Anatomical heterogeneity of Alzheimer disease

Based on cortical thickness on MRIs

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ABSTRACT

Objective: Because the signs associated with dementia due to Alzheimer disease (AD) can be heterogeneous, the goal of this study was to use 3-dimensional MRI to examine the various patterns of cortical atrophy that can be associated with dementia of AD type, and to investigate whether AD dementia can be categorized into anatomical subtypes.

Methods: High-resolution T1-weighted volumetric MRIs were taken of 152 patients in their earlier stages of AD dementia. The images were processed to measure cortical thickness, and hierarchical agglomerative cluster analysis was performed using Ward's clustering linkage. The identified clusters of patients were compared with an age- and sex-matched control group using a general linear model.

Results: There were several distinct patterns of cortical atrophy and the number of patterns varied according to the level of cluster analyses. At the 3-cluster level, patients were divided into (1) bilateral medial temporal–dominant atrophy subtype (n = 52, ~34.2%), (2) parietal-dominant subtype (n = 28, ~18.4%) in which the bilateral parietal lobes, the precuneus, along with bilateral dorsolateral frontal lobes, were atrophic, and (3) diffuse atrophy subtype (n = 72, ~47.4%) in which nearly all association cortices revealed atrophy. These 3 subtypes also differed in their demographic and clinical features.

Conclusions: This cluster analysis of cortical thickness of the entire brain showed that AD dementia in the earlier stages can be categorized into various anatomical subtypes, with distinct clinical features. *Neurology*® 2014;83:1936–1944

GLOSSARY

AD = Alzheimer disease; **CDR** = Clinical Dementia Rating; **D** = diffuse atrophy subtype; **EOAD** = early-onset Alzheimer disease; **FP** = frontoparietal subtype; **FT** = frontotemporal subtype; **LP** = left parietal–dominant subtype; **MF** = medial frontal/temporal subtype; **MT** = medial temporal subtype; **NC** = normal cognition; **P** = parietal-dominant subtype; **RP** = right parietal–dominant subtype.

The clinical presentation of dementia due to Alzheimer disease (AD) is heterogeneous.[1–6] Neuropathologic studies have suggested that there are 3 distinct pathologic subtypes in terms of distribution of amyloid plaques and neurofibrillary tangles.[7] Pathologic findings from autopsied cases are the gold standard for investigating anatomical heterogeneity; however, the autopsy findings usually represent advanced stages of the disease, and cannot map the entire brain because of region-of-interest–based methods. Instead, imaging studies that incorporate a large number of patients assessing the entire cerebral cortex may demonstrate anatomical heterogeneity of AD dementia–induced degeneration at the earlier stages.

To our knowledge, only a few imaging studies have investigated the structural heterogeneity of AD dementia. A voxel-based morphometry study classified 40 patients into 4 subgroups according to atrophy patterns in the medial temporal, posterior lateral cortices, and posterior

Supplemental data at Neurology.org

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cingulate–precuneus.[8] However, there have been no reports of anatomical subgroups for AD dementia using surface-based morphometry, a sensitive method that measures actual cortical thickness across the entire cortical mantle using 3-dimensional MRIs.[9] The objective of this study was to examine variability in surface-based morphometry cortical atrophy patterns of the entire cerebral cortex and then use cluster analyses to determine whether AD dementia can be categorized into distinct anatomical subgroups. As this disease progresses, the left-right hemispheric functional and degenerative asymmetries decrease[10,11] and the cortical degeneration becomes widespread. Therefore, this study only included participants who were in their early stages of AD dementia.

METHODS

Participants. Of 296 patients with AD dementia who were evaluated at Samsung Medical Center's Memory Disorders Clinic from June 2006 to December 2010 and completed neuropsychological tests as well as high-resolution 3.0-tesla T1-weighted MRI, we excluded all patients with a Clinical Dementia Rating (CDR)–Sum of Boxes ≥5. We also excluded patients with familial AD of the autosomal-dominant inheritance type. The final study population therefore consisted of 152 patients with AD dementia with global CDR of 0.5 to 1 and CDR–Sum of Boxes ≤4.5.[2,12,13]

All patients underwent detailed clinical interviews before their neurologic examinations and neuropsychological tests were conducted. Two fellowship trained behavioral neurologists (S.W. Seo and D.L. Na) made a diagnosis of probable AD dementia using the criteria outlined by NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association).[14] Laboratory tests were conducted to rule out other causes of dementia, and included complete blood counts, vitamin B_{12}, folate levels, a metabolite profile, thyroid function tests, and syphilis serology. Patients were excluded if they had a cerebral, cerebellar, or brainstem infarction, hemorrhage, tumors, hydrocephalus or severe cerebral white matter hyperintensities (deep white matter ≥2.5 cm and caps or band ≥1.0 cm), or severe head trauma.

We recruited 72 individuals with normal cognition (NC) to serve as age- and sex-matched controls for the 152 patients with AD dementia for MRI cluster analyses. The NC controls were all characterized by the following: (1) no history of neurologic or psychiatric disorders, (2) normal cognitive function determined using neuropsychological tests, and (3) a normal activities of daily living score as determined using the Seoul–Instrumental Activities of Daily Living test (with a score <8).[15]

Standard protocol approvals, registrations, and patient consents. All patients provided written informed consent and the study was approved by the institutional review board of Samsung Medical Center.

Neuropsychological tests. All participants underwent tests with a standardized neuropsychological battery, the Seoul Neuropsychological Screening Battery,[16–18] the details of which are described in appendix e-1 on the *Neurology*® Web site at Neurology.org.

Image analyses. ***MRI acquisition.*** Brain MRIs were acquired using a 3.0-tesla MRI scanner (Achieva; Philips Medical Systems, Best, the Netherlands) including 3-dimensional T1-weighted images, as has been described in our previous study.[19]

Measurements of cortical thickness. T1-weighted images were processed using an automated anatomical pipeline for measuring cortical thickness, as described previously.[20] Details for cortical thickness measurements are described in appendix e-2.

Cluster analyses. Cluster analyses were performed using the whole-brain cortical thickness for each of the 152 patients with AD dementia. A total of 78,570 vertex points from each subject were used in the analyses after removing noncortical regions on the surface model. To cluster patients according to the relative involvement of each cortical region, rather than global atrophy alone, the variations in global atrophy between patients were compensated by normalizing the vertices to mean cortical thickness.[21] Ward's clustering linkage method[21,22] was used to combine pairs of clusters at each step while minimizing the sum of square errors from the cluster mean. Each of the 152 patients with AD dementia was placed in their own cluster and then progressively clustered with others. The cluster analysis results are shown as a dendrogram (figure 1).

Statistical analyses. A detailed description for statistical analyses is included in appendix e-3. All statistical analyses were conducted using PASW Statistics 18 software (SPSS Inc., Chicago, IL).

To estimate the anatomical differences between AD dementia subtypes and NC, the general linear model and random field theory were applied using the SurfStat toolbox[23] (see appendix e-4 for details). We reported cortical regions reaching a significant vertex level with random field theory corrected $p < 0.05$. We compared cortical atrophy patterns of AD dementia subtypes with each other using the same method as above.

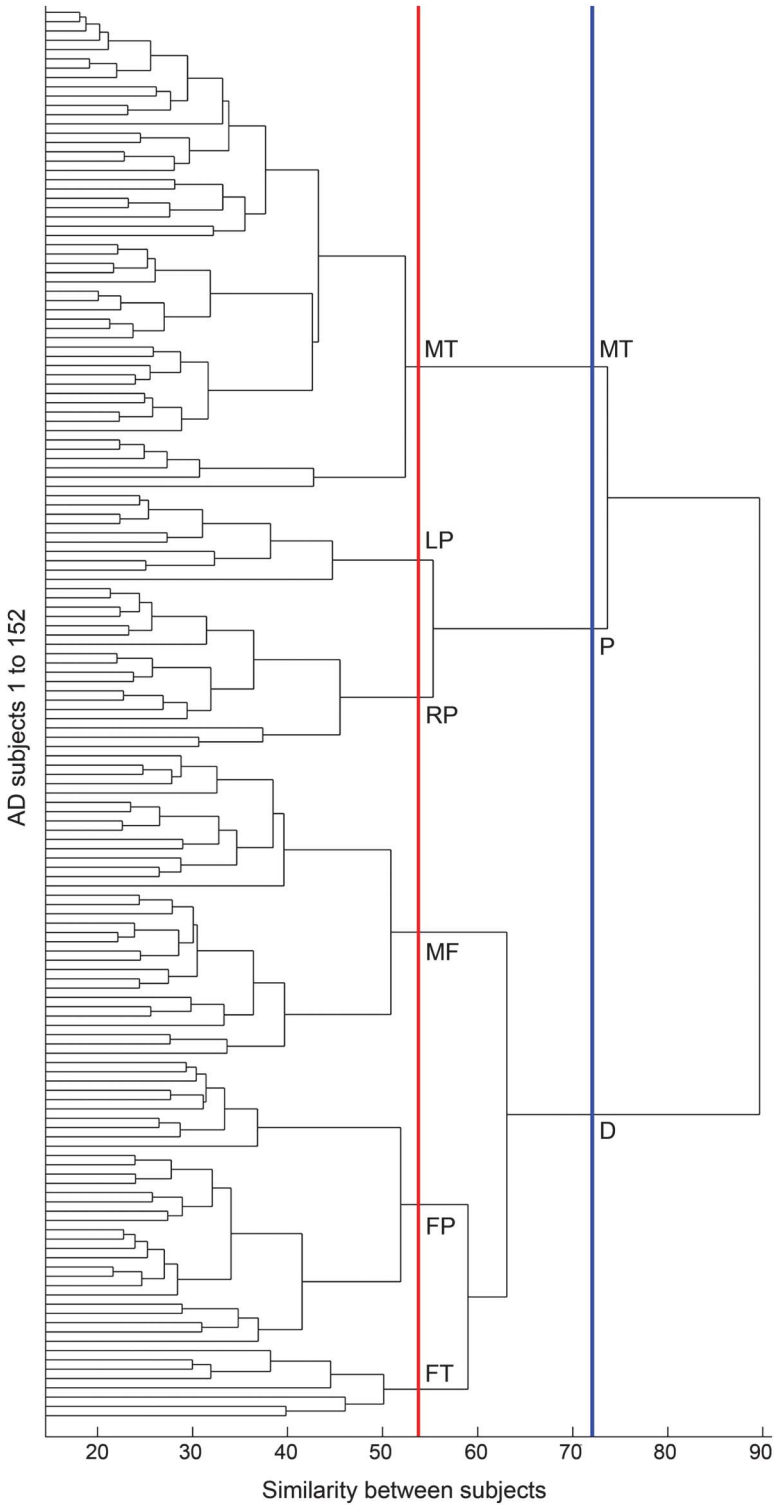
To provide validation for the clustering, principal component analysis was used, which is a multivariate method that can be used to detect correlations in a set of variables. It involves the acquisition of a set of basis vectors with a linear combination that can represent the measured data optimally.[24] We chose the first 2 principal components, which can be explicated as the optimal reflection of the full data, showing the highest variability.[21]

RESULTS

AD dementia subtypes identified by cluster analyses. At the 3-cluster level (figure 2A), the patients were divided into the following: (1) medial temporal subtype (MT subtype, n = 52, ~34.2%) in which the bilateral medial temporal lobes were predominantly involved with additional involvement of anterior and posterior cingulate cortices; (2) parietal-dominant subtype (P subtype, n = 28, ~18.4%) in which the bilateral parietal areas, precuneus, and bilateral dorsolateral frontal areas were involved, with little involvement of medial temporal areas; and (3) diffuse atrophy subtype (D subtype, n = 72, ~47.4%) in which nearly all association cortical areas were involved except for the orbitofrontal and occipital areas.

At the 4-cluster level (figure e-1A), the MT subtype (n = 52, 34.2%) and the P subtype (n = 28, ~18.4%) that were identified at the 3-cluster level were unchanged. D subtype, however, was subdivided into 2 subtypes: the medial frontal/temporal

Figure 1 Dendrogram created by cluster analysis of cortical thickness



The distance along the x-axis represents the measure of similarity between patients, such that the shorter the distance, the greater the similarity between patients. The blue and red lines represent the clustered 3 or 6 subtypes of AD dementia, which are illustrated in figure 2. AD = Alzheimer disease; D = diffuse atrophy subtype; FP = frontoparietal subtype; FT = frontotemporal subtype; LP = left parietal-dominant subtype; MF = medial frontal/temporal subtype; MT = medial temporal-dominant subtype; P = parietal-dominant subtype; RP = right parietal-dominant subtype.

subtype (MF subtype) in which the bilateral superior frontal gyrus and medial temporal areas were dominantly involved (n = 33, ~21.7%); and the D subtype (n = 39, ~25.7%).

At the 5-cluster level (figure e-1B), the MT (n = 52, ~34.2%), P (n = 28, ~18.4%), and MF (n = 33, ~21.7%) subtypes identified at the 4-cluster level were unchanged. D subtype was subdivided into the frontoparietal subtype (FP subtype, n = 31, ~20.4%) and the frontotemporal subtype (FT subtype, n = 8, ~5.3%). The FP subtype involved the frontal and parietal areas diffusely. The FT subtype involved the temporal and inferior parietal area, and partially involved the frontal area.

Finally, at the 6-cluster level (figure 2B), the MT (n = 52, ~34.2%), MF (n = 33, ~21.7%), FP (n = 31, ~20.4%), and FT (n = 8, ~5.3%) subtypes were unchanged. The P subtype, however, was divided according to interhemispheric asymmetry: the left parietal–dominant subtype (LP subtype) in which the left inferior parietal, lateral temporal, and lateral frontal areas were dominantly involved, with relative sparing of the medial temporal area (n = 10, ~6.6%); and the right parietal–dominant subtype (RP subtype) in which the right parietal, lateral temporal, and lateral frontal areas were dominantly involved (n = 18, ~11.8%). Comparisons of cortical thickness among the 6 AD dementia subtypes confirmed that these subtypes were reliably distinguished (figure e-2).

Principal component analyses. Details on how these subtypes were identified via principal component analyses are described elsewhere (figure e-3 and appendix e-5). The 3 subtypes identified via principal component analyses are presented in figure e-3.

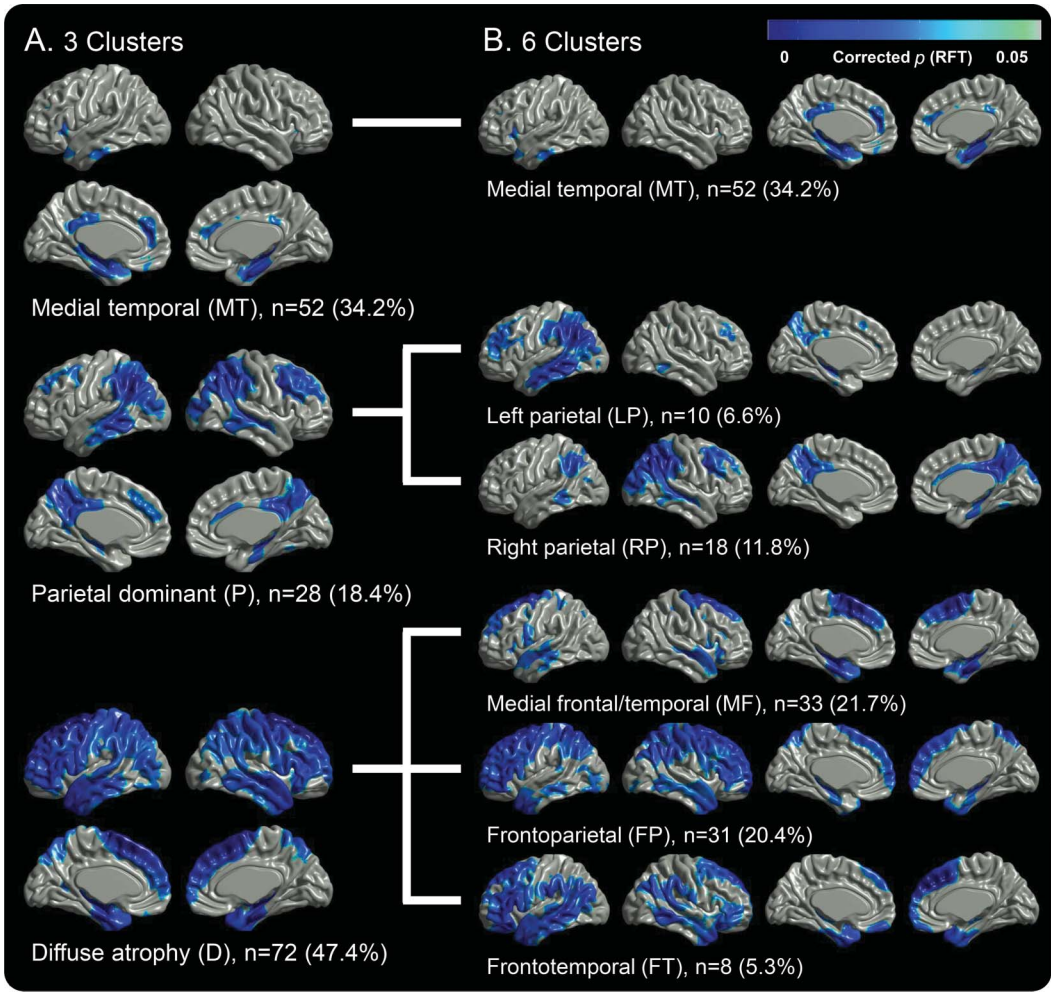
Demographic and clinical characteristics among 3 subtypes of AD dementia. The demographics of the 3 AD dementia subtypes and the NC group were compared (table 1). Among the 3 subtypes, patients in P subtype were the youngest, had the youngest age at onset, and had the highest number of education years. Meanwhile, patients in D subtype had the lowest mean cortical thickness (table 1).

Cognitive characteristics among 3 subtypes of AD dementia. To compare the neuropsychological test results, we used standard scores (*z* scores) because the age, sex, and education years were different among the AD dementia subtypes. The *z* scores were derived based on age- and education-adjusted norms.[18]

Compared with patients in other subtypes, those in P subtype scored the worst on most tests except for language function (table 2).

Comparisons of subtypes at the 6-cluster level are presented in appendix e-6 and tables e-1 and e-2.

Figure 2 Statistical maps of cortical atrophy in each of the 3 (A) or 6 (B) subtypes



These subtypes were identified from cluster analysis compared with controls (corrected for multiple comparisons using random field theory [RFT] at a vertex-wise significance level of $p < 0.05$). The results show the relationship between the 3 and 6 subtypes.

Each subgroup of D subtype showed significantly different demographic and cognitive characteristics in comparison with other AD dementia subtypes (appendix e-7).

DISCUSSION Our major finding is that AD dementia is an anatomically heterogeneous disease and may not be one disease. The cluster analysis based on cortical atrophy patterns showed that patients diagnosed with AD dementia can be categorized into anatomically different subtypes, with 3 to 6 subtypes according to the level of clustering. We further identified some demographic and clinical differences among these AD dementia subtypes in accordance with structural differences.

At the 3-cluster level, we identified MT, P, and D subtypes. Although we limited the analysis to patients in earlier stages of the disease, these results were largely in line with a recent pathologic study that identified 3 AD dementia subtypes based on the distribution and density of neurofibrillary tangles.[7] The 3 subgroups from the pathology study were limbic-predominant (14.3%), hippocampal-sparing (10.9%), and typical AD (74.8%),[7] which may respectively correspond to MT subtype (34.2%), P subtype (18.4%), and D subtype (47.4%) in our study. The frequency of typical presentation in our study (D subtype, 47.4%), however, was lower compared with the previous pathology study (74.8%). This discrepancy may be attributable to different disease stages between the 2 studies. We presume that some patients with MT subtype in earlier stage may lose the distinctive pattern and become D subtype as disease progresses.

Among the 3 subtypes, patients in the P subtype had distinct demographic and clinical features. They were younger (57.1 ± 7.84 years) at the age at onset than the other 2 subtypes (D: 72.2 ± 6.37; MT: 69.8 ± 7.77) and the sex proportion was nearly equal (female percentage: 53.6%) as opposed to the other 2 subtypes in which women outnumbered men

Table 1 Demographic and clinical characteristics of the study population

				AD subtypes (n = 152)			
	NC (n = 72)	AD dementia (n = 152)	*p* Value[a]	MT subtype (n = 52)	P subtype (n = 28)	D subtype (n = 72)	*p* Value[b]
Age at MRI, y	71.3 ± 5.76	71.8 ± 8.90	0.636	72.9 ± 7.49[c]	60.4 ± 7.88[d,e]	75.5 ± 6.19[c]	<0.001[f,g]
Age at onset, y	—	68.6 ± 9.04		69.8 ± 7.77[c]	57.1 ± 7.84[d,e]	72.2 ± 6.37[c]	<0.001[f,g]
Sex, female, n (%)	51 (70.8)	101 (66.4)	0.512	38 (73.1)	15 (53.6)	48 (66.7)	0.211[h]
Education, y	9.84 ± 4.51	9.35 ± 5.65	0.485	8.40 ± 5.42[b]	12.4 ± 4.30[a,c]	8.86 ± 5.94[b]	0.006[f,g]
Ds duration, mo	—	38.8 ± 21.58		36.9 ± 20.4	39.1 ± 19.5	40.0 ± 23.3	0.737[f]
ICV, cm^3	$1.34 \times 10^6 \pm 1.21 \times 10^5$	$1.32 \times 10^6 \pm 1.19 \times 10^5$	0.492	$1.32 \times 10^6 \pm 1.25 \times 10^5$	$1.36 \times 10^6 \pm 1.22 \times 10^5$	$1.32 \times 10^6 \pm 1.12 \times 10^5$	0.216[f]
Mean CTh	3.02 ± 0.11	2.85 ± 0.13	<0.001[g]	2.91 ± 0.13[c]	2.86 ± 0.12	2.81 ± 0.13[a]	<0.001[f,g]
***APO* ε4 genotype, n (%)**	10/49 (20.4)	55/123 (44.7)	0.003[g]	20/42 (47.6)	6/24 (25.0)	29/57 (50.9)	0.091[h]
K-MMSE	28.6 ± 1.23	21.0 ± 3.94	<0.001[g]	21.5 ± 3.88	21.5 ± 3.33	20.5 ± 4.18	0.347
CDR-SB	0	3.34 ± 0.89		3.20 ± 0.90	3.18 ± 0.94	3.50 ± 0.86	0.108

Abbreviations: AD = Alzheimer disease; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CTh = cortical thickness; D subtype = diffuse atrophy subtype; Ds = disease; ICV = intracranial volume; K-MMSE = Korean version of Mini-Mental State Examination; MT subtype = medial temporal–dominant subtype; NC = normal control; P subtype = parietal-dominant subtype.
Data are presented as mean ± SD. CDR-SB scored out of 18; K-MMSE scored out of 30.
[a] The *p* value for the comparison between the AD dementia and control groups.
[b] The *p* value for the comparison across the three AD subtypes.
[c] Significant difference ($p < 0.05$) between P subtype and the other subtypes.
[d] Significant difference ($p < 0.05$) between MT subtype and the other subtypes.
[e] Significant difference ($p < 0.05$) between D subtype and the other subtypes.
[f] Analysis of variance followed by Bonferroni post hoc test was used.
[g] Significant *p* values (<0.05).
[h] The χ^2 test was used.

Table 2 Neuropsychological test results

	AD subtypes			
	MT subtype (n = 52)	P subtype (n = 28)	D subtype (n = 72)	*p* Value
Attention				
Digit Span Forward	−0.34 ± 1.15	−0.48 ± 1.02	−0.22 ± 0.96	0.515
Digit Span Backward	−0.46 ± 1.13[a]	−1.18 ± 0.88[b]	−0.69 ± 1.02	0.014[c]
Language and related function				
K-BNT	−2.64 ± 2.60	−3.87 ± 3.63	−2.86 ± 2.46	0.157
Visuospatial function				
RCFT copy	−1.04 ± 1.90[a]	−5.77 ± 5.82[b,d]	−1.90 ± 2.25[a]	<0.001[c]
Memory				
SVLT, immediate recall	−1.32 ± 0.83[a]	−2.26 ± 1.25[b,d]	−1.51 ± 0.84[a]	<0.001[c]
SVLT, delayed recall	−2.08 ± 0.79[a]	−2.71 ± 0.91[b,d]	−1.96 ± 0.79[a]	<0.001[c]
SVLT, recognition	−1.95 ± 1.21[a]	−3.11 ± 2.39[b,d]	−1.82 ± 1.39[a]	0.001[c]
RCFT, immediate recall	−1.51 ± 0.59[a]	−2.29 ± 0.81[b,d]	−1.53 ± 0.72[a]	<0.001[c]
RCFT, delayed recall	−1.69 ± 0.68[a]	−2.28 ± 0.92[b,d]	−1.68 ± 0.68[a]	0.001[c]
RCFT, recognition	−1.63 ± 0.98	−2.15 ± 1.59[d]	−1.37 ± 1.14[a]	0.018[c]
Frontal executive function				
COWAT, semantic fluency–animals	−1.12 ± 0.94	−1.46 ± 0.87	−1.07 ± 1.12	0.226
COWAT, semantic fluency–supermarket items	−0.90 ± 0.83[a]	−1.64 ± 0.76[b,d]	−1.04 ± 0.83[a]	0.001[c]
COWAT, phonemic fluency with 3 letters	−0.62 ± 0.94[a]	−1.29 ± 1.00[b]	−0.97 ± 0.86	0.011[c]
Stroop test, color reading	−1.20 ± 1.20[a]	−3.89 ± 1.94[b,d]	−1.52 ± 1.31[a]	<0.001[c]

Abbreviations: AD = Alzheimer disease; COWAT = Controlled Oral Word Association Test; D subtype = diffuse atrophy subtype; K-BNT = Korean version of Boston Naming Test; MT subtype = medial temporal–dominant subtype; P subtype = parietal-dominant subtype; RCFT = Rey–Osterrieth Complex Figure Test; SVLT = Seoul Verbal Learning Test.
Data are shown as mean ± SD. All data are *z* scores. Analysis of variance followed by Bonferroni post hoc test was used.
[a] Significant difference ($p < 0.05$) between P subtype and the other subtypes.
[b] Significant difference ($p < 0.05$) between MT subtype and the other subtypes.
[c] Significant *p* values ($p < 0.05$).
[d] Significant difference ($p < 0.05$) between D subtype and the other subtypes.

(D: 66.7%; MT: 73.1%). The proportion of females with hippocampal-sparing AD (37%) was also lower than for limbic-predominant AD (69%) in the pathologic study.[7] Although the P subtype appeared to have lower *APO* ε4 frequency than the other subtypes, this difference did not reach statistical significance. Previous studies have demonstrated that patients with early-onset AD (EOAD) seldom carry the *APO* ε4 allele.[7,25]

Our patients with P subtype had a distinct clinical phenotype regarding cognitive deficit profile with attention, visuospatial, and frontal-executive functions being significantly impaired in comparison to the other 2 subtypes. These neuropsychological findings may be consistent with the observed cortical thinning in patients with P subtype that predominantly affected bilateral parietal cortices, precuneus, and dorsolateral frontal cortices. Decreased attention in our patients with P subtype may be associated with dorsolateral prefrontal and parietal dysfunction, and visuoconstructive deficits may primarily be attributed to cortical thinning in parietal areas. The precuneus is known to be associated with a broad range of highly integrated tasks, such as executive function, retrieval of episodic memory, visuospatial imagery, and self-processing operations.[26–28] We therefore assume that the precuneus damage in our patients with P subtype might have also contributed to their impaired attention, visuospatial function, and executive function. Because the medial temporal area was relatively spared in the P subtype, we expected that performance on tests of episodic memory would be better in this type than in the other subtypes. Contrary to our expectations, however, all scores for memory function tests were also the worst in patients with P subtype. It is possible that memory deficits in these patients may be associated with deficits in attention and working memory, which are related to dorsolateral prefrontal and parietal dysfunction. Alternatively, precuneus damage or its extension to the retrosplenial region (see figure 2), which has been demonstrated to be important

in episodic memory, may have also contributed to the memory impairment.[29] In summary, our patients with P subtype are largely in line with patients with EOAD who show predominant parietal symptoms and signs,[30] disproportionate atrophy in the precuneus compared with late-onset AD,[31] and the hippocampal-sparing group seen in a pathologic study.[7]

Our P subtype was further divided into LP and RP subtypes; these 2 subtypes showed differences in neuropsychological test performance. Patients with LP subtype had lower scores on tests that demand language function such as naming, verbal memory, and oral word fluency. However, the patients with RP subtype performed worse on visuospatial function tests. These findings are in line with previous reports of left-right asymmetries: greater leftward asymmetry for neurofibrillary tangles or cortical atrophy is observed in the aphasic phenotype,[6,32] whereas greater hypometabolism on the right side is associated with visuospatial dysfunction.[1,10] In addition, it may be possible that an extreme form of LP subtype may represent logopenic progressive aphasia whereby patients present with progressive language disturbance, which is similar to the conduction aphasia associated with strokes in the region of the inferior parietal lobe. Anatomical substrates for logopenic aphasia localize mainly to the left temporal–parietal junction with additional left dorsolateral prefrontal regions,[33] which largely overlap the lesions of our LP subtype.

Our P subtype may not follow Braak staging, because parietal and frontal cortices are known to be regions where amyloid deposition may occur only in later stages (stage V). However, a previous report suggested that the origin and spread of pathology in AD cases does not always follow Braak staging.[7] They also demonstrated that the cortical atrophy patterns on MRI differed among the pathologic subtypes of AD dementia.[34]

In contrast to patients with P subtype, patients with MT subtype were older and predominantly women (73.1%), with a higher frequency of *APO* ε4 allele carriers (MT vs $p = 47.6\%$ vs 25.0%). This sex difference might result from age-related reductions in sex hormone (estrogen). Estrogen is known to increase neurogenesis in the hippocampus, and an alteration in the response of the hippocampus to estrogen may cause age-related changes in the female brain.[35,36] Second, a preclinical study showed that *APO* ε4 affects the brains of women more than men.[37] At the same time, *APO* ε4 may have regionally specific effects in the medial temporal lobe.[38] Therefore, in the elderly AD population, women more than men may have a more vulnerable medial temporal cortex, resulting in the MT subtype.

The MT subtype shares several clinical characteristics with subtypes from studies that were labeled as limbic neurofibrillary tangle dementia,[39] tangle-predominant dementia,[40] or limbic-predominant AD.[7] These subsets of late-onset AD are associated with older age and female predominance, in which neurofibrillary tangles were predominant in the allocortical regions with few isocortical tangles.[7,39,40] Patients with MT subtype also had cortical thinning in the anterior and posterior cingulate cortices. Therefore, we presume that the involvement of the posterior cingulate–retrosplenial cortex, along with medial temporal lesions, contributes to memory dysfunction in these patients. Although the anterior cingulate cortex is associated with the expectation of tasks, attention, modulation of emotion, and motivation, its role in the behavioral manifestations of this MT subtype needs to be further clarified.

Patients with D subtype were the oldest and had the lowest mean cortical thickness among the 3 subtypes. The level of female predominance was between the ranges of the other 2 subtypes. The proportion of patients carrying the *APO* ε4 allele was higher than the P subtype, but similar to the MT subtype. The neuropsychological profiles of the D subtype were not significantly different from those of the MT subtype. This subtype may be compatible with typical AD dementia, as observed in a pathologic study.[7]

In conclusion, based on cortical thickness measurements, it appears that there are at least 3 major subtypes of AD dementia: (1) the parietal-dominant atrophy, younger onset, equal sex, low *APO* ε4 subtype; (2) the medial temporal/cingulate-dominant atrophy, older onset, female dominance, high *APO* ε4 subtype; and (3) the diffuse atrophy subtype with characteristics in between. It is possible that with a larger group of participants, a total of 4 to 6 distinctive subtypes could be characterized based on patterns of atrophy. Consideration of this heterogeneity in the patterns of atrophy and the associated neurobehavioral decrements may be important when planning future preventative and treatment strategies, because the subtypes described in this study may have different responses to treatment. In addition, these subtypes may have different courses of disease progression. Because P subtype was similar to EOAD in demographics and cognitive function, we presume the disease progression of P subtype may follow the pattern of EOAD. Previous studies have revealed that typically EOAD has a rapid cognitive decline with rapidly occurring cortical atrophy.[19,30] In contrast, MT subtype, which is similar to limbic-predominant late-onset AD, may have a slower cognitive decline with slower cortical thinning.[4,7,19]

There are some limitations to this study. First, the participants were not studied using amyloid-PET imaging, their CSF was not assayed for β-amyloid peptides/tau, and postmortem pathologic studies

were not performed. Thus, we cannot completely exclude the possibility that our sample may include participants with other forms of dementia. Second, the younger age of the patients with AD dementia might alter the relative distribution of subtypes, because the previous study showed the strong effects on the proportion of different pathologic subtypes. Future studies examining these factors may enable a better understanding of the pathologic basis of these subtypes.

AUTHOR CONTRIBUTIONS

Young Noh, MD, Seun Jeon, MS: conception and design, data analysis and interpretation, manuscript writing. Jong Min Lee, PhD, Sang Won Seo, MD: collection and assembly of data, data analysis and interpretation. Geon Ha Kim, MD, Hanna Cho, MD, Byoung Seok Ye, MD, Cindy W. Yoon, MD, Hee Jin Kim, MD: collection and assembly of data, data analysis and interpretation. Juhee Chin, PhD: collection and assembly of data, data analysis and interpretation. Kee Hyung Park, MD: data analysis and interpretation. Kenneth M. Heilman, MD: data analysis and interpretation, revision of the manuscript for intellectual content. D.L. Na, MD: conception and design, data analysis and interpretation, revision of the manuscript for intellectual content.

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