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Review

Alzheimer's disease as homeostatic responses to age-related myelin breakdown

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Abstract

The amyloid hypothesis (AH) of Alzheimer's disease (AD) posits that the fundamental cause of AD is the accumulation of the peptide amyloid beta (Aβ) in the brain. This hypothesis has been supported by observations that genetic defects in amyloid precursor protein (APP) and presenilin increase Aβ production and cause familial AD (FAD). The AH is widely accepted but does not account for important phenomena including recent failures of clinical trials to impact dementia in humans even after successfully reducing Aβ deposits.

Herein, the AH is viewed from the broader overarching perspective of the myelin model of the human brain that focuses on functioning brain circuits and encompasses white matter and myelin in addition to neurons and synapses. The model proposes that the recently evolved and extensive myelination of the human brain underlies both our unique abilities and susceptibility to highly prevalent age-related neuropsychiatric disorders such as late onset AD (LOAD). It regards oligodendrocytes and the myelin they produce as being both critical for circuit function and uniquely vulnerable to damage. This perspective reframes key observations such as axonal transport disruptions, formation of axonal swellings/sphenoids and neuritic plaques, and proteinaceous deposits such as Aβ and tau as *by-products of homeostatic myelin repair processes*. It delineates empirically testable mechanisms of action for genes underlying FAD and LOAD and provides "upstream" treatment targets. Such interventions could potentially treat multiple degenerative brain disorders by mitigating the effects of aging and associated changes in iron, cholesterol, and free radicals on oligodendrocytes and their myelin.

Keywords: Aging; Oligodendrocyte; Peroxisome; BACE; Neuregulin; Apolipoprotein; Prevention; Ubiquitin; α-Synuclein; TDP-43; FTLD

1. Introduction

The myelin model of the human brain proposes that the processes of myelin development, maintenance, and its eventual breakdown are essential to understanding our species' unique cognitive and behavioral trajectories through life (Fig. 1). The model's lifespan perspective delineates the interplay between the continuous developmental process of myelination and degenerative processes acting on several prominent vulnerabilities of oligodendrocytes and the myelin they sustain. These vulnerabilities make oligodendrocytes and their myelin the "weakest link" that will succumb to a variety of suboptimal genetic variants and environmental insults. The model proposes that the production, maintenance, and repair of the human brain's pervasive myelin sheaths underlie our species' unique vulnerability to highly prevalent neuropsychiatric disorders ranging from schizophrenia to degenerative disorders such as Alzheimer's disease (AD) (Bartzokis, 2002, 2004a,b, 2005).

The myelin model helps integrate congruous as well as incongruous aspects of familial AD (FAD) and late onset AD (LOAD) phenomenology into a continuum of later-life cognitive decline that leads to the very high prevalence of AD observed in the older ages of the human lifespan. Aging- and disease-related myelin damage is viewed in the context of the brain's continual homeostatic attempts to

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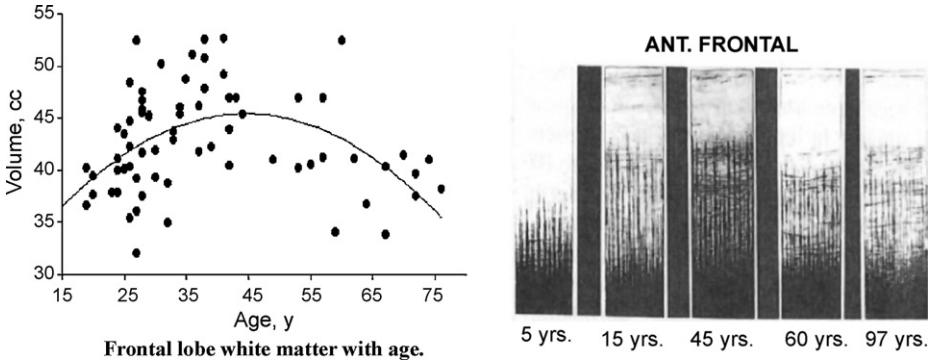

Fig. 1. Quadratic (Inverted U) Trajectories of Human Brain Myelination Over the Lifespan. Myelination (*Y*-axis) versus age (*X*-axis) in frontal lobes of normal individuals. Left panel: in vivo MRI data (Bartzokis et al., 2001) using inversion recovery images that are most sensitive to the high cholesterol levels in myelin and are optimal for tracking myelination. Right panel: postmortem myelin stain data of frontal lobe cortex depicting *intracortical* myelination (from Kaes, 1907 adapted and reproduced in Kemper, 1994). The data were acquired 100 years apart yet the two samples of *normal* individuals show remarkably similar frontal lobe myelination trajectories, both reaching a peak at age 45. A very similar matching pattern (not shown—see Bartzokis, 2007) is observed in temporal lobe.

repair such damage. In what follows, the genetic defects that gave rise to the amyloid hypothesis (AH) of AD namely, amyloid precursor protein (APP) and γ-secretase complex and its presenilin (PS1 and PS2) mutations, will be examined from the perspective of myelin maintenance and repair processes. The roles of genes that affect the much more prevalent LOAD, namely β-site APP cleavage enzyme 1 (BACE1), Apolipoprotein E (ApoE) alleles, tau, ubiquitin, TAR DNA binding protein 43 (TDP-43), and iron-regulated proteins that include APP and α-synuclein (αSyn), will also be assessed from this same perspective.

By necessity this report will examine the often ignored, but ultimately inescapable, role of evolution. Evolution has shaped the human brain through the use of pre-existing genes and their protein products for *multiple* roles and functions (Jacob, 1977). This multiplicity of roles results in the dazzling complexity and redundancy on which normal brain function is based. Myelin, a relatively recent evolutionary development of the first vertebrates (fish), plays a critical role in the complex connectivity of the human brain (Bartzokis, 2004a,b). The model suggests that myelin maintenance and repair employ the same molecular processes involved in producing the proteinaceous lesions that define prevalent disorders such as AD, Parkinson's diseases (PD), dementia with Lewy bodies (DLB), and frontotemporal lobar degeneration (FTLD). It asserts that the age-related increase in the need for maintenance and repair (Fig. 1), together with genetic variability in the efficiency and effectiveness of these processes, *secondarily* result in the production of the lesions that define these diseases (Figs. 2 and 3).

This wider evolutionary perspective serves to counterbalance the prevailing focus on Aβ as the core pathology of AD and reframes this key protein (as well as tau) as a *byproduct* of the myelin repair process rather than the principal cause of AD. The model helps explain why the first three large scale attempts to treat human AD by removing Aβ using active immunization (Holmes et al., 2008), reducing Aβ production by inhibiting the key γ-secretase enzymatic step (with Flurizam), and dissolving amyloid deposits (with Alzamed) have failed to impact the clinical syndrome, even though they may have *succeeded* in eliminating brain amyloid (Holmes et al., 2008). The model ultimately helps outline novel prevention and treatment interventions (Bartzokis and Altshuler, 2003; Bartzokis, 2004a, 2007), and cautions against several pitfalls associated with the massive pharmacological discovery effort focused on directly influencing the amyloidogenic pathway in the brain (Patton et al., 2006).

1.1. Why an overarching hypothesis of human brain "Alzheimerization"?

It has become increasingly apparent that the major age-related degenerative brain disorders represent co-deposition of several proteins such as Aβ, tau, αSyn, TDP43, etc. (Duyckaerts et al., 2009; Jellinger, 2009; Nelson et al., 2007; Schneider et al., 2007) (see Sections 6 and 7 below). At a *minimum*, AD itself represents a co-deposition of at least two proteins, Aβ and tau (reviewed in Duyckaerts et al., 2009; Jellinger, 2009). These multiple pathologies can reduce the relationship of any single lesion type to clinical symptoms (Nelson et al., 2007) and has resulted in calls for reconsidering the current pathologic diagnostic criteria (Jellinger, 2009). The myelin model considers brain circuits in their entirety (Figs. 2 and 3) and offers a viable mechanistic approach that complements and integrates the lesion-based pathologic approach as well as the genetic approach that forms the basis the AH.

The overarching mechanistic/evolution-based approach of the myelin model can be exemplified by briefly considering it in the context of recent modifications to the AH. Increased amyloid Aβ deposition is the ultimate manifestation of known forms of FAD and is an important process in the pathogenesis of AD (Hardy and Selkoe, 2002; Selkoe, 1999; Thal et al., 2002). The AH was modified to account for the weak association between neuritic plaque lesion load