Atlas-based quantification with machine-learning based characterization of DTI from patients with mild cognitive impairment and Alzheimer’s disease

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Introduction Alzheimer’s disease (AD) is the most common cause of dementia in elderly. Palliative treatment and care are the only available options. Disease-modifying treatments are being developed, but the many failed treatment trials among AD patients highlight the importance of targeting therapies to the preclinical and very early clinical phases of AD. MRI-based methods being pursued for early detection of AD-related anatomical alterations have focused on quantitative volume measurement of structures from T1-weighted images, thought to be indicators of neuronal loss. More recent studies suggest the possibility that diffusion tensor imaging (DTI) might be more sensitive than T1-weighted images in detecting early AD pathology. For example, DTI quantification methods such as voxel-based analysis (VBA) and tract-based special statistics (TBSS) have identified spatial distribution of AD-related anatomical changes in early clinical stages. However, these approaches may not be sensitive enough to detect AD pathology in widely distributed brain regions and these methods are not necessarily suitable for detecting abnormalities in single patients. In this study, we applied a machine-learning framework to complement findings from VBM and TBSS. First, we used principal component analysis (PCA) to characterize DTI-detectable anatomical alterations in AD. Next, we used support vector machine (SVM) to investigate a “hyper-plane” that differentiates AD patients from cognitively normal individuals. To systematically reduce the vast amount of anatomical location information (a million voxels in DTI) to a manageable, yet effective, amount suitable for PCA and SVM, we started with an atlas-based approach using an advanced automated technique that can parcellate DTIs into 148 anatomical brain structures to perform structure-by-structure measurements of DTI-derived parameters.

Methods DTI (fractional anisotropy (FA) and mean diffusivity (MD) maps) from 63 participants (19 AD patients, 22 patients with amnestic mild cognitive impairments (aMCI) and 22 cognitively normal, age-matched controls (NC)) were used in the analysis. In the three years after the DTI scan, 6/22 aMCI patients converted to AD (aMCI-C), and 3/22 NC individuals converted to aMCI (NC-C). DTI scans were acquired using a 3T scanner equipped with 8.0 G/cm gradient units. The parameters were: single-shot echo-planar imaging, 30 orientations, b-value 700 s/mm², 50 - 60 gapless whole-brain axial sections of 2.2 mm thickness, matrix 96 x 96, field of view 212 x 212 mm. The JHU-MNI Eve atlas was transformed to each individual’s DTI using affine transformation followed by large deformation diffeomorphic metric mapping. The FA and MD of each brain structure were measured, which resulted in a matrix: (148 structures) x (2 scalar maps), called an atlas-based special statistics (ABM). PCA: PCA was performed on all ABMs. The principal components that correlated with a diagnosis of AD (p < 0.05, corrected for multiple comparison) were extracted. SVM: SVM was trained using ABM from 19 AD patients and 19 NC individuals who were stable for 3 years after the scan. A radial basis function was applied as the kernel, and ten-fold cross-validation was used to assume the classification accuracy. The resultant hyper-plane was then applied to ABM from 22 aMCI patients to investigate the ability to differentiate aMCI-C patients from aMCI patient who remained stable for less 3 years after the scan (aMCI-S). DTI calculations and diffeomorphic transformations were performed with MRIStudio.

Results and Discussion: PCA: The first 46 principal components explained 95% of the variance of ABMs. Among them, the 1st principal component had the strongest correlation with a diagnosis of AD (Spearman’s rank T= -4.97145, p= 5.3987e-06). The projections of the 1st principal component indicated that individuals with aMCI-C or NC-Cs had features similar to those of AD patients (Fig. 1). The vector maps of the 1st principal component indicated brain areas with FA reductions and MD increases related to AD (Fig. 2). SVM: The trained hyper-plane differentiated ADs from NCs with a sensitivity of 0.67, a specificity of 0.95 and a positive likelihood ratio of 15 (ten-fold cross-validation). The hyper-plane differentiated aMCI-C from aMCI-S with a sensitivity of 0.67, a specificity of 1, and a positive likelihood ratio > 67. Atlas-based DTI quantification combined with PCA detected widespread FA reductions and MD increases related to AD and not previously seen in studies using VBM and TBSS. SVM-based classification could rule in future conversion from aMCI to AD with high specificity. Other modalities or methods will be required to increase the sensitivity.

Conclusion: Atlas-based quantification with machine-learning based characterization of DTI detects widespread anatomical alterations related to early AD. This method is applicable to single individuals and could be used to rule in future conversion from aMCI to AD with high specificity. Replication in a different dataset is warranted.

Bibliography:
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Fig.1: Projections of the 1st principal component. Negative values indicate “AD likely.”

Fig.2: Vector maps of the 1st principal component. Weights are relative, and have no applicable units. Widespread FA reductions (upper row) and MD increases (lower row) related to AD, indicated by atlas-based image quantification using PCA.