The diagnostic value of template-derived regional DTI metrics in mild cognitive impairment and Alzheimer's disease

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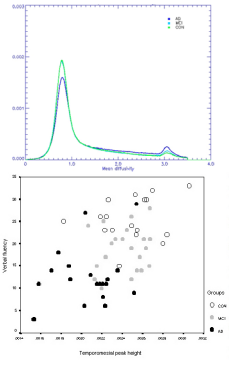
SYNOPSIS: Diffusion tensor imaging can non-invasively and reliably measure microstructural alterations of brain tissue and has proved useful for the characterization of neurodegenerative diseases. In Alzheimer's disease (AD) diffusivity and anisotropy seem to be modulated by the underlying neurobiological processes, making them candidates for surrogate markers. We probed the usefulness of regional histogram-based diffusivity markers for the characterization of the disease progress in terms of clinical stages (controls, mild cognitive impairment [MCI], AD) and cognitive functioning. Histogram analysis separated mild AD, but not MCI from controls. Significant interrelations with memory tests were found across groups, especially for temporomesial parenchymal diffusivity.

INTRODUCTION: Neuroimaging in AD and at-risk syndromes as amnestic mild cognitive impairment is expected to provide tools for early diagnosis, prognosis of conversion to AD and for monitoring disease progression. Diffusion tensor imaging (DTI) can reveal ultrastructural alterations of brain tissue which in the case of AD follow a sequential anatomical order.[1] Studies in AD and MCI so far mostly used manual tracing of regions and attributed diffusivity and anisotropy changes to such AD-related neuropathology.[2-12] In this retrospective cross-sectional study we targeted the question to which degree global and template-derived regional DTI histogram-based quantities parallel the clinical categorization and cognitive performance and may thus assist drug trials as candidate surrogate markers.

METHODS: Subjects: We retrospectively included 19 patients with Alzheimer's disease (AD; 68.6±8.5 yrs, MMSE 22.4 [9–30]), 23 patients with MCI (67.1±6.7 yrs, MMSE 27.5 [22–30]) and 17 healthy elderly control subjects (MCI; 68.9±7.9 yrs, MMSE 28.6 [27–30]). Diagnoses were based on interdisciplinary consensus using medical, neurological and neuropsychological (CERAD battery) findings beside structural MRI, according to Petersen criteria for MCI[12] and DSM-IV and NINCD-ADRDA[13] for AD. Concomitant white matter lesions were tolerated whereas vascular dementia, major neurological disease or depression were exclusion criteria. **Data acquisition and post-processing:** For DTI a spin echo type echo planar imaging sequence with diffusion gradients in six directions was applied (1.5 T, TR 4200 ms, TE 120 ms, matrix 128x128, 24 axial slices, 3 mm thickness, 1 mm gap, 1.875x1.875x4 mm^3; b=0 s/mm^2 [b_0] and b=880 s/mm^2 [3 repeats]). Mean diffusivity (*D*) and fractional anisotropy maps were calculated from the effective diffusion tensor.[14] Data quality and homogeneity was assessed using bootstrap analysis of *D*- and FA-maps[15] delivering 95%-confidence intervals and variation coefficients from each 100 resamples. For the global level a common volume covered by all datasets was determined from the overlap of the normalized (SPM'99) b_0-images; for regional analysis template masks (temporolateral, temporomesial, hippocampal, posterior cingulate) were defined in the parcellation of the MNI MRI single brain and transformed into individual space by applying an inverted deformation matrix gained from the normalization of coregistered b_0-images. Histograms were generated for maps with (D>1.8x10^{-3} mm^2/s) and without (D>3.5x10^{-3} mm^2/s) clearance from macroscopic CSF. From T1-weighted images (124 sagittal slices) brain parenchyma fractions (BPF) of the common volume were calculated using SPM´99 segmentation. **Statistics:** Histogram means and normalized peak heights were tested for group differences (MANCOVA, univariate post-hoc-tests, Bonferroni correction, age and gender as covariates, significance level (SL): 0.05)). Effect sizes of DTI metrics and CERAD scores indicating group overlap were calculated. Interrelations between histogram metrics and selected CERAD tests (delayed verbal recall [DVR], word savings, total word list count, categorial verbal fluency, MMSE) were analysed using partial correlations (SL 0.01) corrected for age.

RESULTS: Bootstrap analysis indicated that for *D* and FA disease effects were dissociated from data quality. *D* was clearly superior to FA in terms of reliability as indicated by smaller average coefficients of variation. We could not identify an effect of AD on global brain FA and focussed on *D* for further analysis. **Group comparisons:** Mild AD could be separated from age-matched controls. In AD we found significantly reduced peaks heights globally (fig., top) and in all subregions (p=[0.001–0.009] and increased mean *D* in the bilateral temporomesial (p=0.001) and posterior cingulate region (p=0.03). AD and CON were best separable using temporomesial peak height (effect size (ES) 1.59), still inferior to DVR test (ES 3.52). MCI could not be differentiated from CON in this study sample. **Interrelations with CERAD** across groups were not significant on the global level, but significant between temporomesial peak heights (fig., bottom) and all subscores (r=[0.390–0.482], p<0.005) and posterior cingulate peak heights and word savings (r=0.435; p=0.001). Correlations with temporomesial *D* were slightly lower. **Effect of *D*-thresholding:** *D*-thresholding at 1.8x10^{-3} mm^2/s resulted in BPFs highly correlated (r=0.83) with those from high resoluted T1-images. Both BPF measures were significantly correlated with mean *D*. Relaxing the CSF-threshold enhanced group differences between AD and CON and slightly increased correlations with CERAD subtests.



DISCUSSION: Histogram diffusivity analysis confirmed the separability of mild AD from controls and showed diffusivity of regional, especially temporomesial metrics to be more strongly interrelated with memory tests than global markers. In this sample, DTI could not detect the subtle neuropathological changes expectable in MCI in contrast to previous reports using manual tracing of the hippocampus [10,11]. In conclusion, template-derived temporomesial DTI metrics proved useful in detecting mild AD, but not MCI and correlates reasonably well with cognitive impairment. They may thus represent a useful adjunct biomarker for predicting the further course in established AD.

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