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Neuroimaging

Prediction of Alzheimer's disease pathophysiology based on cortical thickness patterns

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Abstract

Introduction: Recent studies have shown that pathologically defined subtypes of Alzheimer's disease (AD) represent distinctive atrophy patterns and clinical characteristics. We investigated whether a cortical thickness–based clustering method can reflect such findings.

Methods: A total of 77 AD subjects from the Alzheimer's Disease Neuroimaging Initiative 2 data set who underwent 3-T magnetic resonance imaging, [^{18}F]-fluorodeoxyglucose-positron emission tomography (PET), [^{18}F]-Florbetapir PET, and cerebrospinal fluid (CSF) tests were enrolled. After clustering based on cortical thickness, diverse imaging and biofluid biomarkers were compared between these groups.

Results: Three cortical thinning patterns were noted: medial temporal (MT; 19.5%), diffuse (55.8%), and parietal dominant (P; 24.7%) atrophy subtypes. The P subtype was the youngest and represented more glucose hypometabolism in the parietal and occipital cortices and marked amyloid-beta accumulation in most brain regions. The MT subtype revealed more glucose hypometabolism in the left hippocampus and bilateral frontal cortices and less performance in memory tests. CSF test results did not differ between the groups.

Discussion: Cortical thickness patterns can reflect pathophysiological and clinical changes in AD.

Keywords: Alzheimer's disease; Cortical thickness; Alzheimer's Disease Neuroimaging Initiative; Magnetic resonance imaging; Positron emission tomography

1. Introduction

Aggregations of amyloid-beta (Aβ) and tau protein are the two main pathologic hallmarks of Alzheimer's disease (AD). Although the aggregation of Aβ is known to precede the tau pathology in AD, the earlier role of tau aggregation in the pathogenesis of AD and aging has been reemphasized [1,2]. The accumulation of tau has been noted in the transentorhinal cortices with normal aging and such tau aggregation is known to accelerate the spread of Aβ pathology in the AD brain [1–3]. Moreover, the accumulation of tau proteins

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[1]All the data used in preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). 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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correlates very closely with cognitive decline and brain atrophy including hippocampal atrophy [4,5]. Hence, defining AD based on the tau pathology in the brain would enable a better understanding of the clinical implications of tau accumulation in this disease.

Recently, neuropathologically defined subtypes of AD have represented distinctive clinical characteristics and brain structural changes such as (1) typical generalized atrophy involving medial temporal (MT) lobes; (2) limbic predominant atrophy; (3) and hippocampus-sparing atrophy [6,7]. Because pathologic assessment cannot be easily applied to most of AD subjects in vivo, our group recently investigated whether clustering of AD subjects based on magnetic resonance imaging (MRI) cortical thickness patterns can replicate autopsy-based findings. Interestingly, the MRI cortical thickness pattern–based clustering was comparable with the autopsy-based classification of AD in an earlier report [8]. However, there was no assessment in that previous study as to whether the new clustering method based on cortical thickness patterns can also reflect pathophysiological changes in AD. If so, this would potentially provide additional clinical information on structural brain magnetic resonance (MR) images and, thus, further knowledge of the underlying pathogenesis as well as prognosis of the disease.

We investigated whether the new cortical thickness–based clustering methodology could be replicated in a multicenter, international data set. We also sought to determine whether this clustering method reflected the pathophysiological status of AD as assessed by [^{18}F]-fluorodeoxyglucose (FDG)-positron emission tomography (PET), [^{18}F]-Florbetapir PET, and cerebrospinal fluid (CSF) Aβ and tau protein tests.

2. Methods

2.1. Participants

Data used for the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI is described in Supplementary Methods. We selected 89 AD subjects from the ADNI-2 study who had high-resolution 3-T T1-weighted MRI, baseline FDG-PET, baseline Florbetapir-PET, and available baseline CSF results. Among these 89 subjects, 12 cases were excluded because of segmentation errors in MRI cortical thickness analysis and a total of 77 subjects were included for analyses. For comparison and to obtain representative MR images of each group, we also used data from 42 subjects with normal cognition in the ADNI-2 who underwent the baseline and 2 year follow-up imaging and baseline CSF studies and remained normal at 2-year follow-up assessments.

2.2. Image analysis

2.2.1. MRI analysis

2.2.1.1. MRI acquisition

We followed ADNI procedure in our current analysis. Briefly, we used screening 3-T T1-weighted MRI sequence with rapid gradient echo (MPRAGE) images with a 1.2-mm-slice thickness. Subjects who underwent 1.5 T MRI or MRI sequence with enhanced spoiled gradient were not included because of greater signal-to-noise ratio or less compatibility between sequences. All data were downloaded from LONI (as of October 2014). Additional details regarding data acquisition are available elsewhere (http://www.adni-info.org).

2.2.1.2. Measurements of cortical thickness

The cortical thickness of the initial cohort of 89 AD subjects was measured as described previously [9]. Three-Tesla T1-weighted MRI images were processed using a standard Montreal Neurological Institute (MNI) anatomic pipeline (version 1.1.9; http://wiki.bic.mni.mcgill.ca/index.php/CIVET). We registered all native volumetric T1 images into a standardized stereotaxic space using a linear transformation [10]. An N3 algorithm was used to correct for intensity nonuniformities using inhomogeneities in the magnetic field [11]. The corrected volumetric images were then classified into white matter, gray matter (GM), CSF, and background using an Intensity-Normalized Stereotaxic Environment for Classification of Tissues algorithm [12]. The surfaces of the inner and outer cortices were automatically extracted using a Constrained Laplacian-Based Automated Segmentation with Proximities algorithm [13]. Finally, the Euclidean distances between linked vertices on the inner and the outer surface were calculated for the cortical thickness measurement [14].

2.2.1.3. Cluster analyses

We performed hierarchical agglomerative cluster analysis using Statistics and Machine Learning Toolbox implemented in MATLAB version 8.2.0.29 R2013b (MathWorks, Natick, MA, USA) in which each patient begins in his or her own cluster and at each step the two most "similar" clusters are combined until the last two clusters are combined into a single cluster with all patients. We used the whole-brain cortical thickness for the clustering: a total of 78,570 vertex points (without noncortical regions) for each of the 77 AD subjects. To cluster patients according to the thinning patterns of each cortical region, rather than a global atrophy, the variations in global atrophy between patients were compensated for by normalizing the cortical thickness values from vertices to a mean cortical thickness [15]. The Ward's clustering linkage method [15,16] was used to combine pairs of clusters. The clustering begins with each patient in his or her own cluster (n = 77, size 1 each). At each step, the Ward's method chooses which pair of clusters to be combined next by merging the pair of clusters while minimizing the sum of square errors (the two most similar clusters) from the cluster mean. For instance, n-1 clusters are formed in the first step (one cluster of size 2). Then, n-2 clusters are formed in the second step (two clusters of size 2 or one cluster of size 3 including the cluster formed in step 1). The algorithm continues until all patients are merged into a single large cluster (size n). Finally, each of the 77 AD patients was placed in their own cluster and then progressively clustered with others. The cluster analysis results are shown as a dendrogram (Fig. 1).