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High-dimensional morphometry

Integrated cortical structural marker for Alzheimer's disease

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ABSTRACT

In this article, we propose an approach to integrate cortical morphology measures for improving the discrimination of individuals with and without very mild Alzheimer's disease (AD). FreeSurfer was applied to scans collected from 83 participants with very mild AD and 124 cognitively normal individuals. We generated cortex thickness, white matter convexity (aka "sulcal depth"), and white matter surface metric distortion measures on a normalized surface atlas in this first study to integrate high resolution gray matter thickness and white matter surface geometric measures in identifying very mild AD. Principal component analysis was applied to each individual structural measure to generate eigenvectors. Discrimination power based on individual and combined measures are compared, based on stepwise logistic regression and 10-fold cross-validation. Global AD likelihood index and surface-based likelihood maps were also generated. Our results show complementary patterns on the cortical surface between thickness, which reflects gray matter atrophy, convexity, which reflects white matter sulcal depth changes and metric distortion, which reflects white matter surface area changes. The classifier integrating all 3 types of surface measures significantly improved classification performance compared with classification based on single measures. The principal component analysis-based approach provides a framework for achieving high discrimination power by integrating high-dimensional data, and this method could be very powerful in future studies for early diagnosis of diseases that are known to be associated with abnormal gyral and sulcal patterns.

1. Introduction

Progressive gray matter atrophy that spreads from the medial temporal lobe to the parietal and prefrontal cortices is a prominent characteristic of the neurodegeneration that accompanies Alzheimer's disease (AD) (Braak and Braak, 1991). Disruption of white matter integrity and decreases in white matter volume have also been observed around the temporal lobe, corpus callosum and inferior longitudinal fasciculus in AD patients (Guo et al., 2010), and around bilateral parahippocampal and temporal gyri in individuals with mild cognitive impairment (MCI) (Stoub et al., 2006; Xie et al., 2006). Moreover, a recent study found white matter integrity degradation in cognitively normal individuals at risk for amnestic MCI, whereas gray matter structures were relatively preserved in these individuals (Zhuang et al., 2012). These results indicate that white matter changes may be induced by different pathologic origin compared with gray matter atrophy. And these local white matter volume and integrity changes are likely associated with geometric distortion to the white matter surface. Taken together, cortical geometric features, which represent white matter atrophy, and cortical gray matter thickness may provide complementary information on AD progress. Therefore, integrating these features may increase predictive power for identifying patients with AD at an early stage.

Recent developments of surface-based modeling (SBM) in magnetic resonance imaging (MRI) (Apostolova and Thompson, 2008; Dickerson et al., 2011) have enabled us to capture subtle changes of geometric features of the cortical mantle. As an alternative to widely used region of interest (ROI) analysis (Jack et al.,

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1999) and voxel-based morphometry (Hamalainen et al., 2007), these surface-based methods model the cortical gray matter mantle and its interfaces with the white matter and cerebrospinal fluid as geometrical mesh structures. SBM achieves inter-subject registration of individual cortical mantle surfaces to a template based on high-dimensional diffeomorphic maps (Apostolova and Thompson, 2008; Fischl et al., 1999; Miller, 2004), providing gray matter thickness measures sensitive to submillimeter changes in neuropsychiatric diseases (Im et al., 2008).

Several studies have shown that combined multivariate or multimodal data—structural MRI including cortical thickness, volume, and tensor-based morphemotry, functional MRI, FDG-PET, and nonimaging data including cerebrospinal fluid biomarker and neurocognition—could improve diagnostic power (Desikan et al., 2009; Fan et al., 2008; Hinrichs et al., 2011; Kim and Lee, 2012; Park et al., 2012; Zhang et al., 2011), and combining cortical gray matter thickness and white matter surface measures could increase prediction accuracy in autism (Ecker et al., 2010). In this article, we present the first study to integrate cortical white matter surface geometric and cortical thickness measures on the cortical surface vertices to discriminate very mild AD from cognitively normal controls. SBM was used to generate the following 3 cortical measures: (1) thickness, which reflects gray matter atrophy; (2) convexity, which reflects white matter sulcal depth changes; and (3) metric distortion, which reflects white matter surface area changes. The surface geometric measures (i.e., convexity and metric distortion) reflect the widening and shallowing of the cortical folding pattern. As these cortical measures represent related but different aspects of neuropathologic changes, we hypothesized that integrating surface geometric measures along with cortical thickness would increase the power of discriminating individuals with very mild AD from age-matched healthy subjects.

2. Methods

2.1. Participants

Participants from the Knight Alzheimer Disease Research Center at Washington University School of Medicine were included this study. All participants were administered the Clinical Dementia Rating scale (CDR) (Morris, 1993) and diagnosis and staging of dementia of the Alzheimer type (McKhann et al., 1984). Within our sample, 124 individuals received a CDR of 0 (i.e., controls), and 83 received a CDR of 0.5 with a concurrent diagnosis of dementia of the Alzheimer type (i.e., very mild AD). Demographic data are reported in Table 1.

2.2. MRI acquisition and image processing

All MR scans were collected on a 1.5-Tesla Siemens VISION system. The MR scanning protocol included the collection of 2–4 3D magnetization-prepared rapid acquisition with gradient echo (MPRAGE) volumes (repetition time = 9.7 ms, echo time = 4.0 ms, flip angle = 10°, voxel resolution 1 × 1 × 1.25 mm^3, acquisition time = 6.5 minutes per scan). The MPRAGE scans for each subject were aligned with the first and averaged to create a low-noise image volume.

Table 1
Demographic data of all subjects

	Cognitively normal control (CDR = 0), N = 124	Very mild AD (CDR = 0.5), N = 83	Comparison (p value)
Gender (M/F)	42/82	40/43	$\chi^2 = 4.26$, $p = 0.039$
Age (mean/SD)	74.7 ±10.2	75.0 ± 8.6	t = −0.23, $p = 0.82$

Key: AD, Alzheimer's disease; CDR, clinical dementia rating.

All MR images were processed using FreeSurfer (FS) v4.0.2. Manual quality assurance procedures were carried out by a trained rater to correct geometric inaccuracies or topologic defects. Although on average 30–60 minutes were required to complete the quality assurance procedure per scan, we did not record the exact time or type of correction and the rater was blinded as to the CDR of the subjects. It would have been valuable to know whether more clinically severe cases required more correction.

In this study, the following 3 cortical measures were provided by FS:

- Cortical thickness (thk), calculated as the shortest distance between the pial surface and white surface at each vertex.
- Average convexity (sulc), calculated as the integral movement distance of each white surface vertex during spherical inflation. It captures large-scale geometric features and in the meantime is insensitive to small-scale local noise (Fischl et al., 1999).
- Local metric distortion (Jacobian), calculated as the ratio of a triangle on the registered sphere and the triangle on the white surface (before spherical inflation), normalized for the total area of the white surface (Wisco et al., 2007).

These parameters capture complementary information of the cortical surface (i.e., cortical mantle thickness, white surface folding depth, and surface area distortion) for each participant. They were registered and reindexed into FS's template "fsaverage" surface during the spherical surface inflation and registration process, followed by 20-mm FWHM smoothing kernel. We chose a relatively small smoothing kernel size (as opposed to 35 mm) to allow for good localization and sensitivity while reducing the impact of registration misalignment because of the relatively large sample size (Lerch and Evans, 2005).

2.3. Statistical analysis

Multiple surface-based cortical measures suffer from dimensionality problems with 163,842 vertices for each hemisphere. This oversampling problem (i.e., the number of variables being far larger than the number of observations) can lead to unreliable classifier performance (Duin, 2000; Park et al., 2012; Ramirez et al., 2010). Several machining learning methods, such as partial least squares (Andersen et al., 2012; Ramirez et al., 2010; Thiele et al., 2013; Westman et al., 2011, 2012) and support vector machine (Davatzikos et al., 2008; Fan et al., 2008; Kloppel et al., 2008; Lerch et al., 2008; Magnin et al., 2009; O'Dwyer et al., 2012; Plant et al., 2010; Wee et al., 2011), which can extract feature variables based on subjects' label structure, have demonstrated to be effective in data dimensionality reduction while achieving good classification performance. These learning methods have been developed into a variety of algorithms that have been applied to both structural and functional MR data in studies of AD and MCI patients.

The more traditional but effective way to reduce data dimensionality while preserving topographical distribution is to use manifold-learning method, such as principal component analysis (PCA). The PCA procedure on surfaces has been described in detail in Joshi et al. (1997); Wang et al. (2001) and applied extensively by our group for analysis of deformation-based subcortical structural shape (Csernansky et al., 2004a; Goldman et al., 2011; Mamah et al., 2012; Wang et al., 2001, 2003, 2007). Here, we applied this method to the analysis of cortical thickness and geometric measures, indexed on the "fsaverage" template surface where all subjects' vertices were in correspondence via the previously mentioned registration and reindexing procedure. Because the