Mapping Ventricular Expansion and its Clinical Correlates in Alzheimer's Disease and Mild Cognitive Impairment using Multi-Atlas Fluid Image Alignment

Yi-Yu Chou[1], Natasha Leporé[1], Christina Avedissian[1], Sarah K. Madsen[1], Xue Hua[1], Clifford R. Jack, Jr. [2], Michael W. Weiner[3], Arthur W. Toga[1], Paul M. Thompson[1], and the Alzheimer's Disease Neuroimaging Initiative

[1] Laboratory of Neuro Imaging, UCLA Department of Neurology, Los Angeles, CA, USA
[2] Mayo Clinic College of Medicine, Rochester, MN
[3] Depts. Radiology, Medicine & Psychiatry, UC San Francisco, San Francisco, CA

Abstract. We developed an automated analysis pipeline to analyze 3D changes in ventricular morphology; it provides a highly sensitive quantitative marker of Alzheimer's disease (AD) progression for MRI studies. In the ADNI image database, we created expert delineations of the ventricles, as parametric surface meshes, in 6 brain MRI scans. These 6 images and their embedded surfaces were fluidly registered to MRI scans of 80 AD patients, 80 individuals with mild cognitive impairment (MCI), and 80 healthy controls. Surface averaging within subjects greatly reduced segmentation error. Surface-based statistical maps revealed powerful correlations between surface morphology at baseline and (1) diagnosis, (2) cognitive performance (MMSE scores), (3) depression, and (4) predicted future decline, over a 1 year interval, in 3 standard clinical scores (MMSE, global and sum-of-boxes CDR). We used a false discovery rate method (FDR) method based on cumulative probability plots to find that 40 subjects were sufficient to discriminate AD from normal groups. 60 and 119 subjects, respectively, were required to correlate ventricular enlargement with MMSE and clinical depression. Surface-based FDR, along with multi-atlas fluid registration to reduce segmentation error, will allow researchers to (1) estimate sample sizes with adequate power to detect groups differences, and (2) compare the power of mapping methods head-to-head, optimizing cost-effectiveness for future clinical trials.

Keywords: brain MRI, fluid registration, segmentation, surface modeling, statistical mapping, Alzheimer's disease, population studies

1 Introduction

Alzheimer's Disease (AD) is the commonest type of dementia [1]; it is characterized by progressive neuronal degeneration and cognitive decline, affecting ~5-10% of those over age 65 and 30-40% of those over 90. Mild cognitive impairment (MCI) is a transitional zone between normal aging and early AD, in which subjects exhibit subtle but measurable cognitive impairments; 6-25% of MCI subjects per year transition to AD [2]. As candidate treatments emerge, imaging measures are vital to track disease progression, to map the anatomical trajectory of AD and MCI-related pathology, and reveal factors (risk genes, treatments) that influence progression.

Ventricular expansion appears to provide the greatest sensitivity [3] as a quantitative marker of disease progression in AD in serial MRI studies. Given the urgent need to quantify factors affecting progression from MCI or normal aging to AD, we developed an automated brain mapping technique to map and analyze lateral ventricular dilation in 80 AD patients, 80 individuals with MCI, and 80 healthy subjects by automatically extracting surface-based 3D anatomical models from MRI databases. We also studied correlations between ventricular morphology and Mini-Mental State Exam, Clinical Dementia Rating global scores, sum-of-boxes scores, ApoE genotype, educational level and depression severity. We correlated baseline ventricular expansion with subsequent clinical decline over a 1-year follow-up period, and evaluated the statistical power of our method by reducing the sample size to determine how many subjects would be sufficient using false discovery rate methods and cumulative distribution functions (CDFs). The ultimate goal of this work is to discover which automated measures of disease burden are optimal for (1) predicting conversion from normality to MCI and MCI to AD, and (2) detecting which therapeutic factors may resist neurodegeneration in drug trials.

2 Materials and Methods

2.1 Subjects

240 subjects were scanned as part of the Alzheimer's Disease Neuroimaging Initiative (http://www.loni.ucla.edu/ADNI/) [4], including 80 healthy, 80 individuals with MCI and 80 individuals with Alzheimer's disease. Each of the three groups (AD, MCI, and controls) were age- and gender-matched as closely as possible. As part of a thorough clinical/cognitive assessment at the time of scan acquisition, each subject's mini-mental state examination (MMSE) score, and global and

"sum-of-boxes" clinical dementia ratings [5] were assessed. Our goal was to create statistical maps correlating ventricular morphology and different covariates of interest, including diagnosis (normal, MCI, AD), MMSE, global CDR, and sum-of-boxes CDR, change (over one year) in MMSE, change in global CDR, change in sum of boxes CDR, the ApoE genotype (which confers risk for AD), depression severity and educational level.

2.2 Automated Lateral Ventricle Segmentation and Shape Modeling

Lateral ventricular volumes were automatically estimated for all scans using a "multi-atlas" technique we recently validated [6]. Briefly, a small subgroup of 6 images (2 AD, 2 MCI and 2 normal) were randomly chosen and the lateral ventricles were manually traced in contiguous coronal brain sections. Lateral ventricular surface models were converted into parametric meshes (we refer to these labeled images as 'atlases') [7]. We fluidly registered each atlas and the embedded mesh models to all other subjects, as in [8], treating the deforming image as a Navier-Stokes viscous fluid, as pioneered by Christensen et al. [9], guaranteeing a diffeomorphic mapping. Fluid transforms were applied to the manually traced ventricular boundary using tri-linear interpolation, generating a propagated contour on the unlabeled images. A mesh averaging technique combined the resulting fluidly propagated surface meshes for each image. A medial curve was derived from the line traced out by the centroid of the ventricular boundary. The local radial size was defined as the radial distance between a boundary point and its associated medial curve. Local surface contractions and expansions were statistically compared at equivalent 3D surface locations between groups.

2.3 Ventricular Statistical Maps and Analysis

Surface contractions and expansions were statistically compared between groups at equivalent locations using Student's *t*-tests (2-tailed), and were correlated with different clinical characteristics including diagnosis, cognitive scores, ApoE genotype, clinical scores, and future decline. The associated *P*-values describing the uncorrected significance of group differences were plotted onto the average surface model, as a color-coded map. To assess the power of our method to establish linkages between morphology and different disease measures, we created cumulative distribution function (CDF) plots of the P-values (The p-values are not independent realizations of a random variable over many trials. Rather, it is from the same imaging dataset at different ventricle boundary surfaces). We used the false discovery rate (FDR) method [10] to assign overall significance values to each statistical map, based on the expected proportions of voxels with intensity above the threshold under the null hypothesis. The value for which the CDF plot intersects with the $y = 20x$ line represents the highest value for which at most 5% false positives are expected in the map (The use y=20x line is related to the fact that the observed p-values are limited to the [0 0.05]). This intersection point is called the *q*-value. The *q*-value gives a single overall measure of significance for each *p*-map. If there is no such intersection point (other than the origin), there is no evidence to reject the null hypothesis. Our empirical CDF of *p*-values is the flip of the more common FDR PP plot.

3 Results

3.1 Linking Ventricular Morphology and Clinical Characteristics

Figure 1 shows *p*-maps for each pairwise diagnosis comparison (AD/MCI/Normal), and correlations between ventricular morphology and MMSE score, global CDR, sum of boxes CDR scores, ApoE genotype, educational level and clinical depression, as covariates. The degree of ventricular expansion is strongly associated with diagnosis (with greatest effects for the AD vs normal comparison), MMSE score and clinical depression. The overall significance of these mapping results was confirmed by FDR analysis (**Figure 2**).

3.2 Predicting Future Cognitive Change

ADNI aims to determine how brain imaging changes predict future clinical decline, primarily for drug trial "enrichment", a statistical strategy that empowers drug trials by selecting as candidates those at highest risk for imminent decline. We correlated baseline ventricular morphology with subsequent change over 1 year, in MMSE, global CDR and sum of boxes CDR scores. **Figure 3a** reveals regions where ventricular expansion correlated with future outcomes; all maps were significant overall after multiple comparisons correction with CDF-based FDR (**Figure 3b**).

3.3 Minimal Effective Sample Sizes

To determine how many subjects would suffice to detect statistically significant correlations of ventricular enlargement with diagnosis and with clinical test scores, we randomly threw out subjects from our initial samples, yielding additional 4 groups with different sample size *N*. These groups were chosen to preserve the 1:1:1 ratio between normal, MCI and AD sample sizes, while maintaining the sex balance in all groups As shown in **Figure 4**, 40 subjects were sufficient to discriminate AD from normal groups. 60 and 119 subjects, respectively, were required to correlate ventricular enlargement with MMSE and clinical depression. These studies will allow researchers to estimate sample sizes with adequate power to detect differences between groups, optimizing cost-effectiveness in future trials.

4 Discussion

MRI-based volumetric studies of MCI and Alzheimer's disease have become increasingly common, with a large portion of the work focusing on medial temporal structures such as the entorhinal cortex and hippocampus that degenerate earliest [11][12]. Recently, cortical thickness analyses [13][14] and tensor-based morphometry (TBM) [15] have also been employed to obtain a better overall picture of pathological structural changes, and there is great interest in ranking methods for statistical power, predictive validity, and automation. Ventricular measures show a relatively high effect size in distinguishing disease from normality, even in groups where overall brain volumes provide poor discrimination. Here we used the benefit of multiple atlas segmentations to decrease segmentation error, and FDR methods applied to surfaces, to estimate minimal sample sizes for several disease tracking hypotheses. The FDR curve ranking method, while not a panacea, is an attractive metric allowing algorithm developers to compare the power of different methods head-to-head with the goal of further reducing the minimal sample sizes.

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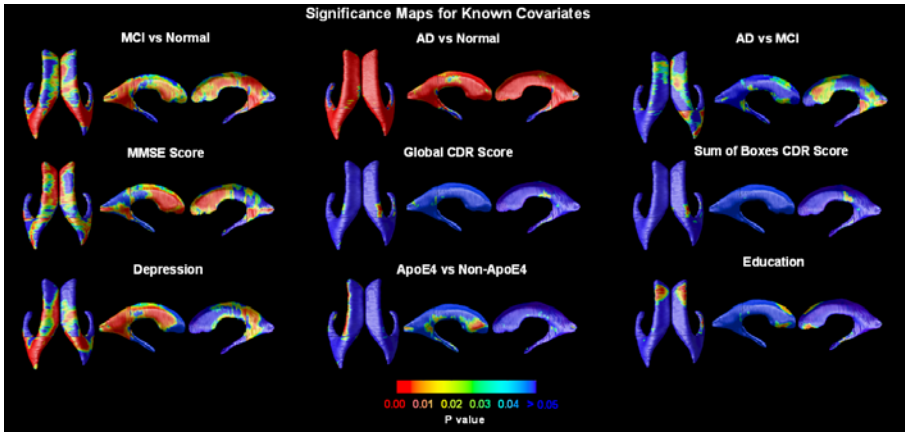

Fig. 1. Significance maps map correlations between local ventricular enlargement and (1) diagnosis (MCI vs. normal, AD vs. normal and AD vs. MCI); (2) cognitive scores (MMSE, Global CDR, and Sum of Boxes CDR); (3) clinical depression scores, (4) ApoE genotype and (5) educational level. **Fig. 2** shows the corrected significance of these maps.

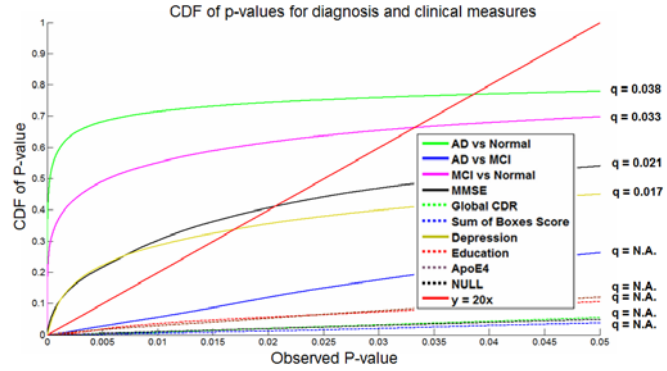

Fig. 2. Cumulative Distribution Functions (CDFs) of significance maps associating ventricular enlargement with diagnosis and clinical measures. Based on FDR q-values, the AD vs. control and MCI vs. control contrast are significant, as are the links between ventricular dilation and (1) MMSE scores, and (2) depression.

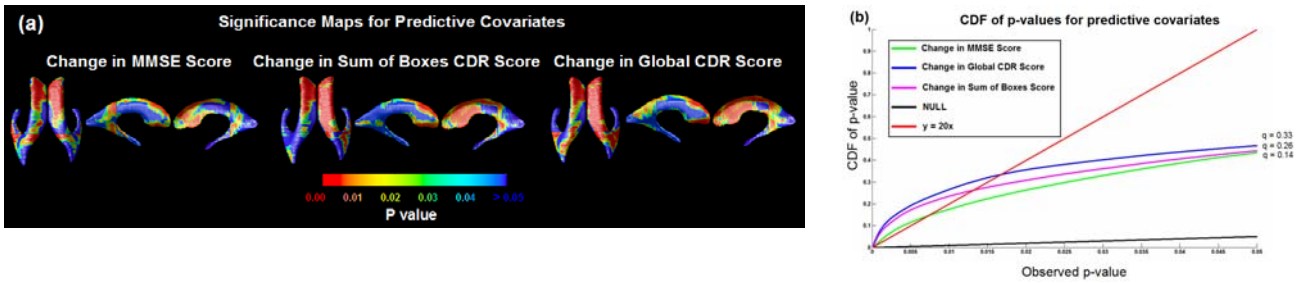

Fig. 3. (a) Significance maps correlate baseline ventricular shape with subsequent decline, over the following year, in 3 commonly used clinical scores. **(b) FDR analysis of future changes.** Correlations were significant between baseline ventricular enlargement and future change in MMSE, Global CDR and Sum of Boxes scores.

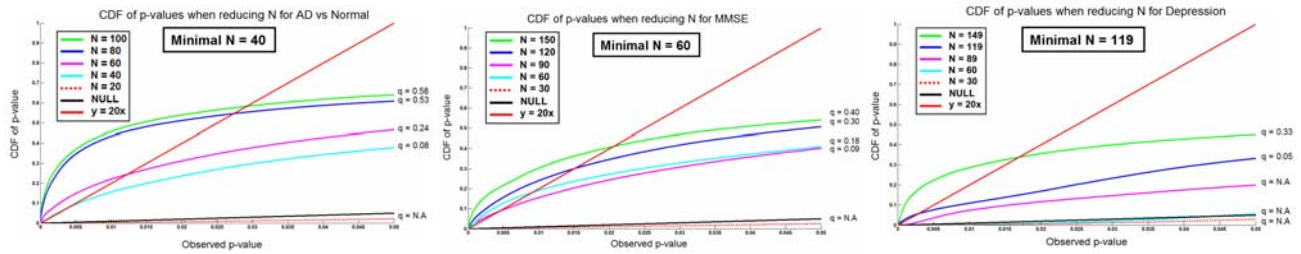

Fig. 4. Effects of Varying the Sample Size. CDFs of *p*-values measuring the effect sizes for discriminating AD from Normal subjects and for other covariates (MMSE and depression scores) as the sample size, N, decreases. *q*-values decrease monotonically with *N*.