Free-water elimination for assessing microstructural gray matter pathology - with application to Alzheimer's Disease

Thomas van Bruggen[1], Hui Zhang[2], Ofer Pasternak[3], Hans-Peter Meinzer[1], Bram Stieltjes[4], and Klaus H. Fritzsche[1,4]

[1]*Division of Medical and Biological Informatics, German Cancer Research Center, Heidelberg, Germany,* [2]*Department of Computer Science & Centre for Medical Image Computing, UCL, London, United Kingdom,* [3]*Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States,* [4]*Division of Quantitative Image-based Disease Characterization, German Cancer Research Center, Heidelberg, Germany*

PURPOSE Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that provides microstructural parameters in white matter tissue by measuring water diffusion. One major confounding factor of the technique is partial volume effects of different tissue types and CSF. A recent study of white matter in a group of ageing subjects [1] used the free-water elimination (FWE) technique [3] to demonstrate the risk of misinterpreting macroscopic effects, such as atrophy, as seemingly microscopic alterations, such as cellular malformation. In gray matter, the low diffusion anisotropy makes DTI-based assessment of microstructure even more challenging. Thus, it is difficult to interpret previously reported findings such as alterations of hippocampal DTI measurements in Alzheimer's disease (AD). Here, we apply and compare two multi-compartment techniques, FWE and the recently proposed neurite orientation dispersion and density imaging (NODDI) [2], in order to assess the hippocampal microstructure in AD, and to separate macroscopic atrophic effects from microstructural alterations in the tissue compartments. FWE assumes two compartments to distinguish tissue from CSF and does not require any special acquisition scheme. NODDI differs from FWE in modeling tissue as two compartments to distinguish the intra- and extra-cellular space and requires at least a two-shell acquisition.

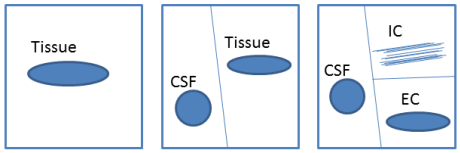

Fig. 1. Schematic depiction of (a) the standard tensor model, (b) the two-compartment model of FWE, and (c) the multi-compartment model with intra- (IC) and extra-cellular space (EC) of NODDI.

METHODS High angular resolution multi-shell diffusion-weighted images (DWI) was obtained from 21 AD patients and 9 healthy controls (HC). 40 non diffusion-weighted volumes and two shells at b-values of 1000 s/mm^2 and 3500 s/mm^2 and 180 directions each were acquired with two repetitions in order to increase SNR. The datasets were corrected for head motion and eddy-currents using FSL. Additionally, T1-datasets were acquired, from which the hippocampi were segmented using Freesurfer and registered with an affine transformation to the DWI datasets in order to serve as volume of interest (VOI) for further analysis.

The standard DTI model, the two-compartment model of FWE, and the NODDI model are illustrated schematically in Fig. 1. The DTI model defines a single compartment. The FWE method adds a CSF compartment that is modeled as an isotropic free diffusion with fractional volume v_{fw}. The remaining tissue compartment is modeled by a diffusion tensor, D_t. The NODDI model also assumes an isotropic CSF compartment (volume fraction v_{iso}). However, the tissue compartment is further divided into an intracellular (IC) compartment (volume fraction $(1-v_{iso})v_{ic}$, also referred to as neurite density), which is modeled as a collection of impermeable sticks, and an extracellular (EC) compartment (volume fraction $(1-v_{iso})(1-v_{ic})$, which is the space surrounding the neurites occupied by glial cells and cell bodies, modeled by a cylindrically symmetric diffusion tensor. NODDI also estimates the orientation dispersion (ODI) of the neurites. All NODDI parameters were extracted based on the two-shell acquisition. The FWE method and standard DTI were applied to the b=1000 s/mm^2 images.

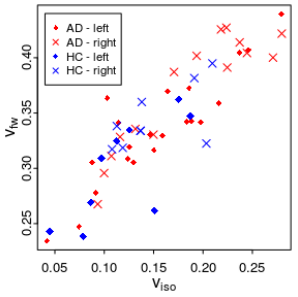

Fig. 2. The isotropic volume fractions as estimated by FWE and NODDI are highly correlating (r=0.91, p<10^{-15})

RESULTS As shown in Fig. 2, we found a high correlation between the FWE and NODDI estimates of the isotropic diffusion compartment in the hippocampus (r=0.91, p<10^{-15}). The FWE estimates of the isotropic volume fraction were consistently higher than the NODDI estimates (see Fig 3a+b). Statistical group comparison by means of t-tests yielded a similar p-value in both cases, v_{iso} (p=0.002) and v_{fw} (p=0.002). v_{iso} and v_{fw} both correlated highly with MD derived from the standard diffusion tensor (r=0.91, p<10^{-15} and r=0.98, p<10^{-15}).

FA was originally introduced as a measure of structural organization. FA_t is a similar measure that is derived from the FWE tensor D_t. NODDI includes two parameters that measure structural organization: ODI and v_{ic} (Fig. 1e). All four measures agreed in not being significantly altered in AD patients (p>0.05).

Hippocampal MD was significantly higher in AD patients when compared to healthy controls (Fig. 1c, p=0.003). Interestingly, after applying FWE, MD_t became significantly lower in AD patients when compared to healthy controls (Fig. 1d, p<10^{-3}). In a further analysis of this finding we found a strong negative correlation between MD_t and neurite density v_{ic} (r=-0.654, p<10^{-7}), whereas MD and v_{ic} did not correlate significantly (r=-0.20, p=0.12). Furthermore, we found a negative correlation between MD_t and v_{fw} (r=-0.59, p<10^{-6}) and between MD_t and v_{iso} (r=-0.70, p<10^{-9}).

DISCUSSION We analyzed the underlying effects of changing DTI indices in AD using two different multi-compartment models of different complexity. Both models supported the finding that the fraction of the free-water compartment is significantly altered in AD, which correlated strongly with changes in MD and implies that this macroscopic effect explains changes in the diffusion tensors. While FWE and NODDI free-water compartments were highly correlated, the values from FWE are quantitatively higher than the values provided by NODDI.

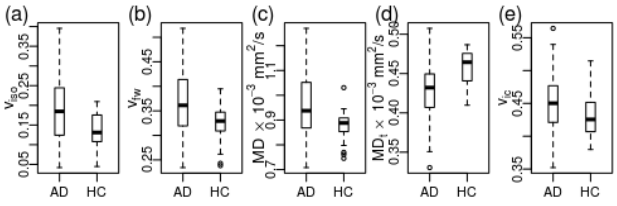

Fig. 3. Boxplots of the isotropic volume fractions, MD (standard and FWE), and neurite density in AD and healthy controls.

This discrepancy may be caused by the fact that the two-shell protocol used here deviates from the optimal acquisition scheme for NODDI, which prescribes lower b-values for both shells (b=700 s/mm^2 and b=2000 s/mm^2). This may also be explained by FWE's assumption of hindered Gaussian diffusion in the tissue compartment, whereas gray matter tissue exhibits both restricted diffusion, in the intra-cellular space, and hindered diffusion, in the extra-cellular space, leading to part of the tissue compartment being misclassified as CSF. Data from the optimized NODDI protocol will be needed to compare the two techniques more definitively. A particularly interesting finding is that the AD group has decreased MD_t. This may be explained by the presence of plaques or other diffusion hindering material in subjects with AD pathology. The strong correlation between MD_t and neurite density suggests that, using the optimized NODDI protocol, the more robustly estimated neurite density may be useful to quantify such pathology directly.

CONCLUSION NODDI and FWE both allow a more in-depth analysis of DTI alterations in AD and, although following very different technical methodologies, agreed in their differentiation of macroscopic and microscopic group effects. Both methods attribute increased MD in AD to an increase in the isotropic water compartment. For CSF estimation, FWE may be advantageous to NODDI, because it works with standard DTI acquisitions. NODDI offers a richer characterization of tissue microstructure beyond CSF estimation and its broad relevance to AD needs to be assessed with data acquired with appropriately optimized multi-shell DWI.

REFERENCES 1) Metzler-Baddeley, et al. Neuroimage 2011 2) Zhang et al., Neuroimage 2012 3) Pasternak et al., MRM 2009