The cortical signature of prodromal AD
Regional thinning predicts mild AD dementia

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ABSTRACT

Objective: We previously used exploratory analyses across the entire cortex to determine that mild Alzheimer disease (AD) is reliably associated with a cortical signature of thinning in specific limbic and association regions. Here we investigated whether the cortical signature of AD-related thinning is present in individuals with questionable AD dementia (QAD) and whether a greater degree of regional cortical thinning predicts mild AD dementia.

Methods: Participants included 49 older adults with mild impairment consistent with mild cognitive impairment (Clinical Dementia Rating [CDR] = 0.5) at the time of structural MRI scanning. Cortical thickness was measured in nine regions of interest (ROIs) identified previously from a comparison of patients with mild AD and controls.

Results: Longitudinal clinical follow-up revealed that 20 participants converted to mild AD dementia (progressors) while 29 remained stable (nonprogressors) approximately 2.5 years after scanning. At baseline, QAD participants showed a milder degree of cortical thinning than typically seen in mild AD, and CDR Sum-of-Boxes correlated with thickness in temporal and parietal ROIs. Compared to nonprogressors, progressors showed temporal and parietal thinning. Using receiver operating characteristic curves, the thickness of an aggregate measure of these regions predicted progression to mild AD with 83% sensitivity and 65% specificity.

Conclusions: Thinning in specific cortical areas known to be affected by Alzheimer disease (AD) is detectable in individuals with questionable AD dementia (QAD) and predicts conversion to mild AD dementia. This method could be useful for identifying individuals at relatively high risk for imminent progression from QAD to mild AD dementia, which may be of value in clinical trials.

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GLOSSARY

AD = Alzheimer disease; ADT = AD signature thickness; AUC = area under the curve; CDR = Clinical Dementia Rating; CDR-SB = CDR Sum-of-Boxes; eTIV = estimated total intracranial volume; EV = entorhinal volume; HV = hippocampal volume; MCI = mild cognitive impairment; MCT = mean cortical thickness; MMSE = Mini-Mental State Examination; MTL = medial temporal lobe; MTLT = medial temporal lobe thickness; OC = older controls; QAD = questionable AD dementia; ROC = receiver operating characteristic; ROI = region of interest; WBV = whole brain volume.

Anatomic abnormalities of brain regions known to be early sites of Alzheimer disease (AD) pathology, such as medial temporal lobe (MTL) regions including the entorhinal cortex and hippocampal formation, can be detected in prodromal AD prior to dementia.1-3 Although it is well known that early in its clinical course AD affects non-MTL neocortical association regions,4,5 there has been little investigation of neocortical anatomy in prodromal AD prior to dementia. The few investigations of cortical anatomic abnormalities in mild cognitive impairment (MCI)6 or prodromal AD7-9 have used techniques that involve exploratory mapping of...
the entire cortex. While these techniques are well suited to disorders in which the localization of pathology is unknown, it is possible to use in vivo imaging and postmortem pathologic data from patients with AD dementia to predict the localization of anatomic abnormalities in prodromal AD. Such an approach employing disease-signature cortical regions of interest (ROIs) is powerful in that it enables hypotheses to be tested about the sequence of involvement of cortical regions in AD progression through comparison of effect sizes from cross-sectional data from patients at different clinical stages in the disease.

Furthermore, there are questions about abnormalities of cortical anatomy in prodromal AD that, to our knowledge, have received no investigation. How do cortical anatomic abnormalities relate to symptoms in the mildest predementia phases of the disease? Which neocortical measures are best in terms of sensitivity and specificity for early diagnosis, and do they improve upon the predictive power of well-accepted morphometric measures, such as volumes of the hippocampal formation, entorhinal cortex, or whole brain?

To address those questions, we studied a sample of individuals with questionable dementia (Clinical Dementia Rating [CDR]10 0.5) whose symptoms and signs were largely similar to MCI. Longitudinal clinical data after the MRI scan were used to classify subjects into progressors to mild AD dementia (CDR 1) vs nonprogressors. A set of AD signature cortical ROIs—found previously in a separate sample of patients with mild AD (CDR 1) to be consistently affected11—was used to extract regional thickness measures which were employed in subsequent analyses. ROI measures were compared in the group of MCI progressors vs nonprogressors, and were also compared to controls and patients with mild AD. In addition, receiver operating characteristic (ROC) curves were generated for the various novel anatomic measures obtained, which were compared to ROC curves for standard morphometric measures. Across all subjects, ROI measures were studied in relation to clinical measures for purposes of clinical validation. Finally, an analysis was performed to demonstrate a map of the spatial pattern of thinning associated with prodromal AD across the cerebral cortex.

**METHODS** Participants, clinical assessment, and MRI data acquisition. Forty-nine volunteer participants (age 64–90, 20 women) were studied, data from some of whom have been published previously.12-15 Participants were recruited from the ongoing longitudinal sample of the Washington University Alzheimer’s Disease Research Center using procedures approved by Washington University’s human subjects committee, and assessed using procedures previously described.16

For the purposes of the present study, the clinical diagnostic categories included questionable dementia of the Alzheimer type (QAD) (CDR Rating = 0.5) and mild AD (CDR Rating = 1). All participants were classified as QAD at the time of baseline MRI scan. Based on annual clinical follow-up, 29 individuals remained with a CDR Rating of 0.5 (nonprogressors) while 20 converted to mild AD (declined to a CDR Rating = 1; progressors).

Multiple (three or four) structural T1-weighted magnetization-prepared rapid gradient echo images were acquired on a 1.5 T Siemens Vision scanner (Siemens Medical Systems, Erlangen, Germany) using the following parameters: repetition time/echo time/inversion time/delay = 9.7/4/20/200 msec, flip angle = 10º, 256 × 256 (1 mm × 1 mm) in-plane resolution, 128 sagittal 1.25 mm slices without gaps. These images were motion-corrected and averaged together during processing. These data are openly available to the community, thanks in part to resources provided by the Washington University Alzheimer’s Disease Research Center (http://www.oasis-brains.org/).

**MRI morphometric data analysis: Automated tissue segmentation and surface reconstruction and alignment of participants.** These methods have been previously described in detail, including the surface-based cortical thickness processing and spherical registration to align subjects’ cortical surfaces.12,17-22 The methods are summarized in appendix e-1 on the Neurology® Web site at www.neurology.org. The Freesurfer software used to analyze and visualize data in this study is freely available (http://surfer.nmr.mgh.harvard.edu).

**MRI morphometric data analysis: Quantification of magnitude of atrophy within regions of interest.** Automated volume measures for whole brain, hippocampus, and entorhinal cortex were adjusted for estimated total intracranial volume (eTIV, calculated as described previously23) by dividing regional volume by eTIV. Nine regions of interest (ROIs) constituting the cortical signature of AD derived from an exploratory cortical thickness analysis comparing 115 older controls to 29 subjects with AD15 were used to generate regional thickness measures for each subject in this study. These adjusted volume and regional thickness measures were used for descriptive purposes and to calculate the mean difference in values of each ROI between the progressor and nonprogressor groups, the percent thinning in progressors relative to nonprogressors (mean thickness of nonprogressor group − mean thickness of progressor group)/mean thickness of nonprogressor group), and the Cohen d effect sizes of progression-related differences for each ROI. In addition, we analyzed a measure of the average thickness of these 9 ROIs (average AD-signature ROI thickness), previously shown to be sensitive to early presymptomatic effects of AD.11

**Statistical analysis.** The eTIV-adjusted volume and regional thickness measures were normalized to a sample of age-matched controls by calcu-
RESULTS Clinical features. Participant characteristics are presented in table 1. For the entire sample, the average duration of clinical follow-up after the MRI scan was 2.7 (SD = 1.7) years with the progressor and nonprogressor groups being followed for 2.3 (SD = 1.1) and 3 (SD = 1.4) years. The progressor and nonprogressor groups did not differ on the basis of age \( [F(1) = 2.7, p = 0.11] \), but they did differ on CDR-SB \( [F(1) = 19.9, p < 0.001] \) and MMSE scores \( [F(1) = 10.1, p < 0.005] \).

Morphometric correlates of symptom severity. Within the entire sample, several cortical thickness measures correlated with the relative severity of cognitive impairment as measured by CDR-SB, including medial temporal \( (r = -0.36, p < 0.01) \), inferior temporal \( (r = -0.30, p < 0.04) \), and superior parietal cortex \( (r = -0.32, p < 0.03) \), with trends \( (p < 0.1) \) for temporal pole \( (r = -0.24) \) and angular gyrus \( (r = -0.28) \). In addition, CDR-SB correlated with average AD-signature thickness \( (r = -0.38, p < 0.01) \), and with mean thickness across the entire cortical mantle \( (r = -0.32, p < 0.03) \).

Similarly, a number of cortical thickness measures correlated with MMSE score: angular gyrus \( (r = 0.45, p < 0.001) \), superior frontal gyrus \( (r = 0.34, p < 0.02) \), superior parietal lobule \( (r = 0.38, p < 0.01) \), supramarginal \( (r = 0.32, p < 0.03) \), mean cortical thickness \( (r = 0.34, p < 0.02) \), and average AD-signature thickness \( (r = 0.35, p < 0.02) \).

As for volumetric measures, the only correlation with CDR-SB or MMSE was observed with entorhinal cortex volume, which showed a trend-level \( (r = -0.24, p < 0.1) \) effect.

Morphometric differences between progressors and nonprogressors. Mean cortical thickness was 3.2% thinner in progressors than nonprogressors [progressors = 2.11 (SD = 0.10) mm, progressors = 2.05 (SD = 0.14) mm; \( F(1) = 4.6, p = 0.037 \), Cohen \( d = 0.54 \)].

As mentioned above, figure 1 (top) illustrates the localization of the nine AD-signature cortical ROIs, derived from a separate sample of 115 OC vs 29 AD. Thinning in prodromal AD (the progressor group) was most prominent in the rostral medial temporal cortex, with thinning (compared to nonprogressors) of 0.28 mm (10.1%, Cohen \( d = 0.79 \)). Three other regions differed \((p < 0.05)\) between the two groups: inferior temporal gyrus (0.17 mm [6.3%] thinning, Cohen \( d = 0.73 \)), superior parietal lobule (0.12 mm [5.8%] thinning, Cohen \( d = 0.70 \)), and temporal pole (0.12 mm [4.7%] thinning, Cohen \( d = 0.51 \)). Two regions showed trends \((p < 0.1)\) toward thinning in prodromal AD: precuneus (0.15 mm [7.03%] thinning, Cohen \( d = 0.52 \)), and angular gyrus (0.1 mm [4.43%] thinning, Cohen \( d = 0.48 \)). Weaker effects in the same direction were observed in the other three ROIs. Group mean and standard error data are shown in figure 1. Additional details are shown in table 2.

The progressor and nonprogressor groups did not differ for whole brain volume \((p > 0.3)\), but both hippocampal \([F(1) = 4.5, p < 0.04, \text{Cohen } d = 0.4]\) and entorhinal \([F(1) = 6.4, p < 0.02, \text{Cohen } d = 0.6]\) volumes were smaller in the progressors than nonprogressors, as expected.

ROC analysis. The goal of this analysis was to provide data to assist in the comparison of the cortical thickness measures of primary interest in this study with morphometric measures employed more widely in previous studies of the prediction of progression to dementia. Rather than discriminant function or logistic regression analysis, ROC was chosen to explore the full spectrum of performance across a range of sensitivity and specificity. Full curves are presented in figures, and here we compare measures by focusing on the peak performance point (highlighted in the figures) that optimized both sensitivity and specificity.

Of the standard volumetric measures, both hippocampal and entorhinal volume outperformed whole brain volume across a wide range of the ROC curve, with the best peak performance by entorhinal cortex (sensitivity and specificity of 72.4% and 65%; hippocampal sensitivity and specificity were 83%
and 50%; figure 2A). Area under the curve (AUC) measures for whole brain volume (WBV), hippocampal volume, and entorhinal volume are 0.59, 0.65, and 0.70.

Since AD is primarily a gray matter disease with important degenerative effects on the cerebral cortex, we hypothesized that, among global measures, mean cortical thickness would be more sensitive than...
whole brain volume, which reflects white matter volume as well as gray matter volume. Therefore, an ROC comparison was made of the predictive classification performance of mean cortical thickness vs whole brain volume. Mean cortical thickness demonstrated predictive classification performance that was better than whole brain volume, with a peak sensitivity of 69% and specificity of 65% (figure 2B) as compared to the peak sensitivity and specificity for whole brain volume of 62% and 55%. AUC measures for WBV and mean cortical thickness are 0.59 and 0.67.

Next, we performed similar analyses of the regional cortical thickness measures. Among all regional thickness measures (figure e-1 and appendix e-1), superior parietal, precuneus, and inferior frontal cortices showed relatively high sensitivity and medial temporal, temporal pole, and superior frontal cortices showed relatively high specificity. Of the nine cortical ROI measures, the medial temporal lobe thickness had the best peak performance, with a sensitivity and specificity of 83% and 55%.

Finally, we compared the predictive classification performance of the average AD-signature thickness vs MTL thickness alone vs entorhinal volume (figure 2C). The AD signature measure performed best, with a sensitivity of 83% and specificity of 65%. AUC measures for hippocampal volume, MTL thickness, and mean AD signature thickness are 0.65, 0.72, and 0.73.

An exploratory analysis of cortical thickness across the entire mantle (figure 3) revealed a pattern of thinning in prodromal AD similar to, but expressed to a lesser degree than, that seen in mild AD.

**DISCUSSION** In this study, we used existing knowledge about regional cortical thinning in a sample of patients with mild AD dementia, many characteristics of which are similar to those of patients with MCI. The magnitude of thinning of certain regions correlates with the relative severity of very mild symptoms in daily life (as measured by CDR-SB) and signs on performance testing (MMSE). Furthermore, the thickness of particular regions of the cerebral cortex known to undergo thinning in mild AD provides a useful measure for the prediction of progression from questionable AD dementia (CDR 0.5) to mild AD dementia (CDR 1).

While extensive investigation has been performed in MCI of certain morphometric measures, such as the volumes of the whole brain, ventricular system, hippocampal formation, and entorhinal cortex, there is scant evidence regarding anatomic abnormalities in other cortical brain regions. Most of the literature on cortical atrophy in MCI has focused on exploratory mapping of atrophy in MCI compared to controls or patients with AD, or in MCI converters to mild AD dementia compared to nonconverters. In the former studies of atrophy in MCI in which the diagnostic outcome is unknown, atrophy patterns are largely similar to, although of lesser magnitude, than those of mild AD dementia. Of the previous investigations that have followed patients clinically after scanning, two demonstrated distributed atrophy patterns in the MCI progressors that are typical of those of patients with AD when comparing MCI progressors to controls, but surprisingly one study showed more widespread atrophy when comparing MCI progressors to nonprogressors, while the other showed much less widespread differences involving only supramarginal, inferior frontal, and hippocampal regions. A third investigation identi-
fied focal ventromedial temporal atrophy. There are no previous comparable data regarding the magnitude of atrophy (% difference) between progressors vs non-progressors. The present data are consistent with previous data indicating that, when AD symptoms are still incipient or very mild, atrophy is already present in a set of heteromodal and limbic cortical regions. These data build on previous results by showing that although a lesser magnitude of atrophy is present in these very mildly affected patients, the spatial pattern is predictable based on what is known about the cortical regions affected in mild AD dementia (when defined using an independent sample).

Besides comparisons between diagnostic patient groups, we also investigated the relationships between regional cortical thickness and relative severity of mild symptoms in daily life (as measured by CDR-SB) and signs of cognitive impairment (as measured by MMSE) within this group of participants. To our knowledge, only one study has investigated the relationship of MMSE to cortical atrophy within a sample restricted to MCI or prodromal AD, and no regions of correlation were found. We observed robust relationships between the average thickness of the nine AD-signature regions and MMSE performance as well as CDR-SB. Such similar relationships, while intuitive, are not inevitable given the frequent dissociation between symptoms in daily life and signs on cognitive testing, particularly in the mildest prodromal stages of the illness. The correlations were anatomically distinct, however, in that CDR-SB correlates most prominently with ventromedial temporal and superior parietal thickness whereas MMSE correlates with superior frontal and lateral parietal thickness. Overall, the strength of the correlations was relatively subtle, as has been the case in previous reports focusing on medial temporal lobe regions. Further investigation will be necessary to determine whether consistent localized brain–behavior relationships can be illuminated through the investi-
Most importantly, measures of the thickness of specific cortical regions known to be affected by AD are useful in predicting progression from questionable dementia to mild AD dementia within a few years. These findings build on a large body of work focused on morphometric measures of the medial temporal lobe in predicting progression from incipient dementia/MCI to AD dementia, expanding now to include regions of the temporoparietal and frontal cortices. The use of ROC analysis illuminates the utility of these measures across a broad spectrum of sensitivity-specificity tradeoffs, allowing the clinician to choose cutpoints depending on the question at hand. Also, by comparing the novel cortical thickness methods to more widely used volumetric measures (the results of which are similar to those of previous studies\(^2,29\)), these analyses further demonstrate the potential utility of thickness measures.

Of the global measures, the average thickness of the cerebral cortex outperforms whole brain volume substantially with respect to predicting progression. This is not surprising given that whole brain volume likely reflects large classes of tissue that are relatively unaffected by AD. Of the regional volume measures, entorhinal volume performed better than hippocampal volume, as has been seen previously.\(^30\) MTL thickness performed better yet in comparison to entorhinal volume, which may relate in part to past observations that thickness appears to be a purer reflection of the effects of AD on cortical morphology while surface area, and therefore volume, are altered substantially by aging.\(^31\) Finally, ROC analysis demonstrated that the average thickness of all nine AD-signature ROIs was the most powerful measure for predicting progression to mild dementia. Compared to MTL ROI measures, such a disease composite measure probably increases sensitivity by including individuals with thinning in additional brain regions involved in the disease and increases specificity by excluding individuals with relative preservation of thickness in those regions (whose relatively isolated MTL thinning may be due to other pathologies).

Several limitations of this study deserve mention. The diagnosis of AD was not confirmed by autopsy or any other imaging markers. Longitudinal MRI measures were not performed. Finally, to translate these measures into biomarkers for use in individual patient diagnostic classification, as has been done with other approaches to cortical morphometric analysis in AD,\(^2,29\) further work is necessary. Yet the robust effects observed provide optimism that this approach to cortical anatomic measurement may be able to achieve such goals.

AUTHOR CONTRIBUTIONS
Dr. Dickerson and Mr. Bakkour performed all statistical analyses.

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