FREE-WATER CORRECTION REVEALS WIDE SPREAD DIFFERENCES BETWEEN STABLE AND CONVERTING MCI SUBJECTS

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Target audience: This abstract is of relevance for all researchers and physicians working with diffusion weighted MRI based group studies.

Purpose Diffusion tensor imaging (DTI) based studies of amnestic mild cognitive impaired (MCI) subjects suggest microstructural alterations even before the appearance of Alzheimer's disease (AD) symptoms [1]. However, with only some of these MCI subjects ultimately converting to AD, and with the MCI subjects being a very heterogeneous group that might consist of a multitude of different atrophic fingerprints, the predictive value of white matter deterioration as a pre-dementia syndrome is limited and the microstructural interpretation of these findings are challenging. Here we applied the diffusion MRI free-water elimination (FWE) [2] technique to compare a group of MCI patients that converted to AD with a group of patients that did not convert. A previous study demonstrated that FWE is essential to disentangle micro- and macroscopic effects in group comparisons, showing that seemingly microscopic alterations in the aging brain can be explained by changes in free-water content of the voxels, caused by macroscopic changes [3]. Here, we find that FWE increases the sensitivity of recognizing very early abnormalities related to the development of Alzheimer's disease (AD) and are able to classify these alterations as being microstructural as opposed to macroscopic in their nature.

Methods

Imaging: Diffusion weighted imaging was performed on a 1.5T (Symphony, Siemens) for 15 AD patients, 15 healthy controls, and 18 MCI subjects with a clinical follow up of three years, during which 10 patients converted to AD. We applied a twice refocused EPI-DTI with the following parameters: TR/TE 4700/78 ms, FOV 240 mm, in-plane resolution of 2.5 mm, 50 axial slices with a thickness of 2.5 mm and no gap, with 6 gradient directions (b=1000 s/mm²) and a b=0 image. This scheme was repeated 10 times.

Diffusivities estimation: All images were corrected for motion and eddy currents (FSL, FLIRT), while compensating the gradient directions. Images were masked (FSL, BET) and the tensor toolkit was used for tensor estimation (https://gforge.inria.fr/projects/ttk). Free-water corrected tensors and free-water maps were calculated following the methods in [2].

TBSS analysis: The full TBSS pipeline was applied using conventional parameters. A permutation test with n=5000 controlled for age was applied to compare the two groups, with p=0.05 as the threshold for significance. Findings are reported for radial diffusivity from standard DTI as well as from FWE DTI measurements, differentiating regions that were found by both methods in agreement and regions that were found by only one of the techniques.

Results

Fig 1A shows a wide spread increase in radial diffusivity found in AD patients compared to HC, with a large overlap of FWE and DTI findings (shown in yellow). A small fraction of voxels is identified only by one of the indices, either the FWE (red) or the DTI (blue) diffusivities. Fig 1B compares between MCI patients that converted to AD and stable MCI patients. The DTI radial diffusivity shows significant increase only on a small subset of the voxels in the corpus callosum. In contrast, the FWE radial diffusivity shows a wide spread pattern of microstructural alteration in the subjects that will convert to AD, and this pattern is similar to the pattern found for AD patients when compared to controls (compare red and yellow in Fig 1B with red and yellow in Fig 1A).

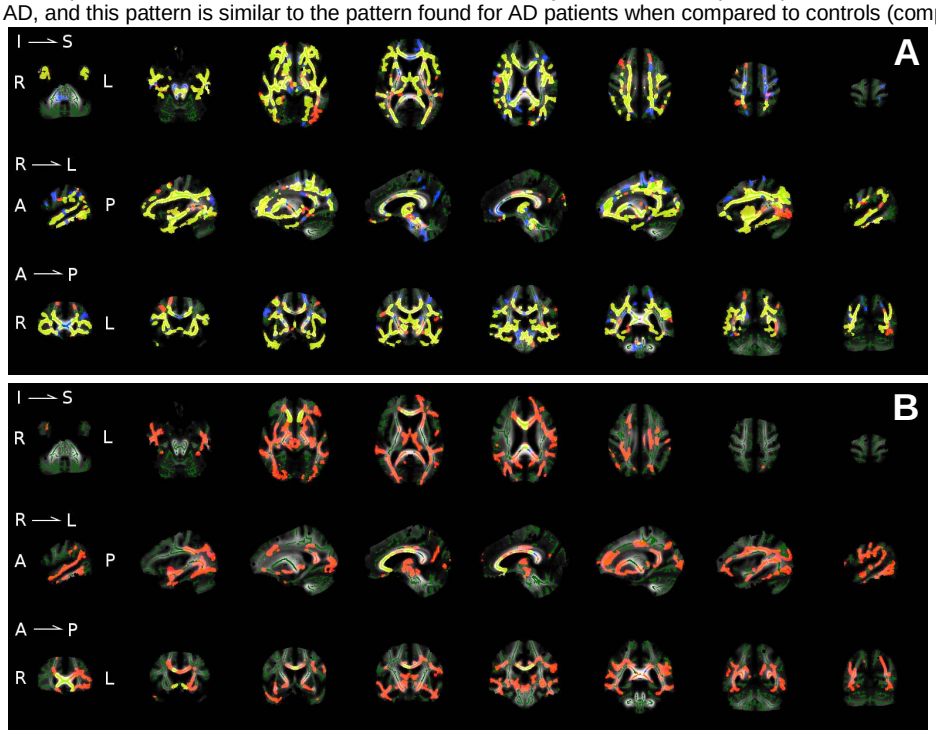

Fig. 1. Differences in radial diffusivity identified by TBSS between (A) Alzheimer patients and healthy subjects and (B) stable and future converting MCI subjects. The FWE reveals that future converting MCI subjects, but not stable MCI subjects, show an abnormality pattern similar to that of AD patients. (Blue - differences found with DTI; Red - Differences found with FWE; Yellow: differences found with both methods, Green: underlying white matter skeleton)

Discussion

By comparing MCI subjects that converted to AD with those that were stable we address an important clinical question of whether MCI subjects with a future conversion to AD already exhibit microstructural changes at the time when they are not yet clinically differentiable from the non-converting MCI subjects. Using FWE we were able to demonstrate that indeed at this early stage of AD there are already widespread alterations, however these alterations are not detected by conventional DTI analysis. The FWE method provides an efficient way to control for volume changes such as those caused by atrophy [3]. Therefore, it is likely that there is large heterogeneity of atrophy levels among the MCI patients that is not specific to those that will convert to AD. When correcting for this heterogeneity, significant microstructural differences emerge, suggesting that the level of axonal deterioration is higher in MCI subjects that will convert to AD. Future research will assess the clinical value of this approach as a diagnostic tool for early detection of AD. Furthermore this approach can be applied on other brain disorders to disentangle the effect of atrophy from that of axonal degeneration.

References:

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