AGE (2012) 34:1093–1110
DOI 10.1007/s11357-011-9357-7

Age-related changes in human and non-human primate white matter: from myelination disturbances to cognitive decline

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Received: 7 August 2011 / Accepted: 1 December 2011 / Published online: 28 December 2011

Abstract The cognitive decline associated with normal aging was long believed to be due primarily to decreased synaptic density and neuron loss. Recent studies in both humans and non-human primates have challenged this idea, pointing instead to disturbances in white matter (WM) including myelin damage. Here, we review both cross-sectional and longitudinal studies in humans and non-human primates that collectively support the hypothesis that WM disturbances increase with age starting at middle age in humans, that these disturbances contribute to age-related cognitive decline, and that age-related WM changes may occur as a result of free radical damage, degenerative changes in cells in the oligodendrocyte lineage, and changes in microenvironments within WM.

Keywords Aging · White matter · Myelination

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Abbreviations

AD	Alzheimer's Disease
ADC	Apparent diffusion coefficient
AxD	Axial diffusivity
CC	Corpus callosum
CSF	Cerebrospinal fluid
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
GM	Gray matter
HA	Hyaluronan
HAS	Hyaluronan synthase
MCI	Mild cognitive impairment
MD	Mean diffusivity
MRI	Magnetic resonance imaging
OPC	Oligodendrocyte progenitor cells
OL	Oligodendrocyte
R_2	Transverse relaxation rate
RD	Radial diffusivity
WM	White matter
WMH	White matter hyperintensities

Introduction

Like other organs, the brain undergoes significant structural and functional changes with increasing age. The nature of these changes and their underlying mechanisms are slowly being identified. It is now clear that the overt pathological changes associated with neurodegenerative diseases, like Alzheimer's

Disease (AD), differ substantially from those that occur during *normative* human brain aging (Terry et al. 1987). Until recently conventional wisdom maintained that normal brain aging is accompanied by gross changes such as decreased weight, ventriculomegaly, and histological evidence of neuronal loss (Jernigan et al. 1991). However, a number of recent studies have suggested that cognitive decline in healthy elderly individuals is not due to neuronal dropout, but a reduction of synaptic and dendritic elements along with changes in white matter (WM; Fjell and Walhovd 2010; Pannese 2011). WM changes with age include a loss in volume, decreased myelin staining, and increased pallor (Kemper 1994). Histological studies have reported a 10–15% loss of myelinated fibers with age (Meier-Ruge et al. 1992; Tang et al. 1997; Marner et al. 2003) and a decline in WM volume (Tang et al. 1997; Marner et al. 2003; Piguet et al. 2009). While important, these studies have limitations that include variable tissue quality, small sample number, a lack of functional correlates, and a cross-sectional design that makes it difficult to discern progression and trajectory of change.

Some of the limitations of histological studies have been overcome with the use of in vivo imaging. In particular, magnetic resonance imaging (MRI) has greatly aided the visualization and quantification of gray matter (GM), WM, and cerebrospinal fluid (CSF) in the brain during aging and disease. Despite low resolution, MRI studies have clear advantages over histological studies including the ability to perform longitudinal assessments, to test subjects for health and neurological status contemporaneously, and the potential for high through-put capacity. Recent advances have expanded the repertoire of measurements that can be made during MRI protocols (Gunning-Dixon et al. 2009). Here, we review recent studies aimed at evaluating the WM changes that accompany ventricular enlargement and atrophy that occur during the course of normative aging. We examine these data in the light of histopathological studies in the monkey that provide insights into the types of disturbances that occur in WM with advanced age. Finally, we speculate on the possible mechanisms that contribute to these changes in WM from a variety of studies in human, non-human primates, and rodents.

Cross-sectional imaging studies in humans

MRI studies of age effects on WM have reported signal abnormalities that are manifested as an increase in hyperintensities (WMH), which are considered to be a result of vascular dysfunction (Yoshita et al. 2005; Debette and Markus 2010), as well as WM volumetric loss and structural changes measured by diffusivity (Sullivan and Pfefferbaum 2006). Studies of age effects on WM volume historically show some disparity of results, such as an age-related loss that is restricted to women (Good et al. 2001; Kruggel 2006), or an increase in WM volume with age (Mortamet et al. 2005). However, other reports, which can vary by technique, number of subjects, screening criterion, age range, or proportion of older participants, have described global decreases of WM volume with age in both sexes (Guttmann et al. 1998; Courchesne et al. 2000; Ge et al. 2002; Allen et al. 2005). Cross-sectional studies also show a loss of WM volume with age in specific regions of the brain, which occurs in both men and women (Raz et al. 1997; Bartzokis et al. 2001; Jernigan et al. 2001; Raz et al. 2004; Allen et al. 2005; Walhovd et al. 2005). A loss of WM volume, which is paralleled by GM loss, is even detectable across a two decade range in otherwise healthy elderly (Lemaitre et al. 2005).

A decline of WM volume or the increase of WMH with age has also been correlated with functional deficits. A loss in frontal lobe WM volume (Brickman et al. 2006) or atrophy of the anterior corpus callosum (CC) of older adults (Jokinen et al. 2007; Gratton et al. 2009) was associated with decreased executive function. Conversely, semantic and short-term memory, stable functions in the healthy elderly, did not correlate with age effects on global or regional WM volumes (Taki et al. 2011). WMH tends to increase with age in the periventricular and deep WM (Piguet et al. 2003) and an increase in the prefrontal cortex is associated with perseverative errors (Gunning-Dixon and Raz 2003). Increased periventricular WMH with age also predicts frontal lobe dysfunction (Soderlund et al. 2006), although the qualitative decline in medial temporal volume may also play a role (Oosterman et al. 2008). Moreover, although the severity of WMH in the elderly varies anatomically, those with the most severe lesions performed more poorly on cognitive tests (Ota et al. 2009). Thus, changes of WMH or WM volume with age, especially in frontal regions of the brain, can have a negative effect on brain function.

Longitudinal imaging studies in humans

Repeated MRI measurements over time can overcome limitations of cross-sectional studies, such as subject

variation, and provide information on the progression of WM changes. Longitudinal analysis of global WM volume over 3.5 years found that WM volume reached a maximum in the 30s in both sexes, but that this was followed by declines that accelerated in the elderly (Liu et al. 2003). Another study found a similar aging pattern that was observed over a 5-year period (Raz et al. 2005). Moreover, WM loss in the prefrontal area of healthy old individuals was found to occur after only 30 months (Raz et al. 2010), suggesting enhanced regional sensitivity to aging. The Baltimore Longitudinal Study reported age-related changes in MRI-derived signal intensity, which was believed to reflect demyelination and changes in water, protein, and mineral content in the old (Davatzikos and Resnick 2002). Results from the same study also reported that while WM volume was stable after 1 year in old subjects (Resnick et al. 2000), it decreased regionally and globally after 4 years (Resnick et al. 2003), suggestive that a critical age threshold was achieved. Functionally, longitudinal studies have shown WM atrophy in the CC of elderly men is associated with cognitive dysfunction (Sullivan et al. 2002). With older subjects 1 year was sufficient to reveal a reduction of frontal WM volume, which correlated with impaired executive function (Cardenas et al. 2011), suggesting an age and or regional susceptibility. These longitudinal studies confirm the cross-sectional results showing WM volumetric loss in the elderly is associated with functional decline.

Longitudinal studies of WMH reveal functional consequences as well. WMH levels in 13 non-demented elderly increased modestly, but significantly, in the cerebrum over 5 years and correlated with psychomotor deficits (Wahlund et al. 1996). In the Austrian Stroke Prevention Study, WMH levels increased steadily over 6 years, and while cognition was stable at 3 years (Schmidt et al. 1999), it was significantly impaired after 6 years (Schmidt et al. 2005; also see Prins et al. 2005). The longitudinal increase of WMH can negatively affect several cognitive domains (Longstreth et al. 2005), including executive function, with an increase of subcortical WMH (Kramer et al. 2007) and mental processing speed, when accompanied by an increase in periventricular WMH (van den Heuvel et al. 2006). A high baseline level of WMH in deep and periventricular WM was most predictive of a longitudinal progression of WMH in the elderly (Sachdev et al. 2007). These results are consistent with cross-sectional studies, in that age-related increases in WMH are progressive and associated with a decline in brain function. There also appears to be a threshold level of detection, as well as functional decline, perhaps a reflection of critical levels of WM damage as a function of aging.

Diffusion tensor imaging in humans

Because WM volumetric studies only assess gross atrophy, they are not able to identify early subtle, regional WM damage or provide insight into relationships of connectivity and function (Gunning-Dixon et al. 2009). Therefore, diffusion tensor imaging (DTI) has been employed to analyze WM tracts by measuring the degree to which water diffusion is restricted (fractional anisotropy, FA). High levels of FA reflect restricted water molecule movement along WM tracts, with the myelin sheaths of axons, axon membranes, and neurofilaments all providing directionality that restricts diffusion (Madden et al. 2009). WM FA tends to decrease with aging in men and women (reviewed in Moseley 2002). Similar to the volumetric data, FA peaks in early middle age when myelination peaks (Kemper 1994) and then declines in the elderly at a rate that parallels or precedes WM volumetric loss (Hasan et al. 2007; Hasan et al. 2008; Hasan et al. 2010; Lebel et al. 2010; Westlye et al. 2010). Regionally, age-related deficits of FA have been described in the genu of the CC centrum semiovale, frontal, and parietal pericallosal WM of men (Pfefferbaum et al. 2000), with a similar pattern found in both sexes (Sullivan et al. 2001). When corrected for partial voluming, FA still decreased in the CC and centrum semiovale with age (Pfefferbaum and Sullivan 2003). In the CC, FA decreases regionally with age in the genu (Abe et al. 2002), but conversely, also in the caudal splenium (Nusbaum et al. 2001), which may reflect technical challenges in the DTI technique (Sullivan et al. 2006). However, additional studies have verified the global decline of FA with age (Hsu et al. 2010), with an antero-posterior gradient of susceptibility (Salat et al. 2005; Minati et al. 2007). Moreover, DTI studies that examined the effects of WMH, ventriculomegaly, and brain atrophy found these to contribute to a decline of FA with age (Bastin et al. 2010). Although WM lesions with age are exacerbated by hypertension, these appear in more posterior regions, a pattern distinct from normal aging (Kennedy and Raz 2009a).

DTI tractography studies allow the quantification of WM microstructure along the extent of specific fiber tracts by the measurement of the level of diffusion along the length of WM (axial) or in the perpendicular (radial) direction. In one study FA declined with age regionally, with increased radial diffusivity (RD), which was attributed to myelin loss (Fjell et al. 2008; for review see Thomason and Thompson 2011). Since FA also declined with age in the genu and the ventromedial prefrontal WM with an increase of mean diffusivity (MD), axial diffusivity (AxD), and RD, this data supports the idea that the frontal cortex is particularly vulnerable to age-related myelin loss (i.e., is age-sensitive; Michielse et al. 2010). A number of studies, using similar techniques, have proposed that the timing and combination of age-related changes in FA, MD, AxD, and RD may reflect a progression of mild to severe WM changes, including demyelination, axonal loss/damage, inflammation, and gliosis (Bennett et al. 2010; Burzynska et al. 2010; Sala et al. 2010; Zhang et al. 2010).

The increase in WM diffusivity has been associated with age-related cognitive decline, especially in the anterior WM (O'Sullivan et al. 2001; Sullivan et al. 2006). However, one study of slightly younger subjects (average age of 65 years) found no loss of FA in anterior and caudal fiber tracts (Madden et al. 2004). But, in a study with a larger subject pool, FA declined with age in the frontal, parietal, and temporal cortices and correlated with deficits in executive function (Grieve et al. 2007). WM deficits were also found to occur to a greater extent in the anterior segments of fiber tracts in the frontal and parietal cortices and increased RD in the anterior tracts corresponded with worse executive performance (Davis et al. 2009). Impairments in working memory, problem solving, and motor function were also correlated with an age-related decrease of FA in anterior and superior fiber tracts, which was interpreted to reflect myelin damage and fluid accumulation in regions around the axon (Zahr et al. 2009). Similar to WM volumetric studies, both sexes are susceptible to the effect of age on WM FA and longitudinal and transverse diffusivity, although with some variation is observed regionally (Sullivan et al. 2010).

Breakdown of myelin and decreased fiber density with age likely affect other functions, such as processing speed. Higher FA and lower RD levels predicted better processing speed in the healthy aged, but not general intelligence or memory, and age-related impairment of cortical connectivity was cited as a global event (Penke et al. 2010). A cross-sectional DTI study found that modifications of FA and ADC with age in the anterior WM correlated with a decline in processing speed and working memory, whereas a decline in episodic memory was linked to changes in central WM (Kennedy and Raz 2009b). Age had the strongest effect on increased diffusivity, particularly in older adults with higher AxD, which correlated with lower processing speed, but not cognitive performance (Burgmans et al. 2011). In sum, DTI measures of microstructural breakdown in myelin and axons with normal aging have been correlated with a decline in complex behaviors and may be reflected in regional sensitivity to aging.

WM and Alzheimer's Disease

Although a thorough overview on MRI studies that examine WM changes with Alzheimer's Disease (AD) is beyond the scope of this review, it is of interest to contrast AD effects on WM versus normal-aged subjects. In an early study that examined the effects of aging and AD on frontal lobe WM, the transverse relaxation rate (R_2), which has high values when myelination is also high, was found to decline in a curvilinear fashion with age and was further exacerbated with AD (Bartzokis et al. 2003). A subsequent report found aging decreased R_2 in the genu, but not the splenium, while AD caused a further decrease in R_2 values in both regions (Bartzokis et al. 2004). A study comparing FA in young, normal old, and mildly demented old adults found that FA declined as a function of age with a rostro-caudal gradient of sensitivity, while mildly demented elderly experienced a distinct WM deterioration in posterior regions (Head et al. 2004). Mildly impaired AD subjects also showed small decrements in FA in the posterior callosum and subcortical WM compared with normal age-matched adults, which correlated with specific functional impairments (Kavcic et al. 2008). A similar result showed that normal aged and mildly cognitively impaired (MCI) subjects differed from AD, in that the latter had a differential decrease of FA in the left anterior temporal lobe, consistent with disease progression (Damoiseaux et al. 2009). Interestingly, lower FA was associated significantly with coincident AD and vascular brain injury (Back et al. 2011). Given that AD and vascular brain injury are commonly co-

morbid (Sonnen et al. 2009), it is possible that earlier findings of lower FA in AD patients reflected vascular disturbances as opposed to a specific effect of AD pathology.

Salat et al. (2009) described an AD-specific decline in WM volume in the parahippocampal and entorhinal cortices, regions that traditionally suffer from atrophy with AD. Longitudinal scans that contrasted subjects with stable MCI and those that converted to AD showed increased WM atrophy in the temporal lobe (Davatzikos et al. 2011). WMH assessed in aged and early AD cases found the burden of periventricular and deep WM was similar, but there was an exacerbation of global cognitive decline with early AD (Burns et al. 2005). Consistent with these earlier studies is the report of the progressive increase of hyperintensities in the posterior periventricular WM and the splenium when comparing normal, mild cognitively impaired, and AD subjects (Yoshita et al. 2006).

Thus, age-related WM changes can be distinguished from pathological conditions, with an exacerbated WMH, atrophy, and differential anatomical presentation. However, it is important to note that modification of WM with normative aging has functional consequences and may reflect interactions with coincident brain atrophy.

The non-human primate as a model of normative aging

While the devastating effects of age-related neurodegenerative diseases like AD on the brain constitute an extremely important biomedical problem, it is important to consider the interaction of neurodegenerative disease with two important aspects of normative aging. First, normative aging provides the substrate on which these neurodegenerative diseases are expressed and hence may be a critical permissive factor in their incidence and in their expression. Second, even if neurodegenerative diseases are eliminated, normative aging changes will compromise brain function, albeit at a lesser rate and to a lesser degree.

Given the difficulties in assessing normative aging in humans, a number of investigations have turned to the rhesus macaque to facilitate the study of normative aging changes independent of neurodegenerative changes and postmortem artifacts. In this regard, the first question is to assess the life span of the rhesus monkey to establish some estimates of what might be thought of as equivalencies to humans in terms of the boundaries for young adults, middle-aged, and elderly subjects. Two studies are most pertinent here—one from the Yerkes National Primate Research Center (Tigges et al. 1988) and the other from the Wisconsin National Primate Research Center (Dyke et al. 1986). While these studies used different methods and assessed different cohorts, they generally agree on the following: rhesus monkeys can be considered young adults at between 4 and 5 years of age when they reach sexual maturity. At the other end of the spectrum, Tigges et al. (1988) reported the maximal life span in captivity to be about 35 years of age while Dyke et al. (1986) reported the maximum to be as much as 40 years of age. Taken together, the maximum ages of 35 or 40 likely correspond to the human maximum of 100 to 120 and overall suggest a relationship of approximately 1 to 3 for monkey to human years. From that perspective, monkeys 20 years and over correspond to humans 60 and over while monkeys 30 years and over correspond to humans in their 90s or above. Most of the data on aging monkeys is thus derived from animals between 20 and 30 years of age.

Within this range of elderly monkeys, the most important observation is that the rhesus monkey does not develop AD or other frank neurodegenerative changes. For example, while the rhesus monkey does show accumulation of amyloid in the cortex and some amyloid plaques, the amyloid that does accumulate is mainly the less toxic amyloid-beta (A-beta) 1-40 rather than A-beta 1-42 (Gearing et al. 1996). In addition, the amyloid plaques that do accumulate do not show the distribution typical of AD or evidence of a predilection for the hippocampus and entorhinal cortex (Heilbroner and Kemper 1990). Additionally, there is no relationship between the accumulation of amyloid plaques and cognitive impairments (Sloane et al. 1997). Finally, neurofibrillary tangles are a second critical and diagnostic feature of AD that is particularly related to the death of neurons but there is no clear evidence that neurofibrillary tangles are ever present in the rhesus monkey brain (Kimura et al. 2003; and Finch and Austad, this publication). And while there are a few recent studies that report A-beta and phosphorylated tau in the monkey brain and assert that this makes the rhesus a good model for AD pathology (e.g., Oikawa et al. 2010), none of these papers provide evidence that this pathology leads to the death or loss of neurons.

Nevertheless, a host of studies confirm that rhesus monkeys show age-related cognitive impairments in multiple domains including working memory, recognition memory, and executive function (e.g., Bartus et al. 1978; Rapp and Amaral 1989; Moss et al. 1988; Herndon et al. 1997; Moore et al. 2006). Thus a critical question is to determine what brain changes occur and whether they are diffusely distributed or localized to particular anatomical substrates or loci. Here, we will focus on evidence that neurons in general and cortical gray matter in particular are largely spared in the normal aging monkey brain while myelinated axons in forebrain white matter are particularly vulnerable to pathological changes during normative aging.

Changes in rhesus macaque gray matter and white matter during normative aging

It is clear that the loss of neurons in GM is accompanied by loss of axons and associated loss of myelin in WM. However, even if neurons are preserved, it is possible to have damage to axons or to myelin as an independent process. Differentiating between these two scenarios is particularly difficult in studies of elderly humans where neuron death that characterizes neurodegenerative diseases in general and AD in particular is ubiquitous. This problem is exemplified by the observation that neuron loss can approach 30% before cognitive symptoms can be detected (Gomez-Isla et al. 1996) and more recently structural MRI studies have also provided evidence that brain pathology in AD may precede symptoms by up to a decade (Tondelli et al. 2011). Hence, humans that are characterized as "neurologically normal" may actually be in the prodromal stages of neurodegenerative disease and have significant neuron loss. Because of this, it is particularly difficult to determine if there is a loss of axons and/or myelin independent of neuron loss during normative human aging.

Hence, despite the benign expression of amyloid and the apparent absence of tangles, the first question to be addressed is whether neurons are lost in rhesus macaque GM. Early studies by Brizzee and colleagues (Brizzee et al. 1980) utilized density measures to evaluate the brain of aged monkeys and reported a reduction of neuron density in the CA1 field of the hippocampus and in area 46 of the prefrontal cortex, two areas critical to cognitive function. Despite the limited sampling, this study appeared to corroborate studies of the aging human brain such as Brody (1955) and Ball (1977) that reported similar findings for human brains using similar sampling methods. However, with the advent of stereological methods in the 1980s, simple sampling of density was replaced with systematic random sampling of entire regions and counting of cells using methods that were free of bias due to changes in size or density (Sterio 1984; West et al. 1991). When applied to rhesus monkey brain tissues, these methods consistently documented an absence of age-related neuron loss in motor cortex (Tigges et al. 1990), primary visual cortex (Peters et al. 1997; Hof et al. 2000), prefrontal area 46 (Peters et al. 1994; Smith et al. 2004), as well as the hippocampus (Keuker et al. 2003) and entorhinal cortex (Merrill et al. 2000). The one exception to this is the report by Smith et al. (2004) of cell loss in prefrontal area 8A in the same subjects where these authors report no loss of neurons in adjacent area 46. While it is always impossible to prove the null hypothesis that neurons are not lost and to exclude the possibility raised by Coleman and Flood (1987) that neuron loss may be limited to very specific areas as the observation of Smith et al. (2004) suggests, it seems quite unlikely that cell loss in the cortex is a major factor in normative aging. This assertion is supported by increasing numbers of studies that have confirmed the stability of neuron numbers in normal aging in rodents where cell loss had also been claimed (Rapp and Gallagher 1996, 2002) and in human brain from subjects given careful neuropsychological examination to exclude even the earliest stages of AD (Gomez-Isla et al. 1996). Based on these observations, factors beyond neuron loss have been examined in order to explain age-related cognitive impairments.

Ultrastructural observations of non-human primate cortex with aging

Because of the unavoidable problems of fixation and preservation of human brain that result from post mortem delay, high quality electron microscopic evaluation of ultrastructure in aging human brain is extremely difficult. In contrast, because of the ability to perfusion fix the central nervous system in laboratory

animals, electron microscopic evaluation of neural ultrastructure is feasible. Among the first studies to demonstrate age-related pathology in WM rather than GM were those of Peters and colleagues (Peters et al. 2000). Using electron microscopic analysis of the cerebral cortex of well-fixed rhesus monkey brain, it was observed that while neurons showed normal ultrastructure even in the most elderly monkeys, both intracortical and subcortical WM showed a variety of myelin pathologies. These pathologies did not involve complete demyelination but instead involved splitting of the myelin sheath at either the intraperiod or major dense lines. At these splits, large inclusions of fluid-filled balloons or of dense inclusions were observed. These forms of myelin pathology were observed in subcortical WM of the primary visual cortex (Peters et al. 2000), prefrontal cortex, and the corpus callosum (Peters and Sethares 2002), as well as the anterior commissure (Sandell and Peters 2003) and in the optic nerve (Sandell and Peters 2001). Additionally, there was significant evidence of remyelination, as reflected by the presence of redundant myelin and of increased frequency of paranodes that could reflect a shortening of internodal myelin lengths as damaged myelin was replaced by new myelin (Peters et al. 2001). The significance of this myelin pathology was suggested by the correlation of many of these pathologies with age-related cognitive impairments, suggesting that these actually affect conduction (e.g., Peters et al. 2000).

Recently, both the fluid filled and dense inclusions were quantified in the genu of the corpus callosum and in the cingulum bundle (Bowley et al. 2010). Analyzing randomly selected fields in the electron microscope, it was shown that both forms of pathology increase steadily with age beginning in middle-aged monkeys by 15 years of age (equivalent to a 45-year-old human) where about 2% of fibers shows one or the other form of pathology. This frequency then increases steadily over the life span to almost 8% in monkeys around 30 years of age (equivalent to a 90-year-old human). It was also found that in these same areas, careful examination revealed the presence of degenerating axons inside of sheaths that had also degenerated, suggesting that in many cases, remyelination had failed. While the frequency of degenerating fibers was much less than that of damaged myelin, it followed the same time course, increasing from about 0.2% in middle-aged monkeys to about 0.8% in aged monkeys. One interpretation of this is that with the increasing presence of myelin pathology that axon conduction is impaired, and myelinated fibers may begin to die back.

Neuroimaging of white matter integrity during aging in the non-human primate

Initial studies of monkey brain using MRI focused on straightforward morphometry using T1-weighted images which look much like fresh sections of monkey brain. As illustrated in Fig. 1, these images revealed evidence of brain atrophy with the age-related enlargement of ventricles and of some sulci. In order to determine whether this atrophy involved mainly gray matter, white matter, or was global and involved both, a simple point counting approach was used by randomly placing a grid over a series of equally spaced images and using the Cavalieri estimator to obtain measures of total volume of the brain as well as measures of specific components. As shown in Fig. 2, this simple analysis revealed no age-related change in total brain volume, a finding in agreement with the report of Herndon et al. (1998) showing stability of brain weights at necropsy of nearly 400 monkeys at the Yerkes National Primate Research Center. Since brain weights at necropsy include the weight of CSF in the ventricles and the deep sulci, atrophy in those areas would go undetected. However, subsequent segmentation of the point counting revealed that there was no loss of volume for total forebrain gray matter or for cortical gray matter, observations congruent with the perseveration of cortical neurons described above. In contrast there was a significant loss of WM volume with age and a complementary and significant increase (not shown) in the volume of the ventricles.

These initial observations were derived from a cohort of 14 monkeys stratified into old and young, which was later expanded to include middle-aged monkeys. Using template-driven segmentation to analyze this cohort also revealed a significant loss of WM with stability of GM (Wisco et al. 2008). The loss of WM volume likely reflects the age-related axon degeneration detected by Bowley et al. (2010), but would not reflect the ubiquitous myelin pathology. To address this, DTI scans were acquired on a different cohort of aged monkeys. Analysis of FA changes revealed a significant age-related loss of FA in subcortical WM, including the areas like the corpus callosum, and cingulum bundle known to exhibit

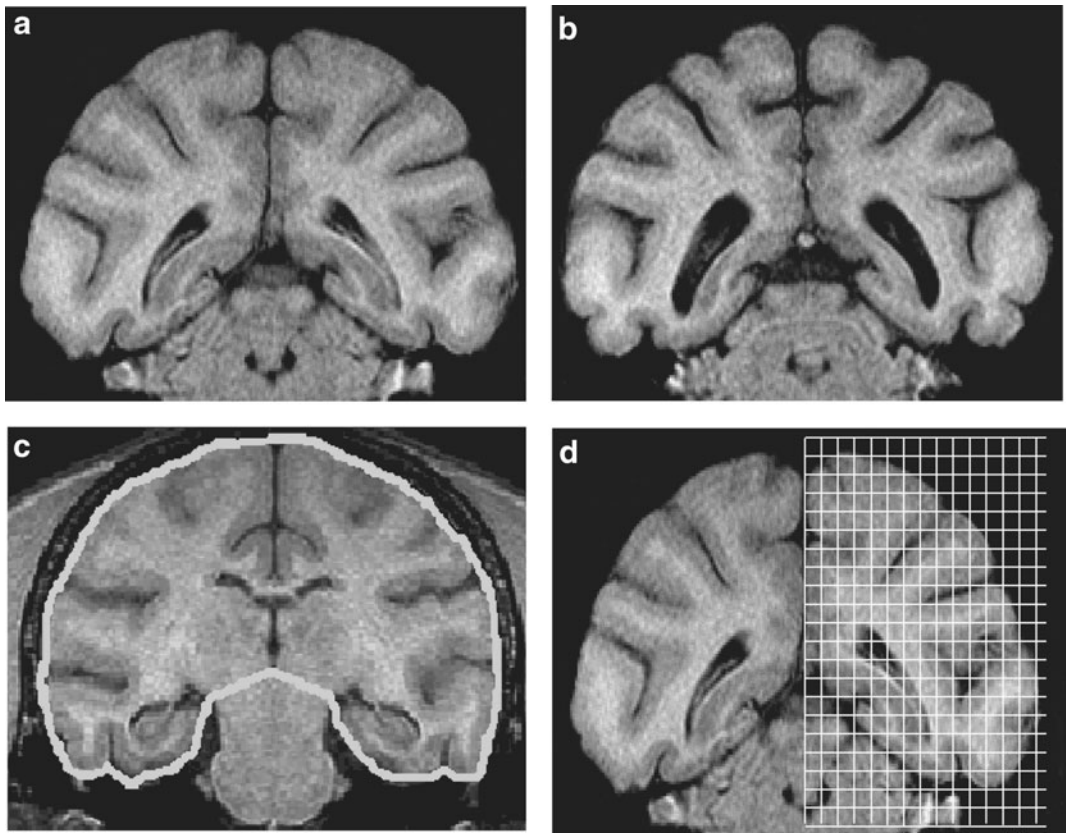
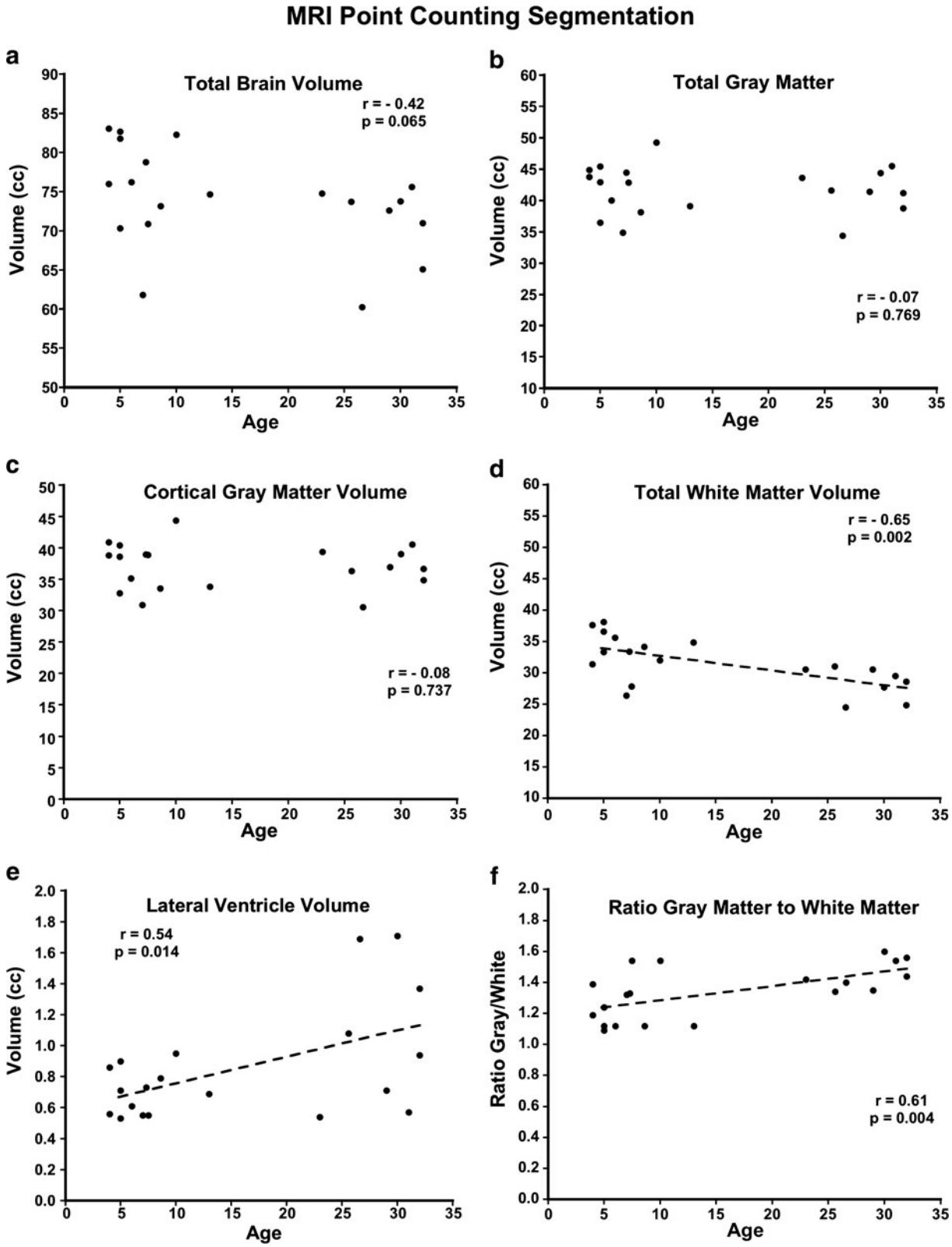


Fig. 1 Matched levels of T1 MRI scans are shown for a 6-year-old young female monkey (**a**) and a 24-year-old female monkey (**b**) where there is obvious enlargement of the atrium of the lateral ventricle. The algorithm used to exclude the brainstem is illustrated by the outline of an MRI scan shown in **c**; the approach of overlaying a point counting grid onto the MRI image and scoring each grid intersection according to the tissue component it overlies is shown in **d**. All scoring was done with the operator blind to the age and sex of the subject

ultrastructual evidence of myelin damage (Makris et al. 2007). This loss of FA likely reflects the increased frequency of fluid and cytoplasm filled inclusions in WM as well as a generalized loss of myelinated fibers confirming the vulnerability of forebrain WM to age-related pathology, independent of loss of GM.

Nevertheless, changes in GM would be predicted even with the stability of neuron numbers for several reasons. First, as myelinated fibers are lost, perhaps due to dying back of fibers with dysfunctional conduction, some atrophy in the deep layers of the cerebral cortex might be expected. Second, as functional inputs to cortical neurons are lost due to either loss of axons or impaired conduction, both loss and dysfunction of synapses might be expected and would likely lead to dendritic atrophy. Indeed there is evidence of both processes. For example, at the microscopic level, some studies have reported a reduction of synapses in the non-human primate neocortex and other areas (Peters et al. 1998; Peters et al. 2008; Hara et al. 2011) while others have reported loss of spines and atrophy of dendrites (Dumitriu et al. 2010; Dickstein et al. 2007). At a more global level, several studies using MRI methods have reported age-related reductions in the thickness or volume of the cerebral cortex or hippocampus (Alexander et al. 2008; Koo et al. 2012; Shamy et al. 2011), a finding compatible with

Fig. 2 An illustration of the relationship of different tissue components to age derived from point counting analysis of two rhesus monkeys. While total brain volume (gray, white, and ventricles) approaches significance (**a**), there is no change in total gray matter (**b**) or in cortical gray matter (**c**). Instead there is a significant age-related loss of white matter (**d**) that is mirrored by an increase in ventricular volume (**e**), leading to an age-related increase in the ratio of gray matter to white matter with age as white matter is lost (**f**) ▶


MRI Point Counting Segmentation
a
Total Brain Volume
r = - 0.42
p = 0.065
Volume (cc)
Age
b
Total Gray Matter
r = - 0.07
p = 0.769
Volume (cc)
Age
c
Cortical Gray Matter Volume
r = - 0.08
p = 0.737
Volume (cc)
Age
d
Total White Matter Volume
r = - 0.65
p = 0.002
Volume (cc)
Age
e
Lateral Ventricle Volume
r = 0.54
p = 0.014
Volume (cc)
Age
f
Ratio Gray Matter to White Matter
r = 0.61
p = 0.004
Ratio Gray/White
Age

atrophy of dendrites and loss of intracortical white matter independent of neuron loss.

Mechanisms of WM changes during normative aging

While the initial cause of myelin pathology is still unknown, Fig. 3 illustrates a possible sequence of processes that may result from the age-related accumulation of myelin pathology and account for many of the observed features, including changes in GM. Thus the splitting of sheaths and increased frequency of fluid and cytoplasmic inclusions likely leads to impaired conduction. As pathology increases and conduction becomes even more impaired, it is plausible that trophic feedback from the target cells back to the neuron of origin would be reduced leading eventually to dying back of the affected axon while shorter collaterals might still be functional. Loss of axon conduction and dying back of axons would be expected to lead to loss of synapses and dendritic atrophy in target neurons. In the extreme, both impaired conduction, axon loss and atrophy of dendrites and synapses constitute a disconnection that could contribute to age-related cognitive impairments. Hence, according to this scenario, a critical question for normal aging is to identify causal mechanisms underlying the myelin pathology as well as to identify possible interventions that could prevent or even reverse these myelin defects.

The mechanisms underlying age-related WM damage remain poorly defined. Chronic hypoperfusion due to damaged small blood vessels has been implicated in age-related WM damage (reviewed by Iadecola 2010). A variety of conditions that reduce cerebral blood flow, including reduced angiogenesis, tortuous arterioles, and hypoxia-induced loss of capillaries, may each result in WM damage in the elderly (Fernando et al. 2004; Brown and Thore 2011). The finding that myelin- and axon-associated free radical injury, as assessed by measurements of distinct isoprostanes, inversely correlated with FA in vascular brain injury independent of AD (Back et al. 2011) support a model whereby vascular changes cause age-related WM damage through oxidative stress.

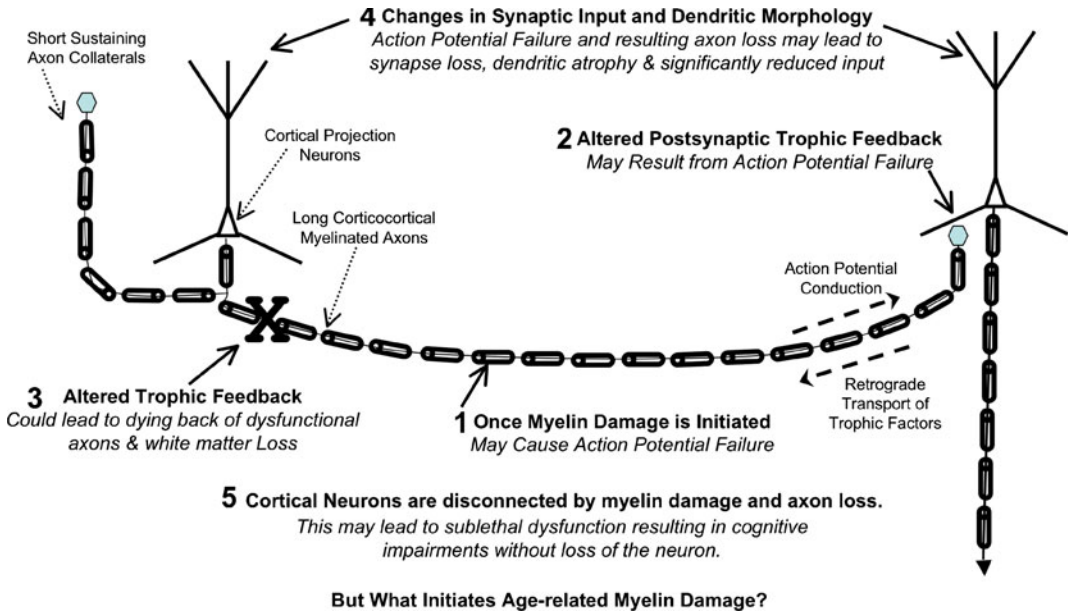


Fig. 3 A model of the possible sequence of events resulting from myelin damage. Once that myelin damage is initiated, (*1*) the type of damage observed may cause failure of action potential conduction as external resistance of compact myelin is lost. Subsequently the loss of normal activation (*2*) may lead to altered trophic feedback that in the extreme could lead to dying back of the individual long axons (*3*) while short local collaterals and the neuronal soma remain intact. (*4*) In addition, the loss of normal activation by action potential failure would be exacerbated by dying back of the axon itself leading to loss of synapses and spines as well as dendritic atrophy on affected neurons. Together (*5*) these changes would effectively "disconnect" parts of the aging brain and lead to cognitive impairments

There is growing evidence that remyelination failure is also a significant contributing mechanism of age-related WM disturbances. Remyelination efficiency decreases with age (Gilson and Blakemore 1993; Shields et al. 1999; Sim et al. 2000). This decline in remyelination efficiency has been linked to impairments in oligodendrocyte progenitor cell (OPC) recruitment and differentiation into myelinating oligodendrocytes (OLs; Sim et al. 2002; Peters and Sethares 2002; Franklin et al. 2002; Ando et al. 2003; Chari et al. 2003; Woodruff et al. 2004; Rist and Franklin 2008). Changes in the transcriptional control of genes that regulate OL differentiation are likely involved in age-related changes in remyelination (Doucette et al. 2010). Indeed, the expression of factors that promote OL differentiation are temporally delayed in older animals (Hinks and Franklin 2000; Franklin et al. 2002). Epigenetic modifications with age to genes involved in the maturation and recruitment of OPCs may contribute to the decline of OPC maturation in older individuals (reviewed by Copray et al. 2009). For example, Shen and co-workers (2008) found decreased histone deacetylation and repressive methylation in OLs in aged mice.

Broader cell-intrinsic changes to OPCs may underlie remyelination failure and the accumulation of WM damage with aging. In particular, telomere function progressively declines with age in mice, leading to activation of p53 associated with DNA damage (Ferrón et al. 2004; Sahin and Depinho 2010). As a result, cellular pathways that promote apoptosis and cellular senescence become activated contributing to compromised progenitor cell functions within tissues, tissue atrophy, and physiological impairment in a wide variety of organ systems. Indeed, studies in humans support the hypothesis that shortening telomere length is associated with age-associated disease (Cawthon et al. 2003).

A striking recent study by Jaskelioff et al. (2011) utilized a transgenic mouse model in which mice with shortened dysfunctional telomeres can be induced to reactivate telomeres, resulting in reduced DNA damage signaling. Telomerase reactivation in late generation mice that had demonstrated degenerative phenotypes in multiple organ systems resulted in reversal of degeneration. In particular, somatic telomerase reactivation reversed neurodegeneration, including recovery of OPCs, evidence of improved myelination, and functional recovery in a number of behavioral tests. These data strongly support the hypothesis that cell-intrinsic changes in OPCs contribute to age-related WM disturbances, and suggest the exciting possibility that reversal of these changes can promote WM regeneration.

Alterations within the WM microenvironment of aged individuals may also contribute to WM damage and remyelination failure. In particular, reactive astrogliosis is linked to the inhibition of OPC maturation and remyelination failure in a number of conditions (Keirstead et al. 2005; Skripuletz et al. 2010). Both Notch signaling and bone morphogenetic proteins induced during reactive astrogliosis have been implicated in blocking OPC differentiation and remyelination (e.g., John et al. 2002; Wang et al. 2011). Astrogliosis is a reliable marker of mammalian brain aging in both GM and WM (Brizzee et al. 1968; Sturrock 1980; Hughes and Lantos 1987; Sloane et al. 2000; Cargill et al. 2011). Thus, the signals associated with astrogliosis may promote remyelination failure during normative aging.

Astrogliosis may also influence OPC maturation in the elderly CNS through alterations to extracellular matrix. In particular, the glycosaminoglycan hyaluronan (HA) may restrict OPC differentiation and limit remyelination (reviewed by Sherman and Back 2008) with advanced aging. HA is synthesized at the inner face of cell membranes by one of three transmembrane HA synthases (HAS1-3), then extruded into the extracellular matrix. It is a non-sulfated, linear molecule comprised of repeating units of (β,1→4)-D-glucuronic acid-(β,1→3)-*N*-acetyl-D-glucosamine that reach sizes in excess of 10^6 Da. HA is localized around myelinated fibers in WM, while it is a component of perineuronal nets surrounding neuron cell bodies in GM (Asher et al. 1991; Bignami and Asher 1992; Bignami et al. 1992; Eggli et al. 1992).

HA synthesis and the expression of the HA receptor, the CD44 transmembrane glycoprotein, are significantly elevated by reactive astrocytes following traumatic spinal cord injury (Struve et al. 2005) and in inflammatory demyelinating lesions including those in patients with multiple sclerosis (Back et al. 2005). Transcripts for an HA synthase and CD44 are also elevated immediately following ischemic lesions in the brain (Wang et al. 2001). HA can induce contact inhibition of growth (Morrison et al. 2001) and elevated HA in glial scars has been implicated in the maintenance of glial cell proliferation and maturation (Struve et al. 2005). However, HA can cause remyelination failure by inhibiting OPC maturation in

demyelinated CNS lesions (Back et al., 2005; Sloane et al. 2010). These findings suggest that HA can regulate astrogliosis but also blocks OPCs from maturing into cells that can replace damaged myelin.

The role of HA in the aging nervous system has not been extensively examined. One study utilizing electrophoretic separation of glycosaminoglycans indicated a moderate increase in HA concentration in 30 month-old rat brain tissue compared to tissues from younger animals (Jenkins and Bachelard 1988a). HA is similarly elevated in brains from patients with Alzheimer's disease (Suzuki et al., 1965; Jenkins and Bachelard 1988b; Back et al. 2011) and in aged individuals with vascular brain injury (Back et al. 2011). We recently found that both HA and CD44 are elevated during normative aging in the prefrontal cortex of rhesus and Japanese macaques (Cargill et al. 2011). The most significant increases in HA occurred in the GM, although there was a trend towards increased HA in WM in oldest-old animals. It is possible, therefore, that HA becomes elevated in the aging brain either as a consequence of age-related cell intrinsic changes (e.g., epigenetic alterations) or as a result of age-related vascular brain injury and other events that can trigger HA synthesis or HA degradation.

All together, these studies support a mechanistic model (Fig. 4) in which WM disturbances occur with aging through a combination of vascular changes, cell-intrinsic changes to OPCs and OLs, and age-related changes in the microenvironment of aging WM. It is unclear to what degree cell intrinsic changes, such as telomere shortening, influence either the vascular damage or the response of OLs and OPCs to the resulting oxidative stress that occurs with vascular disease. However, vascular insults likely influence astrogliosis and therefore may contribute to the accumulation of HA, thus indirectly contributing to the failure of OPCs to differentiate into myelinating OLs.

Summary

Investigations of age-related changes in WM have been rapidly evolving from histological examinations to the expanded use of in vivo MRI scans. Results from cross-sectional and longitudinal as well as DTI studies have confirmed WM changes, such as demyelination in specific subregions of the brain, which correlate with cognitive deficits. However, many of these interesting findings in humans have not been directly confirmed by anatomical techniques, hence the value of the non-human primate model. Mechanistic studies in primates and in rodents are starting to reveal some of the potential mechanisms underlying age-related WM disturbances. MRI-based biomarkers are also proving valuable for acute assessment of AD, and differentiate pathology from normal aging patterns. The potential of this field

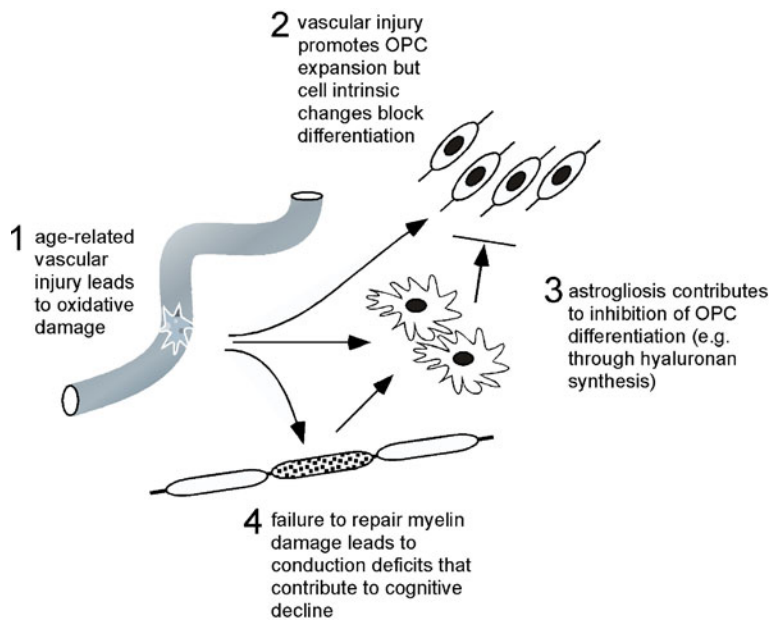


Fig. 4 A model of the possible factors that contribute to myelin damage in aging white matter. (*1*) Vascular brain injury leads to oxidative damage (*2*) that expands the pool of oligodendrocyte progenitor cells. These cells may have cell-intrinsic deficits (e.g., telomere shortening and epigenetic alterations) that prevent their maturation. (*3*) In addition, the injury microenvironment causes gliosis, leading to a non-permissive environment for oligodendrocyte progenitor cell maturation into myelinating cells. The result (*4*) is age-related remyelination failure, contributing to increasing degrees of white matter damage

of study remains great, with the opportunity of providing readily accessible biomarkers of aging, as well as the baseline values for pathological changes in the brain. Validation of MRI metrics in conjunction with molecular markers will be crucial for hypothesis and intervention testing in future investigations.

Acknowledgements This work was supported in part by NIH grants R01 AG031892 (LSS); P51 RR000163 (LSS and SGK; Oregon National Primate Research Center Grant); P01 AG000001 (DLR), R01 AG021133 (DLR), P51 RR000165 (DLR; Yerkes Primate Center Grant).

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