means of clearing damaging protein species.

180 Finally, chronic traumatic encephalopathy (CTE) is caused by mild repetitive head injuries. 3R and  
181 4R tau-positive aggregates are common in CTE, however the tau aggregates that accumulate in  
182 astrocytes are predominantly 4R and localize in astrocytes near small vessels in the cerebral sulci of  
183 the frontal and temporal cortices (McKee et al., 2013, 2015; Stein et al., 2014). Thorn-shaped  
184 astrocytes are also observed subpial and periventricular regions, **an interesting link to ARTAG**  
185 (McKee et al., 2016; Kovacs et al., 2020).

## 186 **5 Do astrocytes contribute to tau pathology spread?**

187 Neurofibrillary tangles have long been acknowledged to follow a stereotypical temporospatial pattern  
188 of spread from the entorhinal cortex as AD progresses (Braak et al., 2011). Recent evidence indicates  
189 that differences in the tau species that deposit in characteristic tau lesions may confer specific  
190 neuronal vulnerabilities and/or prion-like spread of tau (Clavaguera et al., 2013; Dujardin et al.,  
191 2020). Mouse models that express wild-type 3R and 4R human tau isoforms in appropriate ratios  
192 recapitulate the same cell type vulnerabilities that typify human tauopathies when injected with  
193 human tau extracts, including the development of tufted astrocytes in PSP tau-injected mice, and  
194 astroglial plaques in CBD tau-injected mice (He et al., 2020). These data raise the possibility that  
195 astrocytes actively contribute to the spread of pathological forms of tau, **particularly in PSP and**  
196 **CBD**. That tau spreads in a prion-like manner trans-synaptically along anatomical connections was  
197 elegantly shown in transgenic mice in which mutant human (P301L) FTLD-causing tau expression  
198 was restricted to layer II neurons in the entorhinal cortex. Following local tau aggregation, tau  
199 “seeds” were found to spread to the hippocampus and onwards as mice aged (De Calignon et al.,  
200 2012; Liu et al., 2012). Notably, PHF1-positive tau was detected in GFAP-positive astrocytes in the  
201 hippocampus of older mice, suggesting that astrocytes internalise and may contribute to tau spread  
202 (De Calignon et al., 2012) (Figure 1).

203 Heparan sulfate proteoglycans (HSPGs) are a well-conserved group of proteoglycans expressed on  
204 the cell surface of astrocytes and neurons (Turnbull et al., 2001; Sarrazin et al., 2011) that mediate  
205 targeted endocytosis (Turnbull et al., 2001), including that of purified prion proteins *in vitro*  
206 (Schonberger et al., 2003; Horonchik et al., 2005). HSPGs were recently shown to interact with  
207 protein aggregates including  $\alpha$ -synuclein, A $\beta$  and tau (Kanekiyo et al., 2011; Holmes et al., 2013;  
208 Ihse et al., 2017). HSPGs regulate the uptake of synthetic tau fibrils (Holmes et al., 2013) and human  
209 brain-derived tau (Puangmalai et al., 2020) in human immortalised cell lines and mouse primary  
210 neuronal cultures. HSPGs vary in the length of their glycosaminoglycan chains and sulfation  
211 patterns, properties that are important for tau uptake in human embryonic kidney cells (Stopschinski  
212 et al., 2018) and human iPSC derived neurons (Rauch et al., 2018). Interestingly, tau fibrils are  
213 efficiently internalised in a HSPG-dependent manner by primary astrocytes exogenously expressing  
214 transcription factor EB (TFEB), a master regulator of lysosomal biogenesis (Martini-Stoica et al.,  
215 2018). In contrast, monomeric tau appears to be taken up by astrocytes using an HSPG-independent  
216 mechanism (Perea et al., 2019). Together this suggests that multiple mechanisms are involved in tau

## Astrocytes in Tauopathies

217 uptake by astrocytes, that may be specific to tau aggregation state or conformation, as well as the  
218 HSPG profile of the cell type (Tselnicker et al., 2014).

219 HSPGs can also partner with cell surface receptors to mediate the intake of protein aggregates. For  
220 example, HSPGs interact with members of the low-density lipoprotein receptor (LDLR) such as  
221 LRP1, to facilitate A $\beta$  uptake and degradation by astrocytes (Kanekiyo and Bu, 2014; Liu et al.,  
222 2017). Knockdown of LRP1 was recently shown to block the uptake of monomeric and oligomeric  
223 tau in a human neuroglioma cell line, and partially inhibit uptake of sonicated tau fibrils (Rauch et  
224 al., 2020), warranting further investigation into how astrocytic LRP1 may mediate tau uptake and  
225 spread in tauopathies.

226 Astrocytes are an integral part of the glymphatic system of the brain, a clearance system of soluble  
227 proteins and solutes. The astrocytic water channel aquaporin-4 (AQP4), expressed at the astrocyte  
228 end feet, facilitates this process and is important for A $\beta$  clearance (Benarroch, 2007; Iliff et al.,  
229 2012). Disruption to AQP4 may also contribute to tauopathy progression. In a mouse model of CTE,  
230 knockout of AQP4 exacerbated neurofibrillary tau pathology and neurodegeneration (Iliff et al.,  
231 2014). Distinct phosphorylation marks in AQP4 have been reported in human post-mortem ARTAG  
232 samples relative to controls (Ferrer et al., 2018) that are suggested to increase water permeability of  
233 AQP4. However, the functional implications of these modifications in ARTAG remain to be  
234 explored (Han et al., 1998; Kitchen et al., 2015). A recent transcriptional analysis of cognitively-  
235 impaired subjects and controls showed that components of the dystrophin-associated complex, which  
236 anchors AQP4 at the perivascular astrocytic end foot, are associated with phosphorylated tau levels in  
237 the temporal cortex (Simon et al., 2018). This analysis also revealed other astrocyte endfoot  
238 candidate genes that significantly correlate with temporal cortex tau pathology. The authors speculate  
239 that endfoot functions of astrocytes may play a role in the accumulation of tau aggregates throughout  
240 the brain. Although AQP4 might contribute to the clearance of aberrant proteins early in the disease  
241 process, this function could become impaired at later stages, hindering the clearance of pathogenic  
242 tau.

### 243 **6 Tau effects on astrocyte function**

244 In addition to potential roles in tau spread, internalisation of pathological forms of tau has been  
245 shown to disrupt a myriad of astrocytic functions, central for the maintenance and support of  
246 neurons. Oligomeric tau uptake alters calcium signalling and gliotransmitter release (e.g. ATP) via  
247 Ca $^{2+}$ -dependant mechanisms to disrupt post-synaptic currents and downregulate pre- and post-  
248 synaptic markers in neuronal-astrocyte co-cultures (Piacentini et al., 2017), together suggesting that  
249 tau-induced changes to astrocyte function are toxic to neighbouring neurons, at least *in vitro*.  
250 Astrocytes isolated from a transgenic tauopathy model (P301S) expressing a 4R mutant tau isoform  
251 also acquired early functional deficiencies that impaired their ability to support neurons in culture  
252 (Sidoryk-Wegrzynowicz et al., 2017). **Astrocytes from mouse models of tauopathies also show  
253 altered expression of neuronally regulated genes (Hasel et al., 2018), indicating that the accumulation  
254 of abnormal tau species is sufficient to drive transcriptional and likely functional changes in  
255 astrocytes, via altered neuron-astrocyte interactions.** In addition, human astrocytes differentiated from  
256 iPSCs harbouring FTD-causing *MAPT* mutations display an increased vulnerability to oxidative  
257 stress and elevated protein ubiquitination, alongside disease-associated transcriptomic alterations  
258 (Hallmann et al., 2017).

259 The immune-related functions of astrocytes are a major contributor to neuroinflammatory response  
260 that directly alter neuronal integrity in neurodegenerative diseases (Sofroniew and Vinters, 2010). In

261 particular, the complement cascade, which also involves microglia, has an important role in the  
262 accumulation of beta-amyloid pathology (Veerhuis et al., 2011; Lian et al., 2016). C3 is a major  
263 component of the complement cascade and is highly expressed in reactive astrocytes (Liddelow et al.,  
264 2017). C3, as well as its downstream receptor C3aR1, that is mainly expressed by microglia, (Zhang  
265 et al., 2014), is upregulated in postmortem tauopathy brain and correlates with cognitive decline  
266 during disease progression (Litvinchuk et al., 2018). Levels of C3 also correlate with tau amounts in  
267 AD CSF (Wu et al., 2019). Ablation of C3aR or C3 in mouse models of tauopathy reversed neuronal  
268 loss and neurodegeneration (Litvinchuk et al., 2018; Wu et al., 2019), alongside reduced numbers of  
269 GFAP-reactive hypertrophied astrocytes being apparent upon C3aR knockout (Litvinchuk et al.,  
270 2018). These data indicate that complement activation downstream of astrocyte reactivity may be an  
271 important driver of tauopathy.

272 *Astrocytes, together with microglia, are also hypothesized to induce synaptic loss and neurotoxicity*  
273 *in tauopathies, as they do during development (Chung et al., 2013), through dysregulated synaptic*  
274 *pruning (Henstridge et al., 2019). Sleep deprivation is common in AD (Noble and Spires-Jones,*  
275 *2019), where it is believed to be both a cause and consequence of neurodegenerative changes (Noble*  
276 *and Spires-Jones, 2019). Sleep deprivation leads to enhanced tau release and spread (Holth et al.,*  
277 *2019), alongside astrocyte-mediated synapse elimination (Bellessi et al., 2017). It is therefore*  
278 *possible that astrocyte engulfment of tau-containing synapses may be one route by which astrocytes*  
279 *contribute to tau spread in AD.*

280 Ultimately, cross-talk between astrocytes and microglia forms part of a complex innate immune  
281 response that may be exacerbated during tauopathies in response to protein aggregates. Deeper  
282 investigation of these pathways may reveal novel targets that can be exploited to slow or halt disease  
283 progression.

## 284 **7 Discussion**

285 Recent evidence has highlighted that altered astrocyte functions have detrimental consequences for  
286 neurons and may be a driver of neurodegenerative diseases. Astrocytes are closely associated with  
287 the accumulation of pathological forms of tau in tauopathies. There is some evidence that astrocytes  
288 internalise tau aggregates, via mechanisms that are not yet fully understood, and contribute to tau  
289 pathology spread across the brain and tau aggregate clearance via the glymphatic system. However,  
290 astrocytes show significant regional heterogeneity and more work is needed to better understand the  
291 contribution of different astrocyte subtypes in affected brain regions at different disease stages. Such  
292 understanding may aid in the development of astrocyte-targeted therapies for tauopathies. *Astrocyte-*  
293 *targeted therapeutic approaches have been well described elsewhere including by Sadik and*  
294 *Liddelow (2019), and could include antagonists that prevent tau uptake by astrocytes to reduce tau*  
295 *spread, agents that prevent the release of neurotoxic astrocyte secretions or their uptake by neurons,*  
296 *or therapies that restore physiological astrocyte functions including their trophic support for neurons*  
297 *and synapses, maintenance of the blood brain barrier, and roles in the glymphatic clearance of protein*  
298 *aggregates.*

## 299 **7 Conflict of Interest**

300 The authors declare that the research was conducted in the absence of any commercial or financial  
301 relationships that could be construed as a potential conflict of interest.

## 302 **8 Author Contributions**



## Astrocytes in Tauopathies

303 MJR, PBL, LJ, BGP-N and WN wrote and edited the manuscript.

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### 308 **10 References**

309 Acosta, C., Anderson, H. D., and Anderson, C. M. (2017). Astrocyte dysfunction in Alzheimer  
310 disease. *J. Neurosci. Res.* 95, 2430–2447. doi:10.1002/jnr.24075.

311 Ahmed, Z., Bigio, E. H., Budka, H., Dickson, D. W., Ferrer, I., Ghetti, B., et al. (2013). Globular  
312 glial tauopathies (GGT): Consensus recommendations. *Acta Neuropathol.* 126, 537–544.  
313 doi:10.1007/s00401-013-1171-0.

314 Andreadis, A. (2005). Tau gene alternative splicing: Expression patterns, regulation and modulation  
315 of function in normal brain and neurodegenerative diseases. *Biochim. Biophys. Acta - Mol. Basis*  
316 *Dis.* 1739, 91–103. doi:10.1016/j.bbadis.2004.08.010.

317 Benarroch, E. E. (2007). Aquaporin-4, homeostasis, and neurologic disease. *Neurology* 69, 2266 LP  
318 – 2268. doi:10.1212/01.wnl.0000286385.59836.e2.

319 Bellesi, M., de Vivo, L., Chini, M., Gilli, F., Tononi, G., and Cirelli, C. (2017). Sleep loss promotes  
320 astrocytic phagocytosis and microglial activation in mouse cerebral cortex. *J. Neurosci.* 37,  
321 5263–5273. doi: 10.1523/jneurosci.3981-16.2017

322 Besser, L. M., Crary, J. F., Mock, C., and Kukull, W. A. (2017). Comparison of symptomatic and  
323 asymptomatic persons with primary age-related tauopathy. *Neurology* 89, 1707–1715.  
324 doi:10.1212/WNL.0000000000004521.

325 Binder, L. I. (1985). The distribution of tau in the mammalian central nervous system. *J. Cell Biol.*  
326 101, 1371–1378. doi:10.1083/jcb.101.4.1371.

327 Boisvert, M. M., Erikson, G. A., Shokhirev, M. N., and Allen, N. J. (2018). The Aging Astrocyte  
328 Transcriptome from Multiple Regions of the Mouse Brain. *Cell Rep.* 22, 269–285.  
329 doi:10.1016/j.celrep.2017.12.039.

330 Botez, G., Probst, A., Ipsen, S., and Tolnay, M. (1999). Astrocytes expressing hyperphosphorylated  
331 tau protein without glial fibrillary tangles in argyrophilic grain disease. *Acta Neuropathol.* 98,  
332 251–256. doi:10.1007/s004010051077.

333 Bouvier, D. S., Jones, E. V., Quesseveur, G., Davoli, M. A., Ferreira, T. A., Quirion, R., et al. (2016).  
334 High Resolution Dissection of Reactive Glial Nets in Alzheimer's Disease. *Sci. Rep.* 6, 1–15.  
335 doi:10.1038/srep24544.

336 Braak, H., and Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta*  
337 *Neuropathol.* 82, 239–59. doi: 10.1111/j.1750-3639.1991.tb00661.x.

338 Braak, H., Thal, D. R., Ghebremedhin, E., and Del Tredici, K. (2011). Stages of the Pathologic

- 339 Process in Alzheimer Disease: Age Categories From 1 to 100 Years. *J. Neuropathol. Exp.*  
340 *Neurol.* 70, 960–969. doi:10.1097/NEN.0b013e318232a379.
- 341 Bright, F., Ittner, L. M., and Halliday, G. M. (2019). Neuroinflammation in frontotemporal dementia.  
342 *Nat. Rev. Neurol.* 15. doi:10.1038/s41582-019-0231-z.
- 343 Cairns, N. J., Bigio, E. H., Mackenzie, I. R. A., Neumann, M., Lee, V. M. Y., Hatanpaa, K. J., et al.  
344 (2007). Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar  
345 degeneration: Consensus of the Consortium for Frontotemporal Lobar Degeneration. *Acta*  
346 *Neuropathol.* 114, 5–22. doi:10.1007/s00401-007-0237-2.
- 347 Choi, S. S., Lee, H. J., Lim, I., Satoh, J. I., and Kim, S. U. (2014). Human astrocytes: Secretome  
348 profiles of cytokines and chemokines. *PLoS One* 9. doi:10.1371/journal.pone.0092325.
- 349 Chung, W. S., Clarke, L. E., Wang, G. X., Stafford, B. K., Sher, A., Chakraborty, C., et al. (2013).  
350 Astrocytes mediate synapse elimination through MEGF10 and MERTK pathways. *Nature* 504,  
351 394–400. doi: 10.1038/nature12776
- 352 Clavaguera, F., Akatsu, H., Fraser, G., Crowther, R.A., Frank, S., Hench, J., et al. (2013). Brain  
353 homogenates from human tauopathies induce tau inclusions in mouse brain. *Proc Natl Acad Sci*  
354 *U S A.* 110(23), 9535–40. doi: 10.1073/pnas.1301175110.
- 355 Crary, J. F., Trojanowski, J. Q., Schneider, J. A., Abisambra, J. F., Abner, E. L., Alafuzoff, I., et al.  
356 (2014). Primary age-related tauopathy (PART): a common pathology associated with human  
357 aging. *Acta Neuropathol.* 128, 755–766. doi:10.1007/s00401-014-1349-0.
- 358 Darmanis, S., Sloan, S. A., Zhang, Y., Enge, M., Caneda, C., Shuer, L. M., et al. (2015). A survey of  
359 human brain transcriptome diversity at the single cell level. *Proc. Natl. Acad. Sci. U. S. A.* 112,  
360 7285–7290. doi:10.1073/pnas.1507125112.
- 361 De Calignon, A., Polydoro, M., Suárez-Calvet, M., William, C., Adamowicz, D. H., Kopeikina, K. J.,  
362 et al. (2012). Propagation of Tau Pathology in a Model of Early Alzheimer’s Disease. *Neuron*  
363 73, 685–697. doi:10.1016/j.neuron.2011.11.033.
- 364 Dickson, D. W. (2001). Neuropathology of Pick’s disease. *Neurology* 56, S16–S20.  
365 doi:10.1212/WNL.56.suppl\_4.S16.
- 366 Dickson, D. W., Kouri, N., Murray, M. E., and Josephs, K. A. (2011). Neuropathology of  
367 frontotemporal lobar degeneration-Tau (FTLD-Tau). *J. Mol. Neurosci.* 45, 384–389.  
368 doi:10.1007/s12031-011-9589-0.
- 369 Dujardin, S., Commins, C., Lathuiliere, A., Beerepoot, P., Fernandes, A. R., Kamath, T. V., et al.  
370 (2020). Tau molecular diversity contributes to clinical heterogeneity in Alzheimer’s disease.  
371 *Nat. Med.* doi:10.1038/s41591-020-0938-9.
- 372 Falcon, B., Zhang, W., Murzin, A. G., Murshudov, G., Garringer, H. J., Vidal, R., et al. (2018).  
373 Structures of filaments from Pick’s disease reveal a novel tau protein fold. *Nature* 561, 137–  
374 140. doi:10.1038/s41586-018-0454-y.
- 375 Falcon, B., Zivanov, J., Zhang, W., Murzin, A. G., Garringer, H. J., Vidal, R., et al. (2019). Novel tau

## Astrocytes in Tauopathies

- 376 filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. *Nature*.  
377 doi:10.1038/s41586-019-1026-5.
- 378 Ferrer, I., García, M. A., González, I. L., Lucena, D. D., Villalonga, A. R., Tech, M. C., et al. (2018).  
379 Aging-related tau astrogliaopathy (ARTAG): Not only tau phosphorylation in astrocytes. *Brain*  
380 *Pathol.* doi:10.1111/bpa.12593.
- 381 Ferrer, I., López-González, I., Carmona, M., Arregui, L., Dalfó, E., Torrejón-Escribano, B., et al.  
382 (2014). Glial and neuronal tau pathology in tauopathies: Characterization of disease-specific  
383 phenotypes and tau pathology progression. *J. Neuropathol. Exp. Neurol.* 73, 81–97.  
384 doi:10.1097/NEN.000000000000030.
- 385 Fitzpatrick, A. W. P., Falcon, B., He, S., Murzin, A. G., Murshudov, G., Garringer, H. J., et al.  
386 (2017). Cryo-EM structures of tau filaments from Alzheimer's disease. *Nature* 547, 185–190.  
387 doi:10.1038/nature23002.
- 388 Forrest, S. L., Kril, J. J., and Halliday, G. M. (2019). Cellular and regional vulnerability in  
389 frontotemporal tauopathies. *Acta Neuropathol.* 138, 705–727. doi:10.1007/s00401-019-02035-7.
- 390 Forrest, S. L., Kril, J. J., Stevens, C. H., Kwok, J. B., Hallupp, M., Kim, W. S., et al. (2018). Retiring  
391 the term FTDP-17 as MAPT mutations are genetic forms of sporadic frontotemporal  
392 tauopathies. *Brain* 141, 521–534. doi:10.1093/brain/awx328.
- 393 Garwood, C. J., Ratcliffe, L. E., Simpson, J. E., Heath, P. R., Ince, P. G., and Wharton, S. B. (2017).  
394 Review: Astrocytes in Alzheimer's disease and other age-associated dementias: a supporting  
395 player with a central role. *Neuropathol. Appl. Neurobiol.* 43, 281–298. doi:10.1111/nan.12338.
- 396 Goedert, M., and Jakes, R. (1990). Expression of separate isoforms of human tau protein: correlation  
397 with the tau pattern in brain and effects on tubulin polymerization. *EMBO J.* 9, 4225–4230.  
398 doi:10.1002/j.1460-2075.1990.tb07870.x.
- 399 Guerreiro, R. J., Gustafson, D. R., and Hardy, J. (2012). The genetic architecture of Alzheimer's  
400 disease: Beyond APP, PSEN2 and APOE. *Neurobiol. Aging* 33, 437–456.  
401 doi:10.1016/j.neurobiolaging.2010.03.025.
- 402 Guo, T., Noble, W., and Hanger, D. P. (2017). Roles of tau protein in health and disease. *Acta*  
403 *Neuropathol.* 133, 665–704. doi:10.1007/s00401-017-1707-9.
- 404 Habib, N., McCabe, C., Medina, S., Varshavsky, M., Kitsberg, D., Dvir-Szternfeld, R., et al. (2020).  
405 Disease-associated astrocytes in Alzheimer's disease and aging. *Nat. Neurosci.*  
406 doi:10.1038/s41593-020-0624-8.
- 407 Hallmann, A. L., Araúzo-Bravo, M. J., Mavrommatis, L., Ehrlich, M., Röpke, A., Brockhaus, J., et  
408 al. (2017). Astrocyte pathology in a human neural stem cell model of frontotemporal dementia  
409 caused by mutant TAU protein. *Sci. Rep.* 7, 1–10. doi:10.1038/srep42991.
- 410 Han, Z., Wax, M. B., and Patil, R. V (1998). Regulation of Aquaporin-4 Water Channels by Phorbol  
411 Ester-dependent Protein Phosphorylation. *J. Biol. Chem.* 273, 6001–6004.  
412 doi:10.1074/jbc.273.11.6001.

- 413 Hanger, D. P., Anderton, B. H., and Noble, W. (2009). Tau phosphorylation: the therapeutic  
414 challenge for neurodegenerative disease. *Trends Mol. Med.* 15, 112–119.  
415 doi:10.1016/j.molmed.2009.01.003.
- 416 Hasel, P., Dando, O., Jiwaji, Z., Baxter, P., Todd, A.C., Heron, S., Márkus, N.M., McQueen, J.,  
417 Hampton, D.W., Torvell, M., Tiwari, S.S., McKay, S., Eraso-Pichot, A., Zorzano, A., Masgrau,  
418 R., Galea, E., Chandran, S., Wyllie, D.J.A., Simpson, T.I., Hardingham, G.E. (2017). *Nat*  
419 *Commun.* 8:15132.
- 420 He, H. J., Wang, X. S., Pan, R., Wang, D. L., Liu, M. N., and He, R. Q. (2009). The proline-rich  
421 domain of tau plays a role in interactions with actin. *BMC Cell Biol.* 10. doi:10.1186/1471-  
422 2121-10-81.
- 423 He, Z., McBride, J. D., Xu, H., Changolkar, L., Kim, S. jung, Zhang, B., et al. (2020). Transmission  
424 of tauopathy strains is independent of their isoform composition. *Nat. Commun.* 11.  
425 doi:10.1038/s41467-019-13787-x.
- 426 **Henstridge, C.M., Tzioras, M., Paolicelli, R.C. (2019). Glial Contribution to Excitatory and**  
427 **Inhibitory Synapse Loss in Neurodegeneration. *Front Cell Neurosci.* 13:63. doi:**  
428 **10.3389/fncel.2019.00063.**
- 429 Holmes, B. B., DeVos, S. L., Kfoury, N., Li, M., Jacks, R., Yanamandra, K., et al. (2013). Heparan  
430 sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds.  
431 *Proc. Natl. Acad. Sci.* 110, E3138–E3147. doi:10.1073/pnas.1301440110.
- 432 **Holth, J.K., Fritschi, S.K., Wang, C., Pedersen, N.P., Cirrito, J.R., Mahan, T.E., Finn, M.B., Manis,**  
433 **M., Geerling, J.C., Fuller, P.M., Lucey, B.P., Holtzman, D.M. (2019). The sleep-wake cycle**  
434 **regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science.* 363(6429):880-884.**  
435 **doi: 10.1126/science.aav2546.**
- 436 Horonchik, L., Tzaban, S., Ben-Zaken, O., Yedidia, Y., Rouvinski, A., Papy-Garcia, D., et al. (2005).  
437 Heparan sulfate is a cellular receptor for purified infectious prions. *J. Biol. Chem.* 280, 17062–  
438 17067. doi:10.1074/jbc.M500122200.
- 439 Ihse, E., Yamakado, H., Wijk, X. M. Van, Lawrence, R., and Esko, J. D. (2017). Cellular  
440 internalization of alpha- synuclein aggregates by cell surface heparan sulfate depends on  
441 aggregate conformation and cell type. *Sci. Rep.*, 1–10. doi:10.1038/s41598-017-08720-5.
- 442 Iliff, J. J., Chen, M. J., Plog, B. A., Zeppenfeld, D. M., Soltero, M., Yang, L., et al. (2014).  
443 Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury.  
444 *J. Neurosci.* 34, 16180–16193. doi:10.1523/JNEUROSCI.3020-14.2014.
- 445 Iliff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., et al. (2012). A  
446 paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of  
447 interstitial solutes, including amyloid  $\beta$ . *Sci. Transl. Med.* 4. doi:10.1126/scitranslmed.3003748.
- 448 Jellinger, K. A., Alafuzoff, I., Attems, J., Beach, T. G., Cairns, N. J., Crary, J. F., et al. (2015).  
449 PART, a distinct tauopathy, different from classical sporadic Alzheimer disease. *Acta*  
450 *Neuropathol.* 129, 757–762. doi:10.1007/s00401-015-1407-2.

## Astrocytes in Tauopathies

- 451 Jellinger, K. A., and Attems, J. (2007). Neurofibrillary tangle-predominant dementia: Comparison  
452 with classical Alzheimer disease. *Acta Neuropathol.* 113, 107–117. doi:10.1007/s00401-006-  
453 0156-7.
- 454 Josephs, K. A., Hodges, J. R., Snowden, J. S., MacKenzie, I. R., Neumann, M., Mann, D. M., et al.  
455 (2011). Neuropathological background of phenotypical variability in frontotemporal dementia.  
456 *Acta Neuropathol.* 122, 137–153. doi:10.1007/s00401-011-0839-6.
- 457 Jucker, M., and Walker, L. C. (2018). Propagation and spread of pathogenic protein assemblies in  
458 neurodegenerative diseases. *Nat. Neurosci.* 21, 1341–1349. doi:10.1038/s41593-018-0238-6.
- 459 Kamphuis, W., Kooijman, L., Orre, M., Stassen, O., Pekny, M., and Hol, E. M. (2015). GFAP and  
460 vimentin deficiency alters gene expression in astrocytes and microglia in wild-type mice and  
461 changes the transcriptional response of reactive glia in mouse model for Alzheimer's disease.  
462 *Glia* 63, 1036–1056. doi:10.1002/glia.22800.
- 463 Kanekiyo, T., and Bu, G. (2014). The low-density lipoprotein receptor-related protein 1 and amyloid-  
464  $\beta$  clearance in Alzheimer's disease. *Front. Aging Neurosci.* 6, 1–12.  
465 doi:10.3389/fnagi.2014.00093.
- 466 Kanekiyo, T., Zhang, J., Liu, Q., Liu, C. C., Zhang, L., and Bu, G. (2011). Heparan sulphate  
467 proteoglycan and the low-density lipoprotein receptor-related protein 1 constitute major  
468 pathways for neuronal amyloid- $\beta$  uptake. *J. Neurosci.* 31, 1644–1651.  
469 doi:10.1523/JNEUROSCI.5491-10.2011.
- 470 Kersaitis, C., Halliday, G. M., and Kril, J. J. (2004). Regional and cellular pathology in  
471 frontotemporal dementia: Relationship to stage of disease in cases with and without Pick bodies.  
472 *Acta Neuropathol.* 108, 515–523. doi:10.1007/s00401-004-0917-0.
- 473 Kitchen, P., Day, R. E., Taylor, L. H. J., Salman, M. M., Bill, R. M., Conner, M. T., et al. (2015).  
474 Identification and Molecular Mechanisms of the Rapid Tonicity-induced Relocalization of the  
475 Aquaporin 4 Channel. *J. Biol. Chem.* 290, 16873–16881. doi:10.1074/jbc.M115.646034.
- 476 Kovacs, G. G., and Budka, H. (2010). Current concepts of neuropathological diagnostics in practice:  
477 Neurodegenerative diseases. *Clin. Neuropathol.* 29, 271–288. doi:10.5414/npp29271.
- 478 Kovacs, G. G., Ferrer, I., Grinberg, L. T., Alafuzoff, I., Attems, J., Budka, H., et al. (2016). Aging-  
479 related tau astroglial pathology (ARTAG): harmonized evaluation strategy. *Acta Neuropathol.* 131,  
480 87–102. doi:10.1007/s00401-015-1509-x.
- 481 Kovacs, G. G., Robinson, G. L., Xie, S.X., Lee, E.B., Grossman, M., Wolk, D.A., et al. (2017).  
482 Evaluating the Patterns of Aging-Related Tau Astroglial Pathology Unravels Novel Insights Into  
483 Brain Aging and Neurodegenerative Diseases. *J Neuropathol Exp Neurol.* 76(4), 270–288. doi:  
484 10.1093/jnen/nlx007
- 485 Kovacs, G. (2018). Understanding the Relevance of Aging-Related Tau Astroglial Pathology (ARTAG).  
486 *Neuroglia* 1, 339–350. doi:10.3390/neuroglia1020023.
- 487 **Kovacs, G. G. (2020). Astroglia and Tau: New Perspectives. *Front. Aging Neurosci.* 12, 1–14.**  
488 **doi:10.3389/fnagi.2020.00096.**

- 489 Lace, G., Ince, P. G., Brayne, C., Savva, G. M., Matthews, F. E., de Silva, R., et al. (2012). Mesial  
490 Temporal Astrocyte Tau Pathology in the MRC-CFAS Ageing Brain Cohort. *Dement. Geriatr.*  
491 *Cogn. Disord.* 34, 15–24. doi:10.1159/000341581.
- 492 Lane, C. A., Hardy, J., and Schott, J. M. (2018). Alzheimer's disease. *Eur. J. Neurol.* 25, 59–70.  
493 doi:10.1111/ene.13439.
- 494 Leyns, C. E. G., and Holtzman, D. M. (2017). Glial contributions to neurodegeneration in  
495 tauopathies. *Mol. Neurodegener.* 12, 1–16. doi:10.1186/s13024-017-0192-x.
- 496 Lian, H., Litvinchuk, A., Chiang, A. C. A., Aithmitti, N., Jankowsky, J. L., and Zheng, H. (2016).  
497 Astrocyte-microglia cross talk through complement activation modulates amyloid pathology in  
498 mouse models of alzheimer's disease. *J. Neurosci.* 36, 577–589.  
499 doi:10.1523/JNEUROSCI.2117-15.2016.
- 500 Lian, H., Yang, L., Cole, A., Sun, L., Chiang, A. C. A., Fowler, S. W., et al. (2015). NFκB-Activated  
501 Astroglial Release of Complement C3 Compromises Neuronal Morphology and Function  
502 Associated with Alzheimer's Disease. *Neuron* 85, 101–115. doi:10.1016/j.neuron.2014.11.018.
- 503 Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., et al.  
504 (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 541, 481–487.  
505 doi:10.1038/nature21029.
- 506 Sadick, J.S., Liddelow, S.A. (2019). Don't forget astrocytes when targeting Alzheimer's disease. *Br J*  
507 *Pharmacol.* 176(18):3585-3598. doi: 10.1111/bph.14568.
- 508 Ling, H., Kovacs, G. G., Vonsattel, J. P. G., Davey, K., Mok, K. Y., Hardy, J., et al. (2016).  
509 Astroglipathy predominates the earliest stage of corticobasal degeneration pathology. *Brain*  
510 139, 3237–3252. doi:10.1093/brain/aww256.
- 511 Litvinchuk, A., Wan, Y. W., Swartzlander, D. B., Chen, F., Cole, A., Propson, N. E., et al. (2018).  
512 Complement C3aR Inactivation Attenuates Tau Pathology and Reverses an Immune Network  
513 Deregulated in Tauopathy Models and Alzheimer's Disease. *Neuron* 100, 1337-1353.e5.  
514 doi:10.1016/j.neuron.2018.10.031.
- 515 Liu, C., Hu, J., Zhao, N., Wang, J., Wang, N., Cirrito, J. R., et al. (2017). Astrocytic LRP1 Mediates  
516 Brain Aβ Clearance and Impacts Amyloid Deposition. *J. Neurosci.* 37, 4023–4031.  
517 doi:10.1523/JNEUROSCI.3442-16.2017.
- 518 Liu, L., Drouet, V., Wu, J. W., Witter, M. P., Small, S. A., Clelland, C., et al. (2012). Trans-synaptic  
519 spread of tau pathology in vivo. *PLoS One* 7, 1–9. doi:10.1371/journal.pone.0031302.
- 520 Lushnikova, I., Skibo, G., Muller, D., and Nikonenko, I. (2009). Synaptic Potentiation Induces  
521 Increased Glial Coverage of Excitatory Synapses in CA1 Hippocampus. 762, 753–762.  
522 doi:10.1002/hipo.20551.
- 523 Martini-Stoica, H., Cole, A. L., Swartzlander, D. B., Chen, F., Wan, Y. W., Bajaj, L., et al. (2018).  
524 TFEB enhances astroglial uptake of extracellular tau species and reduces tau spreading. *J. Exp.*  
525 *Med.* 215, 2355–2377. doi:10.1084/jem.20172158.

## Astrocytes in Tauopathies

- 526 McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Dirk Keene, C., Litvan, I., et al. (2016).  
527 The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the  
528 diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol.* 131, 75–86.  
529 doi:10.1007/s00401-015-1515-z.
- 530 McKee, A. C., Stein, T. D., Kiernan, P. T., and Alvarez, V. E. (2015). The neuropathology of chronic  
531 traumatic encephalopathy. *Brain Pathol.* 25, 350–364. doi:10.1111/bpa.12248.
- 532 McKee, A. C., Stein, T. D., Nowinski, C. J., Stern, R. A., Daneshvar, D. H., Alvarez, V. E., et al.  
533 (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136, 43–64.  
534 doi:10.1093/brain/aws307.
- 535 McKenzie, A. T., Wang, M., Hauberg, M. E., Fullard, J. F., Kozlenkov, A., Keenan, A., et al. (2018).  
536 Brain Cell Type Specific Gene Expression and Co-expression Network Architectures. *Sci. Rep.*  
537 8, 1–19. doi:10.1038/s41598-018-27293-5.
- 538 Mederos, S., González-Arias, C., and Perea, G. (2018). Astrocyte–Neuron Networks: A Multilane  
539 Highway of Signaling for Homeostatic Brain Function. *Front. Synaptic Neurosci.* 10, 1–12.  
540 doi:10.3389/fnsyn.2018.00045.
- 541 **Noble W, Spires-Jones TL. (2019). Sleep well to slow Alzheimer's progression? *Science*.  
542 363(6429):813-814. doi: 10.1126/science.aaw5583.**
- 543 Oberheim, N. A., Wang, X., Goldman, S., and Nedergaard, M. (2006). Astrocytic complexity  
544 distinguishes the human brain. *Trends Neurosci.* 29, 547–553. doi:10.1016/j.tins.2006.08.004.
- 545 Osborn, L. M., Kamphuis, W., Wadman, W. J., and Hol, E. M. (2016). Astrogliosis: An integral  
546 player in the pathogenesis of Alzheimer's disease. *Prog. Neurobiol.* 144, 121–141.  
547 doi:10.1016/j.pneurobio.2016.01.001.
- 548 Parpura, V., Basarsky, T. A., Liu, F., and Jeftinijatt, K. (1994). Glutamate-mediated astrocyte-neuron  
549 signalling. *Nature* 369, 744–747.
- 550 Perea, J. R., López, E., Díez-Ballesteros, J. C., Ávila, J., Hernández, F., and Bolós, M. (2019).  
551 Extracellular Monomeric Tau Is Internalized by Astrocytes. *Front. Neurosci.* 13, 1–7.  
552 doi:10.3389/fnins.2019.00442.
- 553 Perez-Nievas, B.G., Stein, T.D., Tai, H.C., Dols-Icardo, O., Scotton, T.C., Barroeta-Espar, I., et al.  
554 (2013). Dissecting phenotypic traits linked to human resilience to Alzheimer's pathology. *Brain*.  
555 136(Pt 8), 2510-26. doi: 10.1093/brain/awt171
- 556 Piacentini, R., Li Puma, D. D., Mainardi, M., Lazzarino, G., Tavazzi, B., Arancio, O., et al. (2017).  
557 Reduced gliotransmitter release from astrocytes mediates tau-induced synaptic dysfunction in  
558 cultured hippocampal neurons. *Glia* 65, 1302–1316. doi:10.1002/glia.23163.
- 559 Prince, M., Albanese, E., Guerchert, M., Prina, M., Ferri, C., Mazzotti, D. R., et al. (2014). World  
560 Alzheimer Report 2014: Dementia and Risk Reduction, an Analysis of Protective and  
561 Modifiable Factors. *Alzheimer's Dis. Int.* Available at:  
562 <https://www.alz.co.uk/research/WorldAlzheimerReport2014.pdf>.

- 563 Puangmalai, N., Bhatt, N., Montalbano, M., Sengupta, U., Gaikwad, S., Mcallen, S., et al. (2020).  
564 Internalization mechanisms of brain-derived tau oligomers from patients with Alzheimer ' s  
565 disease , progressive supranuclear palsy and dementia with Lewy bodies. *Cell Death Dis.*  
566 doi:10.1038/s41419-020-2503-3.
- 567 Rauch, J. N., Chen, J. J., Sorum, A. W., Miller, G. M., Sharf, T., See, S. K., et al. (2018). Tau  
568 Internalization is Regulated by 6-O Sulfation on Heparan Sulfate Proteoglycans (HSPGs). *Sci.*  
569 *Rep.* 8, 1–10. doi:10.1038/s41598-018-24904-z.
- 570 Rauch, J. N., Luna, G., Guzman, E., Audouard, M., Challis, C., Sibih, Y. E., et al. (2020). LRP1 is a  
571 master regulator of tau uptake and spread. *Nature* 1, 1–5. doi:10.1038/s41586-020-2156-5.
- 572 **Rodriguez, R. D., and Grinberg, L. T. (2015). Argyrophilic grain disease: An underestimated**  
573 **tauopathy. *Dement. Neuropsychol.* 9, 2–8. doi:10.1590/S1980-57642015DN91000002.**
- 574 Sadick, J. S., and Liddelow, S. A. (2019). Don't forget astrocytes when targeting Alzheimer's  
575 disease. *Br. J. Pharmacol.* 176, 3585–3598. doi:10.1111/bph.14568.
- 576 Saito, Y., Ruberu, N. N., Sawabe, M., Arai, T., Tanaka, N., Kakuta, Y., et al. (2004). Staging of  
577 argyrophilic grains: An age-associated tauopathy. *J. Neuropathol. Exp. Neurol.* 63, 911–918.  
578 doi:10.1093/jnen/63.9.911.
- 579 Santello, M., Toni, N., and Volterra, A. (2019). Astrocyte function from information processing to  
580 cognition and cognitive impairment. *Nat. Neurosci.* 22, 154–166. doi:10.1038/s41593-018-  
581 0325-8.
- 582 Sarrazin, S., Lamanna, W. C., and Esko, J. D. (2011). Heparan Sulfate Proteoglycans. *Cold Spring*  
583 *Harb. Perspect. Biol.* 3, a004952–a004952. doi:10.1101/cshperspect.a004952.
- 584 Schonberger, O., Horonchik, L., Gabizon, R., Papy-Garcia, D., Barritault, D., and Taraboulos, A.  
585 (2003). Novel heparan mimetics potently inhibit the scrapie prion protein and its endocytosis.  
586 *Biochem. Biophys. Res. Commun.* 312, 473–479. doi:10.1016/j.bbrc.2003.10.150.
- 587 Seiberlich, V., Bauer, N. G., Schwarz, L., Ffrench-Constant, C., Goldbaum, O., and Richter-  
588 Landsberg, C. (2015). Downregulation of the microtubule associated protein Tau impairs  
589 process outgrowth and myelin basic protein mRNA transport in oligodendrocytes. *Glia* 63,  
590 1621–1635. doi:10.1002/glia.22832.
- 591 Shigetomi, E., Saito, K., Sano, F., and Koizumi, S. C. (2019). Aberrant calcium signals in reactive  
592 astrocytes: A key process in neurological disorders. *Int. J. Mol. Sci.* 20.  
593 doi:10.3390/ijms20040996.
- 594 Sidoryk-Wegrzynowicz, M., Gerber, Y. N., Ries, M., Sastre, M., Tolkovsky, A. M., and Spillantini,  
595 M. G. (2017). Astrocytes in mouse models of tauopathies acquire early deficits and lose  
596 neurosupportive functions. *Acta Neuropathol. Commun.* 5, 89. doi:10.1186/s40478-017-0478-9.
- 597 Simon, M. J., Wang, M. X., Murchison, C. F., Roese, N. E., Boespflug, E. L., Woltjer, R. L., et al.  
598 (2018). Transcriptional network analysis of human astrocytic endfoot genes reveals region-  
599 specific associations with dementia status and tau pathology. *Sci. Rep.* 8, 1–16.  
600 doi:10.1038/s41598-018-30779-x.



## Astrocytes in Tauopathies

- 601 Sofroniew, M. V, and Vinters, H. V (2010). Astrocytes: biology and pathology. *Acta Neuropathol.*  
602 119, 7–35. doi:10.1007/s00401-009-0619-8.
- 603 Stein, T. D., Alvarez, V. E., and McKee, A. C. (2014). Chronic traumatic encephalopathy: a  
604 spectrum of neuropathological changes following repetitive brain trauma in athletes and military  
605 personnel. *Alzheimers. Res. Ther.* 6, 4. doi:10.1186/alzrt234.
- 606 Stopschinski, B. E., Holmes, B. B., Miller, G. M., Manon, V. A., Vaquer-Alicea, J., Prueitt, W. L., et  
607 al. (2018). Specific glycosaminoglycan chain length and sulfation patterns are required for cell  
608 uptake of tau versus -synuclein and -amyloid aggregates. *J. Biol. Chem.* 293, 10826–10840.  
609 doi:10.1074/jbc.RA117.000378.
- 610 Tselnicker, I. F., Boisvert, M. M., and Allen, N. J. (2014). The role of neuronal versus astrocyte-  
611 derived heparan sulfate proteoglycans in brain development and injury. *Biochem. Soc. Trans.*  
612 42, 1263–1269. doi:10.1042/BST20140166.
- 613 Turnbull, J., Powell, A., and Guimond, S. (2001). Heparan sulfate: Decoding a dynamic  
614 multifunctional cell regulator. *Trends Cell Biol.* 11, 75–82. doi:10.1016/S0962-8924(00)01897-  
615 3.
- 616 Vainchtein, I. D., and Molofsky, A. V. (2020). Astrocytes and Microglia: In Sickness and in Health.  
617 *Trends Neurosci.* 43, 144–154. doi:10.1016/j.tins.2020.01.003.
- 618 Veerhuis, R., Nielsen, H. M., and Tenner, A. J. (2011). Complement in the brain. *Mol. Immunol.* 48,  
619 1592–1603. doi:10.1016/j.molimm.2011.04.003.
- 620 Volterra, A., and Meldolesi, J. (2005). Astrocytes, from brain glue to communication elements: The  
621 revolution continues. *Nat. Rev. Neurosci.* 6, 626–640. doi:10.1038/nrn1722.
- 622 Wang, Y., and Mandelkow, E. (2016). Tau in physiology and pathology. *Nat. Rev. Neurosci.* 17, 5–  
623 21. doi:10.1038/nrn.2015.1.
- 624 Wruck, W., and Adjaye, J. (2020). Meta-analysis of human prefrontal cortex reveals activation of  
625 GFAP and decline of synaptic transmission in the aging brain. *Acta Neuropathol. Commun.* 8,  
626 1–18. doi:10.1186/s40478-020-00907-8.
- 627 Wu, T., Dejanovic, B., Gandham, V. D., Carano, R. A. D., Sheng, M., Hanson, J. E., et al. (2019).  
628 Complement C3 Is Activated in Human AD Brain and Is Required for Neurodegeneration in  
629 Mouse Models of Amyloidosis and Tauopathy Article Complement C3 Is Activated in Human  
630 AD Brain and Is Required for Neurodegeneration in Mouse Models of Amyloidosis and T.  
631 *CellReports* 28, 2111-2123.e6. doi:10.1016/j.celrep.2019.07.060.
- 632 Zamanian, J. L., Xu, L., Foo, L. C., Nouri, N., Zhou, L., Giffard, R. G., et al. (2012). Genomic  
633 analysis of reactive astrogliosis. *J. Neurosci.* 32, 6391–6410. doi:10.1523/JNEUROSCI.6221-  
634 11.2012.
- 635 Zhang, W., Tarutani, A., Newell, K. L., Murzin, A. G., Matsubara, T., Falcon, B., et al. (2020).  
636 Novel tau filament fold in corticobasal degeneration. *Nature* 580. doi:10.1038/s41586-020-  
637 2043-0.

638 Zhang, Y., Chen, K., Sloan, S. A., Bennett, M. L., Scholze, A. R., O’Keeffe, S., et al. (2014). An  
639 RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the  
640 cerebral cortex. *J. Neurosci.* 34, 11929–11947. doi:10.1523/JNEUROSCI.1860-14.2014.

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## 642 **11 Figure legends**

643 **Figure 1.** Astrocytic mechanisms that may contribute to spread of tau pathology. 1) Tau monomers  
644 and aggregates are released from neurons via various mechanisms, including from the pre-synapse, 2)  
645 Astrocytes have specific HSPGs and receptors such as LDR1 that may mediate the uptake of tau  
646 aggregates, 3) These aggregates may be internalised and processed by various mechanisms, include  
647 lysosomal degradation, 4) Disruption of AQP4 in perivascular astrocytic end-feet may contribute to  
648 the disrupted tau clearance and the accumulation of tau aggregates in the CNS.

649 HSPG, heparin sulfate proteoglycan; LDR1, low density lipoprotein receptor-related protein 1;  
650 AQP4, aquaporin-4

651

Disease	PiD	PSP	CBD	AGD	GGT	ARTAG	AD	PART	CTE
<b>Common clinical symptoms</b>	Aphasia, several behavioural changes including and personality changes, cognitive changes at later stages of disease.	Balance and motor deficits, dysphagia and aphagia.	Motor problems (often one-sided), aphagia, dysphagia.	Amnestic mild cognitive impairment often accompanied by neuropsychiatric symptoms.	Behavioural changes, mood swings, short-term memory loss.	Often no cognitive impairment or dementia related symptoms. Focal pathology may correlate with specific deficits, especially in the presence of co-pathology.	Dementia; progressive episodic memory deficits; navigational and multi-tasking difficulties; diverse behavioural and personality changes.	Associated with cognitive impairment and mild AD-like symptoms.	Behavioural changes, mood swings, short-term memory loss.
<b>MAPT cause/risk</b>	Mostly sporadic;  MAPT mutations (exon 9, 10, 11, 12, 13 and intron 9, 10).	Mostly sporadic,  H1/H1c MAPT haplotype increases risk;  MAPT mutations (exon 1, 10, and intron 10);	Mostly sporadic;  H1 MAPT haplotype increases risk;  MAPT mutations (exon 10, 13 & intron 10);	H1 MAPT haplotype may increase risk;  MAPT mutations (exon 10)	H1 MAPT haplotype;  MAPT mutations (exons 1, 10, 11, intron 10).	<i>Depending on sub-type and classification</i>	Mostly sporadic;  APP, PSEN1, PSEN2;  No MAPT mutations	<i>Depending on sub-type and classification</i>	<i>Unknown</i> (external causes)
<b>Primary tau isoforms that</b>	3R	4R	4R	4R	4R	4R	3R & 4R	3R & 4R	3R & 4R

<b>accumulate in lesions</b>									
<b>Affected brain regions</b>	Frontal and temporal cortices.	Precentral cortex, subcortex (globus pallidus, substantia nigra, pontine nuclei, subthalamic nuclei).	Frontal and temporal cortices.	Medial temporal lobe.	Frontal, precentral and/or temporal cortices.	Grey and/or white matter, perivascular, subpial, subependymal.	Entorhinal cortex and hippocampus, spreading to most regions except the cerebellum.	Entorhinal cortex, hippocampus.	Begins focally at depths of cerebral sulci, spreads widely to frontal temporal lobes.
<b>Hallmark astrocytic tau pathology</b>	Ramified	Tufted	Astrocytic plaques	Thorn-shaped & granular fuzzy/bush-like	Globular inclusions	Thorn-shaped & granular fuzzy	<i>None</i>	<i>None</i>	Astrocytic tangles and some thorn-shaped astrocytes.
<b>Cellular localisation of astrocytic tau inclusions</b>	Asymmetric 3R (predominant) or 4R tau inclusions in cell bodies & proximal processes.	Symmetric 4R tau inclusions in proximal processes.	4R tau in distal processes and end feet; thread-like processes are also common.	4R tau inclusions and diffuse staining in cell bodies & proximal-distal processes.	4R globular tau in cell bodies & proximal processes.	4R tau inclusions and diffuse staining in cell bodies & proximal processes.	<i>n/a</i>	<i>n/a</i>	Irregular p-tau lesions (around small vessels).

## Astrocytes in Tauopathies

<b>References</b>	Forrest et al., (2018; 2019); Dickson, (2001; 2011); ; Josephs et al., (2011); Ferrer et al., (2014).	Forrest et al., (2018; 2019); Cairns et al., (2007); Kovacs and Budka, (2010).	Forrest et al., (2018; 2019); Dickson et al., (2011); Ling et al., (2016).	Forrest et al., (2018; 2019); Botez et al., (1999); Saito et al., (2004).	Forrest et al., (2018; 2019); Ahmed et al., (2013).	Forrest et al., (2018; 2019); Kovacs et al., (2016, 2017, 2018, 2020).	Guerreiro et al., (2012); Braak and Braak, (1991); Braak et al., (2011).	Forrest et al., (2018; 2019); Crary et al., (2014); Jellinger et al., (2015).	Forrest et al., (2018; 2019); Stein et al., (2014); McKee et al., (2015; 2016).
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654 **Table 1:** Overview of the **main clinical**, genetic, molecular, and pathological features of tauopathies, including description of astrocyte  
655 abnormalities.

656 PiD, Pick's disease; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; AGD, argyrophilic grain disease; GGT, globular  
657 glial tauopathy; ARTAG, age-related tau astroglipathy; AD, Alzheimer's disease; PART, primary age-related tauopathy; CTE, chronic  
658 traumatic encephalopathy; 3R, 3-repeat tau; 4R, 4-repeat tau.

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