

## UC San Diego

### UC San Diego Previously Published Works

**Title**

White matter mapping is needed

**Permalink**

<https://escholarship.org/uc/item/75x3h7s5>

**Journal**

Neurobiology of Aging, 25(1)

**ISSN**

0197-4580

**Authors**

Jernigan, TL  
Fennema-Notestine, Christine

**Publication Date**

2004

**DOI**

10.1016/j.neurobiolaging.2003.06.002

Peer reviewed

Commentary

## White matter mapping is needed

T.L. Jernigan\*, Christine Fennema-Notestine

*University of California, San Diego and the VASDHS, 9500 Gilman Drive, La Jolla, CA 92093-0949, USA*

Received 23 May 2003; accepted 3 June 2003

### 1. Modern brain maps lack information about oligodendrocyte structure and function

An intriguing hypothesis has been advanced regarding the role of ongoing processes of myelination in the pathogenesis of Alzheimers Disease (Bartzokis, this issue). The protracted course of myelin deposition in dorsal forebrain regions was described over three decades ago in the elegant studies by Yakovlev and Lecours [12]. However, modern imaging methods permit detailed investigation of these processes in living people for the first time, and studies with these techniques have served to emphasize the degree to which ongoing events formerly deemed “maturation” merge with alterations previously associated with involution. For example, recent MRI studies of brain morphology in late childhood and early adulthood [5,7–9] confirm the earlier pathological evidence for continued “whitening” of the substance of the brain long past the point at which total cranial volume is at its peak. It is now clear that exuberant brain growth in the earliest stages of neurodevelopment gives way gradually to a more dynamic interplay between progressive changes, primarily proliferation of oligodendrocytes and myelination (but also in limited cases associated with neurogenesis and neuritic branching), offset by regressive changes (i.e. apoptosis and loss of neuronal processes) that are also occurring from the very beginning of brain development. Thus, the years of life between the end of adolescence and extending through middle age are probably more accurately viewed, not as years of “stability” in brain development (as they have been previously), but as a period during which progressive and regressive changes happen to be in relative balance. The neurobiological implications of ongoing dynamics of brain development during this period are likely to be no less for that coincidence, and the treatise by Bartzokis should provide increased impetus for the needed work of defining these implications.

It is particularly relevant for this discussion that most recent work in neuroimaging has focused on the brain’s

gray matter structures, and, by implication, on neuronal cell populations. Relatively few studies have focused on white matter, and most of these have examined high-signal abnormalities that are well visualized with structural imaging methods. In Fig. 1A, data from our laboratory taken from separate previously published studies of brain development and aging [1,4,9] are presented together. These data were generated concurrently using standardized MR morphometric techniques. Volumes of the total white matter compartment of the cerebrum are plotted against the ages of normal volunteers of different ages ranging from 7 to 99 years. The volumes are expressed as proportions of volume of the supratentorial cranial vault, the average value of which has been reported to change negligibly, if at all, over this age range. Thus, the function is likely to reflect primarily the volume of myelinated white matter. The data from adults 20 to 70 years of age are too sparse to define with any precision the shape of the underlying function, but they are certainly consistent with evidence reviewed by Bartzokis indicating substantial ongoing myelination in adults. Developmental studies have emphasized late myelination in frontal and parietal lobe regions, but the function we observe in the temporal lobe, possibly more relevant to the pathology of early AD, shows a similar (if less striking) pattern, as shown in Fig. 1B. Surprisingly, the pattern is also present within a deep subcortical white matter region which includes the internal and external capsules and surrounds the diencephalon and basal ganglia (Fig. 1C).

The model presented by Bartzokis relies upon evidence for what he refers to as “heterochronologic” development of human white matter. That the process of myelination has differing time courses in different regions is not in doubt; however, a map across the brain revealing the status of myelination at each point during the lifespan does not exist, and, arguably, what does exist is inadequate to provide definitive evidence regarding the hypothesis. If myelination in some deep subcortical regions (as shown in Fig. 1C) continues as long as that in “cortico-cortical” association areas, how then does this relate to the distribution of lesions in AD? The point is not that the known “heterochronicity” of myelination is inconsistent with the model presented by Bartzokis,

\* Corresponding author. Tel.: +1-858-622-5882; fax: +1-858-622-5890.  
E-mail address: tjernigan@ucsd.edu (T.L. Jernigan).

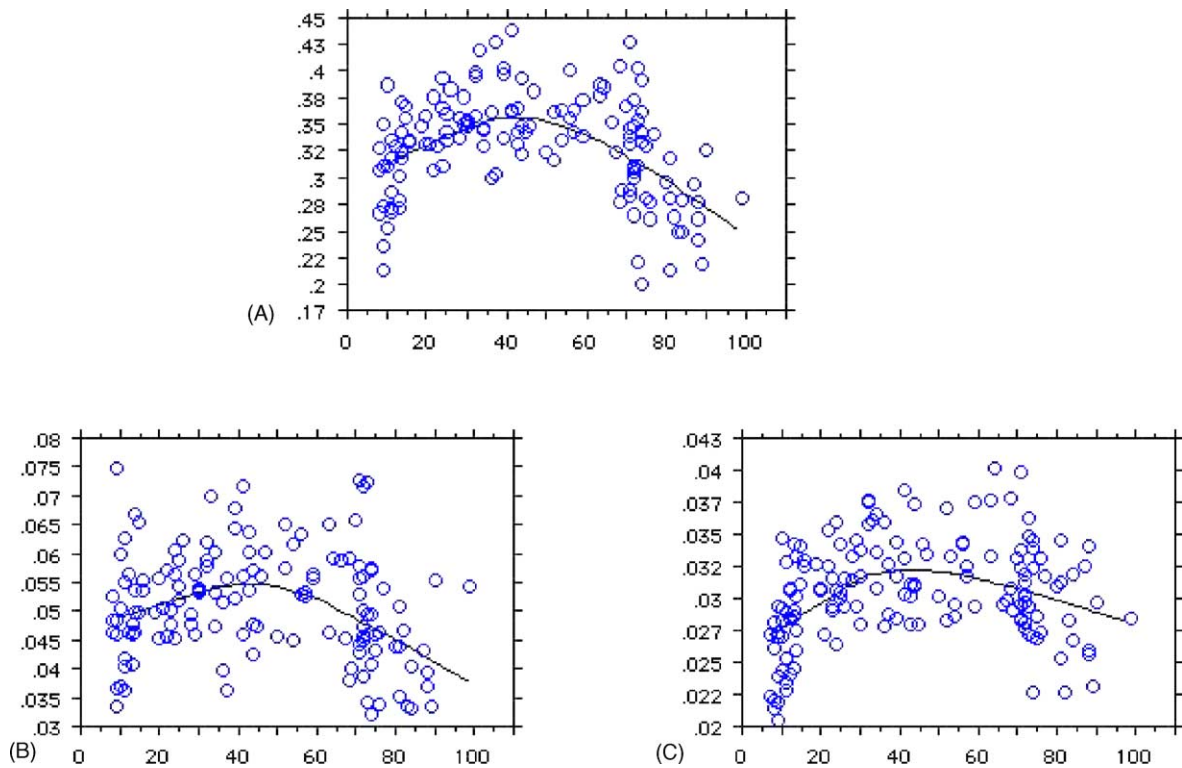


Fig. 1. Normalized white matter volume as a function of age. (A) Cerebral white matter; (B) temporal lobe white matter; (C) deep cerebral white matter.

but that a great deal more information about regional oligodendrocyte function across the age range is needed to test the hypothesis. Recent developments in imaging, for example in diffusion imaging with MR, may speed the acquisition of this information, by providing whole brain maps of myelination-related alterations of diffusion tensors.

The putative role of myelin breakdown in AD also raises important questions about the regional pattern of white matter damage in these patients. Presumably, myelin breakdown, and subsequent loss of or damage to white matter, should exhibit a regional pattern consistent with the known pathology and functional impairments that characterize the disorder. The regional specificity of white matter damage in

AD has received relatively little attention in imaging studies of the disorder to date. We and others have noted the involvement of white matter in the disorder [2,3,6,10,11] but, again, the regionally-specific data are too sparse to weigh heavily either in favor or against the hypothesis under discussion. In Fig. 2A, we present the volumes of temporal lobe white matter in AD patients and age-controls from our studies. It is clear that reduced volume of white matter in this region accompanies the often reported gray matter losses in limbic and neocortical structures. The data from the deep subcortical region surrounding less affected structures (shown in Fig. 2B) suggest less severe effects of the disease on the white matter in this region, consistent

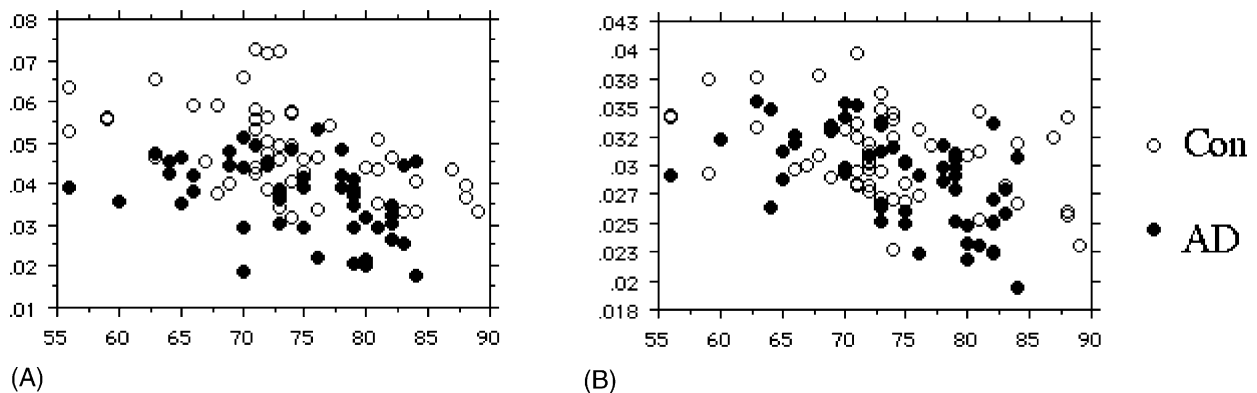


Fig. 2. White matter volume in AD patients and controls as a function of age. (A) Temporal lobe white matter; (B) deep cerebral white matter.

with the hypothesis that cortico-cortical connections may be disproportionately affected. However, there are few, if any, studies that have investigated the regional distribution of AD-related white matter damage systematically, so results of an analysis of the data from these studies would probably be too coarse to militate for or against the hypothesis. The article by Bartzokis will serve the field well if it stimulates more intense scrutiny of myelin loss and alterations of axonal function in AD and other neurodegenerative disorders.

## 2. How do functional alterations attributable to late myelination relate to functional deterioration in AD?

A central theme in the model presented by Bartzokis is a correspondence between the regional distribution of later myelinating neural structures and that of early lesions in evolving AD. The author's position would seem to imply that functions that rely on neural structures not fully mature until very late in development are the first affected in AD. Existing evidence (though fragmentary, as has been noted) would seem to suggest that association regions in the cortex and critical sites of cortico-cortical convergence in the medial temporal lobes are among the later myelinating areas. These regions have certainly been implicated in histopathological studies of AD. However, in at least one respect, the correspondence appears strained. Neuropsychological studies of preclinical and early AD consistently reveal disproportionate effects on memory encoding, retrieval of recently acquired memories, or both. Yet in young people, in whom ongoing myelination is far from complete by present accounts, these functions are arguably at their most robust. Bartzokis speculates that toxicity associated with myelin breakdown affects surrounding tissues, however, in his description of the functional impact of these events he focuses on the effects of the myelin loss itself, i.e. "the resulting decrease in conduction speed and increase in refractory times," and "disconnection of cortico-cortical communication." Why then is the relatively unmyelinated young brain not characterized functionally by weaker mnemonic performance resembling the loss of mnemonic function in the earliest stages of AD?

## 3. Age and glial populations

In summary, the article by Bartzokis outlines a provocative hypothesis about the role of oligodendrocyte functions in AD, and about possible interactions between protracted developmental processes and a neurodegenerative disorder expressed in older people. The article may prompt neuroscientists to consider more carefully the complex functions of glial cells within the neuropil, and to describe any alterations across the life-span in these cell populations. Among

the strengths of the model are a number of testable predictions and hypotheses. Whether or not the model withstands the outcome of these tests, it serves to underscore the lack of understanding of dynamic processes occurring during late brain maturation. To what extent are neurons that remain unmyelinated until later in development contributing to neural computations before that time? If little, then do they mediate novel functions that emerge concurrently with myelination? How do the alterations in neurotransmission that presumably attend late myelination affect the activity and connectivity of neurons that were myelinated at an earlier time? Answers to these questions may come, at least in part, from future imaging studies collecting structural and functional information simultaneously, and would not only bear importantly on the validity of the model under discussion, but would lead to important advances in our understanding of the functional plasticity of the adult brain.

## References

- [1] Archibald SL, Fennema-Notestine C, Gamst A, Riley EP, Mattson SN, Jernigan TL. Brain dysmorphology in individuals with severe prenatal alcohol exposure. *Dev Med Child Neurol* 2001;43:148–54.
- [2] Bronge L, Fernaeus SE, Blomberg M, Ingelson M, Lannfelt L, Isberg B, Wahlund LO. White matter lesions in Alzheimer patients are influenced by apolipoprotein E genotype. *Dement Geriatr Cogn Disord* 1999;10:89–96.
- [3] Englund E, Brun A, Persson B. Correlations between histopathologic white matter changes and proton MR relaxation times in dementia. *Alzheimer Dis Assoc Disord* 1987;1:156–70.
- [4] Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J, Hesselink JR. Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol Aging* 2001;22:581–94.
- [5] Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. *Brain* 1991;114(Pt 5):2037–49.
- [6] Sjobeck M, Englund E. Glial levels determine severity of white matter disease in Alzheimer's disease: a neuropathological study of glial changes. *Neuropathol Appl Neurobiol* 2003;29:159–69.
- [7] Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW. Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage* 1999;9:587–97.
- [8] Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions [letter]. *Nat Neurosci* 1999;2:859–61.
- [9] Sowell ER, Trauner DA, Gamst A, Jernigan TL. Development of cortical and subcortical brain structures in childhood and adolescence: a structural MRI study. *Dev Med Child Neurol* 2002;44:4–16.
- [10] Stout JC, Jernigan TL, Archibald SL, 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.
- [11] Waldemar G, Christiansen P, Larsson HBW. White matter magnetic resonance hyperintensities in dementia of the Alzheimer type: morphological and regional cerebral blood flow correlates. *J Neurol Neurosurg Psychiatry* 1994;57:1458–65.
- [12] Yakovlev PI, Lecours AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, editor. *Regional development of the brain in early life*. Oxford: Blackwell Scientific Publications; 1967. p. 3–70.