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White Matter Degeneration in Vascular and Other Ageing-Related Dementias

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Abstract

Advances in neuroimaging have enabled greater understanding of the progression of cerebral degenerative processes associated with ageing-related dementias. Leukoaraiosis or rarefied white matter (WM) originally described on computed tomography is one of the most prominent changes which occurs in older age. White matter hyperintensities (WMH) evident on magnetic resonance imaging have become commonplace to describe WM changes in relation to cognitive dysfunction, types of stroke injury, cerebral small vessel disease and neurodegenerative disorders including Alzheimer's disease. Substrates of WM degeneration collectively include myelin loss, axonal abnormalities, arteriolosclerosis and parenchymal changes resulting from lacunar infarcts, microinfarcts, microbleeds and perivascular spacing. WM cells incorporating astrocytes, oligodendrocytes, pericytes and microglia are recognised as key cellular components of the gliovascular unit. They respond to ongoing pathological processes in different ways leading to disruption of the gliovascular unit. The most robust alterations involve oligodendrocyte loss and astrocytic clasmatodendrosis with displacement of the water channel protein, aquaporin 4. These modifications likely precede arteriolosclerosis and capillary degeneration and involve tissue oedema, breach of the blood-brain barrier (BBB) and induction of a chronic hypoxic state in the deep WM. Several pathophysiological mechanisms are proposed to explain how WM changes commencing with haemodynamic changes within the vascular system impact on cognitive dysfunction. Animal models simulating cerebral hypoperfusion in man have paved the way for several translational opportunities. Various compounds with variable efficacies have been tested to reduce oxidative stress, inflammation and BBB damage in the WM. **Our review demonstrates that WM degeneration encompasses multiple substrates and therefore more than one pharmacological approach is necessary to preserve axonal function and prevent cognitive impairment.**

Key words: Ageing, astrocytes, clasmatodendrocyte, blood brain barrier, cognitive impairment, post-stroke dementia, stroke, vascular dementia, white matter

Abbreviations used: AD, Alzheimer's disease; APP, amyloid precursor protein; BBB, blood-brain barrier; BCAS, bilateral carotid artery stenosis; BMP4, bone-marrow protein 4; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CFAS, Cognitive Function in Ageing Study; DTI, diffusion tensor imaging; DWML, deep

white matter lesions; GFAP, glial fibrillary acidic protein; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein, dMBP; degenerating form of MBP; MRI, magnetic resonance imaging; OPC, oligodendrocyte precursor cell; PLP, proteolipid protein; PWML, periventricular white matter lesions; SVD, small vessels disease; VCI, vascular cognitive impairment; VaD, vascular dementia; WM, white matter; WMH, white matter hyperintensities; WML, white matter lesions

In this Issue:

The item will contain Figure 3 with text: **In this review, we discuss disintegration of the cellular components of the gliovascular unit in the white matter. This has consequences on blood-brain barrier integrity and is a strong correlate of white matter damage associated with cognitive impairment.** Animal models of cerebral hypoperfusion replicate several features of white matter changes in man. They have been valuable in identifying various agents which target oxidative stress, inflammation and BBB damage.

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Introduction

Ageing related cognitive impairment involves multiple substrates affecting brain structure and function. Neuroimaging evidence shows that white matter (WM) changes are associated with various clinical, sensorimotor, lifestyle, behavioural and cognitive abnormalities, particularly related to the small vessel disease (SVD) syndrome (Pantoni 2010). Imaging evidence reveals that reduced brain volumes, medial temporal lobe atrophy and cortical thinning are related to cognitive dysfunction in both neurodegenerative and cerebrovascular diseases. For example, several imaging studies have found an association between white matter lesions (WML) and global brain atrophy, but it is not clear if this association is independent of shared risk factors (Appelman *et al.* 2009, Schmidt *et al.* 2005). Similarly, lacunar infarcts and microstructural damage in the WM tracts connecting to the cortex may lead to focal cortical thinning with implications for the structural and functional reorganization after stroke (Duering *et al.* 2012). WM changes also contribute to disruption of fronto-subcortical circuits and cortico-cortical disconnectivity (Benjamin *et al.* 2014).

In recent years, the cerebral WM has become an important focus for investigation of mechanisms in brain ageing and dementia. This is consistent with the fact that age *per se* is an important contributor to the progression of WM pathology (Gouw *et al.* 2008b), which relates to increased white matter hyperintensities (WMH) volume and risk factors associated with disability, dementia and death (Inzitari *et al.* 2009). Chronic cerebral hypoperfusion leads to diffuse WM changes, which are strongly correlated with cognitive impairment and depression as well as gait disturbance (Poggesi *et al.* 2011, Longstreth *et al.* 1996). Moreover, carotid artery stenosis is an important risk factor for cerebral WM disease (Kandiah *et al.* 2014, Baradaran *et al.* 2016) and relates to WM damage and cognitive dysfunction (Tomimoto *et al.* 2004, Jokinen *et al.* 2007, Ryberg *et al.* 2011) apparent in subcortical ischemic vascular dementia (VaD) (Shibata *et al.* 2004). Neuropathological examination, albeit with limited sampling has on the whole substantiated various findings identifying the relationship between cerebral and vascular atrophy and cognitive impairment or dementia. The utility of post-mortem imaging of neuropathological specimens, particularly with magnetic resonance imaging (MRI) has further complemented and enabled better understanding of the pathophysiology of the WM (Gouw *et al.* 2008a, Fazekas *et al.* 1991, Fernando *et al.* 2004, McAleese *et al.* 2013).

In this review, we focus on the pathophysiology of the WM in the context of common dementias. We draw on different neuroimaging and neuropathological studies to highlight specific pathologies within the WM that are associated with normal ageing and vascular cognitive disorders in particular. Animal models of cerebral hypoperfusion have also enabled

better understanding on how different cellular and molecular components of the WM alter during ageing-related cerebral hypoperfusion. Although changes in several substrates likely contribute to cognitive impairment, clearly the integrity of the blood-brain barrier (BBB) is an important factor (Wardlaw *et al.* 2013a, Hainsworth *et al.* 2017). The intricately linked gliovascular unit appears a key factor in WM degeneration associated with dementia in which WM changes are prominent, particularly VaD.

Neuroimaging in man

Leukoaraiosis or rarefied white matter was first described as a decreased signal on computed tomography to denote diffuse WM changes (Hachinski *et al.* 1987). More recently, WMH on T2-weighted or FLAIR MRI have been widely analysed to primarily relate to the presence of cerebral SVD (Wardlaw *et al.* 2013b) (Figure 1). WMH are also common in neurodegenerative dementias including Alzheimer's disease (AD) (Prins & Scheltens 2015, Gouw *et al.* 2008a, Frings *et al.* 2014). Their presence in neurodegenerative diseases could reflect pathological processes other than those involved in SVD. However, the prevalence and volumes of WMH as seen on brain T2-weighted MRI increase exponentially with age (de Leeuw *et al.* 2001). In the general population, the prevalence of WMH or WMLs ranges from 11 to 21% in adults aged 64 years and increases to 94% at age 82. Women tend to have a higher degree of WMH than men (Sachdev *et al.* 2016). WMH are more common and extensive in patients with cardiovascular risk factors and symptomatic cerebrovascular disease. In a meta-analysis study (Debette & Markus 2010), WMH were reported to be linked to an increased risk of stroke, dementia and death. These risks are increased in the general population although not consistently in high risk subjects with a history of stroke or vascular disease. The heritability of WMH has been shown to be as high as 45-73% in some cohorts (Atwood *et al.* 2004, Turner *et al.* 2004, Adib-Samii *et al.* 2015). Recent genome-wide association studies have even identified specific loci on chromosome 17 (Fornage *et al.* 2011, Adib-Samii *et al.* 2013). The high heritability of both periventricular white matter hyperintensities (PWMH) as well as deep white matter hyperintensities (DWMH) has also been recognised (Sachdev *et al.* 2016). WMH volumes and their confluency appear to be relevant predictors of subsequent progression of WM damage (Schmidt *et al.* 1999, Ovbiagele & Saver 2006). In an attempt to explain WM degenerative mechanisms, WM changes within the centrum semiovale have been anatomically designated as periventricular white matter (PWML) and deep white matter lesions (DWML) or deep subcortical lesions. DWML have greater tendency to become confluent and may extend periventricularly such that further regional classification of the WM can be difficult.

WMHs are also associated with a more rapid or greater decline in global cognitive performance, executive function, and processing speed (Bolanzadeh *et al.* 2012, Prins & Scheltens 2015). Other studies report an association between periventricular WMH and executive dysfunction or slowing of processing speed, than subcortical WMH (Duering *et al.* 2014). We previously reported that in older stroke survivors, cognitive processing speed and performance as measures of attention were significantly associated with whole WMH volume in the frontal lobe, whereas memory impairment was associated with volumes of WMH in the temporal lobe (Burton *et al.* 2004). In accord with this PWML and DWML sub-regions have been associated with different clinical phenotypes (Kee Hyung *et al.* 2011). However, there is some controversy whether PWML or DWML are of more importance but this could depend on the definition of boundaries between the periventricular and deep WM if the coursing fibres are used as territory markers (Kovari *et al.* 2007). Irrespective of these findings, there is still lack of robust data on whether WMH in different sub-regions e.g. PWML or DWML have differential effects on cognitive function.

Diffusion tensor imaging (DTI) is currently widely used to investigate WM damage in the living brain (Croall *et al.* 2017, Gouw *et al.* 2008a). DTI utilises measures of water diffusion to monitor microstructural alterations in WM tracts. DTI parameters of fractional anisotropy and mean diffusivity provide more specific information on correlates of cognitive function than conventional MRI. Thus, DTI shows progressive reduction in fractional anisotropy and increased mean diffusivity with increasing age, particularly in regions of interest within the centrum semiovale (Salat *et al.* 2005). DTI parameters incorporating microstructural changes within the fibres are correlated with performance in cognitive domains associated with the frontal lobe including executive function, working memory and processing speed. By use of lesion-symptom mapping data and information from probabilistic WM atlases, it appears that the anterior thalamic radiation is the major anatomical structure impacting on processing speed. These findings provide support for the role of frontal-subcortical circuits in cerebral SVD and vascular cognitive impairment (Duering *et al.* 2011, Kalaria & Ihara 2013, Benjamin *et al.* 2014). Furthermore, parallel studies using magnetic resonance spectroscopy suggest a positive correlation between the neuronal marker N-acetyl aspartate-creatine (NAA/Cr) and fractional anisotropy whereas a negative correlation with mean diffusivity. These findings strengthen the evidence that DTI identifies axonal dysfunction or loss, or both along WM tracts in ageing and in cerebral SVD (Charlton *et al.* 2006, Nitkunan *et al.* 2006). Consistent with the microstructural abnormalities, a recent meta-analysis showed that overall cerebral blood flow was low in regions which developed WMH (Shi *et al.* 2016).

Pathological substrates of WMH

The cerebral WM comprises myelinated axons and various glial cells including myelinating oligodendrocytes, oligodendrocyte progenitor cells or NG2-glia, astrocytes and microglia (Table 1). These cellular structures embedded in the extracellular matrix are nourished by a network of capillaries extending from the perforating or medullary end arteries. The pathological correlates of WMH comprise several patterns including myelin pallor or swelling, tissue rarefaction associated with loss of oligodendrocytes, diffuse axonal injury with thinning and varicosities, loosening of axon-oligodendrocyte adhesion and gliosis (Gouw *et al.* 2011, Deramecourt *et al.* 2012, Skrobot *et al.* 2016, Hinman *et al.* 2015) (Figure 1). The tissue changes include lacunes, microinfarcts, microbleeds and perivascular spacing accompanied by degrees of arteriolosclerosis. Depending upon whether it is PWML or DWML, patterns of gliosis may be variable with macrophages present or absent around cavitations and perivascular regions of reactive astrogliosis (Simpson *et al.* 2007a). Although few diffuse amyloid deposits may be evident, cerebral amyloid angiopathy or microatheromas are generally not evident in the WM (Kalaria *et al.* 2012). Microarray studies have further demonstrated that compared to normal appearing WM, in DWML there was differential expression of key genes associated with the immune response, proteolysis, cell cycle progression and control, as well as ion transport (Simpson *et al.* 2009).

As routine pathological sampling is likely to underestimate the burden of WML (Kalaria 2016), some years ago we initiated identification of WML by post-mortem MRI (Fernando *et al.*). This technique was then adopted in the Cognitive Function in Ageing Study (CFAS) allowing MRI directed sampling for further histopathological assessment of lesional and normal appearing WM (Fernando *et al.* 2004). Using this post-mortem approach, CFAS showed that WM pallor is related to dementia, independently of age and gender. PWML are very common in ageing with 87% of non-demented and 95% of demented exhibiting variable degrees of changes (Matthews *et al.* 2009). The odds ratios for dementia with severe PWML was 4.3 (95% CI 1.9–9.8) whereas DWML are seen in greater than 86% of those over 65 years. DWMLs are also less common with 60% frequency in non-demented and 73% in demented individuals and the odds ratios for dementia with severe DWML was 3.3 (1.6–6.8). A combined diagnosis including both WML and histological evidence for SVD was greater in the demented group (32%) compared to non-demented group (24%) with an odds ratio for dementia of 2.9 (1.6–5.5) (Matthews *et al.* 2009).

Vascular pathology and related tissue ischaemic injury

WM vascular changes are most prominent in VaD (Deramecourt *et al.* 2012). However, all neurodegenerative dementias bear some degree of vascular pathology ranging from 61% in frontotemporal dementias to 82% in AD (Toledo *et al.* 2013). Some of this pathology is invariably associated with the WM in the form of SVD. Previous imaging and pathological studies indicated that the medullary arteries and WM of the frontal lobe are especially susceptible to a haemodynamic derangement, leading to much more severe WM damage, than for example in the temporal lobe, during ageing and vascular disease (Furuta *et al.* 1991, Ihara *et al.* 2010). Age-related arteriosclerotic changes and segmental loss of vascular smooth muscle cells along lengths of both the medullary and perforating arteries disrupting flow in the distal arteries and affecting perfusion of the deep WM with the creation of an hypoxic environment (Fernando *et al.* 2006, Kalaria *et al.* 2015).

In the CFAS (Matthews *et al.* 2009), WM vascular pathology as a gross measure was frequently observed with frequency of 71% in non-demented versus 84% in demented subjects. This was most frequently evident as SVD with 60% of elderly non-demented subjects exhibiting these features. Both arteriolosclerosis and perivascular spacing were significantly greater in the DWML compared to normal appearing WM. Quantitative assessment of vascular wall atrophy depicted by the sclerotic index reveals high values (>0.3) are characteristic of most ageing-related dementias and SVD and particularly CADASIL (Fernando *et al.* 2006, Craggs *et al.* 2013). However, sclerotic indices of vessels within the frontal WM did not differentiate post-stroke demented subjects from those who remained stable although there was increased sclerosis in VaD compared to AD subjects (Foster V and RNK, unpublished observations). This was consistent with reductions in cerebral blood flow and cerebral perfusion in elderly stroke survivors who developed delayed dementia (Mori *et al.* 1994, Firbank *et al.* 2011). It is plausible that perforating vessels are already affected as a consequence of ageing prior to induction of infarcts (Brown *et al.* 2009).

The microvascular network within the WM though less dense is equally vulnerable as that in the neocortex. The endothelium of capillaries is activated as indicated by increased expression of the intercellular adhesion molecule in relation to basement membrane collagen IV (Fernando *et al.* 2006). The activation is often accompanied by proliferation of microglia, which release proteases and free radicals to promote further damage over time to components on the extracellular matrix (Rosenberg 2017). As in the cortex, basement membranes within arterioles and capillaries are thickened and undergo intimal thickening. The microvascular network may also show severe distortions in terms of tortuosity, coiling and kinking with the

deep WM (Brown *et al.* 2009), which coincides with leukoariaosis. Consistent with low tissue oxygen tension, within DWML there is induction of hypoxia-inducible factors 1 α and 2 α as well as key hypoxia-regulated proteins such as matrix metalloproteinase-7 and neuroglobin (Fernando *et al.* 2006). These observations are consistent with elevated concentrations of the vasoconstrictor endothelin 1, reflecting abnormal regulation of WM perfusion (Barker *et al.* 2014). However, it is not clear at what threshold point diffuse WM damage implied by the microvascular changes tips over to impact on cognitive function.

Lacunar infarcts (up to 15 mm in size) and microinfarcts are the most common types of vascular pathology related tissue changes in the WM with less frequency of microbleeds or hemosiderin accumulation (Figure 1). In the recent CFAS, cortical microinfarcts were significantly related to higher deep WML scores whereas PWML were related to microinfarcts in subcortical regions (Ince *et al.* 2017). Microbleeds or hemosiderin deposits on histological examination were evident in the WM but their incidence do not appear to be strongly associated with either the burden of WMH or SVD pathology (Janaway *et al.* 2014). Lacunar infarcts are produced when ischaemic damage is focal and of sufficient severity to result in a small area of necrosis, whereas diffuse WM change is considered a form of rarefaction or incomplete infarction where there may be selective damage to several cellular components. Recent imaging studies suggest the pathophysiology of lacunes and WMH is intimately linked and that more than 90% of lacunes evolve at the edge of WMH with a proximal predilection along the course of perforating vessels supplying the WM (Duering *et al.* 2013). This association suggests that hypoperfused area or penumbral region at the edge of the degenerating WM is highly vulnerable to infarction. Lacunes are independently associated with cognitive impairment with up to 37% incidence in elderly subjects (Makin *et al.* 2013, Jokinen *et al.* 2011).

Previous imaging studies have indicated that the size of dilated PVS within the centrum semiovale was correlated with worsening cognitive function, particularly verbal memory (MacLulich *et al.* 2004). Widened perivascular spaces in the WM increase with ageing and are a frequent occurrence in all dementias (Fernando *et al.* 2006, Kalaria 2016) (Figure 1). It is likely that the increased burden and insufficiency in the drainage of the interstitial fluid (Pollock *et al.* 1997) and degraded protein products (Weller *et al.* 2008, Jellinger 2007) into the lymphatic systems play a role in PVS enlargement within the WM.

Myelin loss and cellular implications

Plasma membranes of oligodendrocytes wrap around axons to form the protective myelin sheath (Emery 2010). Myelin is tightly regulated by interplay between intrinsic oligodendrocytic and

extrinsic signals originating from astrocytes and non-glia WM cells and extracellular matrix components (Mitew *et al.* 2014, Itoh *et al.* 2011). These signals determine oligodendrocyte precursor cell (OPC) differentiation to generate dense myelin around receptive axons. Many of these regulatory mechanisms are essential for WM maintenance and repair (Fancy *et al.* 2011, van der Knaap & Bugiani 2017). Of the four common myelin associated proteins namely myelin-associated glycoprotein (MAG), myelin basic protein (MBP), myelin oligodendrocyte glycoprotein and proteolipid protein (PLP), MAG is highly susceptible to ischemia, being expressed only adaxonally removed from the oligodendrocyte cell body. MBP and PLP are expressed throughout the myelin sheath.

Increased WM degeneration is evident by the greater accumulation of degenerating form of MBP (dMBP) (Ihara *et al.* 2010). This is remarkably corroborated by decreased ratios of MBP and PLP which reflect ante-mortem WM ischemia and oligoemia or cerebral **hypoperfusion** in subjects with SVD and VaD compared to AD and ageing controls (Barker *et al.* 2013). In the CFAS cohort, loss of myelin in both the DWML and PWML was evident. However, the area of MBP loss in PWML was associated with a dense feltwork of subependymal glial fibrillary acidic protein (GFAP)-positive processes (Simpson *et al.* 2007a). PWML was also characterized by loss of ependymal cells, leaving gaps in the ependymal lining of the ventricle. The breakdown of the ventricular lining may lead to back-diffusion of the cerebrospinal fluid and contribute to lesion pathogenesis in the periventricular caps (Figure 1).

We previously showed that myelin density in the WM is most reduced in VaD compared to AD and other less prevalent dementias (Ihara *et al.* 2010, Sjobeck *et al.* 2005, Deramecourt *et al.* 2012). However, quantitative analysis determined by myelin index scores suggests all dementias regardless of primary aetiology whether vascular or neurodegenerative show degrees of myelin loss compared to ageing controls (Figure 2). Cognitively normal ageing controls also exhibit considerable myelin loss in relation to pathologically undamaged or intact WM with minimal vascular pathology. Our bivariate analysis revealed that decreased myelin index (increased severity) in the frontal WM was strongly correlated with MMSE and CAMCOG scores, decreased executive function including attention and calculation (Foster V and RK, unpublished observations). This is perhaps not surprising as loss of myelin may lead to disruption of one or more of cortico-subcortico pathways between the frontal cortex and the limbic system or those involving the anteromedial thalamic fibres (see above). The loss of myelin would impact on not only the long-term structural integrity and viability of axons but also essential trophic support impairing the delivery of glycolysis products for mitochondria within the fibres (Nave & Werner 2014). It is thought that rather than any direct toxic effect on

myelin, residing oligodendrocytes are likely vulnerable to the hypoxic environment within the lesional deep WM and impact on myelination (Nedergaard *et al.* 2003).

Axonal Integrity

Axonal pathology has been studied in several ageing-related disorders including AD (Adalbert & Coleman 2013) and SVD (Gouw *et al.* 2011, Hinman *et al.* 2015). It was estimated that about half of the axons in the cerebral WM are myelinated and between age 20 and 80 years up to 45% of WM myelinated fibres are lost with thinner fibres being most affected (Marner *et al.* 2003). Axon density may further be affected by direct infarcts or by “dying back” processes (Adalbert & Coleman 2013). To assess whether axons were similarly affected in regions of myelin loss, we estimated the density of axons in MRI defined lesional i.e. DWML compared to normal appearing WM. Analysis using 3-dimensional stereological methods suggested that while estimated axon numbers was replicated, surprisingly axonal density (expressed as length density) in lesional areas (DWML) was not different to normal WM (Highley *et al.* 2014). The relative axonal preservation in this context of myelin loss parallels with that of multiple sclerosis. However, in CADASIL which is characterised as an aggressive cerebral SVD and exhibits severe WM pathology, SMI32 antibody immunoreactive axons signifying damage were invariably increased in tandem with 24-45% greater arteriolosclerosis (Craggs *et al.* 2014). The regional variability in degrees of axonal damage as revealed by SMI32 immunoreactivity suggests that early changes occur in the frontal lobe with a gradual WM disconnection involving the parietal and temporal lobes. These observations also imply differential stenosis and sclerosis of arterioles in the WM lead to the widespread axonal abnormalities although the U fibres are generally spared. The disruption of the cortico-cortical or cortico-subcortical networks in the WM of the frontal lobe may explain the motor deficits and executive dysfunction in severe SVD.

Glial cells in the WM

Besides myelin, abnormalities in axons, microvessels and glial cells particularly astrocytes and oligodendrocytes are of interest as possible substrates of WMH that correlate with cognitive impairment. Different to rodents, the human WM contains abundant astrocytes which appear to be largely of the fibrous type as opposed to the protoplasmic type. WM cell bodies of human astrocytes are larger and their processes are not aligned with myelinated fibres displaying an elongated morphology like in rodents (Lundgaard *et al.* 2014). The key glial cell type of the WM is the oligodendrocyte, which originates as the oligodendrocyte precursor cell (OPC). The proliferation and migration of OPCs appears to be controlled by astrocytes as they are the main

producers of the platelet-derived growth factor-alpha (PDGF) in the CNS (Richardson *et al.* 1988). Loss of astrocytic function could therefore impact on oligodendrocytes and contribute to WM integrity. In addition, the WM is endowed with a host of microglia, macrophages and pericytes, which are all derived from the same lineage. **Ischaemic injury instigates differential responses during the temporal sequence and spatial distribution of these cells.**

Astrocytes Astrocytes are one of the fundamental glial cells in the WM (Abbott *et al.* 2006). They are important in creating the appropriate milieu and providing energy for oligodendrocytes and axons (Funfschilling *et al.* 2012). Astrocytes also contribute to maintenance of WM integrity and function by orchestrating the control of ion–water homeostasis and preventing intra-myelin oedema (Benfenati & Ferroni 2010). Astrocytic end-feet processes cover more than 90% of the microvasculature and play a crucial role in maintenance of the BBB in the WM. The panglial syncytium, comprising a network of astrocytes, oligodendrocytes and ependymal cells interconnected by gap junctions disperses the water and ions (Depienne *et al.* 2013). In vitro and in vivo studies show that astrocytes can also positively enhance myelination and remyelination. Astrocytes of the WM exhibit regressive changes during ageing and apparently express markers of apoptosis (Kobayashi *et al.* 2002). However, we found that the total astrocyte population in the frontal WM declined in tandem with increased astrocytic clasmatodendrosis in older age (Chen *et al.* 2016). Experimental evidence from brain slices showed that astrocytic clasmatodendrosis occurs rather acutely initiated by acidosis (~pH 5) and energy failure induced by mitochondrial inhibition (Hulse *et al.* 2001). The cellular changes are characterised by cytoplasmic swelling and vacuolation of the soma, with beading and fragmentation of the dendritic processes, leading to irreversible injury via an autophagy-like process (Qin *et al.* 2010). These alterations in cell morphology are directly related to changes in cell function (Hulse *et al.* 2001, Hinson *et al.* 2007). It is plausible that recurrent changes in perfusion pressure or chronic hypoperfusion may alter the local milieu to cause astrocytic clasmatodendrosis and disruption of gliovascular interactions, which progressively worsen with ageing.

We previously noted markers of both myelin and axon damage including the myelin index and immunoreactivities of dMBP, amyloid precursor protein and SMI32 in the WM tended to be increased in post-stroke demented subjects (Foster *et al.* 2014, Akinyemi 2014). However, it was astrocytic clasmatodendrosis in the DWML remote from any infarction that separated the post-stroke demented from post-stroke stable subjects (Chen *et al.* 2016). These observations are consistent the reduced distribution of metallothionein I/ II reactive astrocytes in

the subcortical layers of subjects with Binswanger's disease (Zambenedetti *et al.* 2002) and regressive astroglial changes in the deep WM of a subject with Binswanger's leukoencephalopathy and mixed dementia (AD combined with cerebrovascular disease) (Sahlas *et al.* 2002) although not necessarily associated with demyelination *per se* (Popescu *et al.* 2010). However, Tomimoto (Tomimoto *et al.* 1996, Tomimoto *et al.* 1997) had prior demonstrated that there were significantly more fibrinogen and immunoglobulins in brains exhibiting clasmotodendrosis than those without, which implicated dysfunction of the BBB (Kraig & Chesler 1990, Qin *et al.* 2010). These observations collectively suggest that clasmotodendrosis is an important pathological gauge for disruption of gliovascular interactions with implications for the BBB (Abbott *et al.* 2006).

Microglia The WM predominantly contains ramified bipolar microglia and is devoid of large amoeboid microglia. Microglia may be associated with several functions within the WM including surveillance at the BBB and clearance of myelin debris at sites of WM damage (Lampron *et al.* 2015, Skripuletz *et al.* 2013). In earlier studies, using CD68 as a marker, we observed higher numbers of total microglia in WML, with higher levels in DWML and a trend to higher expression in PWML (Simpson *et al.* 2007b). We further observed that although microglial activation i.e. cells with more retracted processes occurs in both PWML and DWML there were differences in their distribution. PWML contained significantly more activated microglia, expressing major histocompatibility complex class II, the costimulatory molecules B7-2, CD40 and the replication licensing protein mini-chromosome maintenance protein 2. This means the pathogenesis in the PWML contained the ramified, activated microglia reflects an immune activation likely resulting from disruption of the BBB as different from that in the DWML with opposed to the more innate, amoeboid phagocytic cells. We observed that CD68 positive activated amoeboid cells were increased in DWML in post-stroke demented subjects compared to non-demented survivors (YH *et al.*, unpublished observations).

Pericytes Pericytes have multiple functions beyond contractile control of blood flow, providing paracrine signals during angiogenesis and phagocytic activity. They are further specialised as a vital component of the BBB and their processes wrap around the length of capillaries to form close contacts with endothelial cells through peg and socket junctions, gap junctions and adhesion plaques (Hall *et al.* 2014). PDGF- β expressed by endothelial cells recruits pericytes expressing PDGF receptor- β (PDGFR- β) to the capillary wall and inhibition of the signal results in fewer recruited pericytes to the vessel, causing vessel leakage, tortuosity, formation of

microaneurysms, and microbleeds (Carmeliet & Jain 2011). While there is experimental evidence to suggest pericytes are impaired in ischaemic injury (Hall et al. 2014), we have noted markedly decreased number of pericytes per capillary length in all dementias with marked loss in VaD (Ding *et al.* 2017). In contrast, although there was evidence of fibrinogen leakage and reduced oxygenation of the underlying WM of the parietal cortex (precuneus), there was a lack of significant reduction in PDGFR- β reactivity used as a marker of pericytes in AD (Miners *et al.* 2017).

Oligodendrocytes In addition to myelination, remyelination and myelin maintenance, oligodendrocytes have vital roles in the metabolic support of axons. Deficits in such support would impact on neurodegeneration (Bradl & Lassmann 2010). WM oligodendrocytes decrease with ageing and express DNA damage markers such as 8-hydroxy deoxyguanosine (Al-Mashhadi *et al.* 2015). Our findings suggest that oligodendrocyte cell sizes are reduced in DWML likely caused by hypoperfusion or oligoemia. The degenerative changes in oligodendrocytes appear to be a preliminary step towards cell death in the chronic hypoxic environment (Ihara et al. 2010). Oligodendrocyte loss is compensated by differentiating OPCs, which increase during hypoxia/ischemia-induced injury, as an adaptive response for remyelination. OPCs in the adult brain also contribute to WM homeostasis also by interacting with the endothelium and pericytes (Figure 3). When the platelet-derived growth factor α receptor (PDGFR- α) and the +13 isoform of microtubule-associated protein-2 (MAP-2+13) were used as markers, some of the oligodendroglial cells showed a T-shaped pattern of cytoplasmic labelling for MAP-2+13. These cells assuming the morphology of pre-myelinating oligodendrocytes were more frequent in the PWML than in the DWML, particularly at lesion margins. These findings suggested that there may be some attempt by OPCs to remyelinate although greater repair mechanisms may be impaired by age and by degree of pathology (Boulanger & Messier 2014). The paucity of OPCs in DWML may also relate to the hypoxic environment within the deep WM with selective effects on oligodendroglial lineage components. Consistent with this notion, remyelinating oligodendrocytes were reported to be lost in the centre of severely demyelinated WM but proliferated in the perilesional WM (Simpson et al. 2007a).

Gliovascular Interactions and the Blood- Brain Barrier in WM

The concept of the gliovascular unit in the WM is in keeping with the model of the neurovascular unit in the grey matter (Figure 3). The principal components of the gliovascular unit comprising astrocytes juxtaposed to microvessels largely in form of capillaries play a

prominent role in maintaining homeostasis of the BBB. Disturbances in cells forming this unit may critically dysregulate exchange between the blood and the WM tissue. The unit, however, also incorporates pericytes with links to OPCs and microglia (Maki *et al.* 2015a). There is similarly an oligovascular niche, which entails interactions between oligodendrocytes and endothelial cells (Rajani & Williams 2017).

Tight junction proteins such as claudin-V and zona-occludin-1 form tight junction complexes which contribute to the integrity of the BBB (Simpson *et al.* 2010). Abnormalities in these proteins have been observed in a number of disorders associated with BBB dysfunction (Sandoval & Witt 2008, Weiss *et al.* 2009). Quantification of these proteins to assess disruption of tight junctions and use as surrogate markers of BBB permeability indicated that these were not significantly affected in MRI defined DWML although there was widespread albumin extravasation (Simpson *et al.* 2010, Goodall *et al.* 2017). In contrast, loss of astrocytes and retraction of the end-feet which express the transmembrane protein aquaporin 4 (AQP4) that forms channels selective for water mobility (Nagelhus & Ottersen 2013) was severely affected in the DWML (Chen *et al.* 2016). The anchoring of AQP4 from the cytoplasm of astrocytes to the extracellular matrix is dependent on the dystrophin-associated protein complex. Dystrophin connects the filamentous actin in the cytoskeleton to β -dystroglycan, which in turn is bound by laminin and agrin of the basement membranes (Nagelhus & Ottersen 2013). Since capillary basement membranes, the key elements for fluid drainage from the parenchyma are secreted by astrocyte end-feet, the loss of AQP4 would also impair the integrity of basement membranes (Carare *et al.* 2008, Yao *et al.* 2014). Altered AQP4 distribution in the retracted processes and the swelling of astrocytic cell bodies thus impacts on water mobility or water homeostasis and the local microcirculation (Taniguchi *et al.* 2000, Badaut *et al.* 2002).

Contribution of laboratory animal studies

Several animal models have been developed to gain mechanistic insights into the pathophysiology of the WM matter and enable translation to the clinic (Duncombe *et al.* 2017). While efficient models to examine the sequelae of global and focal ischaemic injury have been useful, they have been limited to fully explore various features of WM changes in the context of cerebral hypoperfusion and cerebral SVD. To simulate specific aspects of WM changes resulting from reduced perfusion of the WM, we have focussed on models of bilateral common carotid artery occlusion in rats (referred to as two-vessel occlusion), bilateral common carotid artery stenosis (BCAS) in mice and recently developed bilateral common carotid artery gradual occlusion in rats and mice (Nishio *et al.* 2010, Kitamura *et al.* 2012, Hattori *et al.* 2016b).

The original BCAS experimental model (Shibata *et al.* 2004) established in mice is most relevant to produce cerebral hypoperfusion (Tomimoto *et al.* 2003) by reducing blood flow in both cortical and subcortical structures over a sustained period (Hattori *et al.* 2016a). The BCAS model shares several pathological consequences with cerebral SVD including microinfarcts, microhaemorrhages and WM disruption (Holland *et al.* 2015, Hase *et al.* 2017). BCAS causes gliovascular changes with marked increases in microvessel diameter, vascular wall disruption, and fibrinoid necrosis, microhaemorrhages, and BBB alterations. The GCAS model (Hattori *et al.* 2016b) similarly induces gradual and continuous reduction of cerebral blood flow with replication of several histological, radiological, and behavioural features associated with cerebral hypoperfusion leading to vascular cognitive impairment.

We previously showed that BCAS impaired cognitive function as indicated by longer latencies in the radial arm maze paradigm, impairing nesting ability and causing greater anxiety behaviour. The radial arm maze latencies in older mice (21 months) with BCAS were longer compared to those in younger (3 month) mice indicating greater impairment of hippocampal dependent learning and working memory (Wolf *et al.* 2017). However, at 4 months after BCAS surgery, WM disintegration is quite severe as evident by atrophy along the whole length of the corpus callosum. Consistent with this, MBP was much reduced in the 21 month old mice that may already be compromised by ageing (Wolf *et al.* 2017). Chronic cerebral hypoperfusion leads to a rapid disruption of key proteins critical to the stability of the axon-glia connection, which is mediated by a diversity of molecular events (Reimer *et al.* 2011). As early as 3 days, hypoperfusion damages the paranodal septate-like junctions of myelinated axons. With continued hypoperfusion there is progressive reduction of the paranodal Neurofascin signal and loss of septate-like junctions. Concurrent with paranodal disruption, the nodal length is increased with changes in the spatial distribution of MAG. The APP23 mice show a progressive loss of myelin associated glycoprotein and NF186 from 6 to 12 months, disordered distribution of myelin basic protein, and extended relocation of the channel proteins Nav1.6 and AnkG beyond the primary nodal region in the corpus callosum. These observations suggest WM integrity is compromised along axons at intermodal, paranodal, and Ranvier's nodal sites. These changes can be protected by galantamine treatment (Zhai *et al.* 2016).

Ageing exacerbates the effects to induce more severe WM degeneration and cognitive phenotypes. Thus, consequences of cerebral hypoperfusion including myelin loss, severe loss of oligodendrocytes, activation of inflammatory processes and cognitive impairment were more severe in aged mice (Duncombe *et al.* 2016, Wolf *et al.* 2017). While there could be an attempt for myelin replacement as suggested by increased number of immunolabelled NG2 cells even in

old BCAS mice (Wolf *et al.* 2017), these changes including the preservation of oligodendrocytes can be attenuated by environmental enrichment (EE) intervention more so by limited (3 hours per day) rather than full-time exposure to EE (Hase *et al.* 2017). Moderate level of EE or physical activity appears more beneficial in sustaining WM integrity than no enrichment after chronic hypoperfusion. One of the targets which is critical for the protection of the WM is the cerebral endothelium (Trigiani & Hamel 2017). However, WM integrity in the aged mouse is vulnerable to prolonged cerebral hypoperfusion and hypoxic stress, and loses its ability to also recruit cyclic AMP response element-binding protein (CREB)-mediated oligodendrogenesis for responding to WM injury and stress (Miyamoto *et al.* 2013b). Assessment of CREB-mediated oligodendrogenesis in the WM could be one mechanism to elucidate the effects of limited exposure to EE against WM damage.

BCAS induced WM damage evolves in parallel with bone marrow protein 4 (BMP4) upregulation in pericytes, promoting angiogenesis but inducing astroglialogenesis at the expense of OPC proliferation and maturation (Uemura *et al.* 2017). Since this aggravates WM damage subsequent to chronic hypoperfusion the regulation of BMP4 signalling is a potential therapeutic strategy for treating WM degeneration (Uemura *et al.* 2017). The recent identification of a novel pathway in which astrocyte-derived brain derived nerve growth factor supports oligodendrogenesis (Miyamoto *et al.* 2015) is yet another approach for the amelioration of WM integrity by promoting OPCs, which may serve as a reserve for generating mature oligodendrocytes in damaged WM. In perivascular regions of cerebral WM, pericytes may interact functionally with OPCs to support each other given that pericyte numbers increased when they were maintained in OPC-conditioned media (Maki *et al.* 2015a). However, prior to myelin loss OPCs rapidly responded to WM changes by producing metalloproteinase (MMP)-9 to cause BBB leakage and neutrophil infiltration, indicating that OPCs mediate early injury in WM under disease conditions (Seo *et al.* 2013).

Long-term BCAS induces thickening of carotid artery walls and consequent prolonged reduction in cerebral blood flow (Hase *et al.* 2016). Compensation through collateral flow is not able to prevent reduction in cerebral blood flow but the reduction in flow likely instigates damage in the deep WM particularly targeting oligodendrocytes (Shibata *et al.* 2004, Nishio *et al.* 2010, Washida *et al.* 2010, Maki *et al.* 2011b). Cerebral hypoperfusion therefore also contributes to disconnectivity between cerebral cortices and subcortical structures that result in cognitive and motor deficits (Yamauchi *et al.* 2000, Jokinen *et al.* 2007, Ryberg *et al.* 2011, Ihara *et al.* 2010).

Consistent with the increased degeneration of astrocytes in the deep WM (Chen et al. 2016, Tomimoto et al. 1997), typical clasmatodendrosis identified by damaged fibrous astrocytes with enlarged cell bodies and loss of processes is also evident in BCAS mice. The percentage of clasmatodendrocytes per all GFAP-positive astrocytes was negatively correlated with WM volumes. This was accompanied by profound disruption of AQP4 immunoreactivity (Figure 4) and increased degrees of microglial activation/proliferation. Interestingly, long-term treatment with the pleiotropic compound cilostazol, which is a phosphodiesterase III inhibitor and an antiplatelet agent, ameliorated gliovascular damage and working memory impairments after BCAS possibly acting by protecting the endothelium (Kitamura *et al.* 2017). Preventing chronic cerebral hypoperfusion therefore ought to reduce BBB disruption and maintain the gliovascular integrity.

The astrocytic end-feet AQP4 dislocation caused by BCAS presumably enhances WM pathology due to a disturbance in water homeostasis (Figure 4). These studies suggest that BCAS instigates flow changes and pathological alterations in small arteries and capillaries of the WM leading to breach of the BBB (Mueller 1982, Tang *et al.* 1993, Tomimoto et al. 1996). Such spatial dissociation between the vascular basement membrane and the astrocyte end-feet also occurs in brains of spontaneously hypertensive rats with middle cerebral artery occlusion (MCAO) (Yamashita *et al.* 2009). The basement membrane/extracellular matrix linking endothelial cells are key in maintaining the integrity of the neuro- or gliovascular units, which can be disrupted by tissue plasminogen activator treatment. Microglia in older BCAS mice exhibited striking activation in the area of degraded myelin compared to young adult or old control mice (Wolf et al. 2017). Minocycline, a proposed anti-inflammatory and microglia inhibitor, restored WM function related to a reduction in the number of microglia associated with alterations in myelinated axons induced by cerebral hypoperfusion (Manso *et al.* 2017).

Given the different cellular alterations occurring in the hypoperfused WM, several translational approaches have been attempted. Reactive astrocytes express activated p38 mitogen activated protein kinases (p38 MAPK) and pro-inflammatory transcription factor nuclear factor (NF)-kB (Saggu *et al.* 2016) besides producing reactive oxygen species (ROS) (Nahirnyj *et al.* 2013) and reinforcing cellular inflammation (Cuadrado & Nebreda 2010). Therefore, targeting astrocytes with agents that return them to a quiescent phenotype (Choudhury & Ding 2016) could be protective for the WM. Similarly, identifying molecular targets (Wang *et al.* 2013) of microglial activation and microglial suppressant agents similar to minocycline (Cai *et al.* 2006, Ma *et al.* 2015), ethyl pyruvate (Shen *et al.* 2010), edaravone (Miyamoto *et al.* 2014, Miyamoto *et al.* 2013a) and autophagy inhibitors such as (3-

methyladenine) could attenuate microglial activation (Yang *et al.* 2014) and protect against the WM from further damage. The overproduction of ROS, pro-inflammatory cytokines and matrix metalloproteinases (e. g. MMP-2, MMP-9) (Ihara *et al.* 2001, Miyamoto *et al.* 2014) by microglia or other glial cells promotes BBB disruption and glial activation (Nakaji *et al.* 2006, Wake *et al.* 2009).

Other approaches such as aliskiren, a direct renin inhibitor, or Tempol, a superoxide scavenger may also target oxidative stress to reduce WM damage (Dong *et al.* 2011). Telmisartan, an angiotensin II Type 1 receptor blocker with anti-inflammatory and antioxidative effects was protective against WM damage (Washida *et al.* 2010). WM damage is exacerbated by adrenomedullin deficiency, which induces oxidative stress and hyperglycemia. Thus adrenomedullin is another potentially important target in the control of ischemic WM injury (Mitome-Mishima *et al.* 2014). Adrenomedullin was shown to also promote arteriogenesis and angiogenesis, inhibit oxidative stress and attenuate WM damage (Maki *et al.* 2011b, Maki *et al.* 2011a). In addition, it promoted regeneration of oligodendrocytes subsequent to WM changes (Maki *et al.* 2015b).

Summary and Perspectives

WM degeneration is common in ageing and ageing-related dementias. It is clear that high burden of WML is associated with cognitive decline and dementia. WML have been conveniently demarcated as PWML and DWML. Post-mortem imaging and neuropathological studies suggest different aetiologies are associated with periventricular and deep WM changes. However, PWML and DWML need to be better evaluated in terms of loss of specific functions. Multiple substrates including arteriolosclerosis, myelin loss and gliosis within the degenerating WM collectively appear to contribute to cognitive impairment. The integrity of the gliovascular unit instigated by astrocytic clasmatodendrosis is paramount to maintenance of the BBB and WM physiological function. Besides astrocytes, interactions between other cellular components of the gliovascular unit need to be carefully evaluated. The roles of microglia, perivascular macrophages and pericytes also need to be better defined. Animal models of cerebral hypoperfusion where the WM has been the focus have provided several insights into the pathophysiology and some novel cellular interactions including the oligovascular niche. Animal models have enabled testing of different agents targeting detrimental processes such as oxidative stress and inflammation. While many of these are reasonably efficacious further refinements are needed to identify the most effective strategy for the protection of the WM.

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Author contribution

Yoshiki Hase generated the original data and corrected several drafts of the review.

Karen Horsburgh provided intellectual input and corrected drafts of the review.

Masafumi Ihara conceived some aspects of review and corrected drafts of the review.

Raj N. Kalaria conceived the review, wrote the original manuscript and corrected several drafts and obtained the funding.

Conflict of interest

The co-authors have no disclosures with regard to this report. There are no conflicts of interest.

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Table 1: Neuroimaging and pathological features associated with WM Degeneration and Dementia

Feature	Methodological details	Degree/ Frequency of change	Association with CI/Dementia
WMH (T2 weighted MRI)	Total or ROI (PWML, DWML) WMH volumes assessed by voxels	Increased with age	Strong
Vascular pathology score (range)‡	Pathological scoring system, 1-20.	Score of >10	Weak
White Matter Score	WM pathology scoring system, 0-3.	Scores 2-3	Moderate
Myelin Index (MI); myelin loss (demyelination)	Myelin density scoring system, quartiles.	MI score of >50%	Strong
Sclerotic Index (SI)	Arteriolosclerosis measuring system	SI > 300µm	Unclear
Arteriolosclerosis	Semi-quantitative scoring system (0-3)	Score of 2-3	Weak
Hyalinosis, lipohyalinosis, fibroid necrosis	WM, cortical and subcortical grey matter	Moderate	Unknown
WM Endothelium	Density of GLUT1 immunostain	Moderate	Weak
Basement membranes	Density of COL4 immunostain	Thickening	Weak
Pericytes	Counts in COL4 immunostained sections	Loss	Strong
Oligodendrocyte changes	Density in H&E sections	High	Unclear
Oligodendrocyte precursor cells (OPCs)	Density of GLUT1 immunostain	Low	Unknown
Axonal loss	Density length determined by 3 D stereology	Low	Unclear
Axonal abnormalities	SMI32 and APP immunostains	Variable	Moderate

Complete infarctions (macroscopic), arterial territorial infarctions	Cortical and subcortical regions in H&E stained sections	Moderate	Weak
Lacunar infarcts	Counts in H&E sections	Moderate	Moderate
Small or microinfarcts	Counts in H&E sections	High	Strong
Microbleeds	Counts in H&E sections	Low	Unknown
Microspongy form change	Semi-quantitative scoring system (0-3)	Moderate	Unknown
Perivascular spacing	Semi-quantitative scoring system (0-3)	Moderate	Moderate
Gliosis: astrocytosis	Density of GFAP, CD68 immunostain	Variable	Moderate
Microglia/Macrophages	Density of CD68 immunostain	Moderate	Unknown

Data summarised from several sources (Craggs et al. 2013, Deramecourt et al. 2012, Ihara et al. 2010, Lammie *et al.* 1997, Skrobot et al. 2016). ‡Vascular pathology scores were derived as described previously (Deramecourt et al. 2012). Abbreviations: DWML, deep white matter lesions; MRI, magnetic resonance imaging; PWML, periventricular lesions; ROI, region(s) of interest; WMH, white matter hyperintensity; WM, white matter.

Figure legends

Figure 1: White matter lesions visualised by conventional MRI and histopathological staining in an 80 year old man with vascular cognitive impairment. A-B, Confluent WMH seen in the axial planes of 2-T Weighted MRI from two different subjects. Areas of hypersignals can be seen in the deep and perivascular WM (*). C, WM rarefaction and myelin loss in the deep WM. Arrows show perivascular spacing around two arterioles. D, Partial image of a lacunar infarct in the temporal lobe WM H&E stained section showing. E, A microinfarct (arrow) in the frontal lobe WM. F, a microaneurysm with hyalinised vessels and microbleeds in WM of the parietal lobe. Stains: C, luxol fast blue stained section; D-F, H&E stained sections. Magnification bar: C=150 μ m; D=250 μ m; E,F=100 μ m.

Figure 2: Figure showing increasing loss of myelin density in different disorders with increasing vascular pathology. Means (SE) for n=10-12 subjects show calculated myelin index (MI) values of the frontal WM in controls and patients with various dementias. Mean MI values for subjects were significantly different from Controls †P=0.034 and from undamaged myelin *P<0.01; Abbreviations: Controls, aged controls, PSND, post-stroke non-demented, PSD, post-stroke dementia, VaD, vascular dementia, Mix, mixed dementia, AD, Alzheimer's disease.

Figure 3: Schematic diagram of the interactions between major cellular components within the brain WM. WM microvessels are associated with astrocytes, oligodendrocyte precursor cells (OPCs), microglia/macrophages and pericytes. The gliovascular unit of the WM is formed by astrocyte end-feet juxtaposed to the WM endothelium and glial and endothelial cells functionally interact with each other in a paracrine manner. Together with astrocytes, pericytes are important players within the gliovascular unit modulating vessel diameters. The oligovascular niche is formed by OPCs and the endothelium where an exchange of soluble signals (e.g. trophic factors or chemical messengers) plays an important role in sustaining oligodendrocyte homeostasis and WM integrity. Microglial processes are closely associated with the brain endothelium in a fraction of cerebral microvessels

Figure 4: Images from C57BL/6J mice studies showing astrocyte degeneration in the WM. GFAP (astrocyte marker) and aquaporin-4 (AQP4) distribution in the corpus callosum. A-B, Representative images of double immunofluorescent staining for

GFAP and AQP4 in the corpus callosum. In sham, AQP4 was normally distributed around the vessels within the astrocytic end-feet (A) (arrow heads), whereas in hypoperfused mice (BCAS mice), AQP4 was abnormally distributed at the periphery of GFAP-positive astrocytes or clasmatodendrocytes (damaged astrocytes) (B). Scale bar represents 10 μ m.