Longitudinal Changes in the Centroid Size of the Corpus Callosum as a New Biomarker for Diagnosis of Alzheimer's Disease

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Introduction

Pathologic abnormalities in Alzheimer's disease (AD) appear to begin 10-20 years before cognitive symptoms. Although currently no treatment can significantly alter the course of the disease, several neuroprotective therapeutic agents are in clinical trial that promise to slow the disease process. Thus, it is critical to identify affected individuals while they are still cognitively normal, prior to overt synaptic and neuronal loss, so new therapies have a chance to preserve normal brain function. Most imaging studies on the prodromal phase of AD have focused on alterations in the medial temporal lobe, including the hippocampus and entorhinal cortex. This abstract proposes a new biomarker that separates AD from normal aging based on longitudinal structural MRI scans. The biomarker is the relative change with respect to time of the *centroid size* (S) of the mid-sagittal cross-sectional area of the corpus callosum (CC). Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we show that S *increases* with time in both normal aging and AD. However, the change in S (ΔS) is significantly greater in AD as compared to normal control (NC) subjects. Therefore, we suggest that ΔS can be used as a reliable biomarker to predict conversion from mild cognitive impairment (MCI) to AD.

Table 1: Subject demographics

	Sex (M, F)	Mean age at BL (years)
AD (n=23)	12, 11	73.53 ± 2.18
MCI (n=23)	11, 12	73.69 ± 2.39
NC (n=23)	11, 12	73.67 ± 2.20

MRI Data

We obtained 69 pairs of longitudinal pre-processed high-resolution T1-weighted scans from the ADNI database (http://adni.loni.ucla.edu). Each pair consisted of a baseline (BL) scan and a two-year follow-up (FU) scan. Subject demographics are shown in Table 1. The average period between the BL and FU scans was 2.08 ± 0.07 years. Of the 23 MCI subjects, 11 had converted to AD after two years, while the diagnosis of the rest remained unchanged.

Image Analysis

The images were skull-stripped using the *brainwash* module of the ART package (http://www.nitrc.org/projects/art) to estimate the intra-cranial volume (ICV). A newly developed multi-atlas-based automatic CC segmentation method (submitted as a separate abstract) was used to find the cross-sectional region of the CC on the mid-sagittal section of the brain. Figure 1 shows an example of the detected CC on BL and FU scans of an AD patient. Two measures were calculated from the detected CC: the area (A) and the centroid size (S). To compute S, m=200 uniformly sampled landmarks $\mathbf{x}_i$ (i=1, 2, …, 200) were located on the perimeter of the CC with the first landmark $\mathbf{x}_1$ being the tip of the rostrum of the CC. The remaining landmarks were obtained by computing the *Fourier descriptors* of the border of the CC and sampling the truncated Fourier series fit at uniform intervals equal to 0.5% of the circumference. The centroid size is essentially the root-mean-square of the distances between the centroid and the landmarks, given by: $S = \sqrt{(1/m)\sum_i \|x_i - \bar{x}\|^2}$.

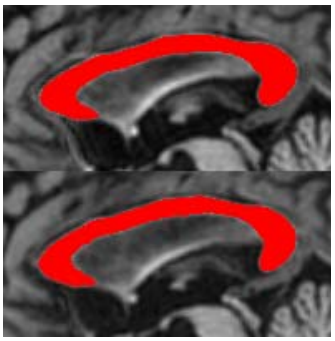

Figure 1: Automatically detected CC on BL (top) and FU (bottom) scans in an AD patient. At BL: A = 604.25 mm^2 and S = 484.35 mm; at FU: A = 589.25 mm^2, and S = 495.58 mm.

Statistical Analysis

The ICV was correlated with A at both BL (r=0.385; p=0.001) and FU (r=0.362; p=0.002); and with S at both BL (r=0.477; p<10^{-4}) and FU (r=0.475; p<10^{-4}). Thus we used the ICV as a covariate in a general linear model to determine whether A, or S, are different between groups at BL or FU. This analysis revealed no statistically significant differences between A or S either at BL or FU. We then applied paired samples t-tests to determine whether there are changes in time in A or S. In all three groups, area significantly decreased (Table 2) and S significantly increased (Table 3) from BL to FU. Next, we applied a one-way ANOVA to determine whether the significant longitudinal changes in A or S are different between the three groups. No significant differences in ΔA were found between the three groups. However, one-way ANOVA revealed statistically significant differences in ΔS (F=3.46; p<0.037) between the three groups. Post-hoc independent-samples t-tests showed that ΔS is significantly larger in AD as compared to NC (p=0.006). However, the MCI group was not significantly different from either the AD or NC groups. Next, we examined whether ΔS can be used to classify the MCI subjects into converters or non-converters to AD. Using the results in Table 3, we used the threshold of ΔS>4 mm to indicate conversion to AD. This simple criterion correctly classified 18 of the 23 MCI cases (9 converters and 9 non-converters) for an overall accuracy of 78%.

Table 2: Change in CC area in 2 years

	mean ΔA (mm^2)	95% CI	P-value
AD	-11.1	(-15.6, -6.5)	<10^{-4}
MCI	-9.4	(-17.9, -0.8)	<10^{-4}
NC	-10.6	(-14.6, -6.5)	0.033

Table 3: Change in CC centroid size in 2 years

	mean ΔS (mm)	95% CI	P-value
AD	6.3	(4.0, 8.7)	<10^{-4}
MCI	5.1	(2.3, 8.0)	0.001
NC	2.2	(0.3, 4.1)	0.023

Discussion

Our analysis revealed that both normal aging and AD are associated with significant CC atrophy as well as significant increase in the centroid size of the CC which likely reflects overall brain atrophy. However, while CC area change ΔA does not differentiate between AD and NC subjects, the change in centroid size ΔS in two years is significantly greater in AD relative to NC subjects. In fact, as can be seen in Table 3, there is very little overlap between the 95% confidence intervals (CI) of ΔS in AD (4.0, 8.7) and NC (0.3, 4.1). The variability in the evolution of S in time is larger in MCI (95% CI: 2.3 – 8.0) than the other groups. This reflects the fact that the MCI group includes a combination of individuals with normal aging as well as those affected by early AD. The main finding of this paper is that ΔS may be an indirect index of brain atrophy which can be precisely and automatically measured and is useful as a biomarker of AD. This index increases with age in both normal aging and AD, however, the rate of increase in AD is significantly higher than in normal controls. This index therefore has potential as a diagnostic marker for predicting conversion to AD in MCI subjects.

Conclusion

The main conclusion of this paper is that an increase of greater than 4 mm in S over a period of 24 months is a strong indication of conversion from MCI to AD. However, CC atrophy measured by its area is present in both AD and normal aging to the extent that it cannot be used to distinguish between the two.

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