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Variations in cortical thickness with dementia severity in Alzheimer's disease

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ABSTRACT

Previous magnetic resonance imaging (MRI) studies have used volumetric methods to investigate cerebral atrophy and showed its linear pattern with the measure of dementia severity in Alzheimer's disease (AD). This study analyzed the phase- and region-specific changes in cortical thickness with dementia severity. In 43 normal controls and 60 AD patients with clinical dementia rating (CDR) (0.5, $n = 21$; 1, $n = 28$; 2, $n = 11$), the cortical thickness was measured using automated surface-based analysis of MRI data. Statistical analyses were performed to investigate overall the hemispheric mean thicknesses as well as the topography of cortical atrophy based on vertices in the groups. No significant difference in cortical thickness was observed for the mild (from CDR = 0.5 to 1) stage of dementia. In contrast, a significant reduction of cortical thickness occurred from CDR = 1 to 2. Topographic analysis of cortical atrophy showed that the significant cortical thinning in CDR = 0.5 relative to normal was found in most association cortices, with this being more extensive than previously reported. There were significant cortical atrophies between CDR = 1 and 2 in the frontal, inferolateral temporal, inferior parietal lobule, medial occipital, and posterior-cingulated regions. Our results confirm and extend previous findings, suggesting that widespread cortical thinning occurs before the onset of dementia (from normal to CDR = 0.5), and that once dementia starts, cortical atrophy in association cortices accelerates in moderate AD (from CDR = 1 to 2).

Alzheimer's disease (AD), the most common cause of dementia, is a progressive neurodegenerative condition characterized histologically by the presence of neurofibrillary tangles and neuritic amyloid plaques [1]. These microscopic changes are accompanied by macroscopic and progressive cortical atrophy, as demonstrated *in vivo* by magnetic resonance imaging (MRI). Assessing the progression of cerebral atrophy with disease severity and uncovering the course of structural degeneration may contribute to the early diagnosis of AD and the development of appropriate clinical therapies. Hence, it is important to identify a reliable quantitative index of structural cerebral changes and to detect the phase- and region-specific patterns of cortical decreases using a standardized measure of dementia severity.

Several previous MRI studies have used region of interest (ROI)-based or gross volumetric methods to investigate structural changes in the brain associated with AD. These studies have demonstrated that the decreases in the volumes of the entire brain and specific regions such as the hippocampus and entorhinal cortex increase with the severity of dementia [2,9]. However, analyzing the entire brain volume will not elucidate regional changes, and manually segmented ROI-based analyses are intensive labor and suffer from intra- and inter-rater reliability issues. In comparison, voxel-based morphometry (VBM) is an observer-independent automatic methodology that is implemented across the cortex. However, this method also exhibits limited accuracy in the measurement of cortical morphology, especially in brain regions where fine anatomic details are often obscured by a partial volume effect. Measuring the thickness of the cortical surface has been proposed for overcoming this problem, which has the advantage of providing a localized quantitative description of cortical atrophy (in millimeters) and enabling more precise measurement in deep sulci as a cortical sheet.

Previous studies that employed MR volumetry using cortical measurement techniques analyzed the data based on the assumption that brain atrophy varies linearly with disease severity [19,24]. The first study that applied a cortical thickness measurement to the analysis of AD also showed linear relationships between disease severity and cortical thickness decrease [13]. The cortical thickness

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Table 1
Demographic characteristics of normal controls and AD patients with varying degrees of dementia severity

	Normal (CDR = 0) (n = 43)	CDR = 0.5 (n = 21)	CDR = 1 (n = 28)	CDR = 2 (n = 11)
Age (years)	68.7 ± 5.7 (55–83)	71.1 ± 7.2 (58–84)	71.3 ± 8.5 (49–83)	71.1 ± 9.8 (55–87)
Sex (males/females)	21/22	5/16	8/20	4/7
Education (years)	10.7 ± 4.7 (0–18)	9.2 ± 5.5 (0–18)	7.5 ± 5.5 (0–18)	8.0 ± 4.3 (0–16)
MMSE score	29.2 ± 1.2 (24–30)	23.8 ± 2.6 (18–28)[a]	20.5 ± 4.4 (10–27)[a,b]	15.6 ± 4.8 (10–23)[a,b,c]

Data are mean ± S.D. (range) values.
[a] Bonferroni *post hoc* test differs from normal ($P \leq 0.05$).
[b] Bonferroni *post hoc* test differs from CDR = 0.5 ($P \leq 0.05$).
[c] Bonferroni *post hoc* test differs from CDR = 1 ($P \leq 0.05$).

study in AD most recently published showed the patterns of cortical thinning with the progression of disease from mild cognitive impairment (MCI) to AD, but it did not analyzed a specific pattern in AD [22]. The most accurate way to monitor changes in MR volumetry would be to perform longitudinal studies, but this is difficult since most clinical and research settings do not allow multiple MRI scans covering the entire range of disease severity to be performed. Moreover, most of these studies have involved ROI-based or gross volumetric analyses, which were based on measures of the percentage volume loss or brain-boundary shift integral of the entire brain [2,9].

In this study we analyzed the phase- and region-specific changes in cortical thickness using automated surface-based methods according to dementia severity in normal controls and AD patients. Dementia severity was quantified using the clinical dementia rating (CDR) [16].

Three-dimensional T1-weighted spoiled-gradient (SPGR) echo images were obtained from 60 patients with AD who visited the Memory Disorder Clinic of Samsung Medical Center, Seoul, South Korea. All the patients fulfilled the criteria for probable AD proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association [15]. Diagnostic procedures included a clinical interview, neurological examination, and a battery of neuropsychological tests. Laboratory tests including complete blood count, blood chemistry, vitamin B_{12}/folate, syphilis serology, and thyroid function tests did not reveal the cause of the dementia in any of the patients. Conventional brain MRI scans (T1- and T2-weighted, and FLAIR images) confirmed the absence of territorial cerebral infarction, brain tumor, and other structural lesions. The CDR and Mini-Mental State Examination (MMSE) [5] were measured. The AD patients were divided into three clinical groups according to their CDR as follows: 0.5, n = 21; 1, n = 28; 2, n = 11. The control group consisted of 43 healthy volunteers who had no history of neurological or psychiatric illnesses or abnormalities in neurological examinations. The cognitive functioning of the control subjects was confirmed to be within normal limits as assessed by MMSE and neuropsychological testing. Demographic and clinical data of the participants are presented in Table 1. We obtained informed consents from all the patients and controls, and the study was approved by the Institutional Review Board of the hospital.

The group characteristics were compared using an analysis of variance with a Bonferroni *post hoc* test. The age and duration of education did not differ between the groups, but the sex ratio did. Therefore, sex was entered as a covariate in group comparisons.

Three-dimensional T1-weighted SPGR echo images were acquired using a 1.5-T MRI scanner (GE Signa, Milwaukee, WI) with the following imaging parameters: coronal slice thickness, 1.5 mm; echo time, 7 ms; repetition time, 30 ms; number of excitations, 1; flip angle, 45°; field of view, 22 cm × 22 cm; matrix size, 256 × 256 pixels.

The native MRI images were registered into a standardized stereotaxic space using a linear transformation [4]. Images were corrected for intensity nonuniformity resulting from inhomogeneities in the magnetic field [23]. The registered and corrected volumes were classified into white matter, gray matter, cerebrospinal fluid, and background using an advanced neural-net classifier [26]. The surfaces of the inner and outer cortex were automatically fitted using the Constrained Laplacian-Based Automated Segmentation with Proximities (CLASP) algorithm [10]. The reconstructed hemispheric cortical surfaces consisted of a triangular mesh of 81,920 elements. The inner and outer surfaces had the same number of vertices, and there was a close correspondence between the counterpart vertices of the inner and outer cortical surfaces. The cortical thickness was defined as the Euclidean distance between these linked vertices [12].

To compare the thicknesses of corresponding regions between participants at a vertex level, the thickness values were spatially normalized using surface-based two-dimensional nonlinear registration [20]. Using the transformation, thickness information on the vertices was transformed into an average template. For global analysis, averaged values of the thickness of the whole surface in each hemisphere were analyzed.

Diffusion smoothing with a full-width half-maximum of 20 mm was used to blur each cortical thickness map, which increased the signal-to-noise ratio and statistical power [12,13]. Global and regional cortical thicknesses in the normal and CDR groups (CDR = 0, 0.5, 1, and 2) were compared using an analysis of covariance (ANCOVA) with sex as a covariate.

ANCOVA revealed that the mean cortical thickness was significantly affected by the dementia severity (CDR = 0, 0.5, 1, and 2) for both hemispheres (Table 2). Bonferroni *post hoc* tests indicated that the mean cortical thickness was significantly less in each of CDR = 0.5, 1, and 2 than in normal subjects. The mean cortical thickness was significantly less (by about 0.3 mm) for CDR = 2 than for CDR = 0.5 or 1, whereas there was no significant difference between CDR = 0.5 and CDR = 1.

Table 2
Statistical tests (ANCOVA) of between-subjects effects (normal and CDR = 0.5, 1, and 2) for left and right hemispheres for the mean cortical thickness (in millimeters)

	Normal (CDR = 0)	CDR = 0.5	CDR = 1	CDR = 2	F	P
Left	3.17 ± 0.18	2.91 ± 0.23[a]	2.93 ± 0.25 [a]	2.65 ± 0.25[a,b,c]	27.267	<0.0001
Right	3.18 ± 0.18	2.94 ± 0.25 [a]	2.96 ± 0.22 [a]	2.65 ± 0.25[a,b,c]	27.080	<0.0001

[a] Bonferroni *post hoc* test differs from normal ($P \leq 0.05$).
[b] Bonferroni *post hoc* test differs from CDR = 0.5 ($P \leq 0.05$).
[c] Bonferroni *post hoc* test differs from CDR = 1 ($P \leq 0.05$).

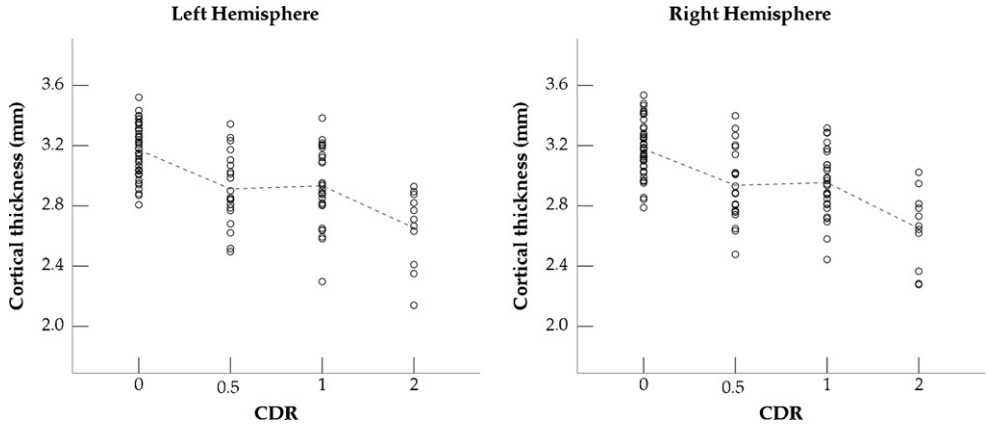

Fig. 1. Mean cortical thickness vs. CDR for each hemisphere. The plots show decreases in the cortical thicknesses from normal to CDR = 0.5 and from CDR = 1 to 2 in both hemispheres.

The mean cortical thickness in hemispheric regions is plotted against CDR in Fig. 1, in which the lines connecting mean values show the pattern of cortical thickness change according to CDR. The slope was not constant, in that the decrease in thickness was greater from normal to CDR = 0.5 and from CDR = 1 to 2.

In order to reveal any region specificity in these changes, cortical thickness analysis was performed on a vertex-by-vertex basis. The differences in the mean cortical thickness at each vertex between groups are mapped on an average-surface model in Fig. 2A for normal to CDR = 0.5, CDR = 0.5–1, and CDR = 1–2. The significant localized differences in cortical thickness, as revealed by ANCOVA, are shown in Fig. 2B. The cortical surface model comprised 40,962 vertices, and correction of the thresholds for multiple comparisons was needed to reduce the false-positive rate. We performed false-discovery-rate (FDR) correction for multiple comparisons at a corrected *P*-value of 0.05 [8]. Bonferroni *post hoc* tests confirmed the regions showing statistically significant differences in cortical thickness between normal and CDR = 0.5, CDR = 0.5 and 1, and CDR = 1 and 2. As shown in Fig. 2B, significant cortical thinning in CDR = 0.5 relative to normal was found extensively throughout both hemispheres, except for the superior motor and sensory areas, and the orbital, prefrontal, and partial areas of the right parietal and both occipital lobes. The difference in the mean cortical thickness between normal and CDR = 0.5 was higher in the medial temporal area (parahippocampal gyrus and uncus) than in other areas (the difference in mean value was 0.6–0.8 mm). Although the difference between CDR = 0.5 and 1 was also greater in the medial temporal region (0.2–0.4 mm) than any other regions, it did not reach statistical significance. Significant cortical thinning in CDR = 2 relative to CDR = 1 was detected in the frontal and inferolateral temporal regions. In the parietal lobe, significant differences were evident in the transition area between the parietal and temporal lobes, including the inferior parietal lobule. In the medial view, significant cortical thinning appeared in occipital and right frontal lobes. Differences were also present in the posterior cingulate region in both hemispheres. Larger differences in the mean thickness values between CDR = 1 and 2 were particularly evident in the temporal, posterior cingulate, and right medial occipital regions (0.6–0.8 mm).

Our study, which involved a large sample of normal controls and AD patients, showed that the overall cortical thickness reduces as the disease severity increases. Previous volumetric studies that used the MMSE score to quantify the severity of dementia found a significant relationship between the regional or whole brain volume and the MMSE score [18,24]. Longitudinal studies have also found that volumetric brain atrophy is correlated with MMSE scores [9,25]. In most of these studies, the relationship between the severity measure of the disease and brain atrophy was assumed to be linear. In our study, rather than using MMSE, which reflects only the cognitive aspects of dementia, we used the CDR, which clinically stages not only the cognitive deficits but also the functional impairments of dementia [17]. The results showed that the cortical thickness decreased nonuniformly as the CDR increased from 0.5 to 2. Although the dementia severity differed within the earlier (from CDR = 0.5 to 1) stage, no significant reduction in the regional mean thickness was noted. In contrast, the mean cortical thickness was significantly less in CDR = 2 than in CDR = 1 in large cortical areas.

Many previous studies have suggested that the cortical volume decrease in the early stages of AD occurs in the specific areas centered on the medial temporal lobes [7,9], and that an obvious decrease of cortical volume throughout the neocortex occurs during moderate AD [25]. Our comparison of CDR = 0.5 with the normal group showed that the most remarkable cortical thinning occurred in the medial temporal area, with the superior motor and sensory cortices being relatively spared, which is consistent with previous reports [12,25]. However, cortical thinning in very mild AD (CDR = 0.5) was much more widespread than expected, which is not consistent with previous volumetric studies. That is, our vertex-by-vertex analysis revealed that although the hippocampal region showed the greatest difference in mean cortical thickness, statistically significant cortical atrophy appeared to be more diffuse than previously reported. Recent analyses have shown that presymptomatic progressive atrophy is not limited to the medial temporal lobe, involving the inferolateral temporal lobe, parietal lobe, and posterior cingulate [3,6]. A significantly thinned cortical thickness of the frontal and superior parietal areas have been noted in MCI [22]. Pathological studies also have shown that neurofibrillary tangles or neuritic plaques are widely distributed even in MCI, including in the neocortex and limbic areas [14]. Moreover, *in vivo* amyloid imaging using PET has demonstrated the presence of amyloid deposits in the frontal and parietal lobes even in mild AD [11]. Our findings thus could be consistent with these previous studies, and extend previous findings, suggesting that the surface-based cortical measurement employed in the present study can detect subtle cortical atrophy in very mild AD. We also propose that cortical changes at a structural level could occur across the cortex in the stage before onset, and that the significant cortical thinning in CDR = 0.5 relative to normal might reflect the accumulation of such structural changes.

We found that the significant cortical changes between CDR = 1 and 2 occurred mainly in the frontal, temporal, and medial occipital regions. In addition, the posterior cingulate region showed significant cortical thinning, with the difference in mean cortical thickness being greatest between CDR = 1 and 2. A previous

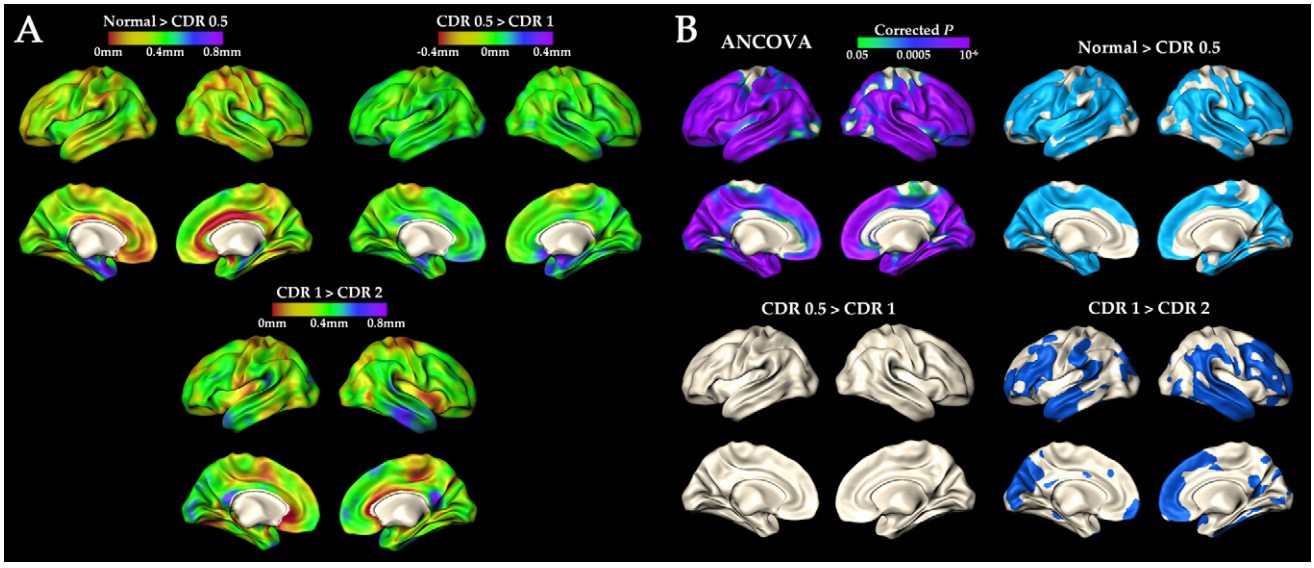

Fig. 2. Regional maps of the differences in the mean cortical thickness (A) and statistical maps (B) between groups: normal to CDR = 0.5, CDR = 0.5–1, and CDR = 1–2.

study showed that a temporoparietal volume loss that had already occurred at baseline (MMSE score of 17.7) progressed into frontal and occipital loss at the later stages of AD, and that the loss was greatest in the frontal and temporal regions (corresponding to the average MMSE score decreasing from 17.7 to 12.9) over a 2-year period [25]. Other studies have also found that lateral regions of the temporal lobe and frontal lobe were associated with disease progression in patients with mild and moderate AD [13,21]. Our regional pattern of cortical loss in CDR = 2 (with an average MMSE score of 15.6) is thus in agreement with these previous studies. The posterior cingulate area is significantly related to disease progression [6,13,21], which supports the data reported here. Previous studies have found that involvement of the frontal region in cortical atrophy occurs later in the disease [21,25]. However, from our results we propose a different interpretation that the remarkable cortical thickness decrease in these regions, even in the frontal region, could result from the acceleration of atrophy at the moderate stage that had gradually occurred before.

In summary, our data demonstrate a phase- and region-specific pattern of cortical thickness reduction in a large data set grouped by standardized and widely used severity measures (CDR), which could contribute to the planning of clinical trials in AD. The 3D surface-based cortical thickness analysis conform previous studies and provide an additional finding that widespread cortical thinning in large cortical areas occurs before the onset of dementia (from normal to CDR = 0.5), and that once dementia starts, cortical atrophy in association cortices accelerates in moderate AD. For future work, the use of a longitudinal design could be more valid than a cross-sectional study in demonstrating the cortical thickness changes as a function of dementia severity.

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