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Predicting progression from mild cognitive impairment to Alzheimer's disease using longitudinal callosal atrophy

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Abstract

Introduction: We investigate whether longitudinal callosal atrophy could predict conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD).

Methods: Longitudinal (baseline + 1-year follow-up) MRI scans of 132 MCI subjects from the Alzheimer's Disease Neuroimaging Initiative were used. A total of 54 subjects did not convert to AD over an average (±SD) follow-up of 5.46 (±1.63) years, whereas 78 converted to AD with an average conversion time of 2.56 (±1.65) years. Annual change in the corpus callosum thickness profile was calculated from the baseline and 1-year follow-up MRI. A logistic regression model with fused lasso regularization for prediction was applied to the annual changes.

Results: We found a sex difference. The accuracy of prediction was 84% in females and 61% in males. The discriminating regions of corpus callosum differed between sexes. In females, the genu, rostrum, and posterior body had predictive power, whereas the genu and splenium were relevant in males.

Discussion: Annual callosal atrophy predicts MCI-to-AD conversion in females more accurately than in males.

Keywords: Alzheimer's disease; Mild cognitive impairment; Brain; Corpus callosum; Magnetic resonance imaging; Shape analysis; Longitudinal analysis

1. Introduction

Mild cognitive impairment (MCI) is generally considered as the prodromal phase of Alzheimer's disease (AD). It is of great importance to identify individuals with MCI who are likely to progress to AD in the near future, for it would allow for early intervention.

Significant efforts have been made to find biomarkers that predict conversion from MCI to AD. The potential biomarkers include genetic, CSF proteins, cognitive measurements, glucose metabolism (FDG-PET), and structural/functional brain abnormalities (magnetic resonance imaging [MRI], fMRI). In a comprehensive review of a number of studies, Landau et al. [1] compared these biomarkers in predicting conversion using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI). They found 73%–88% specificity but a disappointing sensitivity of around 40% for all these biomarkers in classification. Another notable study of predicting conversion is that of Killiany et al. [2].

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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They used structural MRI to predict conversion and found the entorhinal cortex, the banks of the superior temporal sulcus, and the anterior cingulate most useful with 75% accuracy, but low specificity 48%. Davatzikos et al. [3] tried the combined information from MRI and CSF biomarkers in prediction and reported top accuracy of 61.7% in their analysis. Thus, more studies are required to find a way to improve the accuracy in predicting MCI-to-AD conversion.

Up to now, almost all efforts have been made based on baseline measures. Given the neurodegenerative nature of AD progression, we conjecture that observing temporal changes in brain structures may improve the accuracy in predicting conversion and provide a measure for the progression to AD. In addition, observing the temporal change within each subject could naturally diminish potential confounding factors in prediction because the progression in AD may depend on factors such as sex, age, education, and diet. The heterogeneity in cohorts may be a reason of poor accuracy in existing classification studies. The insidious manner of progression in AD requires reliable and accurate measures to detect subtle structural changes in the brain over a fairly short time period, say, at most 1 year. The hippocampus and medial temporal lobes are main targets as neuroimaging markers for AD, but measurements to detect subtle changes reliably and accurately are difficult. Therefore, we focus on the corpus callosum (CC) as the mid-sagittal plane cross-sectional area of the CC is well visualized in structural MRI scans and can be reliably measured with good accuracy [4].

The CC is the largest white matter tract interconnecting the cerebral hemispheres. Both cross-sectional and longitudinal studies have reported atrophy of the CC in MCI and AD [4–8]. CC atrophy has been proposed as a consequence of two possible mechanisms: direct myelin breakdown [9,10], and Wallerian degeneration wherein callosal fibers are lost as a result of distal injury to the callosal projecting neurons [11]. However, the use of longitudinal CC atrophy to predict future MCI conversion to AD has not been studied extensively.

Therefore, this study aims to investigate whether patterns of longitudinal CC atrophy predict conversion from MCI to AD. To the best of our knowledge, this is the first attempt to predict future MCI conversion to AD using longitudinal structural callosal change from MRI scans. For this purpose, we used longitudinal scans from 132 MCI subjects in ADNI. Annual change in CC thickness profile was calculated for each subject from two MRI scans that were 1 year apart. A logistic regression model with fused lasso regularization [4] was trained on the callosal thickness profiles and used for predicting conversion.

2. Methods

2.1. Subjects

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). The primary goal of the ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. The Principal Investigator of the ADNI is Michael W. Weiner, MD, VA Medical Center and University of California-San Francisco. The first phase, ADNI1, was intended to enroll 800 subjects, including normal controls, MCI, and AD subjects. For up-to-date information, see www.adni-info.org.

In our longitudinal study of CC atrophy we used the ADNI1 "3-year complete standardized data set" [12], which includes 1.5-T longitudinal structural MRI scans from 148 individuals initially diagnosed as MCI. Summaries of demographic and diagnostic data were downloaded in October, 2013. We divided the MCI subjects into two groups, those whose diagnoses indicated a conversion to AD at any time within 3 years after their initial evaluation (mild cognitive impairment-converted [MCI-C]) and those who did not convert (mild cognitive impairment-nonconverted [MCI-NC]) during the follow-up period. Note that the later group includes subjects who may convert at a later unknown time or not convert at all. Therefore, our classification can be considered to be between incipient AD patients vs. "others". ADNI1 followed nonconverters for up to 7.5 years (mean = 5.5, SD = 1.6). In ADNI1, the subjects were classified as MCI when their Mini-Mental State Examination (MMSE) score was between 24 and 30 (inclusive) and had a memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a clinical dementia rating (CDR) of 0.5, absence of significant levels of impairment in other cognitive domains, especially preserved activities of daily living, and an absence of dementia. The subjects were considered as mild AD if their MMSE score was in the 20–26 range (inclusive), had a CDR of 0.5 or 1.0, and met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD. Cognitive assessment and imaging were conducted at baseline, 6 months, and 12 months, and yearly thereafter [13]. Preliminary examination showed a difference in the sex ratio between the MCI-C and MCI-NC groups. A description of the demographic data is given in Table 1.

2.2. MRI imaging

Subject scans were 1.5 T, T1-weighted magnetization prepared rapid gradient echo images, using matrix sizes of 192 × 192 × 160–170 or 256 × 256 × 166–184. The in-plane voxel dimensions were 0.94 to 1.25 mm, whereas the slice thickness was kept very close to 1.2 mm. Repetition