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Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease

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Abstract

A hypothetical model of Alzheimer's disease (AD) as a uniquely human brain disorder rooted in its exceptional process of myelination is presented. Cortical regions with the most protracted development are most vulnerable to AD pathology, and this protracted development is driven by oligodendrocytes, which continue to differentiate into myelin producing cells late into the fifth decade of life. The unique metabolic demands of producing and maintaining their vast myelin sheaths and synthesizing the brain's cholesterol supply make oligodendrocytes especially susceptible to a variety of insults. Their vulnerability increases with increasing age at differentiation as later-differentiating cells myelinate increasing numbers of axonal segments. These vulnerable late-differentiating cells drive the protracted process of intracortical myelination and by increasing local cholesterol and iron levels, progressively increase the toxicity of the intracortical environment forming the basis for the age risk factor for AD. At older ages, the roughly bilaterally symmetrical continuum of oligodendrocyte vulnerability manifests as a progressive pattern of myelin breakdown that recapitulates the developmental process of myelination in reverse. The ensuing homeostatic responses to myelin breakdown further increase intracortical toxicity and results in the relentless progression and non-random anatomical distribution of AD lesions that eventually cause neuronal dysfunction and degeneration.

This process causes a slowly progressive disruption of neural impulse transmission that degrades the temporal synchrony of widely distributed neural networks underlying normal brain function. The resulting network "disconnections" first impact functions that are most dependent on large-scale synchronization including higher cognitive functions and formation of new memories. Multiple genetic and environmental risk factors (e.g. amyloid β-peptide and free radical toxicity, head trauma, anoxia, cholesterol levels, etc.) can contribute to the cognitive deficits observed in aging and AD through their impact on the life-long trajectory of myelin development and breakdown. This development-to-degeneration model is testable through imaging and post mortem methods and highlights the vital role of myelin in impulse transmission and synchronous brain function. The model offers a framework that explains the anatomical distribution and progressive course of AD pathology, some of the failures of promising therapeutic interventions, and suggests further testable hypotheses as well as novel approaches for intervention efforts.

Keywords: Aging; Alzheimer; Myelin; Degeneration; Development; White matter; Oligodendrocytes; Amyloid; Tau; Neurons

1. Impact of myelin on human brain function and degeneration

Alzheimer's disease (AD) is a uniquely human disease whose single most important risk factor is age [29,248]. Non-human models that mimic this disease with fidelity have not been discovered despite the old age that many animals achieve in captivity. Even though much progress has been made, a genetically engineered animal model that has most of the features of AD has been difficult to create [133,206]. The age risk factor is present in both sporadic (non-genetic) and genetic forms of the disorder. Increased amyloid β-peptide (Aβ) oligomer deposition is the ultimate manifestation of genetic forms of AD and is an important early event in the pathogenesis of AD [104,209,235]. However, even though gene defects that increase Aβ production can accelerate the disease process in familial AD and disorders such as Down's syndrome, detectable AD pathology does not develop until the early adult years (typically over age 30) and clinical symptoms do not appear until years to decades later despite the presence of the abnormal genes and their products from birth [208,246].

By itself, the size of the human brain cannot be the uniquely human risk factor, since other animals with even larger brains (elephants, dolphins, etc.) do not develop AD

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cortical pathology despite achieving long life spans. Disproportionate over-development of specific brain regions such as the temporal or frontal lobes is also apparently not uniquely human since recent data indicate that, compared to other higher primates, those lobes may not be disproportionately larger than other brain regions when controlling for body size [211]. The human brain does, however, have disproportionately greater white matter volume (approximately 20%) compared to the other higher primates that do not develop AD-like pathology [211] and the percentage of brain dry weight accounted by myelin in human brain (35%) is substantially (30%) higher compared to rodents [171].

Human white matter is also unique in its "heterochronologic" development (some regions myelinate on a different timeline than others) [116,192] as well as the very long myelination timeline of the cortical association regions [10,14,21,121,266]. Myelination of axons from the prefrontal and other association areas (temporal and parietal lobes) continues until the end of the fifth decade [14,21,49,87,121,266]. This protracted myelination trajectory represents the entirety of the human life span in evolutionary terms (e.g. prior to the 1900s, relatively few individuals lived past the age of 50). These same late-myelinating neocortical regions are most vulnerable to developing the pathognomonic lesions of AD consisting of amyloid-rich extracellular neuritic plaques (NP) and tau-rich intraneuronal neurofibrillary tangles (NFT) [28,235]. Alocortical brain regions, such as the hippocampus, develop these lesions only after the neocortical association regions while the heavily/early myelinated primary motor and sensory regions are resistant to these changes and develop them only later in the disease process [28,235]. The available data on human myelination suggests that the temporal lobe, and specifically the basal and parahippocampal regions, has the most protracted cycle of myelination into the fifth and even sixth decades of life [14,21,27,121].

The production and maintenance of myelin is essential for normal brain function. Myelination results in saltatory conduction of action potentials that markedly increases (>10-fold) signal transmission speed [254]. Speed makes it possible to integrate information across the highly distributed neural networks that underlie higher cognitive functions [10,14,82,97,155,222]. In addition to faster communication across long distances, faster conduction velocity can also facilitate information flow by allowing for precise temporal coding of high-frequency bursts of neuronal activity [273]. Once myelin's function in saltatory conduction is compromised (even without frank loss of a myelin segment), not only is transmission velocity reduced but there is also a marked increase in the refractory period of the axon. This increase in refractory period can be as much as 34 times higher than the value obtained from the non-demyelinated portion of the same axon [77].

Aging-associated reduction in the number of fast conducting CNS axons of as much as 50% has been demonstrated in cats [264]. Human stereological studies estimate that the total length of myelinated axons is reduced by 27–45% in old age, primarily through loss of fibers with small diameter [177,232] which myelinate later in development [131] and are most susceptible to Aβ pathology [28]. This aging-related myelin breakdown negatively impacts cognitive performance in primates [173,184] and humans [87,174,243] (Bartzokis et al., unpublished data). The age-related loss of myelin function may also explain the conduction delays observed in aging animals and humans [4,67] and patients with AD [231]. Myelin loss may also underlie the reduced myelin staining in post mortem studies of aging and the aging-related loss of brain volume [14,21,121,157].

Disruptions due to conduction delays, changes in transmission refractory times, or temporal dispersion of impulses of myelinated tracks [77,148,232,254,264] may have the greatest impact on synchronization of impulses on which normal brain functions depend [69,76,230]. The susceptibility to the disruption of timing of impulses would be most apparent for brain functions that depend on highly distributed neural networks such as functions involved in encoding and retrieval of new memories and integration of higher executive functions [61,73,76,154,245]. These are the last functional areas to myelinate and the first to deteriorate with normal aging in monkeys [173,184] and humans [1,10,75,174,184,256]. These same functions seem to be most impacted in preclinical and early AD [10,26,28,40,62,81,130].

2. Oligodendrocytes: the most vulnerable cells in the brain

Oligodendrocytes, the CNS cells that produce myelin and underlie the protracted course of human brain development, are unique in at least five ways that are directly pertinent to the model. First and possibly most important, is the unique relationship of oligodendrocytes to the production of cholesterol. All brain cholesterol is synthesized de novo by oligodendrocytes and the human brain, which is approximately 2% of the body by weight, contains approximately 25% of the body's membrane cholesterol [65,163]. Cholesterol is present in much higher concentrations in plasma membranes, which contain 90% of all cholesterol, than in most intracellular membranes [270]. Cholesterol accounts for 28% of the brain's lipid weight [164]. The highly specialized plasma membranes that form myelin are especially enriched in cholesterol, accounting for 40% of their lipid content that is approximately twice the concentration of plasma membranes [172,200]. It is thus not surprising that myelin membrane changes are found to drive brain lipid changes with age as well as species differences in membrane composition (for review see Rouser et al. [200]).

Cholesterol is asymmetrically distributed in the lipid bilayer of membranes. In plasma membrane, cholesterol is enriched by 85% in the inner (cytofacial) leaflet [205]. In the unique myelin membrane bilayer, this asymmetry is

reversed with its outer (exofacial) leaflet (exposed to the extracellular environment) being enriched by 40% compared to the cytofacial leaflet [223]. This very high exofacial distribution contributes to three properties of cholesterol that are directly pertinent to the model. First, since cholesterol does not bind as much water as the polar phospholipids in the membrane bilayer, membranes with higher cholesterol levels are relatively dehydrated and promote closer membrane-to-membrane contact which, amongst other things, may contribute to the tight packing achieved by myelin [227]. However, this membrane packing ability is disrupted by byproducts of lipid oxidation, which could predispose myelin to breakdown and possibly degrade its electrical insulation properties necessary for saltatory conduction [184,227]. Second, its exofacial cholesterol enrichment may contribute to the free exchange of cholesterol from oligodendrocytes to neurons and astrocytes with the aid of apolipoproteins, an exchange that is not observed for most other lipid components of membranes [200,262]. Finally, the low water binding produced by high cholesterol levels in myelin may promote the hydrophobic ends of Aβ aggregates to preferentially interact with and damage myelin (for review see [226,262,263]).

The dependence of the brain on oligodendrocyte-produced cholesterol has implications for CNS development and its continual functional plasticity. In gray matter, cholesterol deficits can directly impact neuronal plasticity as CNS synaptogenesis and dendritic outgrowth are promoted by oligodendrocyte-derived cholesterol and the impairment of these remodeling processes may interfere with new learning [74,145,250]. The critical role of cholesterol in brain function could make even subtle genetic influences on the apolipoproteins involved in its transport (e.g. apolipoproteins D, E, J, and L) have clinically important impacts on multiple neuropsychiatric diseases [10,253] as well as AD [91,106,110,138,262,263].

Second, oligodendrocytes have the highest iron content of all brain cell types [47,71] and as much as 70% of brain iron is associated with myelin [60]. This is not surprising given that cholesterol and lipid synthesizing enzymes require iron to function [39] and its importance is highlighted by its involvement in oligodendrocyte differentiation. Age-related increases in iron levels may contribute to the increased intracellular oxidation necessary to trigger oligodendrocyte precursors to differentiate [162,189,218] and inadequate iron levels result in poor myelination and mental deficiencies in children [47,197].

Normal ferritin, a spherical protein in which upwards of 90% of tissue non-heme iron is stored [79,166], can sequester and store iron and other transition metals. Many normal as well as pathological processes (anoxia, oxidative stress, etc.) that have been shown to damage oligodendrocytes (see below) can also release iron from ferritin [3,54,66,100,101]. Oligodendrocytes may be more vulnerable than other cells to such iron releases since in addition to containing the highest iron stores, their particular ferritin subunit composition makes iron available with greater ease than in other cells [23,47].

Protection from iron's deleterious effects is an important issue for cellular survival. Recent evidence suggests that elevated iron levels increase the production of amyloid precursor protein (APP) [195] and that the soluble Aβ (the initial Aβ form produced from APP cleavage) can act as an iron chelator [146,274]. However, iron and other transition metals such as copper and zinc can also promote Aβ oligomerization [5,53,85,134,146]. Oligomerization makes Aβ toxic [53,123,238] making the homeostasis of iron and Aβ critically important [52].

Third, the maintenance of their enlarged lipid membrane (myelin sheath) that is up to 600× the surface area of the soma membrane and 100× the weight of the soma [164,257] makes the energy requirements of oligodendrocytes two to threefold higher than other brain cells [47]. The metabolic demands are even higher for precursors and oligodendrocytes that are actively myelinating new axon segments and produce three times their own weight in membrane lipids each day [257]. In adulthood, these differentiating cells are especially abundant intracortically in the association regions of human brain [14,121]. Since approximately 2–3% of the oxygen consumed in normal mitochondrial respiration is obligatorily transformed into free radicals [38,120], cells with high metabolism such as oligodendrocytes may be at risk due to their elevated levels of damaging oxidative reactions. The combination of high lipid and iron content, and high metabolic activity could make oligodendrocytes especially vulnerable to oxidative damage [101] and oxidized lipids are deleterious to the integrity of the myelin sheaths [184,227].

Fourth, oligodendrocytes are markedly heterogeneous based on when in the protracted process of human brain development they differentiated into myelin producing cells. Oligodendrocytes that differentiated late in life ensheath up to 50 smaller diameter axons as opposed to one oligodendrocyte per myelin segment of large CNS motor and primary sensory area axons [261]. These late-differentiating cells cannot produce the same myelin thickness per axon segment as earlier myelinating oligodendrocytes [131]. The thinner, later myelinating sheaths are more susceptible to functional impairment and destruction [177,232]. In addition, later-differentiating oligodendrocytes have different lipid properties, may have a slower rate of myelin turnover, and reduced ability for myelin repair than earlier differentiating cells [107,170,189] (see Bartzokis [9] for further review). Thus, later myelinating neurons of the association areas, like the inferior temporal regions, prefrontal, and temporoparietal regions [21,30,156,266] may be more susceptible to myelin breakdown (and subsequent neuronal degeneration, see below) than early-myelinating neurons in the primary motor and visual areas, which could be more resistant to functional impairment due to differences such as thicker myelin sheaths [108,109,131] (see Bartzokis [9] for further review). This continuum

of development-dependent oligodendrocyte heterogeneity could contribute to the bilaterally enhanced vulnerability of late-myelinating intracortical and subcortical regions to myelin breakdown [10,14,15,18,102,121]. The vulnerability continuum can explain the bilateral and progressive nature of functional impairments as progressively more resistant earlier-myelinating regions succumb to the functional impairments of myelin breakdown [15,16].

Finally, the unique functions, structure, and biochemistry of these cells may all contribute to their high and region-specific vulnerability to a multitude of insults [20]. Oligodendrocytes are more susceptible than neurons and astrocytes to chronic hypoperfusion [120,129,179,185], toxic products of activated microglia such as nitric oxide [153,158,214], iron toxicity [127], and excitotoxicity [2,112,144,147]. In addition, oligodendrocyte precursors are especially vulnerable to oxidative damage, making actively myelinating intracortical and subcortical regions especially vulnerable [7,39,115]. This high vulnerability of precursor cells is manifested in the wide variety of insults such as exogenous glucocorticoids [63,114], excitotoxicity [198], hypothyroidism [194], nutritional deficiencies including iron [47,197,257], other heavy metal toxicity [63,127,167], drugs of abuse such as alcohol [57,105] and cocaine [11,13,169], hypertension [80,93,94], and brain trauma [224,242], which can result in myelination arrests or decrements during the over 5 decade-long developmental trajectory of human myelination [14,21,121,266].

3. Evidence of myelin damage in brain aging and AD

Multiple investigators have suggested that myelin breakdown may be a contributing factor to the pathology of both aging [14,43,98,113,121,157,168,183], and AD [15,17,18,28,44,58,70,96,102,126,139,196,228,233,249]. Widespread and diffuse myelin breakdown has been reported to occur in AD subjects despite the lack of evidence of infarction, Wallerian degeneration, or white matter amyloid angiopathy [15,18,31,34,58,59,72,196] and these white matter deficits are observed at the earliest or preclinical stages of the disease [15,18,58,102]. Some investigators attribute the myelin breakdown to ischemia [33,212] while others consider it to be a primary disease process [15,17,18,31,44,46,58,96,126,225,228,233,241] that may be accelerated by or caused by factors such as oligomeric Aβ [53,128,196,238].

Like adult myelination, the neurodegeneration of AD is not global [28,58,191,193,255]. Rather, the neurons most susceptible to neurodegeneration in AD extend small diameter cortico–cortical axons that myelinate late in life [28,121,232,235]. The susceptibility of this subset of axons to myelin breakdown [107,121,152,170,232] may provide a mechanism through which the apparent progression of cortical AD pathology could occur in a bilateral, predictable pattern that appears to be the reverse of myelination, as suggested by Braak and Braak [26]. For example, the genu of the corpus callosum connects the prefrontal lobes and myelinates in later years compared to the splenium that connects the occipital lobes [18,237,266]. Even in adulthood, the genu has up to 20–30% of its axons unmyelinated compared to less than 7% in splenium, which subserves primary visual pathways predominated by large, heavily myelinated axons [131,178].

In adult humans, the transentorhinal region and the nearby neocortical association areas are particularly poorly myelinated [111,247] cited in [21,27] as is the temporal lobe in general compared to the frontal lobe [14,121]. These same late-myelinating regions are the focus of the very first Aβ deposits and myelin breakdown [58,126,235,236] and are involved in short-term memory formation that depends on synchronization of impulses [76] of widely distributed functional areas [176].

Thus, late-myelinating oligodendrocytes and their precursors are present at the cortical site of Aβ oligomeric deposits observed in aging and AD. The evidence that the pathogenesis of AD is linked to the characteristic neocortical Aβ deposition is well established [104,210,235,236]. Recent data indicate that Aβ becomes toxic when it oligomerizes [149], and myelin can be directly damaged by oligomerized Aβ [123,238,265]. Furthermore, Aβ has been shown to promote oxidative stress and neurotoxicity [136,149,244] and iron has been shown to interact with Aβ to promote the formation of reactive oxygen species [25,160,186,199,219,240,267], for review see Lynch et al. [136]. Increased levels of lipid peroxidation and myelin breakdown have been demonstrated in the myelin of older compared to younger normal individuals [15,18,43] and in the myelin of AD patients compared to normal older subjects [15,18,44], and myelin integrity is disrupted by the products of lipid peroxidation [184,227].

4. From myelin damage to neuronal death

The pathognomonic lesions of AD (NFT and NP) appear in the fourth decade of life and at this stage, neuronal loss is not observed [191]. As the severity and numbers of these lesions progress over the ensuing 30 years, they eventually result in neuronal loss and manifest clinically as AD [27,175]. Myelin damage or loss can contribute to this process as it has marked effects on neuronal survival and function through a variety of mechanisms. The loss of neurotrophic factors produced by oligodendrocytes can adversely affect their underlying neurons [55,258]. A special case of this role is the crucial involvement of oligodendrocytes in neurosteroid production, both as the producer of the cholesterol backbone and as the major producer of neurosteroid precursors [32], which are neurotrophic to axons as well as myelin [187].

In addition, axon myelination markedly reduces neuronal energy expenditure. The loss or dysfunction of axonal myelin would require an estimated increase of up to 5000-fold in neuronal energy expenditure in order to main-

tain neurotransmission levels [107,170]. Approximately 2–3% of the oxygen consumed in normal mitochondrial respiration is obligatorily transformed into free radicals [37,119] and with aging, an increasing percentage of oxygen is converted to superoxide [182,203,220]. The aging-related loss/dysfunction of myelin would result in a further increase in the production of damaging free radicals. Both neurons and especially oligodendroglia (for reasons described above) are very susceptible to damage from free radicals. Free radical (oxidative) damage has been shown to be strongly aging-related [151,216] and has been implicated in the pathophysiology of AD [56,83,95,135, 140,151,161,190,216,217,219].

An increase in neuronal free radical production has also been postulated to contribute to AD tangle-related neuropathology [83,140,161,217]. Oxidation of tau induces its dimerization and polymerization into insoluble filaments [239], the precursor to the intraneuronal NFT, the second pathognomonic lesion observed in AD brain. These damaging oxidative processes are also observed in other neurodegenerative diseases and it is thus not surprising that many other neurodegenerative disorders manifest NFTs while normal individuals rarely do so [207].

In AD, there may be additional paths connecting the early pathology of Aβ oligomer deposits, which is aging-related and can be seen in normal aging individuals [165,209]. In addition, fatty acid oxidative products and cholesterol depletion have been shown to promote tau hyperphosphorylation and polymerization [74,83]. Thus, multiple mechanisms may exist interrelating Aβ oligomer damage to lipid membranes, oxidative stress, and tau polymerization [25,149,160,181,199,240]. In the context of these complex interrelated damaging processes, the heterogeneity observed at post mortem examination with some AD brains containing primarily Aβ pattern of sequelae while others primarily a NFT pattern [8,22,91] may be created by differing combinations of risk factors and could be used in the context of this model to better understand those factors.

5. The developmental framework: explaining the age risk factor of AD

The unique susceptibility of oligodendrocytes to stressors that occur in adulthood as well as treatment interventions (hormone replacement, non-steroidal anti-inflammatory, antihypertensive, cholesterol-lowering, etc.) that modify such stressors could alter the development and subsequent degeneration trajectories of brain myelin. The impact of both insults and myelin-sparing interventions would be preferentially greater on later-myelinating regions. In contrast, these same events would have comparatively less impact on brain regions and functions such as movement and vision, which are subserved by larger axons that became fully and heavily myelinated early in life [15,131]. Damage to vulnerable younger oligodendrocytes and their precursors could thus be a common mechanism of altering brain developmental patterns that, in older age, manifest as a variety of risk factors for AD such as early brain trauma, vascular disease, hypertension, nutritional deficiencies, hypercholesterolemia and reduced hormone levels, etc. through their delayed impact on the subsequent pattern of myelin breakdown associated with aging and aging-related diseases such as AD. These delayed effects would also increase the heterogeneity of symptoms observed in degenerative diseases depending on when the insults occurred in relation to the regions/functions undergoing myelination at that particular time of life of the individual.

The essential role of cholesterol and iron in oligodendrocyte and brain function can be used to exemplify the utility of the developmental prospective of the model in its application to AD. Membrane cholesterol is directly involved in AD pathophysiology in multiple and interrelated ways [24,68,141,165,181]. For example, intramembrane secretases that generate Aβ produce more Aβ when membranes have higher cholesterol content [68,132,260,268]. Oligodendrocytes themselves can produce Aβ [20,84]. This suggests that as myelination progresses, the increasing numbers of oligodendrocytes can directly increase the production of Aβ and also do so indirectly by providing more cholesterol to the rest of the brain cells and thus driving the age-related increase in whole brain cholesterol levels to the peak reached in the fourth decade of life [201]. Unlike other major body lipids, cholesterol cannot be degraded by mammalian tissue (except for minor pathways involved in hormone and bile acid metabolism) and the few ways cholesterol can be removed from brain is by a slow exchange with plasma [164] after hydroxylation [181] or possibly by sequestration in NPs [165]. Deficits in hydroxylation is associated with increased Aβ, tau, and risk for AD [181]. The increasing availability of cholesterol is supported by evidence that cholesterol content of the exofacial leaflet of plasma membranes in brain doubles with age [117,262]. This may set up a scenario of aging-related increase in intracortical toxicity as the production as well as oligomerization of Aβ is promoted by high cholesterol content of lipid bilayers [68,159,181,260,271]. It is thus not surprising that deposits of Aβ oligomers increase with age and are observed in otherwise normal aging individuals [64,252]. Furthermore, epidemiologic studies suggest that elevated peripheral cholesterol levels in midlife may predispose individuals to developing AD in old age [124], and medications which reduce cholesterol synthesis may be beneficial in preventing and possibly treating early AD [50,132,181,213,260,262] possibly by reversing the age-related increase in cholesterol levels in the exofacial leaflet of plasma membrane [122]. The pathognomonic lesions of AD (NFT and NP) also begin to appear in the fourth decade of life but at this stage, there is no neuronal loss [191]. The progression of these lesions over the ensuing 30 years, eventually results in neuronal loss and clinical manifestations as AD [27,175].

In the same time frame, the increasing levels of toxic Aβ aggregates preferentially bind to cholesterol in mem-

branes, disrupt cholesterol transport between cells, and can remove cholesterol from membranes [6] (for review see [262,268]). The toxicity of oligomeric Aβ has been shown to increase with age and myelination [90] and can destroy oligodendrocytes in vitro [265]. As the disease progresses, Aβ oligomer levels rise in patients with preclinical AD [234]. The increasing Aβ oligomer-membrane interactions could thus progressively remove membrane cholesterol levels in older individuals [165,201] and eventually markedly reduce cholesterol levels in individuals who develop AD as has been consistently demonstrated [96,143,196,228]. The cholesterol loss occurs without appreciable loss of phospholipids [96] and much of this cholesterol reduction can be directly attributed to loss of cholesterol-enriched myelin [139]. Finally, deficiency in membrane cholesterol promotes tau phosphorylation and breakdown of microtubule stability and could thus contribute to intraneuronal NFT [74].

Within the developmental framework of the model, these dynamic and interrelated age-related changes in membrane lipids can help explain why treatments that lower cholesterol, blood pressure, inflammation, or replace declining hormone levels in mid-life are associated with reduced risk of developing AD in later life but have not proven effective therapies for patients that have already developed AD [78,80,124,188,272]. The developmental model suggests that cholesterol-lowering medications, as well as other interventions that may lower cholesterol such as hormone treatments, may have markedly different effects at different stages of the disease. Such treatments may ameliorate the process of Aβ production and aggregation in preclinical and possibly even early stages of AD (when cholesterol levels are higher), while being ineffective or possibly exacerbating the destructive disease processes once the disease has progressed (when cholesterol levels are already low) [78,180,213,272].

The developmental framework of the model can also be used to better understand the role of increasing iron levels in brain development and degeneration. Tissue iron is a powerful promoter of oxidation and damaging free radical reactions [101,127] and brain tissue iron levels increase with age from extremely low levels at birth [12,17,19,99,125]. In addition, increased iron levels are associated with excess damage to mitochondria and their DNA [149,251], resulting in an increased percentage of oxygen converted to superoxide with age [182,203,220]. Thus, like increasing cholesterol and myelination, age-related increases in iron levels may be an additional risk factor that contributes to the development of an intracortical environment that makes myelin especially susceptible to damage with increasing age. Increasing cortical iron could thus also contribute to the biological basis for the age risk factor of neurodegenerative disorders such as AD [12,17,19] and environmental or genetic factors that influence brain iron levels could impact the disease process [48,202].

Of special interest to the hypothesis that oligodendrocytes may be involved in the early pathophysiology of aging and AD is the recent data indicating that the process of Aβ oligomerization is mediated in part by transition metal interacting with Aβ and by metal-mediated oxidative stress [52,146]. The observation that iron is consistently found at the core of plaques [219], and that oligomerization of Aβ is promoted by iron and other transition metals such as copper and zinc [5,53,85,134,146], has reinvigorated searches for metal chelation treatments for AD [42,150] for review see [51].

Compared to subcortical gray matter regions, cortical iron levels are low with the very lowest levels occurring in the late-myelinating association cortices [99]. Thus, in the vulnerable late-myelinating cortical regions, the destruction of iron-rich oligodendroglia could be the major extracellular source of transition metal involved in Aβ oligomerization. A destructive spiral of iron release causing Aβ oligomerization followed by further oligodendroglial damage and further iron release could help explain the ever-progressive nature of AD pathophysiology. As described above for the age-related increases in brain cholesterol levels [201], age-related increases in brain iron levels [19,99] could help explain why patients with a genetic predisposition for increased production of Aβ such as Downs syndrome [104] do not develop pathologic lesions of AD until they reach their early to mid-30s despite the production of increased Aβ levels since birth. Only in the early adult years would both adequate iron levels and active cortical myelination occur in the association regions [14,16,99,121]. Together, these developmental processes could form the physiologic basis for age as the major risk factor for AD [16,17,19] and explain the timing of the appearance of its first pathophysiologic markers (NP and NFT) in mid-life [15,18,27]. Animal models have shown that aging renders the brain more vulnerable to Aβ neurotoxicity [90,149]; this aging effect is most notable in higher primates with longer myelination cycles than lower primates and is absent in aged rats [90].

6. Future directions and prevention-focused interventions

The involvement of myelin breakdown in the pathophysiology of brain aging and AD is entirely consistent with the Aβ hypothesis of AD and may help explain some of its apparent weaknesses [104]. Cortical Aβ oligomer deposition, one of the hallmarks of AD, is an age-dependent extracellular process [137], however elevated Aβ oligomers are also observed in white matter [128,196], and Aβ deposits can be observed there [259]. The astrocytic response to Aβ deposits in the white matter is less intense than in cortex, however [128,259], which may contribute to the under appreciation of the impact Aβ may have on white matter and myelin in general [196]. Oligomeric Aβ can damage myelin [123,238,265]. Oligomeric Aβ can also increase lipid peroxidation [229,244], which is increased in AD myelin [44] and disrupts its integrity [227]. The changes associ-

ated with brain aging are critical to the toxic effects of Aβ [90] and to the cytoskeletal response to intracerebrally injected Aβ [149]. This age-related susceptibility and the timing of NP and NFT appearance is consistent with the developmental pattern of regionally increasing intracortical myelination [10,121], cholesterol [117,262], and iron levels [12,16,17,99,125] of the human brain.

The functional impact of myelin breakdown and the resulting decrease in conduction speed and increase in refractory times is supported by observations of increased latency of evoked potential responses in patients with AD and associations between these response speeds and cognitive function [231]. In addition, symmetric and bilateral functional "disconnection" [88,89] of cortico–cortical communication, affecting primarily association regions and higher cognitive functions, are observed in both preclinical and early AD [10,26,28,41,62,81,130].

Thus, various aspects of the pathophysiology of AD suggest that at the earliest stages of this disease, age-related damage to late-differentiating oligodendrocytes and their precursors may predispose to the development of AD [15,18,58,102]. The model suggests novel myelin-centered approaches to treatment interventions earlier in the process may be possible. Multiple promyelinating treatments may already be available [10]. For example, insulin-like growth factor-1 can increase myelination [36,92] and inhibit oligodendrocyte apoptosis during primary demyelination [142]. This effect is observed both in white matter tracts such as the corpus callosum and in cortical gray matter and hippocampal regions, even in the face of nutritional deficiencies known to reduce myelination [45,269].

Thirty years elapse between the onset of the disease (as manifested by the appearance of the first NFT and NP) and the clinical changes suggestive of early AD [175] in the absence of appreciable neuronal loss [191]. Imaging biomarker technology has emerged that is safe, repeatable, and widely available and can track the dynamic changes in brain membranes over the age-span, making it possible to prospectively test the entirety of the model [14,87,221]. Techniques that are especially sensitive to disruption in myelin integrity such as relaxometry, magnetization transfer, and diffusion tensor imaging create the opportunity to prospectively test the later, degeneration phases of the model [10,14,15, 18,19,86,87,103], while techniques that are especially sensitive to myelination can be used to investigate the developmental aspects of the model [10,15,86,221] (Bartzokis et al., unpublished data). Thus, the spectrum of dynamic changes caused by insults as well as therapeutic interventions that may accelerate myelination or remove offensive factors or correct delays in myelination can be investigated.

Imaging biomarkers could be used to identify individuals at high risk for developing cognitive impairments, and prospectively track the effects of treatment interventions aimed at preventing the progression of cognitive impairments in populations that have minimal symptoms or are entirely asymptomatic [10,210,215]. Combining imaging and genetic approaches may provide the opportunity to apply potential treatments in the earliest phases of the disease possibly even before the myelin-damaging process differentiates from "normal" aging. Such a preventive approach could have the benefit of allowing less intense interventions that may be better tolerated and have a larger impact due to its earlier initiation. Thus, low-dose immunologic [204], cholesterol-lowering [50,213], metal chelation [42,150], or antioxidant treatments could prove effective with greatly reduced risk of untoward side effects. In order to achieve these goals in the reasonably near future, these technologies must be safe, widely available, and accessible, and prospective studies demonstrating their utility must be undertaken [15,16].

7. Conclusions

Alzheimer's disease is a relentlessly progressive cortical disorder that in its earliest stages affects cortico–cortical neurons and begins in later-myelinating association cortices. Recent evidence suggests that an understanding of brain aging and the aging-related processes of myelin production and subsequent breakdown may be relevant to creating a useful conceptual model aimed at understanding aging, AD, and possibly other age-related neurodegenerative disorders [35,118] (see Bartzokis [9] for further details). This model posits that because of the unique vulnerability of late-developing oligodendrocytes, myelin breakdown is at the core of the earliest changes involved in both brain aging and AD. Myelin breakdown disrupts brain functions that depend on highly synchronized timing of neuronal impulses and eventually results in functional "disconnections" of association cortical regions, with subsequent loss of neurons and progression to permanent deficits. The loss of synchrony affects progressively more networks, and therefore results in an increasing group of devastating symptoms that we currently refer to as AD. Thus, genetic and/or environmental effects that impact myelin development and breakdown will manifest as risk factors (or protective factors) for the development of AD. This model suggests that many pathological states (e.g. genetic, hormonal, head trauma, hypertension, hypercholesterolemia, substance abuse, etc.) can impact the normal age-related pattern of myelin development and thus impact the pattern of myelin breakdown at older ages.

The model provides a framework that suggests explanations for the special susceptibility of the human brain to AD, the bilateral regional pattern of degenerative NP and NFT lesions and their predictable and non-relenting course, the importance of the age risk factor in the development of both the idiopathic as well as the genetic process resulting in these lesions, the substantial dysfunction despite minimal neuronal destruction in aging and early in the course of AD, and the similarity of neurocognitive deficits observed in aging and preclinical AD.

This temporally expanded model of brain development and its dynamic interaction with brain degeneration creates

the possibility of testing its underlying hypotheses through prospective imaging studies focused on areas of active myelination, combined with neurocognitive evaluations and genetic studies targeting proteins and lipids involved in myelination. The model predicts that medications or other interventions (hormonal, dietary) that protect myelin, enhance myelination, or prevent its breakdown could result in amelioration of deficits in both normal brain aging and aging-related neurodegenerative disorders such as AD.

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References

[1] Albert M. Neuropsychological and neurophysiological changes in healthy adult humans across the age range. Neurobiol Aging 1993;14:623–5.
[2] Alonso G. Prolonged corticosterone treatment of adult rats inhibits the proliferation of oligodendrocyte progenitors present throughout white and gray matter regions of the brain. Glia 2000;31:219–31.
[3] Anggard E. Nitric oxide: mediator, murderer, and medicine [see comments]. Lancet 1994;343:1199–206.
[4] Aston-Jones G, Rogers J, Shaver RD, Dinan TG, Moss DE. Age-impaired impulse flow from nucleus basalis to cortex. Nature 1985;318:462–4.
[5] Atwood CS, Moir RD, Huang X, Scarpa RC, Bacarra NM, Romano DM, et al. Dramatic aggregation of Alzheimer abeta by Cu(II) is induced by conditions representing physiological acidosis. J Biol Chem 1998;273:12817–26.
[6] Avdulov NA, Chochina SV, Igbavboa U, Warden CS, Vassiliev AV, Wood WG. Lipid binding to amyloid beta-peptide aggregates: preferential binding of cholesterol as compared with phosphatidylcholine and fatty acids. J Neurochem 1997;69:1746–52.
[7] Back SA, Gan X, Li Y, Rosenberg PA, Volpe JJ. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. J Neurosci 1998;18:6241–53.
[8] Barker WW, Luis CA, Kashuba A, Luis M, Harwood DG, Loewenstein D, et al. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the state of Florida brain bank. Alzheimer Dis Assoc Disord 2002;16:203–12.
[9] Bartzokis G. Quadratic trajectories of brain myelin content: Unifying construct for neuropsychiatric disorders. Neurobiology of Aging 2003 (in press).
[10] Bartzokis G. Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation. Neuropsychopharmacology 2002;27:672–83.
[11] Bartzokis G, Beckson M, Hance DB, Lu PH, Foster JA, Mintz J, et al. Magnetic resonance imaging evidence of "silent" cerebrovascular toxicity in cocaine dependent. Biol Psychiatry 1999;45:1203–11.
[12] Bartzokis G, Beckson M, Hance DB, Marx P, Foster JA, Marder SR. MR evaluation of age-related increase of brain iron in young adult and older normal males. Magn Reson Imaging 1997;15:29–35.
[13] Bartzokis G, Beckson M, Lu PH, Edwards N, Bridge P, Mintz J. Brain maturation may be arrested in chronic cocaine addicts. Biol Psychiatry 2002;51:605–11.
[14] Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. Arch Gen Psychiatry 2001;58:461–5.
[15] Bartzokis G, Cummings J, Sultzer D, Henderson VW, Nuechterlein KH, Mintz J. White matter structural integrity in aging and Alzheimer's disease: a magnetic resonance imaging study. Arch Neurol 2003;60:393–8.
[16] Bartzokis G, Mintz J, Sultzer D, Marx P, Herzberg JS, Phelan CK, et al. In vivo MR evaluation of age-related increases in brain iron. AJNR Am J Neuroradiol 1994;15:1129–38.
[17] Bartzokis G, Sultzer D, Cummings BJ, Holt LE, Hance DB, Henderson VW, et al. In vivo evaluation of brain iron in Alzheimer's disease and normal controls using magnetic resonance imaging. Arch Gen Psychiatry 2000;57:47–53.
[18] Bartzokis G, Sultzer D, Lu PH, Nuechterlein KH, Mintz J, Cummings J. Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical "disconnection" in aging and Alzheimer's disease. 2003, under review.
[19] Bartzokis G, Sultzer D, Mintz J, Holt LE, Marx P, Phelan CK, et al. In vivo evaluation of brain iron in Alzheimer's disease and normal subjects using MRI. Biol Psychiatry 1994;35:480–7.
[20] Bauer J, Bradl M, Klein M, Leisser M, Deckwerth TL, Wekerle H, et al. Endoplasmic reticulum stress in PLP-overexpressing transgenic rats: gray matter oligodendrocytes are more vulnerable than white matter oligodendrocytes. J Neuropathol Exp Neurol 2002;61:12–22.
[21] Benes FM, Turtle M, Khan Y, Farol P. Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. Arch Gen Psychiatry 1994;51:477–84.
[22] Bird TD, Sumi SM, Nemens EJ, Nochlin D, Schellenberg G, Lampe TH, et al. Phenotypic heterogeneity in familial Alzheimer's disease: a study of 24 kindreds. Ann Neurol 1989;25:12–25.
[23] Blissman G, Menzies S, Beard J, Palmer C, Connor J. The expression of ferritin subunits and iron in oligodendrocytes in neonatal porcine brains. Dev Neurosci 1996;18:274–81.
[24] Bogdanovic N, Bretillon L, Lund EG, Diczfalusy U, Lannfelt L, Winblad B, et al. On the turnover of brain cholesterol in patients with Alzheimer's disease. Abnormal induction of the cholesterol-catabolic enzyme CYP46 in glial cells. Neurosci Lett 2001;314:45–8.
[25] Bondy SC, Guo-Ross SX, Truong AT. Promotion of transition metal-induced reactive oxygen species formation by beta-amyloid. Brain Res 1998;799:91–6.
[26] Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. Neurobiol Aging 1997;18:351–7.
[27] Braak H, Braak E. Temporal sequence of Alzheimer's disease-related pathology. In: Jones E, Peters A, editors. Cerebral cortex: neurodegenerative and age-related changes in structure and function of cerebral cortex, vol. 14. New York: Plenum Press; 1999. p. 475–512.
[28] Braak H, Del Tredici K, Schultz C, Braak E. Vulnerability of select neuronal types to Alzheimer's disease. Ann N Y Acad Sci 2000;924:53–61.
[29] Breteler MM, Claus JJ, van Duijn CM, Launer LJ, Hofman A. Epidemiology of Alzheimer's disease. Epidemiol Rev 1992;14:59–82.
[30] Brody BA, Kinney HC, Kloman AS, Gilles FH. Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. J Neuropathol Exp Neurol 1987;46:283–301.
[31] Bronge L, Bogdanovic N, Wahlund LO. Postmortem MRI and histopathology of white matter changes in Alzheimer brains. A quantitative, comparative study. Dement Geriatr Cogn Disord 2002;13:205–12.

[32] Brown RC, Cascio C, Papadopoulos V. Pathways of neurosteroid biosynthesis in cell lines from human brain: regulation of dehydroepiandrosterone formation by oxidative stress and beta-amyloid peptide. J Neurochem 2000;74:847–59.
[33] Brown WR, Moody DM, Thore CR, Challa VR. Cerebrovascular pathology in Alzheimer's disease and leukoaraiosis. Ann N Y Acad Sci 2000;903:39–45.
[34] Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. Ann Neurol 1986;19:253–62.
[35] Burn DJ, Jaros E. Multiple system atrophy: cellular and molecular pathology. Mol Pathol 2001;54:419–26.
[36] Carson MJ, Behringer RR, Brinster RL, McMorris FA. Insulin-like growth factor I increases brain growth and central nervous system myelination in transgenic mice. Neuron 1993;10:729–40.
[37] Chance B, Sies H, Boveris A. Hydroperoxide metabolism in mammalian organs. Physiol Rev 1979;59:527–605.
[38] Chance SA, Highley JR, Esiri MM, Crow TJ. Fiber content of the fornix in schizophrenia: lack of evidence for a primary limbic encephalopathy. Am J Psychiatry 1999;156:1720–4.
[39] Cheepsunthorn P, Palmer C, Menzies S, Roberts RL, Connor JR. Hypoxic/ischemic insult alters ferritin expression and myelination in neonatal rat brains. J Comp Neurol 2001;431:382–96.
[40] Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Patterns of cognitive decline in presymptomatic Alzheimer Disease. Arch Gen Psychiatry 2001;58:853–8.
[41] Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. Arch Gen Psychiatry 2001;58: 853–8.
[42] Cherny RA, Atwood CS, Xilinas ME, Gray DN, Jones WD, McLean CA, et al. Treatment with a copper–zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. Neuron 2001;30:665–76.
[43] Chia LS, Thompson JE, Moscarello MA. Changes in lipid phase behaviour in human myelin during maturation and aging. Involvement of lipid peroxidation. FEBS Lett 1983;157:155–8.
[44] Chia LS, Thompson JE, Moscarello MA. X-ray diffraction evidence for myelin disorder in brain from humans with Alzheimers disease. Biochem Biophys Acta 1984;775:308–12.
[45] Chowen JA, Goya L, Ramos S, Busiguina S, Garcia-Segura LM, Argente J, et al. Effects of early undernutrition on the brain insulin-like growth factor-I system. J Neuroendocrinol 2002;14:163–9.
[46] Chung TF, Sipe JD, McKee A, Fine RE, Schreiber BM, Liang JS, et al. Serum amyloid A in Alzheimer's disease brain is predominantly localized to myelin sheaths and axonal membrane. Amyloid 2000;7:105–10.
[47] Connor JR, Menzies SL. Relationship of iron to oligodendrocytes and myelination. Glia 1996;17:83–93.
[48] Connor JR, Milward EA, Moalem S, Sampietro M, Boyer P, Percy ME, et al. Is hemochromatosis a risk factor for Alzheimer's disease? J Alzheimers Dis 2001;3:471–7.
[49] Courchesne E, Chisum HJ, Townsend J, Cowles A, Covington J, Egaas B, et al. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. Neuroradiology 2000;216:672–82.
[50] Crisby M, Carlson LA, Winblad B. Statins in the prevention and treatment of Alzheimer disease. Alzheimer Dis Assoc Disord 2002;16:131–6.
[51] Cuajungco MP, Faget KY, Huang X, Tanzi RE, Bush AI. Metal chelation as a potential therapy for Alzheimer's disease. Ann N Y Acad Sci 2000;920:292–304.
[52] Cuajungco MP, Goldstein LE, Nunomura A, Smith MA, Lim JT, Atwood Cs, et al. Evidence that the beta-amyloid plaques of Alzheimer's disease represent the redox-silencing and entombment of A beta by zinc. J Biol Chem 2000;275:19439–42.
[53] Curtain CC, Ali F, Volitakis I, Cherny RA, Norton RS, Beyreuther K, et al. Alzheimer's disease amyloid-beta binds copper and zinc to generate an allosterically ordered membrane-penetrating structure containing superoxide dismutase-like subunits. J Biol Chem 2001;276:20466–73.
[54] Dai L, Winyard PG, Zhang Z, Blake DR, Morris CJ. Ascorbate promotes low density lipoprotein oxidation in the presence of ferritin. Biochim Biophys Acta 1996;1304:223–8.
[55] Dai X, Qu P, Dreyfus CF. Neuronal signals regulate neurotrophin expression in oligodendrocytes of the basal forebrain. Glia 2001;34:234–9.
[56] Davis DR, Anderton BH, Brion JP, Reynolds CH, Hanger DP. Oxidative stress induces dephosphorylation of tau in rat brain primary neuronal cultures. J Neurochem 1997;68:1590–7.
[57] de la Monte SM. Disproportionate atrophy of cerebral white matter in chronic alcoholics. Arch Neurol 1988;45:990–2.
[58] de la Monte SM. Quantitation of cerebral atrophy in preclinical and end-stage Alzheimer's disease. Ann Neurol 1989;25:450–9.
[59] de la Monte SM, Wells SE, Hedley-Whyte T, Growdon JH. Neuropathological distinction between Parkinson's dementia and Parkinson's plus Alzheimer's disease. Ann Neurol 1989;26:309–20.
[60] de los Monteros AE, Korsak RA, Tran T, Vu D, de Vellis J, Edmond J. Dietary iron and the integrity of the developing rat brain: a study with the artificially-reared rat pup. Cell Mol Biol (Noisy-le-grand) 2000;46:501–15.
[61] de Groot J, Zhou S, Carlton SM. Peripheral glutamate release in the hindpaw following low and high intensity sciatic stimulation. Neuroreport 2000;11:497–502.
[62] DeKosky ST, Ikonomovic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, et al. Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. Ann Neurol 2002;51:145–55.
[63] Deng W, McKinnon RD, Poretz RD. Lead exposure delays the differentiation of oligodendroglial progenitors in vitro. Toxicol Appl Pharmacol 2001;174:235–44.
[64] Dickson DW, Crystal HA, Mattiace LA, Masur DM, Blau AD, Davies P, et al. Identification of normal and pathological aging in prospectively studied nondemented elderly humans. Neurobiol Aging 1992;13:179–89.
[65] Dietschy JM, Turley SD. Cholesterol metabolism in the brain. Curr Opin Lipidol 2001;12:105–12.
[66] Double KL, Maywald M, Schmittel M, Riederer P, Gerlach M. In vitro studies of ferritin iron release and neurotoxicity. J Neurochem 1998;70:2492–9.
[67] Dustman RE, Emmerson RY, Shearer DE. Life span changes in electrophysiological measures of inhibition. Brain Cogn 1996;30:109–26.
[68] Ehehalt R, Keller P, Haass C, Thiele C, Simons K. Amyloidogenic processing of the Alzheimer b-amyloid precursor protein depends on lipid rafts. J Cell Biol 2003;160:113–23.
[69] Engel AK, Fries P, Singer W. Dynamic predictions: oscillations and synchrony in top-down processing. Nat Rev Neurosci 2001;2:704–16.
[70] Englund E, Brun A, Alling C. White matter changes in dementia of Alzheimer's type. Brain 1988;111:1425–39.
[71] Erb GL, Osterbur DL, LeVine SM. The distribution of iron in the brain: a phylogenetic analysis using iron histochemistry. Dev Brain Res 1996;93:120–8.
[72] Erkinjuntti T, Benavente O, Eliasziw M, Munoz DG, Sulkava R, Haltia M, et al. Diffuse vacuolization (spongiosis) and arteriolosclerosis in the frontal white matter occurs in vascular dementia. Arch Neurol 1996;53:325–32.
[73] Esposito G, Kirkby BS, Van Horn JD, Ellmore TM, Berman KF. Context-dependent, neural system-specific neurophysiological concomitants of ageing: mapping PET correlates during cognitive activation. Brain 1999;122:963–79.

[74] Fan QW, Yu W, Gong JS, Zou K, Sawamura N, Senda T, et al. Cholesterol-dependent modulation of dendrite outgrowth and microtubule stability in cultured neurons. J Neurochem 2002;80:178–90.
[75] Fazekas F, Schmidt R, Scheltens P. Pathophysiologic mechanisms in the development of age-related white matter changes of the brain. Dement Geriatr Cogn Disord 1998;9(Suppl 1):2–5.
[76] Fell J, Klaver P, Lehnertz K, Grunwald T, Schaller C, Elger CE, et al. Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. Nat Neurosci 2001;4:1259–64.
[77] Felts PA, Baker TA, Smith KJ. Conduction in segmentally demyelinated mammalian central axons. J Neurosci 1997;17:7267–77.
[78] Fillit HM. The role of hormone replacement therapy in the prevention of Alzheimer disease. Arch Intern Med 2002;162:1934–42.
[79] Floyd RA, Carney JM. The role of metal ions in oxidative processes and aging. Toxicol Ind Health 1993;9:197–214.
[80] Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the systolic hypertension in Europe (syst-eur) study. Arch Intern Med 2002;162:2046–52.
[81] Fox NC, Warrington EK, Seiffer AL, Agnew SK, Rossor MN. Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer's disease. A longitudinal prospective study. Brain 1998;121:1631–9.
[82] Fuster JM. Synopsis of function and dysfunction of the frontal lobe. Acta Psychiatr Scand Suppl 1999;395:51–7.
[83] Gamblin TC, King ME, Kuret J, Berry RW, Binder LI. Oxidative regulation of fatty acid-induced tau polymerization. Biochemistry 2000;39:14203–10.
[84] Garcia-Ladona FJ, Huss Y, Frey P, Ghandour MS. Oligodendrocytes express different isoforms of beta-amyloid precursor protein in chemically defined cell culture conditions: in situ hybridization and immunocytochemical detection. J Neurosci Res 1997;50:50–61.
[85] Garzon-Rodriguez W, Yatsimirsky AK, Glabe CG. Binding of Zn(II), Cu(II), and Fe(II) ions to Alzheimer's A beta peptide studied by fluorescence. Bioorg Med Chem Lett 1999;9:2243–8.
[86] Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL. Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis. AJNR Am J Neuroradiol 2002;23:1327–33.
[87] Ge Y, Grossman RI, Babb JS, Rabin ML, Mannon LJ, Kolson DL. Age-related total gray matter and white matter changes in normal adult brain. Part II: quantitative magnetization transfer ratio histogram analysis. AJNR Am J Neuroradiol 2002;23:1334–41.
[88] Geschwind N. Disconnexion syndromes in animals and man. Part II. In: Williams D, editor. Brain: a journal of neurology, vol. LXXXVIII. New York: St. Martins Press Inc.; 1965. p. 585–644.
[89] Geschwind N. Disconnexion syndromes in animals and man. Part 1. In: Williams D, editor. Brain: a journal of neurology, vol. LXXXVIII. New York: St. Martin's Press Inc.; 1965. p. 237–94.
[90] Geula C, Wu CK, Saroff D, Lorenzo A, Yuan M, Yankner BA. Aging renders the brain vulnerable to amyloid beta-protein neurotoxicity [see comments]. Nat Med 1998;4:827–31.
[91] Ghebremedhin E, Schultz C, Thal DR, Rub U, Ohm TG, Braak E, et al. Gender and age modify the association between APOE and AD-related neuropathology. Neurology 2001;56:1696–701.
[92] Goddard DR, Berry M, Butt AM. In vivo actions of fibroblast growth factor-2 and insulin-like growth factor-I on oligodendrocyte development and myelination in the central nervous system. J Neurosci Res 1999;57:74–85.
[93] Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and brain atrophy in the healthy elderly. Neurology 2002;59:713–9.
[94] Goldstein IB, Bartzokis G, Hance DB, Shapiro D. Relationship between blood pressure and subcortical lesions in healthy elderly people. Stroke 1998;29:765–72.
[95] Good PF, Werner P, Hsu A, Olanow CW, Perl DP. Evidence of neuronal oxidative damage in Alzheimer's disease. Am J Pathol 1996;149:21–8.
[96] Gottfries CG, Karlsson I, Svennerholm L. Membrane components separate early-onset Alzheimer's disease from senile dementia of the Alzheimer type. Int Psychogeriatr 1996;8:365–72.
[97] Gould E, Beylin A, Tanapat P, Reeves A, Shors TJ. Learning enhances adult neurogenesis in the hippocampal formation. Nat Neurosci 1999;2:260–5.
[98] Guttmann CR, Jolesz FA, Kikinis R, Killiany RJ, Moss MB, Sandor T, et al. White matter changes with normal aging. Neurology 1998;50:972–8.
[99] Hallgren B, Sourander P. The effect of age on the non-haemin iron in the human brain. J Neurochem 1958;3:41–51.
[100] Halliwell B, Gutteridge JM. Oxygen free radicals and iron in relation to biology and medicine: some problems and concepts. Arch Biochem Biophys 1986;246:501–14.
[101] Halliwell B, Gutteridge JMC. Iron as biological pro-oxidant. ISI Atlas Sci Biochem 1988;1:48–52.
[102] Han X, Holtzman DM, McKeel Jr DW, Kelley J, Morris JC. Substantial sulfatide deficiency and ceramide elevation in very early Alzheimer's disease: potential role in disease pathogenesis. J Neurochem 2002;82:809–18.
[103] Hanyu H, Shindo H, Kakizaki D, Abe K, Iwamoto T, Takasaki M. Increased water diffusion in cerebral white matter in Alzheimer's disease. Gerontology 1997;43:343–51.
[104] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353–6.
[105] Harris SJ, Wilce P, Bedi KS. Exposure of rats to a high but not low dose of ethanol during early postnatal life increases the rate of loss of optic nerve axons and decreases the rate of myelination. J Anat 2000;197:477–85.
[106] Hayashi H, Igbavboa U, Hamanaka H, Kobayashi M, Fujita SC, Wood WG, et al. Cholesterol is increased in the exofacial leaflet of synaptic plasma membranes of human apolipoprotein E4 knock-in mice. Neuroreport 2002;13:383–6.
[107] Hildebrand C, Remahl S, Persson H, Bjartmar C. Myelinated nerve fibres in the cns. Prog Neurobiol 1993;40:319–84.
[108] Hof PR, Cox K, Morrison JH. Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: I. Superior frontal and inferior temporal cortex. J Comp Neurol 1990;301:44–54.
[109] Hof PR, Morrison JH. Quantitative analysis of a vulnerable subset of pyramidal neurons in Alzheimer's disease: II. Primary and secondary visual cortex. J Comp Neurol 1990;301:55–64.
[110] Holtzman DM, Bales KR, Tenkova T, Fagan AM, Parsadanian M, Sartorius LJ, et al. Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 2000;97:2892–7.
[111] Hopf A. Die myeloarchitectonik des isocortex temporalis beim menschen. J Hirnforsch 1954;1:208–79.
[112] Hopkins KJ, Wang G, Schmued LC. Temporal progression of kainic acid induced neuronal and myelin degeneration in the rat forebrain. Brain Res 2000;864:69–80.
[113] Horrocks LA, van Rollings M, Yates AJ. Lipid changes in the ageing brain. In: Davison AN, Thompson RHS, editors. The molecular basis of neuropathology. London: Edward Arnold, Ltd.; 1981. p. 601–30.
[114] Huang WL, Harper CG, Evans SF, Newnham JP, Dunlop SA. Repeated prenatal corticosteroid administration delays myelination of the corpus callosum in fetal sheep. Int J Dev Neurosci 2001; 19:415–25.
[115] Husain J, Juurlink BH. Oligodendroglial precursor cell susceptibility to hypoxia is related to poor ability to cope with reactive oxygen species. Brain Res 1995;698:86–94.
[116] Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 1997;387: 167–78.

[117] Igbavboa U, Avdulov NA, Chochina SV, Wood WG. Transbilayer distribution of cholesterol is modified in brain synaptic plasma membranes of knockout mice deficient in the low-density lipoprotein receptor, apolipoprotein E, or both proteins. J Neurochem 1997;69:1661–7.
[118] Jellinger KA, Stadelmann C. Problems of cell death in neurodegeneration and Alzheimer's Disease. J Alzheimers Dis 2001;3:31–40.
[119] Juurlink BH. Response of glial cells to ischemia: roles of reactive oxygen species and glutathione. Neurosci Biobehav Rev 1997;21:151–66.
[120] Juurlink BH. Response of glial cells to ischemia: roles of reactive oxygen species and glutathione. Neurosci Biobehav Rev 1997;21:151–66.
[121] Kemper T. Neuroanatomical and neuropathological changes during aging and dementia. 2nd ed. New York, NY: Oxford University Press; 1994.
[122] Kirsch C, Eckert GP, Mueller WE. Statin effects on cholesterol micro-domains in brain plasma membranes. Biochem Pharmacol 2003;65:843–56.
[123] Kiuru S, Salonen O, Haltia M. Gelsolin-related spinal and cerebral amyloid angiopathy. Ann Neurol 1999;45:305–11.
[124] Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med 2002;137:149–55.
[125] Klintworth GK. Huntington's chorea—morphologic contributions of a century. In: Barbeau A, Paulson GW, Chase TN, editors. Advances in Neurology, vol. 1. Huntington's chorea, 1872–1972. New York: Raven Press; 1973. p. 353–68.
[126] Kobayashi K, Hayashi M, Nakano H, Fukutani Y, Sasaki K, Shimazaki M, et al. Apoptosis of astrocytes with enhanced lysosomal activity and oligodendrocytes in white matter lesions in Alzheimer's disease. Neuropathol Appl Neurobiol 2002;28:238–51.
[127] Kress GJ, Dineley KE, Reynolds IJ. The relationship between intracellular free iron and cell injury in cultured neurons, astrocytes, and oligodendrocytes. J Neurosci 2002;22:5848–55.
[128] Kurt MA, Davies DC, Kidd M, Duff K, Rolph SC, Jennings KH, et al. Neurodegenerative changes associated with beta-amyloid deposition in the brains of mice carrying mutant amyloid precursor protein and mutant presenilin-1 transgenes. Exp Neurol 2001;171:59–71.
[129] Kurumatani T, Kudo T, Ikura Y, Takeda M. White matter changes in the gerbil brain under chronic cerebral hypoperfusion. Stroke 1998;29:1058–62.
[130] Lakmache Y, Lassonde M, Gauthier S, Frigon JY, Lepore F. Interhemispheric disconnection syndrome in Alzheimer's disease. Proc Natl Acad Sci USA 1998;95:9042–6.
[131] Lamantia AS, Rakic P. Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. J Comp Neurol 1990;291:520–37.
[132] Locatelli S, Lutjohann D, Schmidt HH, Otto C, Beisiegel U, von Bergmann K. Reduction of plasma 24*S*-hydroxycholesterol (cerebrosterol) levels using high-dosage simvastatin in patients with hypercholesterolemia: evidence that simvastatin affects cholesterol metabolism in the human brain. Arch Neurol 2002;59:213–6.
[133] Lopez JC. A beta, tau and the fabrication of tangles. Nat Rev Neurosci 2001;2:681.
[134] Loske C, Gerdemann A, Schepl W, Wycislo M, Schinzel R, Palm D, et al. Transition metal-mediated glycoxidation accelerates cross-linking of beta-amyloid peptide. Eur J Biochem 2000;267:4171–8.
[135] Lovell MA, Ehmann WD, Butler SM, Markesbery WR. Elevated thiobarbituric acid-reactive substances and antioxidant enzyme activity in the brain in Alzheimer's disease. Neurology 1995;45: 1594–601.
[136] Lynch T, Cherny RA, Bush AI. Oxidative processes in Alzheimer's disease: the role of A-beta-metal interactions. Exp Gerontol 2000;35:445–51.
[137] Mackenzie IR. Senile plaques do not progressively accumulate with normal aging. Acta Neuropathol 1994;87:520–5.
[138] Mahley RW. Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 1988;240:622–30.
[139] Malone MJ, Szoke MC. Neurochemical changes in white matter. Aged human brain and Alzheimer's disease. Arch Neurol 1985;42:1063–6.
[140] Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. Free Radic Biol Med 1997;23:134–47.
[141] Marx J. Alzheimer's disease. Bad for the heart, bad for the mind? Science 2001;294:508–9.
[142] Mason JL, Ye P, Suzuki K, D'Ercole AJ, Matsushima GK. Insulin-like growth factor-1 inhibits mature oligodendrocyte apoptosis during primary demyelination. J Neurosci 2000;20:5703–8.
[143] Mason RP, Shoemaker WJ, Shajenko L, Chambers TE, Herbette LG. Evidence for changes in the Alzheimer's disease brain cortical membrane structure mediated by cholesterol. Neurobiol Aging 1992;13:413–9.
[144] Matute C, Sanchez-Gomez MV, Martinez-Millan L, Miled R. Glutamate receptor-mediated toxicity in optic nerve oligodendrocytes. Neurobiology 1997;94:8830–5.
[145] Mauch DH, Nagler K, Schumacher S, Goritz C, Muller EC, Otto A, et al. CNS synaptogenesis promoted by glia-derived cholesterol. Science 2001;294:1354–7.
[146] Maynard CJ, Cappai R, Volitakis I, Cherny RA, White AR, Beyreuther K, et al. Overexpression of Alzheimer's disease amyloid-beta opposes the age-dependent elevations of brain copper and iron. J Biol Chem 2002;277:44670–6.
[147] McDonald JW, Althomsons SP, Hyrc KL, Choi DW, Goldberg MP. Oligodendrocytes from forebrain are highly vulnerable to AMPA/kainate receptor-mediated excitotoxicity. Nat Med 1998;4: 291–7.
[148] McDonald WI, Sears TA. The effects of experimental demyelination on conduction in the central nervous system. Brain 1970;93:583–98.
[149] McKee AC, Kowall NW, Schumacher JS, Beal MF. The neurotoxicity of amyloid beta protein in aged primates. Amyloid 1998;5:1–9.
[150] McLachlan DRC, Dalton AJ, Kruck TP, Bell MY, Smith WL, Kalow W, et al. Intramuscular desferrioxamine in patients with Alzheimer's disease. Lancet 1991;337:1304–8.
[151] Mecocci P, MacGarvey U, Kaufman AE, Koontz D, Shoffner JM, Wallace DC, et al. Oxidative damage to mitochondrial DNA shows marked age-dependent increases in human brain. Ann Neurol 1993;34:609–16.
[152] Meier-Ruge W, Ulrich J, Bruhlmann M, Meier E. Age-related white matter atrophy in the human brain. Ann N Y Acad Sci 1992;673:260–9.
[153] Merrill JE, Ignarro LJ, Sherman MP, Melinek J, Lane TE. Microglial cell cytotoxicity of oligodendrocytes is mediated through nitric oxide. J Immunol 1993;151:2132–41.
[154] Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990;28:597–613.
[155] Mesulam MM. A plasticity-based theory of the pathogenesis of Alzheimer's disease. Ann N Y Acad Sci 2000;924:42–52.
[156] Meyer A. Paul Flechsig's system of myelogenetic cortical localization in the light of recent research in neuroanatomy and neurophysiology part II. Can J Neurol Sci 1981;8:95–104.
[157] Miller AK, Alston RL, Corsellis JA. Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. Neuropathol Appl Neurobiol 1980;6:119–32.
[158] Mitrovic B, Ignarro LJ, Vinters HV, Akers MA, Schmid I, Uittenbogaart C, et al. Nitric oxide induces necrotic but not apoptotic cell death in oligodendrocytes. Neuroscience 1995;65:531–9.

[159] Mizuno T, Nakata M, Naiki H, Michikawa M, Wang R, Haass C, et al. Cholesterol-dependent generation of a seeding amyloid beta-protein in cell culture. J Biol Chem 1999;274:15110–4.
[160] Monji A, Utsumi H, Ueda T, Imoto T, Yoshida I, Hashioka S, et al. The relationship between the aggregational state of the amyloid-beta peptides and free radical generation by the peptides. J Neurochem 2001;77:1425–32.
[161] Montine TJ, Markesbery WR, Zackert W, Sanchez SC, Roberts II LJ, Morrow JD. The magnitude of brain lipid peroxidation correlates with the extent of degeneration but not with density of neuritic plaques or neurofibrillary tangles or with APOE genotype in Alzheimer's disease patients. Am J Pathol 1999;155:863–8.
[162] Morath DJ, Mayer-Proschel M. Iron modulates the differentiation of a distinct population of glial precursor cells into oligodendrocytes. Dev Biol 2001;237:232–43.
[163] Morell P, Jurevics H. Origin of cholesterol in myelin. Neurochem Res 1996;21:463–70.
[164] Morell P, Toews AD. In vivo metabolism of oligodendroglial lipids. In: Norton WT, editor. Oligodendroglia. New York: Plenium Press; 1984. p. 47–86.
[165] Mori T, Paris D, Town T, Rojiani AM, Sparks DL, Delledonne A, et al. Cholesterol accumulates in senile plaques of Alzheimer disease patients and in transgenic APP(SW) mice. J Neuropathol Exp Neurol 2001;60:778–85.
[166] Morris CM, Candy JM, Oakley AE, Bloxham CA, Edwardson JA. Histochemical distribution of non-haem iron in the human brain. Acta Anat (Basel) 1992;144:235–57.
[167] Myers GJ, Davidson PW. Prenatal methylmercury exposure and children: neurologic, developmental, and behavioral research. Environ Health Perspect 1998;106:841–7.
[168] Nielsen K, Peters A. The effects of aging on the frequency of nerve fibers in rhesus monkey striate cortex. Neurobiol Aging 2000;21:621–8.
[169] Niess C, Grauel U, Toennes SW, Bratzke H. Incidence of axonal injury in human brain tissue. Acta Neuropathol (Berl) 2002;104:79–84.
[170] Nieuwenhuys R. Structure and organization of fibre systems. In: Nieuwenhuys R, Tendokelaar JH, Nicholson C, editors. The central nervous system of vertebrates, vol. 1. Berlin: Springer; 1999. p. 113–57 [chapter 3].
[171] Norton WT. Formation, structure, and biochemistry of myelin. In: Siegel GJ, Albers RW, Agranoff BW, Katzman R, editors. Basic neurochemistry, vol. 3. Boston: Little, Brown and Co.; 1981. p. 63–92.
[172] O'Brien JS, Sampson EL. Lipid composition of the normal human brain: gray matter, white matter, and myelin. J Lipid Res 1965;6:537–44.
[173] O'donnell KA, Rapp PR, Hof PR. Preservation of prefrontal cortical volume in behaviorally characterized aged macaque monkeys. Exp Neurol 1999;160:300–10.
[174] O'Sullivan M, Jones DK, Summers PE, Morris RG, Williams SC, Markus HS. Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. Neurology 2001;57:632–8.
[175] Ohm TG, Muller H, Braak H, Bohl J. Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. Neuroscience 1995;64:209–17.
[176] Ojemann GA, Schoenfield-McNeill J, Corina DP. Anatomic subdivisions in human temporal cortical neuronal activity related to recent verbal memory. Nat Neurosci 2002;5:64–71.
[177] Pakkenberg B, Pelvig D, Marner L, Bundgaard MJ, Gundersen HJ, Nyengaard JR, et al. Aging and the human neocortex. Exp Gerontol 2003;38:95–9.
[178] Pandya DN, Seltzer B. The topography of commissural fibers. In: Two hemispheres-one brain: functions of the corpus callosum. Alan R. Liss, Inc.; 1986. p. 47–73.
[179] Pantoni L, Garcia JH. Pathogenesis of luekoaraiosis. Stroke 1997;28:652–9.
[180] Papassotiropoulos A, Lutjohann D, Bagli M, Locatelli S, Jessen F, Buschfort R, et al. 24*S*-hydroxycholesterol in cerebrospinal fluid is elevated in early stages of dementia. J Psychiatr Res 2002;36:27–32.
[181] Papassotiropoulos A, Streffer JR, Tsolaki M, Schmid S, Thal D, Nicosia F, et al. Increased brain beta-amyloid load, phosphorylated tau, and risk of Alzheimer disease associated with an intronic CYP46 polymorphism. Arch Neurol 2003;60:29–35.
[182] Perez-Campo R, Lopez-Torres M, Cadenas S, Rojas C, Barja G. The rate of free radical production as a determinant of the rate of aging: evidence from the comparative approach. J Comp Physiol B 1998;168:149–58.
[183] Peters A, Moss MB, Sethares C. Effects of aging on myelinated nerve fibers in monkey primary visual cortex. J Comp Neurol 2000;419:364–76.
[184] Peters A, Sethares C. Aging and the myelinated fibers in prefrontal cortex and corpus callosum of the monkey. J Comp Neurol 2002;442:277–91.
[185] Petty MA, Wettstein JG. White matter ischaemia. Brain Res Rev 1999;31:58–64.
[186] Pike CJ, Ramezan-Arab N, Cotman CW. Beta-amyloid neurotoxicity in vitro: evidence of oxidative stress but not protection by antioxidants. J Neurochem 1997;69:1601–11.
[187] Plassart-Schiess E, Baulieu EE. Neurosteroids: recent findings. Brain Res Rev 2001;37:133–40.
[188] Posner HB, Tang MX, Luchsinger J, Lantigua R, Stern Y, Mayeux R. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology 2002;58:1175–81.
[189] Power J, Mayer-Proschel M, Smith J, Noble M. Oligodendrocyte precursor cells from different brain regions express divergent properties consistent with the differing time courses of myelination in these regions. Dev Biol 2002;245:362–75.
[190] Pratico D, Clark CM, Liun F, Rokach J, Lee VY, Trojanowski JQ. Increase of brain oxidative stress in mild cognitive impairment: a possible predictor of Alzheimer disease. Arch Neurol 2002;59:972–6.
[191] Price JL, Ko AI, Wade MJ, Tsou SK, McKeel DW, Morris JC. Neuron number in the entorhinal cortex and CA1 in preclinical Alzheimer Disease. Arch Neurol 2001;58:1395–402.
[192] Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 1986;232:232–5.
[193] Regeur L, Jensen G, Pakkenberg H, Evans SM, Pakkenberg B. No global neocortical nerve cell loss in brains from patients with senile dementia of Alzheimer's type. Neurobiol Aging 1994;15:347–52.
[194] Rodriguez-Pena A. Oligodendrocyte development and thyroid hormone. J Neurobiol 1999;40:497–512.
[195] Rogers JT, Randall JD, Eder PS, Huang X, Bush AI, Tanzi RE, et al. Alzheimer's disease drug discovery targeted to the APP mRNA 5′ untranslated region. J Mol Neurosci 2002;19:77–82.
[196] Roher AE, Weiss N, Kokjohn TA, Kuo YM, Kalback W, Anthony J, et al. Increased abeta peptides and reduced cholesterol and myelin proteins characterize white matter degeneration in Alzheimer's Disease. Biochemistry 2002;41:11080–90.
[197] Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: delayed maturation of auditory brainstem responses. Am J Clin Nutr 1998;68:683–90.
[198] Rosenberg PA, Dai W, Gan XD, Ali S, Fu J, Back SA, et al. Mature myelin basic protein-expressing oligodendrocytes are insensitive to kainate toxicity. J Neurosci Res 2003;71:237–45.
[199] Rottkamp CA, Raina AK, Zhu X, Gaier E, Bush AI, Atwood CS, et al. Redox-active iron mediates amyloid-beta toxicity. Free Radic Biol Med 2001;30:447–50.
[200] Rouser G, Kritchevsky G, Yamamoto A, Baxter CF. Lipids in the nervous system of different species as a function of age: brain, spinal cord, peripheral nerve, purified whole cell preparations, and subcellular particulates: regulatory mechanisms and membrane structure. Adv Lipid Res 1972;10:261–360.

[201] Rouser G, Yamamoto A. Curvilinear regression course of human brain lipid composition changes with age. Lipids 1968;3:284–7.
[202] Sampietro M, Caputo L, Casatta A, Meregalli M, Pellagatti A, Tagliabue J, et al. The hemochromatosis gene affects the age of onset of sporadic Alzheimer's disease. Neurobiol Aging 2001;22:563–8.
[203] Sastre J, Pallardo FV, Garcia de la Asuncion J, Vina J. Mitochondria, oxidative stress and aging. Free Radic Res 2000;32:189–98.
[204] Schenk D. Amyloid-beta immunotherapy for Alzheimer's disease: the end of the beginning. Nat Rev Neurosci 2002;3:824–8.
[205] Schroeder F, Woodford JK, Kavecansky J, Wood WG, Joiner C. Cholesterol domains in biological membranes. Mol Membr Biol 1995;12:113–9.
[206] Schultz C, Dehghani F, Hubbard GB, Thal DR, Struckhoff G, Braak E, et al. Filamentous tau pathology in nerve cells, astrocytes, and oligodendrocytes of aged baboons. J Neuropathol Exp Neurol 2000;59:39–52.
[207] Schultz C, Hubbard GB, Rub U, Braak E, Braak H. Age-related progression of tau pathology in brains of baboons. Neurobiol Aging 2000;21:905–11.
[208] Schupf N. Epidemiology of dementia in Down's syndrome. In: Iqbal K, Sisodia SS, Winblad B, editors. Alzheimer's disease: advances in etiology, pathogenesis, and therapeutics. Chichester, UK: John Wiley & Sons, Ltd.; 2001. p. 23–30.
[209] Selkoe DJ. Translating cell biology into therapeutic advances in Alzheimer's disease. Nature 1999;399:A23–31.
[210] Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev 2001;81:741–66.
[211] Semendeferi K, Lu A, Schenker N, Damasio H. Humans and great apes share a large frontal cortex. Nat Neurosci 2002;5:272–6.
[212] Seno H, Inagaki T, Yamamori C, Miyaoka T, Horiguchi J. Dementia of Alzheimer type with and without multiple lacunar infarctions: evaluation of white matter lesions. Neuropathology 2000;20:204–9.
[213] Simons M, Kramer EM, Macchi P, Rathke-Hartlieb S, Trotter J, Nave KA, et al. Overexpression of the myelin proteolipid protein leads to accumulation of cholesterol and proteolipid protein in endosomes/lysosomes: implications for Pelizaeus-Merzbacher disease. J Cell Biol 2002;157:327–36.
[214] Sloane JA, Hollander W, Moss MB, Rosene DL, Abraham CR. Increased microglial activation and protein nitration in white matter of the aging monkey. Neurobiol Aging 1999;20:395–405.
[215] Small GW, Ercoli LM, Silverman DH, Huang SC, Komo S, Bookheimer SY, et al. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. Proc Natl Acad Sci USA 2000;97:6037–42.
[216] Smith CD, Carney JM, Starke-Reed PE, Oliver CN, Stadtman ER, Floyd RA, et al. Excess brain protein oxidation and enzyme dysfunction in normal aging and in Alzheimer disease. Proc Natl Acad Sci USA 1991;88:10540–3.
[217] Smith MA, Casadesus G, Joseph JA, Perry G. Amyloid-beta and tau serve antioxidant functions in the aging and Alzheimer brain. Free Radic Biol Med 2002;33:1194–9.
[218] Smith MA, Rottkamp CA, Nunomura A, Raina AK, Perry G. Oxidative stress in Alzheimer's disease. Biochim Biophys Acta 2000;1502:139–44.
[219] Smith MA, Wehr K, Harris PLR, Siedlak SL, Connor JR, Perry G. Abnormal localization of iron regulatory protein in Alzheimer's disease. Brain Res 1998;788:232–6.
[220] Sohal RS, Sohal BH, Orr WC. Mitochondrial superoxide and hydrogen peroxide generation, protein oxidative damage, and longevity in different species of flies. Free Radic Biol Med 1995;19:499–504.
[221] Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. Nat Neurosci 2003;6:309–15.
[222] Srinivasan R. Spatial structure of the human alpha rhythm: global correlation in adults and local correlation in children. Clin Neurophysiol 1999;1999:1351–62.
[223] Stoffel W, Bosio A. Myelin glycolipids and their functions. Curr Opin Neurobiol 1997;7:654–61.
[224] Stone JR, Okonkwo DO, Singleton RH, Mutlu LK, Helm GA, Povlishock JT. Caspase-3-mediated cleavage of amyloid precursor protein and formation of amyloid beta peptide in traumatic axonal injury. J Neurotrauma 2002;19:601–14.
[225] Stout JC, Jernigan T, Archibald S, Salmon DP. Association of dementia severity with cortical gray matter and abnormal white matter volumes in dementia of the Alzheimer type. Arch Neurol 1996;53:742–9.
[226] Subasinghe S, Unabia S, Barrow CJ, Mok SS, Aguilar MI, Small DH. Cholesterol is necessary both for the toxic effect of Abeta peptides on vascular smooth muscle cells and for Abeta binding to vascular smooth muscle cell membranes. J Neurochem 2003;84:471–9.
[227] Surewicz WK, Epand RM, Epand RF, Hallett FR, Moscarello MA. Modulation of myelin basic protein-induced aggregation and fusion of liposomes by cholesterol, aliphatic aldehydes and alkanes. Biochim Biophys Acta 1986;863:45–52.
[228] Svennerholm L, Gottfries CG. Membrane lipids, selectively diminished in Alzheimer brains, suggest synapse loss as a primary event in early-onset form (type I) and demyelination in late-onset form (type II). J Neurochem 1994;62:1039–47.
[229] Tabner BJ, Turnbull S, El-Agnaf OM, Allsop D. Formation of hydrogen peroxide and hydroxyl radicals from Abeta and alpha-synuclein as a possible mechanism of cell death in Alzheimer's disease and Parkinson's disease (1, 2). Free Radic Biol Med 2002;32:1076–83.
[230] Tallon-Baudry C, Bertrand O, Fischer C. Oscillatory synchrony between human extrastriate areas during visual short-term memory maintenance. J Neurosci 2001;21:RC177.
[231] Tanaka F, Kachi T, Yamada T, Sobue G. Auditory and visual event-related potentials and flash visual evoked potentials in Alzheimer's disease: correlations with mini-mental state examination and Raven's coloured progressive matrices. J Neurol Sci 1998;156:83–8.
[232] Tang Y, Nyengaard JR, Pakkenberg B, Gundersen HJ. Age-induced white matter changes in the human brain: a stereological investigation. Neurobiol Aging 1997;18:609–15.
[233] Terry RD, Gonatas NK, Weiss M. Ultrastructural studies in Alzheimers presenile dementia. Am J Pathol 1964;49:269–81.
[234] Thal DR, Barduzal S, Franz K, Herrmann G, Bode F, Lambrecht E, et al. Giant cell arteritis in a 19-year-old woman associated with vertebral artery aneurysm and subarachnoid hemorrhage. Clin Neuropathol 2001;20:80–6.
[235] Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. Neurology 2002;58:1791–800.
[236] Thal DR, Rub U, Schultz C, Sassin I, Ghebremedhin E, Del Tredici K, et al. Sequence of Abeta-protein deposition in the human medial temporal lobe. J Neuropathol Exp Neurol 2000;59:733–48.
[237] Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW. Growth patterns in the developing brain detected by using continuum mechanical tensor maps. Nature 2000;404:190–3.
[238] Torp R, Head E, Cotman CW. Ultrastructural analyses of beta-amyloid in the aged dog brain: neuronal beta-amyloid is localized to the plasma membrane. Prog Neuropsychopharmacol Biol Psychiatry 2000;24:801–10.
[239] Troncoso JC, Costello A, Watson Jr AL, Johnson GV. In vitro polymerization of oxidized tau into filaments. Brain Res 1993;613:313–6.
[240] Turnbull S, Tabner BJ, El-Agnaf OM, Twyman LJ, Allsop D. New evidence that the Alzheimer beta-amyloid peptide does not spontaneously form free radicals: an ESR study using a series of spin-traps. Free Radic Biol Med 2001;30:1154–62.
[241] Umahara T, Tsuchiya K, Ikeda K, Kanaya K, Iwamoto T, Takasaki M, et al. Demonstration and distribution of tau-positive glial coiled body-like structures in white matter and white matter threads in early onset Alzheimer's disease. Neuropathology 2002;22:9–12.

[242] Uryu K, Laurer H, McIntosh T, Pratico D, Martinez D, Leight S, et al. Repetitive mild brain trauma accelerates Abeta deposition, lipid peroxidation, and cognitive impairment in a transgenic mouse model of Alzheimer amyloidosis. J Neurosci 2002;22:446–54.
[243] van der Flier WM, van den Heuvel DM, Weverling-Rijnsburger AW, Bollen EL, Westendorp RG, van Buchem MA, et al. Magnetization transfer imaging in normal aging, mild cognitive impairment, and Alzheimer's disease. Ann Neurol 2002;52:62–7.
[244] Varadarajan S, Yatin S, Aksenova M, Butterfield DA. Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. J Struct Biol 2000;130:184–208.
[245] Varela F, Lachaux JP, Rodriguez E, Martinerie J. The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2001;2:229–39.
[246] Vlkolinsky R, Cairns N, Fountoulakis M, Lubec G. Decreased brain levels of 2′,3′-cyclic nucleotide-3′-phosphodiesterase in Down syndrome and Alzheimer's disease. Neurobiol Aging 2001;22:547–53.
[247] Vogt C, Vogt O. Allgemeinere ergebnisse unserer hirnforschung. J Psychol Neurol 1919;25:279–462.
[248] Walker LC, Cork LC. The neurobiology of aging in non-human primates. In: Terry RD, Katzman R, Bick KL, Sisodia SS, editors. Alzheimer's Disease. Philadelphia: Lippincott, Williams and Wilkins; 1999. p. 233–43.
[249] Wallin A, Gottfries CG, Karlsson I, Svennerholm L. Decreased myelin lipids in Alzheimer's disease and vascular dementia. Acta Neurol Scand 1989;80:319–23.
[250] Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 2002;416:535–9.
[251] Walter PB, Knutson MD, Paler-Martinez A, Lee S, Xu Y, Viteri FE, et al. Iron deficiency and iron excess damage mitochondria and mitochondrial DNA in rats. Proc Natl Acad Sci USA 2002;99:2264–9.
[252] Wang J, Dickson DW, Trojanowski JQ, Lee VM. The levels of soluble versus insoluble brain Abeta distinguish Alzheimer's disease from normal and pathologic aging. Exp Neurol 1999;158:328–37.
[253] Waterham HR. Inherited disorders of cholesterol biosynthesis. Clin Genet 2002;61:393–403.
[254] Waxman SG. Conduction in myelinated, unmyelinated, and demyelinated fibers. Arch Neurol 1977;34:585–9.
[255] West MJ, Coleman PD, Flood DG, Troncoso JC. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease. Lancet 1994;344:769–72.
[256] West R, Murphy KJ, Armilio ML, Craik FI, Stuss DT. Lapses of intention and performance variability reveal age-related increases in fluctuations of executive control. Brain Cogn 2002;49:402–19.
[257] Wiggins RC. Myelin development and nutritional insufficiency. Brain Res 1982;257:151–75.
[258] Wilkins A, Chandran S, Compston A. A role for oligodendrocyte-derived IGF-1 in trophic support of cortical neurons. Glia 2001;36:48–57.
[259] Wisniewski HM, Bancher C, Barcikowska M, Wen GY, Currie J. Spectrum of morphological appearance of amyloid deposits in Alzheimer's disease. Acta Neuropathol (Berl) 1989;78:337–47.
[260] Wolozin B. Cholesterol and Alzheimer's disease. Biochem Soc Trans 2002;30:525–9.
[261] Wood P, Bunger RP. The biology of the oligodendrocyte. In: Norton WT, editor. Oligodendroglia. New York: Plenum Press; 1984. p. 1–46.
[262] Wood WG, Schroeder F, Avdulov NA, Chochina SV, Igbavboa U. Recent advances in brain cholesterol dynamics: transport, domains, and Alzheimer's disease. Lipids 1999;34:225–34.
[263] Wood WG, Schroeder F, Igbavboa U, Avdulov NA, Chochina SV. Brain membrane cholesterol domains, aging and amyloid beta-peptides. Neurobiol Aging 2002;23:685.
[264] Xi MC, Liu RH, Engelhardt JK, Morales FR, Chase MH. Changes in the axonal conduction velocity of pyramidal tract neurons in the aged cat. Neuroscience 1999;92:219–25.
[265] Xu J, Chen S, Ahmed SH, Chen H, Ku G, Goldberg MP, et al. Amyloid-beta peptides are cytotoxic to oligodendrocytes. J Neurosci 2001;21:RC118.
[266] Yakovlev PI, Lecours AR. Regional development of the brain in early life. Boston: Blackwell Scientific Publications; 1967.
[267] Yang EY, Guo-Ross SX, Bondy SC. The stabilization of ferrous iron by a toxic beta-amyloid fragment and by an aluminum salt. Brain Res 1999;839:221–6.
[268] Yao Z-X, Papadopulos V. Function of beta-amyloid in cholesterol transport: a lead to neurotoxicity. FASEB August 21, online publication.
[269] Ye P, Lee KH, D'Ercole AJ. Insulin-like growth factor-I (IGF-I) protects myelination from undernutritional insult: studies of transgenic mice overexpressing IGF-I in brain. J Neurosci Res 2000;62:700–8.
[270] Yeagle PL. Cholesterol and the cell membrane. Biochim Biophys Acta 1985;822:267–87.
[271] Yip CM, Darabie AA, McLaurin J. Abeta42-peptide assembly on lipid bilayers. J Mol Biol 2002;318:97–107.
[272] Zandi PP, Anthony JC, Hayden KM, Mehta K, Mayer L, Breitner JC. Reduced incidence of AD with NSAID but not H2 receptor antagonists: the Cache County Study. Neurology 2002;59:880–6.
[273] Zhou R, Abbas PJ, Assouline JG. Electrically evoked auditory brainstem response in peripherally myelin-deficient mice. Hear Res 1995;88:98–106.
[274] Zou K, Gong JS, Yanagisawa K, Michikawa M. A novel function of monomeric amyloid beta-protein serving as an antioxidant molecule against metal-induced oxidative damage. J Neurosci 2002;22:4833–41.