Multi-modal MRI analysis with disease specific spatial filtering: initial testing to predict mild cognitive impairment patients who convert to Alzheimer's disease

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Introduction Normalization-based image analysis is one of the most effective methods for image quantification and statistical comparison, and has been applied to diffusion tensor imaging (DTI) analysis, as well as conventional T1- and T2- weighted image analyses. To increase the statistical power to detect abnormalities, sophisticated image-filtering methods (or voxel-grouping methods) have been suggested, such as anisotropic smoothing, skeletonization of the white matter structures, and structure-based image parcellation. These methods could possibly increase the statistical power to detect disease-specific change seen on MRI, without an *a priori* hypothesis. However, the choice of an ideal filter depends on the distribution pattern of the pathology, which is disease-specific. Namely, the filter could most effectively detect disease-related changes when the shape and size of the filters exactly follow the true distribution of the pathology. Moreover, the choice of an image modality to be used depends on the histopathological background of the target disease. For example, DTI is suitable for detecting white matter pathology, but inappropriate for detecting cortical atrophy. Therefore, we hypothesized that we could increase the statistical power to separate a specific disease group, with known pathology, from a control group by combining information extracted from multi-modal MRI using disease-specific filters. This concept was tested as an automated method to predict the conversion from amnestic mild cognitive impairment (aMCI) to Alzheimer's disease (AD). First, we created disease-specific filters for each modality (a Jacobian map from T1-weighted image analysis, a T2 map, and DTI-derived scalar maps) and optimized the combination to calculate a disease score (AD score) for each participant to separate AD patients from the control group. Then, the tool was applied to calculate the disease scores of 22 aMCI patients to determine whether the AD score could predict the future conversion to AD.

Methods (1) Tool development: Multi-modal MR images [a Jacobian map from T1-weighted image analysis, a T2 map, and DTI derived maps of fractional anisotropy (FA), mean diffusivity (MD), parallel diffusivity ($\lambda_{||}$), radial diffusivity ($\lambda_{\perp}$), and Jacobian] from 19 AD patients and 22 cognitively normal, age-matched control participants (NC) were used as a training dataset. DWIs were acquired with co-registered MPRAGE and double-echo FSE using a 3T scanner equipped with 8.0 G/cm gradient units. DTI calculation and a diffeomorphic transformation of multi-modal MR images to the JHU-MNI atlas[1] were performed with MRIStudio[2]. A group comparison between AD and NC was performed for each modality using a voxel-wise, two-sample t-test, and the areas with a $p < 0.05$, after correction for multiple comparisons, were binarized (inside 1, outside 0) to serve as an AD-specific spatial filter. A mean value inside the AD-specific filter was measured for each modality and the combination of the values was optimized using Fisher's linear discriminant analysis to calculate the AD score for each participant. (2) Application to aMCI: Multi-modal MR images from 22 aMCI patients were normalized to the JHU-MNI atlas, and the tool was applied to obtain an AD score for each patient. During the three years after the initial scan, 6 out of 22 patients were converted to AD. A receiver operating characteristic (ROC) analysis was performed to identify the AD threshold score that would distinguish converters from non-converters, and the sensitivity and specificity were calculated. To evaluate the efficacy of multi-modal approach, the areas under the curve (AUC) of each ROC curve (multi-modality and single-modality) were compared. (Ken, as meant? This sentence was a little unclear to me, so I changed it, but I'm not sure what you meant exactly…)

Results and Discussion**:** An AD score did predict conversion from aMCI to AD, with a sensitivity of 0.67 and a specificity of 0.81. Pair-wise comparison of the ROC curves demonstrated that there were significant increases ($p < 0.05$) in AUC when we used a multi-modality approach, compared to a single-modality approach. One possible explanation for the better AUC with the multi-modality approach is that each modality could detect different pathologies that are co-existent in AD (e.g., gray matter atrophy, axonal degeneration, demyelination, and vascular pathology) independently, and the combination could capture the overall pathology of AD better than a single modality only.

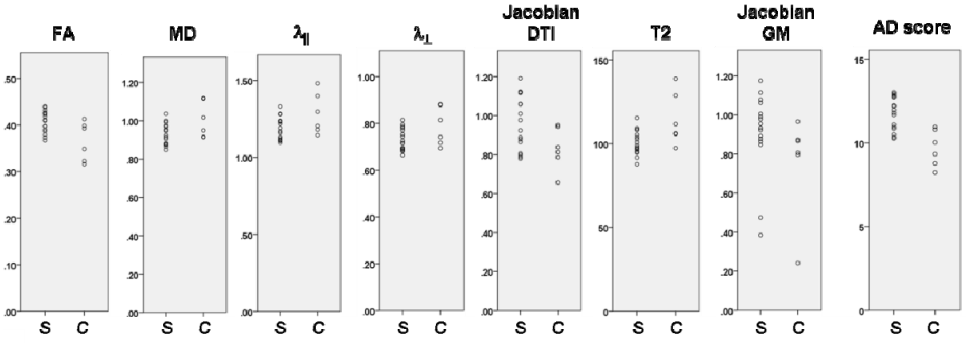

Fig. 1: Comparison of DTI-derived measurements (FA, MD, $\lambda_{||}$, $\lambda_{\perp}$ and Jacobian), T2, Jacobian derived from a T1-weighted image (Jacobian GM), and AD score between aMCI patients who were stable for 3 years after the scans and aMCI patients who converted to AD within 3 years after the scans (c). Each value was measured using a corresponding AD-specific filter. The AD score (multi-modality approach) separated converter from stable aMCI patients better than a single-modality approach.

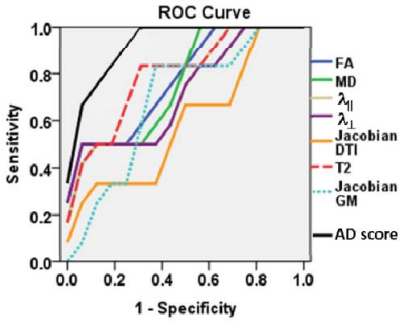

Fig. 2: ROC curves drawn by multi-modality approach (AD score) and single-modality approaches. The AUC of the multi-modality approach was larger than that of single-modality approaches.

Conclusion: Multi-modality MRI analysis, with disease-specific spatial filtering, increased significantly the predictive power to identify aMCI patients who might convert to AD. This method has the potential to quantitatively analyze MRI data to identify patients at risk in clinical settings.

Bibliography:
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