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REVIEW

DIFFUSION TENSOR IMAGING OF WHITE MATTER DEGENERATION IN ALZHEIMER'S DISEASE AND MILD COGNITIVE IMPAIRMENT

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Abstract—Alzheimer's disease (AD) has traditionally been regarded as a disease of the gray matter (GM). However, the advent of diffusion tensor imaging (DTI) has contributed to new knowledge about how changes in white matter (WM) microstructure *in vivo* may be directly related to the pathophysiology of AD. It is now evident that WM is heavily affected in AD, even at early stages. Still, our knowledge about WM degeneration in AD is poor compared to what we know about GM atrophy. For instance, it has not been clear if WM can be directly affected in AD independently of GM degeneration, or whether WM changes mainly represent secondary effects of GM atrophy, e.g. through Wallerian degeneration. In this paper, we review recent studies using DTI to study WM alterations in AD. These studies suggest that microstructural WM affection at pre-AD stages cannot completely be accounted for by concomitant GM atrophy. Further, recent research has demonstrated relationships between increased cerebrospinal fluid levels of Tau proteins and changes in WM microstructure indexed by DTI, which could indicate that WM degeneration in pre-AD stages is related to ongoing axonal damage. We conclude that DTI is a promising biomarker for AD, with the potential also to identify subgroups of patients with especially high degree of WM affection, thereby contributing to more differentiated pre-AD diagnoses. However, more research and validation studies are needed before it is realistic to use this information in clinical practice with individual patients.

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Key words: diffusion tensor imaging, Alzheimer's disease, mild cognitive impairment, CSF biomarkers, Tau proteins, white matter.

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Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; APOE4, apolipoprotein E4; Aβ, amyloid-beta; CSF, cerebrospinal fluid; DA, axonal diffusivity; DR, radial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; GM, gray matter; MCI, mild cognitive impairment; MD, mean diffusivity; NFT, neurofibrillary tangles; ROI, region of interest; SLF, superior longitudinal fasciculus; WM, white matter.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease defined by widespread cognitive impairments accompanied by the presence of neurofibrillary tangles (NFT) and amyloid plaques. The clinical manifestation of AD is seen in the domains of memory and spatial navigation in the early phases of the disease, with affection of almost all cognitive domains including executive function failure, emotional instability, psychosis and both retrograde and anterograde amnesia as the disease progresses. The clinical diagnosis of "probable AD" is typically only confirmed after death by postmortem examinations with positive findings of intraneuronal NFTs and extracellular aggregation of amyloid-beta (Aβ) in the form of plaques (Dubois et al., 2010).

AD has traditionally been considered a disease of the gray matter (GM) of the brain, with white matter (WM) affection often considered secondary to GM damage (Roher et al., 2002). Even though evidence has accumulated that WM is affected in AD (Brun and Englund, 1986), the mechanisms of WM affection in AD remain largely unknown, raising several questions:

- Is WM affection secondary to GM affection or can it also be independent?
- What is the spatial and temporal dynamics of WM affection in AD?
- How is WM degeneration related to other AD-biomarkers, especially cerebrospinal fluid (CSF) biomarkers of amyloid-beta ($A\beta_{1-42}$), NFTs (hyperphosphorylated Tau; p-Tau) and neurodegeneration (total Tau)?

We will review recent research relevant for each of these questions. Although there is currently much focus on WM degeneration in AD, our knowledge is still limited compared to what we know about GM atrophy and other AD biomarkers.

CAN WM AFFECTION IN AD BE INDEPENDENT OF GM DEGENERATION?

There are two main entry points to explain WM changes in AD. WM damage can occur secondary to GM pathology through Wallerian degeneration (Waller, 1850), i.e. degeneration of axons separated from their cell bodies, followed by slower degradation of the myelin sheath. Secondary WM changes may be caused through damage to GM, e.g. from accumulation of Aβ in some form, soluble oligomers, or less likely plaques (Zetterberg et al., 2010), consistent with the amyloid cascade hypothesis of AD (Hardy and Allsop, 1991), or through Aβ-independent pathways (Chételat, 2013; Herrup et al., 2013). Cell death will in turn lead to axonal disruption in WM tracts connecting the affected GM areas, exhibiting Wallerian degeneration. Alternatively to the secondary route, it is possible that different mechanisms can cause WM degradation directly, independently of GM pathology. Several lines of evidence suggest that some of the changes seen in WM are not necessarily secondary to GM changes in AD, but might also reflect processes that originate in WM and play a direct role in the pathogenesis of AD. We will present findings from molecular neurobiology and *in vivo* neuroimaging relevant for the discussion of WM affection in AD.

The first line of evidence for direct WM affection in AD comes from molecular neurobiology. WM degeneration independent of GM lesions has been found in AD in neuropathological studies, attributed to vascular disease (Brun and Englund, 1986), but has also been identified in individuals without co-morbid vascular brain disease (Sjöbeck et al., 2006). Elevated CSF Tau levels in patients (see Info Box) could also be interpreted as coherent with WM affection. Tau exists normally as a family of microtubule-associated proteins, and is primarily located in the axons. By its binding to tubulin, Tau provides stability to, and promotes assembly of microtubules, which are involved both in maintaining cell structure and serve as tracks for axonal transport (Buée et al., 2000). The binding process can be regulated by phosphorylation and de-phosphorylation of the protein (Lee et al., 1989). Hyperphosphorylation of Tau results in the formation of insoluble paired helical filaments which are the main constituents of NFTs, and the resulting loss of binding to microtubule leads to destabilization of axons and axonal degeneration, decline in a range of neuronal functions, and ultimately cell death (Iqbal and Grundke-Iqbal, 2008). While the relationship between Aβ load and NFTs seems complex, and interactions between isoforms of the proteins are plausible (Roberson et al., 2007; Hyman, 2011; Desikan et al., 2012; Manczak and Reddy, 2013), the neurodegeneration and neurocognitive affection in AD may be more strongly related to NFTs than amyloid plaque load (Bennett et al., 2004). As Tau is found primarily in axons, and DTI is sensitive to axonal degeneration, this is supportive of microstructural changes as indexed by DTI playing a central role in the pathogenesis of AD. However, as discussed below, axonal degeneration detectable by DTI is likely occurring both within GM and WM. Further, axonal degeneration, especially in WM, is likely more related to total levels of Tau than the hyperphosphorylated Tau that constitutes the NFTs. Also, increased CSF levels of total Tau do not by themselves constitute strong evidence for primary WM affection, since axonal degeneration may result from even earlier processes, including cell death. A recent very large study of 5542 cases found relationships between CSF biomarkers of Aβ, total Tau and phosphorylated Tau (p-Tau) and neurofilament light, which is a protein expressed in large-caliber myelinated axons (Skillbäck et al., 2013). Although such results cannot be used to make strong inferences about the temporal order or the direction of causality between GM and WM affection, they highlight that a robust relationship can be expected, and that WM by no means is spared in the AD disease process.

Info box

In-vivo biomarkers of AD

Biomarkers can aid in early pre-symptomatic detection of AD. This is crucial for selecting subjects for clinical drug trials, monitoring disease progression, and for eective and rapid treatment of patients. An ideal biomarker should be highly sensitive and specific to the disease, be predictive of the course, and be available without invasive procedures. Two important classes of AD biomarkers discussed in the present paper are structural neuroimaging biomarkers and CSF biomarkers:

- **Structural neuroimaging biomarkers**
  - *Structural MRI:* Degree of atrophy (volume or thickness reductions) correlates with disease progression and cognitive decline, and is predictive of conversion to AD.
  - *Diffusion tensor imaging:* White matter microstructure changes are commonly found in MCI and AD, and DTI shows promise as a stage-marker for AD.
- **CSF biomarkers**
  - *Aβ 42:* Reduced CSF Aβ42 levels are believed to be caused by the aggregation of Aβ42 into plaques, leaving less Aβ free to diuse into CSF. CSF Aβ42 levels are also negatively correlated with plaque load *post mortem* (Formichi et al., 2006), to PiB-PET retention (Fagan et al., 2006) and has reasonable sensitivity and specificity for the diagnosis of AD.
  - *Tau:* Neurofibrillary tangles (NFTs) are believed to be the result of abnormal processing (hyperphosphorylation) of the microtubule-associated protein Tau which is primarily located in the axons (Grundke-Iqbal et al., 1986). Levels of total Tau (Tapiola et al., 1997) and P-Tau (Buerger et al., 2006) measured in CSF correlate positively (total Tau, $r = 0.44$; P-Tau, rho = 0.72) with post-mortem neuropathological findings of NFTs in the brain.