

## 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; A $\beta$ , 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 (A $\beta$ ) 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 A $\beta$  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 A $\beta$ -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 A $\beta$  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 A $\beta$ , 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 elective 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**
  - *A $\beta$  42*: Reduced CSF A $\beta$ 42 levels are believed to be caused by the aggregation of A $\beta$ 42 into plaques, leaving less A $\beta$  free to diffuse into CSF. CSF A $\beta$ 42 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.

Other findings suggesting the possibility that some WM alterations are independent of GM pathology, and might reflect processes closely linked to precipitating factors in the emergence of AD, are altered levels of molecules related to cytoskeleton maintenance and cellular survival in WM of AD brains (Castaño et al., 2013). Similarly, caspase-6 activity – a protease that induces axonal degeneration and cleaves Tau and other proteins – is raised early in AD (Klaiman et al., 2008). In one study of healthy aged individuals, both Caspase-6 activity in entorhinal cortex and in the CA1 region of the hippocampus, and Tau pathology predicted lowered memory scores, while A $\beta$  did not correlate with any cognitive test (Ramcharitar et al., 2013). Oligodendrocyte cell death and reactive gliosis have been demonstrated in AD (Englund and Brun, 1990), and biochemical analyses have suggested that extensive WM axonal demyelination is part of AD pathology (Roher et al., 2002).

The second line of evidence comes from *in vivo* neuroimaging studies, which is the focus of the present review. DTI can be used to index different microstructural properties of WM. The most frequently used DTI metrics are fractional anisotropy (FA), a measure of the degree of directionality of water diffusion in the tissue, and mean diffusivity (MD), a measure of the total diffusion in a voxel, also called the apparent diffusion coefficient (see paper by Concha, (2014), for a thorough discussion of the different diffusion properties). By examining additional diffusion metrics, we are able to obtain information about different properties of the underlying WM than can be obtained from FA and MD alone. Although the exact relationship between diffusion metrics and the underlying neurobiology is highly complex, diffusivity parallel to the principal eigenvector (DA) might reflect axonal damage, and diffusivity perpendicular (DR) to the principal eigenvector is likely more affected by myelination, axonal diameter and axonal packing (Beaulieu, 2002; Song et al., 2003). While less exact than neuropathological studies, the real advantage of neuroimaging is the ability to study the human brain *in vivo*, offering opportunities to describe the dynamics of disease progression longitudinally, and to relate changes in WM microstructure to changing levels of a range of other measures, both clinical and biological.

DTI studies have shown at least partial statistical independence between cortical atrophy in medial temporal lobe structures and alterations in the microstructure of connecting WM in AD (Salat et al., 2010). Bosch and colleagues (Bosch et al., 2012) found FA changes that could be explained by GM atrophy, but in the same study reported that DR changes in several regions were independent of GM atrophy, suggesting possibly different mechanisms accounting for the changes. In other studies, DTI changes are found to be both dependent on, and independent of, GM atrophy (O'Dwyer et al., 2011a; Alves et al., 2012), supporting the possibility that WM changes can be independent of GM changes in AD, but that more than one mechanism might be involved. A study on the temporal dynamics of

GM and WM affection in AD showed widespread DTI changes in mild cognitive impairment (MCI) and AD compared to controls (Agosta et al., 2011). Interestingly, while the correlations between WM and GM abnormalities were widespread in the AD group, WM-GM correlations were confined to the medial temporal lobe in the MCI group, with changes in most WM tracts being independent of GM atrophy. Similar results were found in MCI patients in another study, where microstructural WM damage in the fornix was unrelated to hippocampal atrophy in early MCI, but WM changes in fornix correlated with hippocampal atrophy in subjects that had carried MCI longer (Zhuang et al., 2013). A multi-modal study of MCI patients showed that metabolism, morphometry and FA of selected WM regions all contributed uniquely to explain memory function, indicating that the metrics were sensitive to different properties of brain pathology, all with cognitive consequences (Walhovd et al., 2009). Thus, WM microstructural differences with relations to memory could not be explained by concomitant GM pathology. In a study of regional WM volume, Salat et al. (2009) showed reductions in early phases of AD, although it was not directly tested whether these were independent of GM changes.

Together, evidence from molecular neurobiology and from human *in vivo* neuroimaging studies indicates that WM abnormalities can be at least partly independent of GM changes in the pathogenesis of AD. Although WM and GM changes conceivably will be correlated in progressed AD through, e.g. Wallerian degeneration, it is possible that WM degradation and GM atrophy in initial phases are caused by different events, or that a joint mechanism affects both tissue types. Thus, there is presently not convincing evidence that GM damage is the only cause of WM degradation in early AD.

A theory considering WM damage as primary in AD is the retrogenesis model formulated by Bartzokis et al. (Bartzokis et al., 2007; Bartzokis, 2011), which builds on previous works by Reisberg (Reisberg et al., 1999) and Braak and Braak (Braak and Braak, 1991, 1997). According to this model, the WM degeneration in AD is the reverse of what is seen during myelogenesis. Early myelinated, large-diameter fibers such as primary sensory area axons are affected least and last, while late-myelinated neocortical projection fibers are affected early in AD. Oligodendrocytes that are differentiated late in life myelinate more axonal segments per cell, as opposed to axons myelinated early in life that might have only one oligodendrocyte per myelin sheath. Given an even rate of damage to oligodendrocytes across the brain, this skewed ratio of myelin sheaths per oligodendrocyte would in itself contribute to a susceptibility of myelin breakdown in late myelinated areas such as association tracts. Additionally, the model proposes cholesterol and iron build-up as other risk factors related to oligodendrocytes and demyelination.

Some DTI studies conclude in support of this theory when comparing FA in late and early myelinated fiber tracts in AD (Stricker et al., 2009) and in aging (Brickman et al., 2012). Douaud and colleagues

(Douaud et al., 2011) used the mode of anisotropy (MO) to qualify the higher FA they found in MCI vs. controls in an area of crossing fiber tracts, relating this to relative sparing of one tract (early myelinated motor-related projection fibers) compared to the affected crossing association fibers in the late myelinated superior longitudinal fasciculus (SLF).

While the above studies can be taken in support of the retrogenesis model, other studies' results are not always in favor. According to a recent meta-analysis (Sexton et al., 2011), the effect size for FA in the splenium of the corpus callosum was greater than in the genu (see further discussion of this study below). Following the retrogenesis model, we would expect greater WM alterations in the genu, as it projects to prefrontal cortex and its myelination is more protracted than the splenium, while the reported effect sizes hint at the opposite pattern. Westlye and colleagues (Westlye et al., 2010) determined age at peak FA to describe whether WM tracts were early or late maturing. While the authors observed relatively early maturation of the CST, and protracted development of the dorsal and parahippocampal cingulum as well as the uncinate fasciculi, the timing of when deterioration started did not fit the retrogenesis model well, as the dorsal cingulum and uncinate fasciculus started deteriorating relatively late. Thus, although the retrogenesis theory is intriguing, the evidence so far is not conclusive.

Whether the retrogenesis theory holds or not, cerebrovascular conditions – an important risk factor for AD – are likely central in causing the observed WM damage. However, while mild ischemic WM disease is observed in about 50% of AD-cases (Englund et al., 1989), the newly proposed diagnostic criteria for probable AD from the National Institute of Aging–Alzheimer's Association workgroups specifically treat substantial concomitant cerebrovascular disease as an exclusion criterion (McKhann et al., 2011). Cerebrovascular conditions and AD may be linked through several relevant pathways, including a relationship between cerebrovascular disorders and the major genetic risk factor for sporadic AD, apolipoprotein E4 (APOE4) (Zlokovic, 2013). Still, taking these new criteria into account, we are urged to also look past cerebrovascular disease in the search for pathogenic mechanisms affecting WM in AD. The effects of cerebrovascular disease on WM degeneration in AD will therefore not be discussed specifically in this paper.

### WHAT IS THE SPATIAL AND TEMPORAL DYNAMICS OF WM AFFECTION IN AD?

Having established that WM is affected in AD, and possibly not just dependent on GM pathology, the regions commonly affected and the temporal dynamics of WM changes in AD are important to investigate. Sexton et al. (Sexton et al., 2011) published the first meta-analysis on cross-sectional DTI-studies on AD and MCI. The authors reported data from every study published until February 2010 that compared FA or MD between either AD or MCI and healthy controls, and

reported region of interest (ROI)-based results. The total number of studies was 41, with a total of 2026 participants (617 with AD, 494 with MCI, and 915 controls). The meta-analysis confirmed the commonly reported widespread findings of reduced FA/increased MD in AD and MCI vs. controls. When comparing FA between AD and controls, large effect sizes were reported in the uncinate fasciculus and SLF, medium effect sizes in the genu and splenium of the corpus callosum, frontal- and temporal WM. Effect sizes in the cingulum ranged from small in middle cingulum, medium in anterior and parahippocampal parts, to large in posterior cingulum. The pattern was similar for comparisons between MCI and controls, although different ROIs were examined.

For MD, significant differences between both AD and controls, and between MCI and controls, were found in most all areas studied. The largest effect sizes were located to the hippocampus, and temporal and parietal areas. Studies using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006) or other voxel-based whole-brain analysis methods were not taken into account in the meta-analysis. When methods enabling more specific localization are employed, the affected areas are quite consistently reported in the literature as overlapping with WM areas connecting regions of the episodic temporo-parietal memory network (Buckner and Wheeler, 2001), including the hippocampus, entorhinal, retrosplenial, posterior cingulate and precuneus cortices (Damoiseaux et al., 2009; Acosta-Cabronero et al., 2010; Huang et al., 2012).

In addition to FA and MD, one would expect to see the same pattern of differences between AD and controls as reported by Sexton and colleagues for the absolute diffusion metrics DR and DA. Additionally, the examination of DR and DA lends the possibility for more complex patterns of change in diffusion metrics to be revealed. An increase in FA may be caused either by increased DA, decreased DR, or a combination of the two. An increase in MD can be caused by an increase in any of the three eigenvectors, with or without decreases in the other eigenvectors. It is unlikely that identical mechanisms underlie change in different DTI indices, although a fair degree of overlap is to be expected between these dependent measures (Song et al., 2003). Increased DR in temporal, frontal and parietal regions is commonly reported in AD (Huang et al., 2007). It seems also that the effects are somewhat larger when the absolute diffusion metrics DR and MD, are considered, than the commonly employed composite measures of FA. When considering studies analyzing DA, less consistent results make findings in this DTI metric more difficult to interpret (Agosta et al., 2011; O'Dwyer et al., 2011b; Huang et al., 2012). Although low DA has been related to axonal degeneration in rodent models (Song et al., 2003), a human histology study showed that DA follows a complex, non-monotonous trajectory of change after axonal injury (Concha et al., 2006), and DA has also been reported to increase with age (Madden et al., 2012). Thus, changes in DA seem more complex to

interpret than the other metrics. If increased DA is observed in AD, this will also contribute to reduce group differences in FA, and DR and MD may thus potentially be more sensitive biomarkers of WM-injury in AD.

### LONGITUDINAL DTI STUDIES OF MCI AND AD

Few longitudinal studies on DTI in MCI and AD samples have been published, and the sample sizes are still small. The Alzheimer's Disease Neuroimaging Initiative (ADNI) include DTI in its protocol for ADNI-2 and ADNI-go (Jack et al., 2010), and it may not be until the datasets are released from such multicenter projects that we will see the first large longitudinal follow-up studies on DTI in MCI and AD.

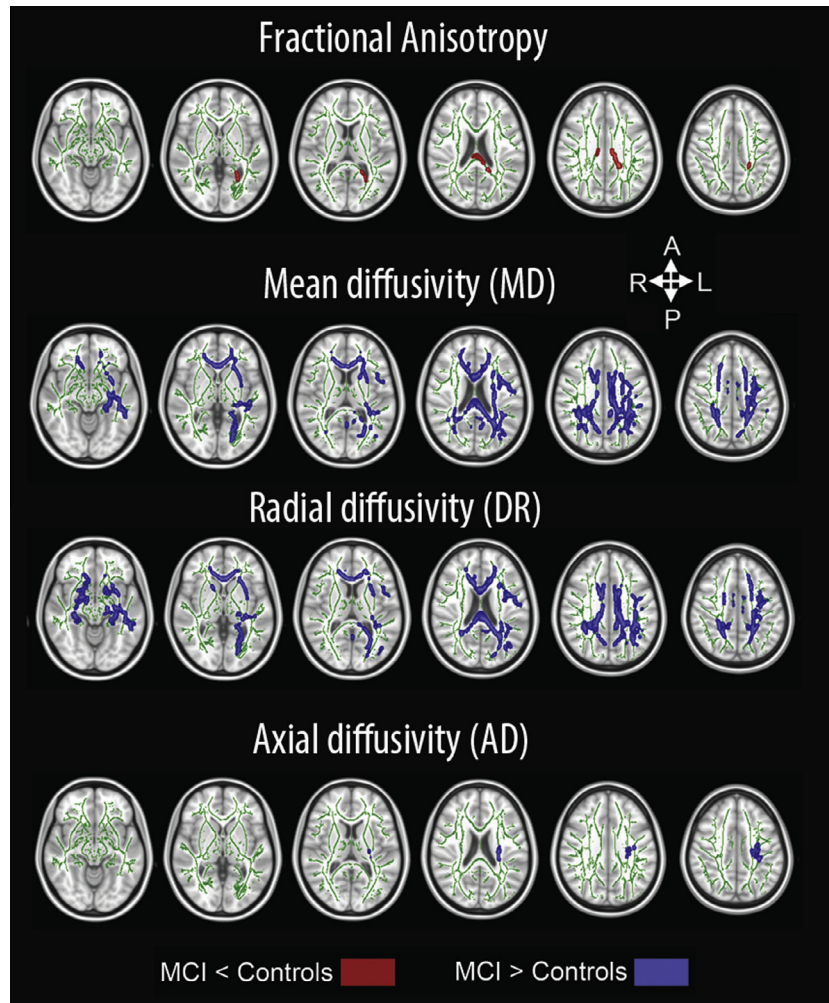
The few studies we are aware of examining DTI in MCI longitudinally still provide some insight into the pathological processes in WM in AD and MCI patient groups. In a study by Teipel and colleagues (Teipel et al., 2010), FA reductions were reported in the corpus callosum in MCI subjects after approximately one year, but no significant differences between MCI and healthy controls with regard to change over time was reported. Three groups of 25 each MCI, AD patients and controls were followed up over the course of 12 months, at four different time-points by Mielke and colleagues (Mielke et al., 2009; Nowrangi et al., 2013). Stable cross-sectional differences between controls and AD were evident throughout all time-points in the splenium of the corpus callosum and in the fornix (lower FA and higher MD in AD), while MCI did not differ significantly from controls. Longitudinally, however, the MCI group did show greater MD increase in the fornix than controls, while the AD group did not show larger change in DTI measures than the other two groups. There were no between group differences in FA change over time. In another study examining DTI longitudinally in AD patients, the authors reported FA reductions and DR increases in the uncinate fasciculus in the AD patients over a period of 1.5 years compared to baseline (Kitamura et al., 2013). The DTI changes were unfortunately not compared to changes in the control group, making it challenging to tell if these are WM changes that could also be seen in normal aging or whether they were specific to AD. The findings by Kitamura et al. are supported by the results from a study using combined cross-sectional and longitudinal samples (Acosta-Cabronero et al., 2012). In the early stages of AD, only DA and MD were elevated compared to healthy controls. As the disease progressed, DA seemed stable while DR increased, and as a result FA was reduced. This pattern was shown when comparing early stage AD with later stage AD, both cross-sectionally and longitudinally over 12 months (Acosta-Cabronero et al., 2012). A similar pattern has been reported by our research group (Amlien et al., 2013). Widespread cross-sectional DTI differences between MCI and controls in FA, MD and DR were detected both at baseline and at follow-up after 2.5 years, while differences in DA were only evident at baseline. When we analyzed longitudinal changes, the same pattern

was found, with MCI showing greater changes in DR and FA than controls over time, and DA being relatively stable (see Fig. 1).

### HOW IS WM DEGENERATION RELATED TO CSF BIOMARKERS OF AD?

CSF measures of Tau proteins may be the most relevant to relate to microstructural WM changes in early AD. While the Tau measured in CSF probably stems from diffusion from intracellular space, the precise mechanisms for this leakage is unknown. CSF Tau levels seem to reflect the extent of ongoing axonal damage, and rapidly elevated levels are seen in acute conditions as stroke where Tau levels are correlated with infarct size (Hesse et al., 2000). Following traumatic brain injury, sharply increased levels of CSF Tau are measured in the acute phase, followed by a relationship between patient improvement and normalization of CSF Tau levels (Zemlan et al., 2002). As a marker of acute axonal injury, we would expect to find elevated CSF Tau levels early in the AD pathogenesis if axonal disruption or damage is indeed an early upstream event. It is possible that ongoing axonal damage in AD leads to an increased and measurable leakage of Tau to CSF, but small-scale axonal damage needs to accumulate over time for it to affect WM microstructure to a degree that can be detectable by DTI with current methods. Axonal degeneration inducing detectable changes in WM microstructure would likely cause elevation of CSF levels of total Tau, not necessarily hyperphosphorylated Tau, which primarily are found intracellularly in GM neurons. Still, results from the large study by Skillbäck et al. (2013) demonstrated relationships between CSF biomarkers of both A $\beta$ 42, total Tau as well as p-Tau and subcortical axonal damage as indexed by neurofilament light.

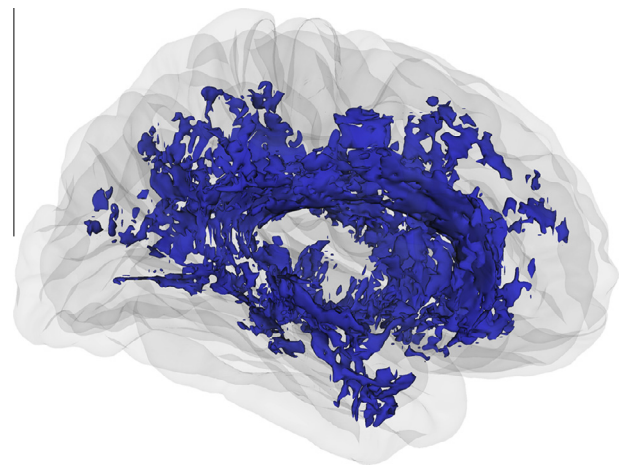
Recently, several research groups have been working to elucidate the relationship between CSF Tau and WM microstructure changes in AD and MCI. Comparing subjects with stable, non-progressing MCI with subjects with MCI who progressed to probable AD in >2 years, Douaud and colleagues (Douaud et al., 2013) found DTI differences at baseline in the left hippocampus, and in WM in the fornix and in the left fimbria, as well as in the SLF. While the DTI measure in the hippocampus was the best single predictor of conversion to AD with 77% accuracy, the combination of CSF Tau, volume and diffusion measures yielded 91% classification accuracy (85% sensitivity, 96% specificity). Another study compared baseline measures of DTI and CSF in declining vs. stable MCI patients over a two to three year period, and found that while DTI was the best predictor of both later MTL atrophy and cognitive decline, CSF total Tau (but not A $\beta$ 42 or P-Tau) was also significantly related to cognitive decline (Selnes et al., 2013). The relationship between DTI and cognitive decline in this sample was significant for DR, MD and FA in parahippocampal WM, where the effects also were largest. For the other tested WM ROIs



**Fig. 1.** Differences in WM microstructure detected by DTI in MCI patients. Different diffusion metrics can be used to differentiate patients with MCI from healthy controls. Effects are often especially strong for MD and DR. Data from [Amlien et al. \(2013\)](#).

(entorhinal, retrosplenial, posterior cingulate, precuneus, supramarginal, middle temporal), a significant relationship was found (except for middle temporal WM) for DR and MD, but not for FA. Employing cross sectional methods, [Stenset et al. \(2011\)](#) reported higher DR and lower FA in posterior cingulate for MCI patients with pathological elevated CSF total Tau levels vs. MCI patients with non-pathological CSF total Tau levels. This initial study led us to follow up the sample longitudinally to explore whether the differences in WM microstructure were still developing or just preexisting at this stage of AD progression. We found that patients with pathological levels of CSF Tau had greater FA reductions and DR increases in the right cingulum and SLF relative to controls over time, but this was not found in MCI patients with non-pathological CSF Tau levels ([Amlien et al., 2013](#)) (see [Fig. 2](#)). This can be interpreted as meaning that those MCI patients with the highest level of on-going axonal degeneration, as evidenced by their pathological levels of CSF Tau, also showed the most rapid deterioration of WM.

While the above studies examined changes in patients with diagnosed AD or MCI, by the time AD and



**Fig. 2.** Reduction of radial diffusion in MCI. Three-dimensional rendering of areas of the WM where MCI patients have larger radial diffusion than age-matched controls. As can easily be seen, effects are widespread across WM. Data from [Amlien et al. \(2013\)](#).

MCI have been diagnosed, the disease has already taken a significant toll on the brain. By studying

preclinical changes in WM in at-risk populations, new insights into the possible early events leading to AD and MCI can be made. In a group of healthy adults with a familial history of AD, CSF Tau and Tau/A $\beta$ 42 ratio at baseline was related to WM microstructure 3.5 years later in areas adjacent to GM structures typically affected in early AD (Bendlin et al., 2012). Higher CSF levels were related to higher MD, DR and DA in WM adjacent to the hippocampus, but not to FA, and not to GM measures. The authors hypothesize that early AD pathology involves axonal or myelin degeneration, while cortical involvement is not detectable until a later stage. In a similar study, Xiong and colleagues (Xiong et al., 2011) examined cognitively normal adult subjects with a familial history of AD, representing a group of subjects with increased probability of being at a prodromal stage of AD and possessing genetic risk factors. At this very early stage, a familial history of AD was associated with age-related reductions in CSF levels of A $\beta$ 42, indicating higher brain levels of  $\beta$ -amyloid. The presence of an APOE4 allele was also related to decreased levels of A $\beta$ 42, but this decrease was stronger in individuals with a family history of AD. While brain volumetric measures did not differ between the groups, subjects with a family history of AD had lower FA in the genu and splenium of the corpus callosum than subjects without a familial history of AD, and for subjects over 55 years, a family history of AD was related to higher CSF total Tau. The above studies provide indications that microstructural WM changes are promising candidate biomarkers for the early detection of AD. Simultaneously, these studies on subjects with risk factors for AD accentuate a limitation that is prevalent in the AD literature. When there is no follow-up of the at-risk normal participants or the MCI patients, it is unknown for how many subjects in a given sample onset of AD is causing the symptoms. Studies of MCI patients without follow-up examinations will include highly heterogeneous samples of individuals both with and without a prodromal AD. Optimally, researchers should have the patience to collect at least clinical follow-up data over a long enough period of time, before making strong conclusions on the biology of AD. However, when the aim is to identify the earliest markers of the disease, conversion may take several years, at least up to 10 years in some cases, making such studies rare (for important exceptions, see e.g. Driscoll et al., 2009). For DTI, no such studies yet exist.

### TARGETS OF INVESTIGATION: BEYOND THE WM-GM DISTINCTION?

DTI metrics seem to be sensitive to pathological WM changes in AD. For different reasons, DTI are much more seldom used to track changes in GM structures, and especially within the cortex. However, there are reasons to expect that some of the pathology detected in WM could potentially also be detectable in GM. For instance, a recent study used T1/T2 contrast to map myelin content within the cortex (Grydeland et al., 2013). Glasser and Van Essen (2011) showed that by exploiting the inverse sensitivity of the T1 and the T2

signal to myelin, it was possible to map myelin content continuously across the cortical mantle. Grydeland et al. (2013) demonstrated an increase in myelin content through childhood development. This was reversed in aging with declining myelin content among older adults. Interestingly, mapping MD from the same voxels showed largely overlapping trajectories. This indicates that MD was related to the same events that caused the myelin content measure to change through life. Interestingly, Cherubini et al. (2010) showed progressive increased MD in the hippocampus, amygdala and caudate in groups of patients with amnesic MCI and mild AD compared to healthy elderly. Thus, although seldom done, there seems to be a great potential for using DTI metrics to measure microstructural alterations also within GM structures. Thus, the neurobiological events detected by DTI scans of WM could be envisioned to also take place in GM. Consequently, investigations testing whether WM in some instances could be selectively affected in very early phases of AD independently of GM should ideally test both tissue classes with the same measures. The possibility that DTI sometimes is more sensitive to early pathology than T1-weighted imaging can thus not easily be interpreted as WM being more affected than GM in general. However, it may be more fruitful to go beyond the distinction of WM and GM, and rather discuss the underlying processes that can be more or less manifested across both WM and GM (see e.g. Grydeland et al., 2012).

### CONSIDERATIONS IN INTERPRETING DTI CHANGES IN AD RESEARCH

One needs to exhibit caution when interpreting absolute diffusion metrics, and it is complicated to attribute underlying biological processes to changes in the measured diffusion metric. This is especially true for diffusion in the principal direction, DA, as this metric is both complex to interpret and seems less reliable than the other metrics (Danielian et al., 2010). Still, several animal studies have demonstrated distinct temporal patterns of diffusivity change during the course of Wallerian degeneration following ischemia, with acute reduced DA caused by axonal damage followed by chronic increase in DR caused at least in part by myelin breakdown (Song et al., 2002, 2003; Sun et al., 2008; Liu et al., 2013). While the effects of specific axonal damage seem reasonably well described, the effects of the diffuse damage caused by neurotoxins show differing results, possibly due to different effects of the neurotoxin studied. Reductions of neurofibrils with intact myelin sheaths in rats by methylmercury led to increased DA, while other DTI metrics remained stable (Kinoshita et al., 1999). Disruption of the axonal cytoskeleton in rats by the neurotoxin iminodipropionitrile led to measured reductions in DA, while DR remained stable (Shepherd et al., 2001). While the results are not conclusive in one direction or the other and probably dependent on which axonal structures are affected by the neurotoxins, as well as

the nature of the lesions, the results provide a good indicator that DA and DR can be independently affected when components making up the axon are disrupted (Beaulieu, 2002). Thus, although FA and MD may be the most often employed measures of WM degeneration in early AD, additional information can be obtained by also studying DR, and possibly DA.

However, while the pathological mechanisms behind diffusion tensor changes are rather well explored in animals, one cannot infer the same pathological mechanisms from animal models alone. Relating DTI changes in humans to other biomarkers, for example CSF levels of total Tau, with known neurobiological mechanisms is thus important, as information from two vectors, both the animal model and knowledge of the neurobiology, can be used to support the claims. Exploring such relations can therefore be very useful for generating hypotheses explaining the mechanisms behind the observed changes.

## SUMMARY AND CONCLUSION

WM changes are detectable at an early stage of the AD pathogenesis, with indications that WM microstructure changes are not always secondary to GM degeneration in AD. Evidence so far indicate that WM and GM degeneration to a certain extent can be disentangled in early stages of the disease, while stronger relationships are more likely at later stages when the degree of GM atrophy has progressed. We suggest to look beyond the distinction between WM and GM per se, and also investigate common and non-common neurobiological events across tissue classes (Grydeland et al., 2013). Combined with CSF total Tau, DTI measures of WM microstructure can be used to aid in prediction of which MCI patients will progress to probably AD. However, more research and validation studies are needed before it is realistic to use this information in clinical practice with individual patients. Developing DTI further as an early biomarker for AD has the potential to lead to improvements in monitoring disease progression, to be used in an enrichment strategy for sample selection and outcome measures in drug trials, and to open up early windows for drug treatment. It is also possible that DTI can be used to identify subgroups of MCI patients with especially high degree of WM affection, thus contributing to better differentiated pre-AD diagnoses.

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## REFERENCES

- Acosta-Cabronero J, Alley S, Williams GB, Pengas G, Nestor PJ (2012) Diffusion tensor metrics as biomarkers in Alzheimer's disease. *PLoS ONE* 7:e49072.
- Acosta-Cabronero J, Williams GB, Pengas G, Nestor PJ (2010) Absolute diffusivities define the landscape of white matter degeneration in Alzheimer's disease. *Brain* 133:529–539.
- Agosta F, Pievani M, Sala S, Geroldi C, Galluzzi S, Frisoni GB, Filippi M (2011) White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology* 258:853–863.
- Alves GS, O'Dwyer L, Jurcoane A, Oertel-Knöchel V, Knöchel C, Prvulovic D, Sudo F, Alves CE, Valente L, Moreira D, Fußer F, Karakaya T, Pantel J, Engelhardt E, Laks J (2012) Different patterns of white matter degeneration using multiple diffusion indices and volumetric data in mild cognitive impairment and Alzheimer patients. *PLoS ONE* 7:e52859.
- Amlien IK, Fjell AM, Walhovd KB, Selnes P, Stenset V, Grambaite R, Bjørnerud A, Due-Tønnessen P, Skinningsrud A, Gjerstad L, Reinvang I, Fladby T (2013) Mild cognitive impairment: cerebrospinal fluid tau biomarker pathologic levels and longitudinal changes in white matter integrity. *Radiology* 266:295–303.
- Bartzokis G (2011) Alzheimer's disease as homeostatic responses to age-related myelin breakdown. *Neurobiol Aging* 32:1341–1371.
- Bartzokis G, Lu PH, Mintz J (2007) Human brain myelination and amyloid beta deposition in Alzheimer's disease. *Alzheimers Dement* 3:122–125.
- Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR Biomed* 15: 435–455.
- Bendlin BB, Carlsson CM, Johnson SC, Zetterberg H, Blennow K, Willette AA, Okonkwo OC, Sodhi A, Ries ML, Birdsill AC, Alexander AL, Rowley HA, Puglielli L, Asthana S, Sager MA (2012) CSF T-Tau/A $\beta$ 42 predicts white matter microstructure in healthy adults at risk for Alzheimer's disease. *PLoS ONE* 7:e37720.
- Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE (2004) Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. *Arch. Neurol.* 61:378–384.
- Bosch B, Arenaza-Urquijo EM, Rami L, Sala-Llonch R, Junqué C, Solé-Padullés C, Peña-Gómez C, Bargalló N, Molinuevo JL, Bartrés-Faz D (2012) Multiple DTI index analysis in normal aging, amnesic MCI and AD. Relationship with neuropsychological performance. *Neurobiol Aging* 33:61–74.
- Braak H, Braak E (1991) Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol* 82:239–259.
- Braak H, Braak E (1997) Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging* 18:351–357.
- Brickman AM, Meier IB, Korgaonkar MS, Provenzano FA, Grieve SM, Siedlecki KL, Wasserman BT, Williams LM, Zimmerman ME (2012) Testing the white matter retrogenesis hypothesis of cognitive aging. *Neurobiol Aging* 33:1699–1715.
- Brun A, Englund E (1986) A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. *Ann Neurol* 19:253–262.
- Buckner RL, Wheeler ME (2001) The cognitive neuroscience of remembering. *Nat Rev Neurosci* 2:624–634.
- Buerger K, Ewers M, Pirttilä T, Zinkowski R, Alafuzoff I, Teipel SJ, DeBernardis J, Kerkman D, McCulloch C, Soininen H (2006) CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. *Brain* 129:3035–3041.
- Buée L, Bussièrè T, Buée-Scherrer V, Delacourte A, Hof PR (2000) Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Rev* 33:95–130.
- Castaño EM, Maarouf CL, Wu T, Leal MC, Whiteside CM, Lue L-F, Kokjohn TA, Sabbagh MN, Beach TG, Roher AE (2013) Alzheimer disease periventricular white matter lesions exhibit specific proteomic profile alterations. *Neurochem Int* 62:145–156.
- Cherubini A, Péran P, Spoletini I, Di Paola M, Di Iulio F, Hagberg GE, et al (2010) Combined volumetry and DTI in subcortical structures of mild cognitive impairment and Alzheimer's disease patients. *J Alzheimers Dis* 19(4):1273–1282. <http://dx.doi.org/10.3233/JAD-2010-091186>.
- Chételat G (2013) Alzheimer disease: A $\beta$ -independent processes—rethinking preclinical AD. *Nat Rev Neurol* 9:123–124.



- Concha L (2014) A macroscopic view of microstructure: Using diffusion-weighted images to infer damage, repair, and plasticity of white matter. *Neuroscience* 276:14–28.
- Concha L, Gross DW, Wheatley BM, Beaulieu C (2006) Diffusion tensor imaging of time-dependent axonal and myelin degradation after corpus callosotomy in epilepsy patients. *Neuroimage* 32:1090–1099.
- Damoiseaux JS, Smith SM, Witter MP, Sanz Arigita EJ, Barkhof F, Scheltens P, Stam CJ, Zarei M, Rombouts SA (2009) White matter tract integrity in aging and Alzheimer's disease. *Hum Brain Mapp* 30:1051–1059.
- Danielian LE, Iwata NK, Thomasson DM, Floeter MK (2010) Reliability of fiber tracking measurements in diffusion tensor imaging for longitudinal study. *Neuroimage* 49:1572–1580.
- Desikan RS, McEvoy LK, Thompson WK, Holland D, Brewer JB, Aisen PS, Sperling RA, Dale AM, Alzheimer's Disease Neuroimaging Initiative (2012) Amyloid- $\beta$ -associated clinical decline occurs only in the presence of elevated P-tau. *Arch Neurol* 69:709–713.
- Douaud G, Jbabdi S, Behrens TEJ, Menke RA, Gass A, Monsch AU, Rao A, Whitcher B, Kindlmann G, Matthews PM, Smith S (2011) DTI measures in crossing-fibre areas: increased diffusion anisotropy reveals early white matter alteration in MCI and mild Alzheimer's disease. *Neuroimage* 55:880–890.
- Douaud G, Menke RAL, Gass A, Monsch AU, Rao A, Whitcher B, Zamboni G, Matthews PM, Sollberger M, Smith S (2013) Brain microstructure reveals early abnormalities more than two years prior to clinical progression from mild cognitive impairment to Alzheimer's disease. *J Neurosci* 33:2147–2155.
- Driscoll I, Davatzikos C, An Y, Wu X, Shen D, Kraut M, Resnick SM (2009) Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. *Neurology* 72:1906–1913.
- Dubois B, Feldman HH, Jacova C, Cummings JL, DeKosky ST, Barberger-Gateau P, Delacourte A, Frisoni G, Fox NC, Galasko D (2010) Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol* 9:1118–1127.
- Englund E, Brun A (1990) White matter changes in dementia of Alzheimer's type: the difference in vulnerability between cell compartments. *Histopathology* 16:433–439.
- Englund E, Brun A, Gustafson L (1989) A white-matter disease in dementia of Alzheimer's type – clinical and neuropathological correlates. *Neurobiol Aging* 4:87–102.
- Fagan AM, Mintun MA, Mach RH, Lee S-Y, Dence CS, Shah AR, LaRossa GN, Spinner ML, Klunk WE, Mathis CA, DeKosky ST, Morris JC, Holtzman DM (2006) Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid A $\beta$ 42 in humans. *Ann Neurol* 59:512–519.
- Formichi P, Battisti C, Radi E, Federico A (2006) Cerebrospinal fluid tau, A $\beta$ , and phosphorylated tau protein for the diagnosis of Alzheimer's disease. *J Cell Physiol* 208:39–46.
- Glasser MF, Van Essen DC (2011) Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. *J Neurosci* 31(32):11597–11616. <http://dx.doi.org/10.1523/jneurosci.2180-11.2011>.
- Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI (1986) Abnormal phosphorylation of the microtubule-associated protein tau (tau) in Alzheimer cytoskeletal pathology. *Proc Natl Acad Sci U S A* 83:4913–4917.
- Grydeland H, Walhovd KB, Tamnes CK, Westlye LT, Fjell AM (2013) Intracortical myelin links with performance variability across the human lifespan: results from T1- and T2-weighted MRI myelin mapping and diffusion tensor imaging. *J Neurosci* 33:18618–18630.
- Grydeland H, Westlye LT, Walhovd KB, Fjell AM (2012) Improved prediction of Alzheimer's disease with longitudinal white matter/gray matter contrast changes. *Hum Brain Mapp* 34:2775–2785.
- Hardy J, Allsop D (1991) Amyloid deposition as the central event in the aetiology of Alzheimer's disease. *Trends Pharmacol Sci* 12:383–388.
- Herrup K, Carrillo MC, Schenk D, Cacace A, Desanti S, Fremeau R, Bhat R, Glicksman M, May P, Swerdlow R, Van Eldik LJ, Bain LJ, Budd S (2013) Beyond amyloid: getting real about nonamyloid targets in Alzheimer's disease. *Alzheimers Dement* 9(452–458):e1.
- Hesse C, Rosengren L, Vanmechelen E, Vanderstichele H, Jensen C, Davidsson P, Blennow K (2000) Cerebrospinal fluid markers for Alzheimer's disease evaluated after acute ischemic stroke. *J Alzheimers Dis* 2:199–206.
- Huang H, Fan X, Weiner M, Martin-Cook K, Xiao G, Davis J, DeVos M, Rosenberg R, Diaz-Arrastia R (2012) Distinctive disruption patterns of white matter tracts in Alzheimer's disease with full diffusion tensor characterization. *Neurobiol Aging* 33:2029–2045.
- Huang J, Friedland RP, Auchus AP (2007) Diffusion tensor imaging of normal-appearing white matter in mild cognitive impairment and early Alzheimer disease: preliminary evidence of axonal degeneration in the temporal lobe. *AJNR Am J Neuroradiol* 28:1943–1948.
- Hyman BT (2011) Amyloid-dependent and amyloid-independent stages of Alzheimer disease. *Arch Neurol* 68:1062–1064.
- Iqbal K, Grundke-Iqbal I (2008) Alzheimer neurofibrillary degeneration: significance, etiopathogenesis, therapeutics and prevention. *J Cell Mol Med* 12:38–55.
- Jack CR, Bernstein MA, Borowski BJ, Gunter JL, Fox NC, Thompson PM, Schuff N, Krueger G, Killiany RJ, DeCarli CS, Dale AM, Carmichael OW, Tosun D, Weiner MW, Alzheimer's Disease Neuroimaging Initiative (2010) Update on the magnetic resonance imaging core of the Alzheimer's disease neuroimaging initiative. *Alzheimers Dement* 6:212–220.
- Kinoshita Y, Ohnishi A, Kohshi K, Yokota A (1999) Apparent diffusion coefficient on rat brain and nerves intoxicated with methylmercury. *Environ Res* 80:348–354.
- Kitamura S, Kiuchi K, Taoka T, Hashimoto K, Ueda S, Yasuno F, Morikawa M, Kichikawa K, Kishimoto T (2013) Longitudinal white matter changes in Alzheimer's disease: a tractography-based analysis study. *Brain Res* 1515:12–18.
- Klaiman G, Petzke TL, Hammond J, LeBlanc AC (2008) Targets of caspase-6 activity in human neurons and Alzheimer disease. *Mol Cell Proteomics* 7:1541–1555.
- Lee G, Neve RL, Kosik KS (1989) The microtubule binding domain of tau protein. *Neuron* 2:1615–1624.
- Liu M, Gross DW, Wheatley BM, Concha L, Beaulieu C (2013) The acute phase of Wallerian degeneration: longitudinal diffusion tensor imaging of the fornix following temporal lobe surgery. *Neuroimage* 74:128–139.
- Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen N-K, Song AW (2012) Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochim Biophys Acta* 1822:386–400.
- Manczak M, Reddy PH (2013) Abnormal interaction of oligomeric amyloid- $\beta$  with phosphorylated Tau: implications to synaptic dysfunction and neuronal damage. *J Alzheimers Dis* 36:285–295.
- McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 7:263–269.
- Mielke MM, Kozauer NA, Chan KCG, George M, Toroney J, Zerrate M, Bände-Roche K, Wang M-C, Vanzijl P, Pekar JJ, Mori S, Lyketsos CG, Albert M (2009) Regionally-specific diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 46:47–55.
- Nowrangi MA, Lyketsos CG, Leoutsakos J-MS, Oishi K, Albert M, Mori S, Mielke MM (2013) Longitudinal, region-specific course of diffusion tensor imaging measures in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement* 9:519–528.
- O'Dwyer L, Lamberton F, Bokde AL, Ewers M, Faluy YO, Tanner C, Mazoyer B, O'Neill D, Bartley M, Collins DR, Coughlan T, Prvulovic D, Hampel H (2011a) Using diffusion tensor imaging and mixed-effects models to investigate primary and secondary white matter degeneration in Alzheimer's disease and mild cognitive impairment. *J Alzheimers Dis* 26:667–682.

- O'Dwyer L, Lambertson F, Bokde AL, Ewers M, Faluyi YO, Tanner C, Mazoyer B, O'Neill D, Bartley M, Collins DR, Coughlan T, Prvulovic D, Hampel H (2011b) Multiple indices of diffusion identifies white matter damage in mild cognitive impairment and Alzheimer's disease. *PLoS ONE* 6:e21745.
- Ramcharitar JM, Afonso V, Albrecht SA, Bennett D, LeBlanc AC (2013) Caspase-6 activity predicts lower episodic memory ability in aged individuals. *Neurobiol Aging* 34:1815–1824.
- Reisberg B, Franssen EH, Hasan SM, Monteiro I, Boksay I, Souren LEM, Kenowsky S, Auer SR, Elahi S, Kluger A (1999) Retrogenesis: clinical, physiologic, and pathologic mechanisms in brain aging, Alzheimer's and other dementing processes. *Eur Arch Psychiatry Clin Neurosci* 249:S28–S36.
- Roberson ED, Scearce-Levie K, Palop JJ, Yan F, Cheng IH, Wu T, Gerstein H, Yu GQ, Mucke L (2007) Reducing endogenous tau ameliorates amyloid-induced deficits in an Alzheimer's disease mouse model. *Science* 316:750–754.
- Roher AE, Weiss N, Kokjohn TA, Kuo Y-M, Kalback W, Anthony J, Watson D, Luehrs DC, Sue L, Walker D, Emmerling M, Goux W, Beach T (2002) Increased A $\beta$  peptides and reduced cholesterol and myelin proteins characterize white matter degeneration in Alzheimer's disease. *Biochemistry* 41:11080–11090.
- Salat DH, Greve DN, Pacheco JL, Quinn BT, Helmer KG, Buckner RL, Fischl B (2009) Regional white matter volume differences in nondemented aging and Alzheimer's disease. *Neuroimage* 44(4):1247–1258. <http://dx.doi.org/10.1016/j.neuroimage.2008.10.030>.
- Salat DH, Tuch DS, Van der Kouwe A, Greve DN, Pappu V, Lee SY, Hevelone ND, Zaleta AK, Growdon JH, Corkin S (2010) White matter pathology isolates the hippocampal formation in Alzheimer's disease. *Neurobiol Aging* 31:244–256.
- Selnes P, Aarsland D, Bjornerud A, Gjerstad L, Wallin A, Hessen E, Reinvang I, Grambaite R, Auning E, Kjærøvik VK, Due-Tønnessen P, Stenset V, Fladby T (2013) Diffusion tensor imaging surpasses cerebrospinal fluid as predictor of cognitive decline and medial temporal lobe atrophy in subjective cognitive impairment and mild cognitive impairment. *J Alzheimers Dis* 33:723–736.
- Sexton CE, Kalu UG, Filippini N, Mackay CE, Ebmeier KP (2011) A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 32. 2322.e5–e18.
- Shepherd TM, Thelwall PE, Wirth ED (2001) Non-lethal disruption of the axonal cytoskeleton alters water diffusion in spinal cord white matter. *Proceedings of the 9th ISMRM*.
- Sjöbeck M, Haglund M, Englund E (2006) White matter mapping in Alzheimer's disease: a neuropathological study. *Neurobiol Aging* 27:673–680.
- Skillbäck T, Zetterberg H, Blennow K, Mattsson N (2013) Cerebrospinal fluid biomarkers for Alzheimer disease and subcortical axonal damage in 5,542 clinical samples. *Alzheimers Res Ther* 5:47.
- Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TEJ (2006) Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage* 31:1487–1505.
- Song S-K, Sun S-W, Ju W-K, Lin S-J, Cross AH, Neufeld AH (2003) Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *Neuroimage* 20:1714–1722.
- Song S-K, Sun S-W, Ramsbottom MJ, Chang C, Russell J, Cross AH (2002) Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17:1429–1436.
- Stenset V, Bjornerud A, Fjell AM, Walhovd KB, Hofoss D, Due-Tønnessen P, et al (2011) Cingulum fiber diffusivity and CSF T-tau in patients with subjective and mild cognitive impairment. *Neurobiol Aging* 32(4):581–589. <http://dx.doi.org/10.1016/j.neurobiolaging.2009.04.014>.
- Stricker NH, Schweinsburg BC, Delano-Wood L, Wierenga CE, Bangen KJ, Haaland KY, Frank LR, Salmon DP, Bondi MW (2009) Decreased white matter integrity in late-myelinating fiber pathways in Alzheimer's disease supports retrogenesis. *Neuroimage* 45:10–16.
- Sun S-W, Liang H-F, Cross AH, Song S-K (2008) Evolving Wallerian degeneration after transient retinal ischemia in mice characterized by diffusion tensor imaging. *Neuroimage* 40:1–10.
- Tapiola T, Overmyer M, Lehtovirta M, Helisalmi S, Ramberg J, Alafuzoff I, Riekkinen P, Soininen H (1997) The level of cerebrospinal fluid tau correlates with neurofibrillary tangles in Alzheimer's disease. *Neuroreport* 8:3961–3963.
- Teipel SJ, Meindl T, Wagner M, Stieltjes B, Reuter S, Hauenstein K-H, Filippi M, Ernemann U, Reiser MF, Hampel H (2010) Longitudinal changes in fiber tract integrity in healthy aging and mild cognitive impairment: a DTI follow-up study. *J Alzheimers Dis* 22:507–522.
- Walhovd KB, Fjell AM, Amlien IK, Grambaite R, Stenset V, Bjornerud A, Reinvang I, Gjerstad L, Cappelen T, Due-Tønnessen P, Fladby T (2009) Multimodal imaging in mild cognitive impairment: metabolism, morphometry and diffusion of the temporal–parietal memory network. *Neuroimage* 45:215–223.
- Waller A (1850) Experiments on the section of the glossopharyngeal and hypoglossal nerves of the frog, and observations of the alterations produced thereby in the structure of their primitive fibres. *Philos Trans R Soc Lond* 140:423–429.
- Westlye LT, Walhovd KB, Dale AM, Bjornerud A, Due-Tønnessen P, Engvig A, Grydeland H, Tamnes CK, Østby Y, Fjell AM (2010) Life-span changes of the human brain white matter: diffusion tensor imaging (DTI) and volumetry. *Cereb Cortex* 20:2055–2068.
- Xiong C, Roe CM, Buckles V, Fagan A, Holtzman D, Balota D, Duchek J, Storandt M, Mintun M, Grant E, Snyder AZ, Head D, Benzinger TLS, Mettenberg J, Csernansky J, Morris JC (2011) Role of family history for Alzheimer biomarker abnormalities in the adult children study. *Arch Neurol* 68:1313–1319.
- Zemlan F, Rosenberg WS, Luebbe PA, Campbell TA, Dean GE, Weiner NE, Cohen JA, Rudick RA, Woo D (2002) Quantification of axonal damage in traumatic brain injury. *J Neurochem* 72:741–750.
- Zetterberg H, Blennow K, Hanse E (2010) Amyloid  $\beta$  and APP as biomarkers for Alzheimer's disease. *Exp Gerontol* 45:23–29.
- Zhuang L, Sachdev PS, Trollor JN, Reppermund S, Kochan NA, Brodaty H, Wen W (2013) Microstructural white matter changes, not hippocampal atrophy, detect early amnesic mild cognitive impairment. *PLoS ONE* 8:e58887.
- Zlokovic BV (2013) Cerebrovascular effects of apolipoprotein E: implications for Alzheimer disease. *JAMA Neurol* 70:440–444.