Topography of cortical thinning in subcortical vascular mild cognitive impairment and subcortical vascular dementia

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Topography of cortical thinning in subcortical vascular mild cognitive impairment and subcortical vascular dementia

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<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

<ABSTRACT>

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Background: Amnestic mild cognitive impairment (MCI) is known to be a preclinical stage of Alzheimer's disease (AD). Likewise, an MCI associated with small vessel disease (subcortical vascular mild cognitive impairment, svMCI), might be a forme froste of subcortical vascular dementia (SVaD). There have been few studies that investigated cortical thinning in SVaD or svMCI that may be another important variable, in addition to white matter ischemia, contributing to clinical manifestations of these two disorders.
***Objectives*:** The purpose of this was 1) to compare cortical thinning between SVaD and AD, and 2) to determine if svMCI differs from SVaD in the distribution of cortical atrophy, which may help understand the hierarchy between svMCI and SVaD and how svMCI evolves into SVaD.
***Methods*:** Participants were 20 patients with SVaD, 34 patients with svMCI, 115 patients with AD, and 96 healthy subjects (NC) who were imaged with MRI including three-dimensional volumetric images for cortical thickness analysis across the entire brain. Differences in the pattern of cortical thinning between AD versus SVaD and svMCI versus SVaD were analyzed by applying analysis of covariance on a vertex-by-vertex basis.
***Results*:** Relative to NC, AD groups showed cortical thinning distributed in temporoparietal association cortices including the medial temporal lobe. In contrast, SVaD groups showed cortical thinning primarily distributed in all frontal areas, with this being most pronounced in prefrontal cortices followed by premotor and motor cortices. Comparison between the AD and SVaD groups revealed that SVaD groups showed cortical thinning mainly in the frontal region while AD groups showed cortical thinning predominantly in the temporoparietal regions. Compared to NC, svMCI groups showed

cortical thinning in inferior frontal and orbitofrontal gyri, anterior cingulate, insula, superior temporal gyrus, parahippocampal gyrus, cuneus, and lingual gyrus, while cortical thinning in SVaD groups involved all these areas plus middle and superior frontal gyri, medial frontal gyrus, anterior portion of lateral temporal gyrus, and fusiform gyrus.

***Conclusions*:** This study showed that the topography of cortical thinning of SVaD is distinct from that of AD, suggesting that the underlying mechanisms underlying these two disorders may be quite different. This study also demonstrated that there is a hierarchy between svMCI and SVaD, suggesting that svMCI defined with this criteria may be a transitional state between normal cognition and SVaD.

Key words : small vessel disease, dementia, mild cognitive impairment, subcortical, cortical thinning, cortical atrophy

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I. INTRODUCTION

Vascular dementia (VaD) comprises many subtypes. These include multi-infarct dementia in which dementia is caused by recurrent multiple-territory infarctions, and single-infarct dementia in which even a single-territory infarction or lacune when occurring in a strategically important brain region can cause persistent and profound dementia. A third type, one of the most common VaDs especially in Asian countries, is subcortical VaD (SVaD).[1] SVaD results from small vessel disease that produces multiple lacunes or ischemic changes in the subcortical gray matter and cerebral white matter.[2]

Multi-infarct and single-infarct dementia exhibit diverse clinical features that vary according to the involved vessels, whereas SVaD is relatively homogeneous in terms of both lesion location and clinical manifestations. Cognitive impairments in SVaD are probably related to ischemic interruption of frontal subcortical circuits [3, 4] or disruption of cholinergic pathways that traverse the subcortical white matter. [5] These neural networks may be affected even in early stages of SVaD, which supports mechanisms for cognitive deficits and neurobehavioral symptoms such as apathy, abulia, aspontaneity, agitation, disinhibition, frontal executive dysfunctions, and relatively mild memory dysfunction due to inadequate retrieval strategies.[3, 4] These clinical characteristics of SVaD are quite distinct from those of Alzheimer's disease (AD), in which temporoparietal regions are predominantly affected in the earlier stages of the disease, resulting in memory loss of encoding-deficit type, anomia, and visuospatial dysfunction, with frontal dysfunctions only appearing in

later stages of AD. In addition, focal neurologic signs and vascular parkinsonism associated with ischemic changes are much more common in SVaD than in AD.

Recent studies suggest that SVaD and AD (which are the two most common dementias) overlap pathologically, in that patients who are clinically diagnosed with SVaD also have coassociated AD pathology, and vice versa.[6] Furthermore, some autopsy studies have shown that pure VaD is rare.[7] However, differentiating SVaD from AD is still important for therapeutic interventions, especially as more specific therapies are developed.

There has recently been considerable interest in detecting dementia in its earliest stage. Many studies suggested that mild cognitive impairment (MCI), especially of the amnestic type, is a prodromal stage for AD. Likewise, there must be a preclinical stage of SVaD (an MCI associated with small vessel disease), which was termed subcortical vascular MCI (svMCI) in this study. The clinical importance of svMCI might be higher than those of other types of MCI since management of risk factors and drug treatment could prevent the evolution of svMCI to SVaD. Nonetheless, the clinical and imaging characteristics of svMCI have not been well defined (Table 1).[8-13]

Table 1. Previous reported articles in svMCI.

Authors	Subjects	Types of study	Results	Diagnostic criteria
Meyer et al, 2002	10 svMCI	Longitudinal (3.72+/-2.94years)	During 3.72+/-2.94years of follow-up of normal subjects, 12 of 291 developed subcortical small vessel dementia. Of those, ten patients had prodromal MCI.	Modified Petersen's criteria + focal neurological sign + small vessel features (Detail description for small vessel features have not been mentioned)
Frisoni et al, 2002	29 svMCI	Longitudinal (32+/-8 months)	Twenty-nine patients with MCI-V, MCI-V patients showed a poor performance on frontal tests and impairment of balance and gait. Of those followed for at least 40 months, 50 % of patients with MCI-V had died.	Modified Petersen's criteria +modified criteria for subcortical vascular dementia (SVD) by Erkinjuntti
galluzzi et al, 2005	29 svMCI	Cross-sectional	Letter fluency, digit span forward, EPS stance and gait, and irritability were best prediction of svMCI.	Modified Petersen's criteria +modified criteria for subcortical vascular dementia (SVD) by Erkinjuntti.
Mendonca et al, 2005	15 svMCI	Cross-sectional	Of forty MCI, 15 were found to have subcortical vascular features.	modified Petersen's criteria + Hachinski ischemic score + small vessel features (Detail description for small vessel features have not been mentioned)
Zanetti et al, 2006	34 with mcd-MCI	Longitudinal (3years)	Of 34 with mcd-MCI, nine evolved to subcortical VaD	Multiple domain MCI + ischemic changes shown by CT (Detail description for small vessel features have not been mentioned)
Bomboi s et al, 2007	170 consecutive MCI patients	Cross-sectional	Of 170 MCI, Subcortical hyperintensities were found in 157 patients	NA

One of the diagnostic hallmarks of SVaD and svMCI is the presence of ischemic changes or lacunes in magnetic resonance imaging (MRI). Ischemic rating alone, however, cannot predict the dementia severity or differentiate SVaD or svMCI from AD or amnestic MCI for several reasons: (1) The ischemic change is a nonspecific phenomenon arising from a variety of etiologies including degenerative processes, (2) the clinical manifestations of ischemia are unpredictable since many ischemic lesions can be asymptomatic, and (3) the pathology of AD and SVaD can coexist. As mentioned above, the cognitive decline in a patient with SVaD or svMCI is secondary to disruption of frontal subcortical circuits or cholinergic pathways. Thus, cortical changes in SVaD or svMCI may be more strongly correlated with neuropsychological deficits than with white matter ischemia per se. Also, the regional distribution of cortical changes may help differentiate SVaD or svMCI from other degenerative dementia or MCI.

Cortical changes in patients with SVaD or svMCI have been studied with functional imaging techniques such as single-photon-emission computed tomography (SPECT) [14] and positron-emission tomography (PET).[15] In contrast, no MRI studies have specifically identified the distribution pattern of cortical thinning in SVaD or svMCI. MRI results would reflect cortical atrophy more directly than SPECT or PET results since the alteration of perfusion or metabolism in functional images can be affected by such factors as metabolic disturbances and drug therapy other than cortical atrophy per se. Furthermore, it is debatable whether decreased

cortical activity in glucose PET reflects true cortical hypometabolism or a partial volumetric effect that is secondary to cortical atrophy.[16]

The aim of this study was to compare the regional distribution of cortical thinning of SVaD with that of AD by quantifying the thickness of the cortical mantle across the entire brain using automated three-dimensional (3D) image processing. Another aim was to determine if the severity and distribution of cortical atrophy differ between svMCI and SVaD, which may help understand the hierarchy between svMCI and SVaD and possibly how svMCI evolves into SVaD.

II. MATERIALS AND METHODS

1. Participants

A. Patients

The patient groups consisted of 20 patients with SVaD and 34 patients with svMCI who underwent high-resolution T1-weighted volumetric MRI scans at Samsung Medical Center, Seoul, Korea between January 2004 and December 2006. SVaD patients met the criteria for VaD described by the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) [17] and also fulfilled the imaging criteria proposed by Erkinjuntti et al..[18] These patients therefore showed multiple cognitive dysfunction as well as focal neurological symptoms or signs that included corticobulbar signs (facial palsy, dysarthria, dysphagia, or pathologic laughing or crying), pyramidal signs (hemiparesis, hyperactive deep tendon reflexes, or extensor plantar responses), or parkinsonism (short-step gait, festination

gait, shuffling gait, decreased arm swing while walking, rigidity, bradykinesia, or postural instability). The presence of significant ischemia associated with small vessel disease was defined according to the imaging criteria proposed by Erkinjuntti et al.. Diagnosis of svMCI was based on the following criteria modified from those proposed by Petersen et al. [19]: (1) subjective cognitive complaints by the patient or his/her caregiver, (2) normal general cognitive function as measured by a score on the Korean version of the Mini-Mental State Examination (MMSE) above the 16th percentile of age- and sex-matched norms, (3) normal activities of daily living (ADL) as judged by both an interview with a clinician and the standardized ADL scale described below, (4) objective cognitive decline below the 16th percentile of norms on standardized neuropsychological tests, (5) presence of focal neurological symptoms or signs described earlier, (6) significant small vessel ischemic changes without territory infarction on brain MRI as described below, and (7) absence of dementia. The presence of significant ischemic changes associated with small vessel disease was defined as high signal intensities (HSI) on T2-weighted or FLAIR images that fulfilled the following criteria: (1) HSI of periventricular white matter (caps or rim) longer than 10 mm, and (2) HSI in deep white matter consistent with extensive white matter lesion or diffusely confluent lesion ≥25 mm in maximum diameter. When defining deep white matter, HSI evident in the axial slice just above the top of lateral ventricles was considered to be a periventricular white matter lesion, while HSI evident in the second or more axial slices above the top of the lateral ventricles were considered to be deep white matter lesions. These patients

who met these operational svMCI criteria also fulfilled the grade 3 of the Fazekas criteria.[20]

B. Controls

Control groups consisted of 115 patients with probable AD and 96 normal-cognition (NC) patients who underwent high-resolution T1-weighted volumetric MRI scans at Samsung Medical Center, Seoul, Korea between January 2004 and December 2006. All the AD 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.[21] The NC group had no history of neurological or psychiatric illnesses and showed normal findings in neuropsychological tests.

All the subjects underwent a clinical interview and neurological examination. The absence of secondary causes of cognitive deficits was assessed by laboratory tests including complete blood count, blood chemistry, vitamin B_{12}/folate, syphilis serology, and thyroid function tests. Detailed criteria of exclusion were described in Table 2. Conventional brain MRI scans (T1-weighted, T2-weighted, and FLAIR images) confirmed the absence of territorial cerebral infarctions, brain tumors, and other structural lesions. The study was approved by the Institutional Review Board of Samsung Medical Center. The demographic features of the patients are detailed in Table 3.

2. Clinical interview (CRCD protocol)

Clinical interview for all the subjects will be performed according to Clinical Research Center for Dementia (CRCD) protocol. The CRCD protocol has been designed to assess 1) cognition, 2) activities of daily living (ADL), 3) behavioral and psychological symptoms of dementia (BPSD), and 4) etiologies of dementia. CRCD protocol contains basic information, past and family medical history, current medication history, interview for cognitive function (interview of memory, language, visuospatial function, attention, judgement, and abstract thinking), and Mini-Mental State Examination (MMSE), Clinical Dementia Rating Scale (CDR), Global Deterioration Scale (GDS), activities of daily living scales (physical and instrumental), abnormal behavior [Neuropsychiatry Inventory (NPI) and Geriatric Depression scale], and Hachinski ischemic scale.

Table 2. Check lists of exclusion for participants.

Check lists		Yes	No
A primary caregiver willing to accept responsibility for supervising the evaluations assessing the condition of the patient throughout the study, and for providing input to efficacy assessments in accordance with all protocol requirements.			
Any condition other than svMCI that could explain the patient's cognitive impairment.			
Medical disease	Abnormal thyroid function tests		
	Vitamin B12 or folate deficiency		
	Syphilis		
	Metabolic encephalopathy		
Neurological and Psychiatric disease	A current DSM-IV Axis I diagnosis that may interfere with the evaluation of natural course of disease.		
	Mental Retardation		
	A history of encephalitis, brain tumor, hemorrhage and aneurysm		
	A history of head trauma that may cause a loss of consciousness.		
A disability that may prevent the patient from competing all study requirements	Blindness, deafness, severe language difficulty		
	Sick-sinus syndrome, sino-atrial block, second or third degree atrio-ventricular block		
	A current diagnosis of severe or unstable asthmatic conditions (COPD)		
	A current diagnosis of active, uncontrolled peptic ulceration or GI bleeding		
	DM that may be uncontrolled by insulin		
	Chronic renal failure that may be uncontrolled by dialysis.		
	Malignancy		

Table 3. Demographic variables and Mini-Mental State Examination (MMSE) scores of subjects.

	NC *N*=96	AD *N*=115	SVaD *N*=20	svMCI *N*=34
Age: years, mean±SD	67.7±6.3	72.7±6.9*	74.2±6.1*	70.6±6.4*
Sex: female, *N* (%)	54 (56.3%)	80 (69.6%)	11 (55.0%)	15 (44.1%)
Education: years, mean±SD	10.8±4.8	8.5±5.4*	7.2±5.5*	10.1±4.8
MMSE,mean±SD	28.6±1.5	17.7±5.4*	19.0±5.1*	26.2±2.2*,†

N: number of subjects, NC: normal cognition, AD: Alzheimer's disease, SVaD: subcortical vascular dementia, svMCI: subcortical vascular mild cognitive impairment, SD: standard deviation. *P<0.05 between NC and AD, NC and SVaD, or NC and svMCI; †P<0.05 between SVaD and AD, or SVaD and svMCI

3. Neuropsychological tests

All patients and controls underwent neuropsychological tests using a standardized neuropsychological battery the Seoul Neuropsychological Screening Battery (SNSB).[22] This battery contains tests for attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructive function, verbal and visual memory, and frontal/executive function. Among these, the tests comprised the digit span (forward and backward), the Korean version of the Boston Naming Test (K-BNT),[23] the Rey-Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-min delayed recall, and recognition), Seoul Verbal Learning Test (SVLT; three learning-free-recall trials of 12 words, 20-min delayed-recall trial for these 12 items, and a recognition test), Contrasting program, Go/no-go, Fist-edge-palm test, Alternating hand movement, Alternating squares and triangle, Luria loop, phonemic and semantic Controlled Oral Word Association Test (COWAT), and Stroop Test

(word and color reading of 112 items during a 2-min period) (Table 4). Age-, sex-, and education-specific norms for each test based on 447 normal subjects were used. The scores of these scorable cognitive tests were classified as abnormal when they were below the 16th percentiles of the norms for the age-, sex-, and education-matched normal subjects.

Table 4. Tests that are included Seoul Neuropsychological Screening Battery

Cognitive Domain	Neuropsychological Tests	Scorable items
Attention	Digit Span: Forward / Backward Letter Cancellation	Forward / Backward (9 / 8)
Language & Related Functions	Spontaneous Speech / Comprehension / Repetition Korean-Boston Naming Test (K-BNT) Reading / Writing Finger Naming / Right-Left Orientation / Calculation / Body Part Identification Praxis Test: Buccofacial, Ideomotor	S-K-BNT (15) Calculation (12)
Visuospatial Functions	Korean-Mini Mental State Examination (K-MMSE): Drawing Rey Complex Figure Test (RCFT): Copy	RCFT: Copy (36)
Memory	K-MMSE: Registration/ Recall Seoul Verbal Learning Test (SVLT) RCFT: Immediate & Delayed Recalls/ Recognition	SVLT (36 + 12+ 12 = 60) RCFT (36 + 36+ 12 = 84) K-MMSE(orientation) = 6
Frontal / Executive Functions	Motor impersistence Contrasting Program / Go-No-Go Test Fist-Edge-Palm / Alternating Hand Movement Alternating Square & Triangle / Luria Loop Controlled Oral Word Association Test (COWAT): - Semantic (Animal, Supermarket) - Phonemic (Korean version of FAS) Korean-Color Word Stroop Test (K-CWST)	Motor impersistence (3) Contrasting / Go-No-Go Test (3/3) Fist-Edge-Palm (3) Luria Loop (3) Animal (20) Phonemic (15) Color reading (20)
General Cognition Indices	K-MMSE Global Deterioration Scale (GDS) Clinical Dementia Rating Scale (CDR)	Total score (300)

4. Image acquisition and processing, and cortical thickness measurement

3D T1-weighted spoiled-gradient echo MRI images from 265 subjects (20 with SVaD, 34 with svMCI, 115 with probable AD, and 96 with NC) were acquired using a 1.5-tesla 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, 22×22 cm; and matrix size, 256×256 pixels. Several preprocessing steps were applied to measure the cortical thickness. Images were processed using the standard Montreal Neurological Institute (MNI) anatomic pipeline. The native MRI images were registered into a standardized stereotaxic space using linear transformation.[24] The N3 algorithm was used to correct images for intensity nonuniformities resulting from inhomogeneities in the magnetic field.[25] The registered and corrected volumes were classified into white matter, gray matter, cerebrospinal fluid, and background using a 3D stereotaxic brain mask and the Intensity-Normalized Stereotaxic Environment for Classification of Tissues (INSECT) algorithm.[26] The surfaces of the inner and outer cortices were automatically extracted using the Constrained Laplacian-Based Automated Segmentation with Proximities (CLASP) algorithm.[27]

The presence of areas of white matter hyperintensity (WMH) on MRI scans of SVaD patients makes it difficult to completely delineate the inner cortical surface with correct topology. A semiautomated method was used to overcome this technical limitation, in which the region with WMH was manually outlined and substituted it for the intensity of normal tissue (Figure 1).

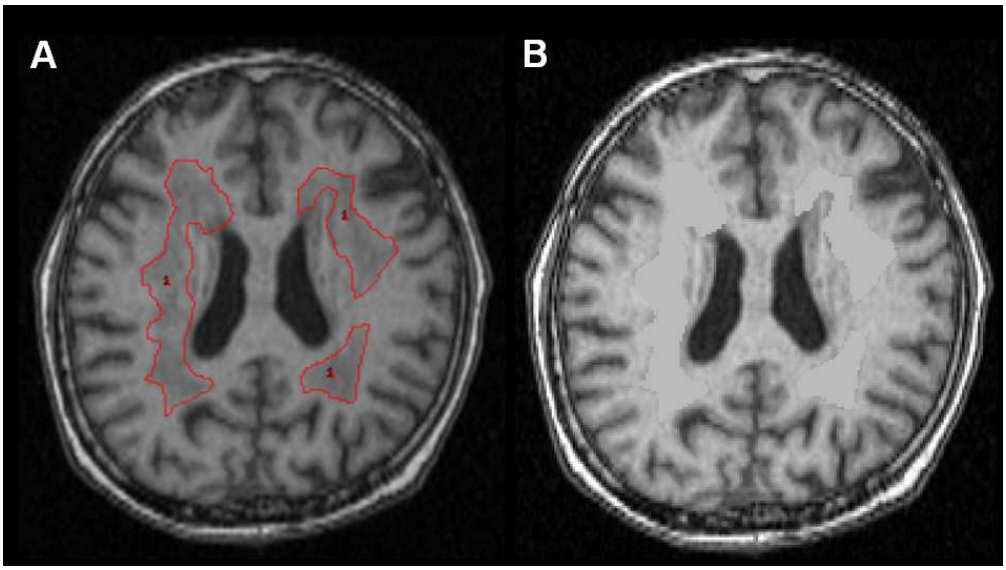

Figure 1. New semiautomated method for tissue classification in patients with svMCI and SVaD. First, white matter hyperintensities (WMHs) were manually traced (A), and then these WMHs were replaced by normal-appearing white matter (B).

Preprocessing for spoiled-gradient echo MRI was performed using Analyze 7.5 (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). A trained investigator blinded to clinical information manually traced WMHs in 20 SVaD patients and 34 svMCI patients. Tracing was performed in three orthogonal viewing planes, and directly on axial images for WMH. Then manually traced WMHs were replaced by normal-appearing white matter intensity. The cortical thickness was defined as the Euclidean distance between linked vertices of the inner and outer surfaces.[28] The thickness values were calculated in native space of the brains rather than in Talairach space so as to increase the amount of statistically significant data.[29] Since the cortical surface models were extracted from MRI volumes transformed into stereotaxic space, the cortical thickness was measured in native

space by applying an inverse transformation matrix to cortical surfaces and reconstructing them in native space.[30] These assessment items were summarized in Table 5.

Table 5. Assessment items in this study.

Demographic variables (CRCD protocol)
age, gender, duration of education, height, weight, level of economy, handedness, occupation, activity of lesure, social activity, sleep, smoking, alcohol drinking, exercise
Past history: head trauma, CO intoxication, stroke, brain surgery
Associated disease: hypertension, DM, hyperlipidemia, heart disease, obesity, homocysteinemia
Family history: dementia, stroke, other degenerative disease
Medication history: antiplatelet agents, NSAIDs, Hormone, osteoporosis
Vital signs and Neurological examinations:
BP, pulse rate, body temperature, body weight, neurologic examinations including PEPS
Neuropsychological examination: SNSB (see text)
Assessment of ADL and behaviors
ADL: Physical ADL, Instrumental ADL
Behavior: CGA-NPI, FBI
Laboratory tests
CBC, Blood chemistry, Apo E polymorphism, Homocysteine, CRP
MRI (T1, T2, FLAIR, Gradient echo axial imaging, SPGR)
Severity of ischemic changes, number of lacunes and microbleeds, and cortical thickness

5. Intrarater reliability

The intrarater reliability of this new semiautomated method for tissue classification was assessed by the investigator tracing WMHs twice (1 month apart) in eight randomly selected patients.

6. Nonlinear registration of cortical surface

To compare the thicknesses of corresponding regions between subjects, the thickness values were spatially normalized using surface-based two-dimensional registration with a sphere-to-sphere warping algorithm, in which the vertices of each subject were nonlinearly registered to a surface group template. An improved

surface registration algorithm and an unbiased iterative group template showing enhanced anatomic detail were employed.[31] Using the transformation, thickness information on the vertices was transformed to an unbiased iterative group template. For global and lobar regional analysis, data of 30 normal subjects that had previously been manually categorized to lobes, and which had shown high interrater reliability,[32] were registered to the template. The template then took the label of maximum probability in each vertex. An individual cortical surface of a subject was registered to the precategorized template and automatically divided into frontal, temporal, parietal, and occipital lobes. Averaged values of the thickness of the whole vertex in each hemisphere and lobar region were used for the global analysis.

7. Statistical analysis

Diffusion smoothing with a full-width half-maximum of 20 mm was used to blur each map of the cortical thickness, which increased both the signal-to-noise ratio and statistical power.[28, 30] The localized differences between the NC, AD, and SVaD groups were analyzed by applying ANCOVA on a vertex-by-vertex basis, and statistical maps of differences in cortical thickness between groups were constructed on a surface model, with age, sex, and education entered as covariates. A Bonferroni post-hoc analysis was performed using the following contrasts: (1) AD<NC, (2) SVaD<NC, and (3) AD<SVaD. The same procedure was applied to the NC, svMCI, and SVaD groups, with the Bonferroni post-hoc analysis performed using the following contrasts: (1) svMCI<NC, (2) SVaD<NC, and (3) SVaD<svMCI. The cortical surface model contained 40,962 vertices, and the

thresholds for multiple comparisons were corrected to reduce the false-positive rate.[33] The false-discovery-rate correction for multiple comparisons was performed at a corrected probability value of $P<0.05$. In order to calculate thickness differences between the test and retest, Spearman's correlation was performed for the overall thickness. To assess local differences in cortical thickness measurements, the groupwise absolute mean of the thickness difference was computed at every vertex of the cortical surface atlas according to $\frac{\sum_{j=1}^{8}\left|T_{ij}^{1st}-T_{ij}^{2nd}\right|}{8}$ for the *i*th vertex, where *j* is the subject and *T* is the cortical thickness. Vertex-based paired *t*-tests were used to detect regions where the thickness differed significantly between the test and retest.

III. RESULTS

1. Results of neuropsychological tests

Results of neuropsychological test were compared between groups only for subjects in whom the time interval between MRI and neuropsychological testing was less than 3 months. The data from the neuropsychological testing in the four study groups are presented in Table 6.

ANCOVA showed that impairment in all cognitive domains was greater in patients with SVaD and those with AD than in NC subjects. Comparison between the SVaD and AD groups revealed that AD patients showed greater impairment in delayed recall/recognition of SVLT and recognition of Rey figures, whereas SVaD showed greater impairment in phonemic and semantic COWAT.

The results of neuropsychological tests were compared between the SVaD and svMCI groups using ANCOVA. Compared to NC subjects, patients with svMCI showed greater impairment in all cognitive domains except in attention, recognition of Rey figures, contrasting program, alternating squares and triangles, Luria loop, and Stroop word-reading test. Comparison between the SVaD and svMCI groups revealed that SVaD patients showed greater impairment in all cognitive domains except in recognition of Rey figures, alternating hand movement, and Luria loop, whereas the impairment in svMCI patients was no greater in any of the cognitive domains.

Table 6. Results of neuropsychological tests in the NC, AD, SVaD, and svMCI groups.

Neuropsychological tests (possible maximum score)	NC	AD	SVaD	svMCI
Attention				
Digit span: forward	5.9±1.6 (63)	4.7±1.3 (105)*	4.4±1.2 (18)*	5.8±1.3 (33)*
Digit span: backward	3.7±1.1 (63)	2.8±1.2 (104) *	2.3±1.0 (18)*	3.4±1.0 (33)†
Language and related disorders				
K-BNT (60)	47.2±8.6 (63)	29.6±11.5 (101)*	28.1±7.7 (17)*	41.7±9.9 (33)*,†
Visuospatial function				
RCFT (36)	32.8±3.7 (63)	21.4±11.0 (103)*	21.4±8.4 (16)*	28.5±7.4 (33)*,†
Memory				
SVLT: sum of three free recall trials (12+12+12=36)	20.7±3.8 (63)	8.9±4.7 (106)*	10.5±4.2 (17)*	14.5±4.8 (33)*,†
SVLT: delayed recall (12)	7.0±1.7 (63)	0.6±1.4 (106)*,†	1.7±1.9 (17)*	2.1±0.4 (33)*,†
SVLT: recognition score (true positive+true negative) (24)	21.0±2.3 (58)	14.6±3.4 (89)*,†	16.9±3.4 (17)*	19.0±2.6 (32)*,†
RCFT: immediate recall (36)	15.3±6.1 (63)	2.2±2.6 (104)*	3.8±3.7 (16)*	9.0±6.0 (33)*,†
RCFT: delayed recall (36)	15.0±5.5 (63)	1.5±2.5 (103)*	3.8±3.7 (16)*	8.9±5.6 (33)*,†
RCFT: recognition score (true positive+true negative) (24)	19.7±3.0 (59)	14.5±3.9 (86)*,†	16.9±2.8 (15)*	18.6±2.1 (31)
Frontal/executive function				
Contrasting program	1.6% (1/63)	36.5% (38/104)*	55.6% (10/18)*	9.1% (3/33)†
Go/no-go	6.3% (4/63)	67.3% (70/104)*	72.2% (13/18)*	30.3% (10/33)*,†
Fist-edge-palm test	1.6% (1/63)	47.6% (50/105)*	66.7% (12/18)*	18.2% (6/33)*,†
Alternating hand movement	9.5% (6/63)	44.3% (47/106)*	61.1% (11/18)*	30.3% (10/33)*
Alternating squares and triangle	4.8% (3/63)	27.2% (28/103)*	44.4% (8/18)*	6.1% (2/33)†
Luria loop	1.6% (1/63)	25.2% (26/103)*	33.3% (6/18)*	12.1% (4/33)
COWAT: Semantic (animal)	16.5±4.2 (62)	8.0±3.7 (90)*	6.7±3.4 (18)*	11.2±4.5 (32)*,†
Semantic (supermarket)	19.6±5.3 (62)	8.8±4.3 (90)*,†	5.6±3.7 (18)*,†	11.7±5.0 (32)*,†
Phonemic (sum of three phonemes)	26.4±11.2 (61)	11.6±8.0 (93)*,†	4.4±5.1 (19)*	14.0±7.6 (34)*,†
Stroop test				
word reading (2 min; 112)	111.4±2.0 (62)	90.5±28.5 (80)*	76.8±32.3 (15)*	105.5±13.4 (32)†
color reading (2 min; 112)	96.7±16.1 (62)	36.8±22.7 (79)*	34.2±30.5 (16)*	58.3±25.2 (32)*,†

K-BNT: Korean version of the Boston Naming Test, RCFT: Rey-Osterrieth

Complex Figure Test, SVLT; Seoul Verbal Learning Test, COWAT: Controlled Oral Word Association Test. *P<0.05 between NC and AD, NC and SVaD, or NC and svMCI; †P<0.05 between SVaD and AD, or SVaD and svMCI

2. Intrarater reliability of cortical thickness measurement

The correlation coefficient of overall cortical thickness was 0.908 (P=0.002) (Figure 2). Figure 3 shows maps of the absolute thickness-measurement variability for the test–retest comparisons. This figure shows that the mean absolute thickness difference was less than 0.2 mm for the bulk of the cortex except for both insular regions. None of the differences were statistically significant.

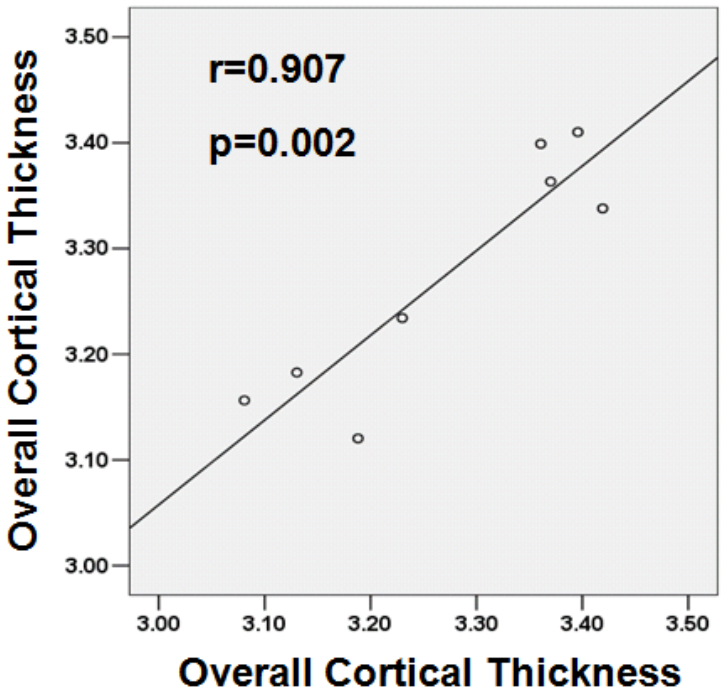

Figure 2. The correlation coefficient of overall cortical thickness for test–retest comparisons.

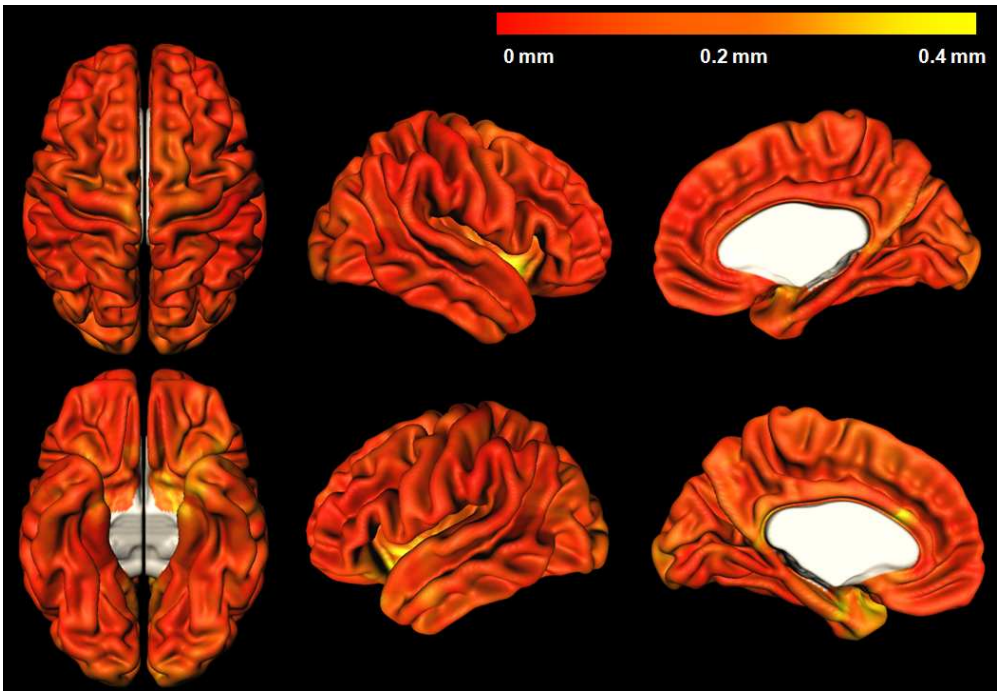

Figure 3. Maps of thickness-measurement variability for test–retest comparisons. The measurement variability was less than 0.2 mm for most of the cortex for the test–retest comparison except for both insular regions.

3. Overall and lobar cortical mean thickness

The cortical thickness across the entire cortices was compared between SVaD and AD patients using ANCOVA. The results showed that overal cortical thickness differed among the NC, AD, and SVaD groups ($F(2,225)=71.934$, $P<0.001$). Bonferroni post-hoc tests showed that the overall cortical thickness in the NC group differed from those in the AD and SVaD groups, but there was no difference between the AD and SVaD groups (Figure 4A).

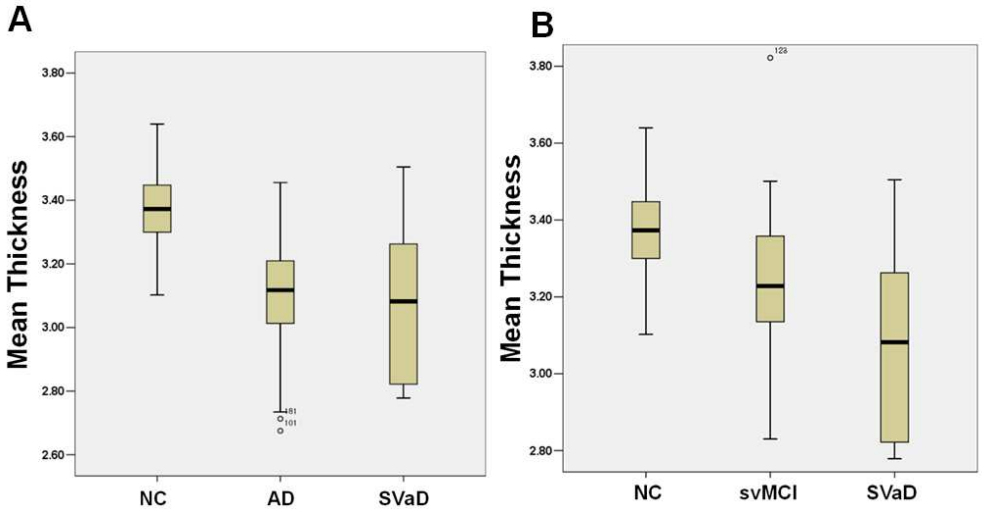

Figure 4. Age-, sex-, and education-corrected differences in overall cortical thickness. Overall cortical thickness of the normal group differs from those of AD and SVaD groups, but there was no difference between the AD and SVaD groups (A). Overall cortical thickness of svMCI is between that of normal-cognition (NC) and SVaD groups, suggesting that svMCI may be a transitional stage between normal cognition and SVaD (B).

This trend was also present in post-hoc tests for the temporal, parietal, and occipital lobes, whereas there was a significant difference between the AD and SVaD groups in the frontal lobe (Table 7).

ANCOVA also revealed that the overall cortical thickness differed among the NC, svMCI, and SVaD groups ($F(2,144)=28.421$, $P<0.001$). Bonferroni post-hoc tests showed that the overall cortical thickness in the NC group differed from those in the svMCI and SVaD groups, and that this also differed between the svMCI and SVaD groups (Figure 4B). This trend was also present in post-hoc tests for the frontal and temporal lobes, whereas in the parietal and occipital lobes there was no

difference between the NC and svMCI groups but there was a difference between the svMCI and SVaD groups (Table 7).

Table 7. Cortical thickness in the frontal, temporal, parietal, and occipital lobes in the NC, AD, SVaD and svMCI groups (mean±SD, in mm).

Lobe	NC (*N*=96)	AD (*N*=115)	SVaD (*N*=20)	svMCI (*N*=34)
Overall	3.455±1.119	3.107±1.162*	3.066±0.228*	3.242±0.189*,†
Frontal	3.431±0.140	3.205±0.165*,†	3.072±0.271*	3.256±0.217*,†
Temporal	3.513±0.127	3.164±0.212*	3.209±0.234*	3.376±0.186*,†
Parietal	3.167±0.116	2.948±0.171*	2.984±0.220*	3.150±0.195†
Occipital	3.1029±0.137	2.888±0.215*	2.856±0.254*	3.012±0.248†

*P<0.05 between NC and AD, NC and SVaD, or NC and svMCI; †P<0.05 between SVaD and AD, or SVaD and svMCI.

4. Topography of cortical atrophy

The statistical significance of cortical thinning was mapped onto an average-surface model in the NC, AD, and SVaD groups (Figure 5). Relative to the NC group, AD patients showed cortical thinning in the entire cortex except for the sensorimotor cortices. The differences were most significant in the medial temporal lobe, temporoparietal association cortex, posterior medial parietal lobule, and prefrontal cortex (Figure 5A). Relative to the NC group, SVaD patients showed cortical thinning in the frontal, temporal, and occipital cortices, with preservation of the precuneus, inferior, and superior parietal lobules, and sensorimotor cortices (Figure 5B). Comparison between the AD and SVaD groups revealed that SVaD patients showed cortical thinning in the inferior portion of prefrontal cortex, lateral orbitofrontal gyrus, and anterior cingulate gyrus. Relative to SVaD, AD patients

showed cortical thinning in the superior parietal lobule, left temporal and parietal association cortex, and left medial temporal lobe (Figure 5C). The statistical significance of cortical thinning was mapped onto an average-surface model in the NC, svMCI, and SVaD groups (Figure 6). Relative to the NC group, cortical thinning of svMCI was most significant in the inferior frontal gyrus, orbitofrontal gyrus, medial frontal gyrus, cuneus, and superior temporal gyrus (Figure 6A). Comparison between the svMCI and SVaD groups revealed that SVaD patients showed cortical thinning in the prefrontal gyrus, anterior cingulate, insula, superior temporal gyrus, temporoparietal association cortex, lingual gyrus, and cuneus (Figure 6C). To further illustrate the magnitude of these effects, Figure 7 presents cortical thickness data in representative vertex points from the left medial frontal gyrus, prefrontal gyrus, and left orbitofrontal gyrus for the NC, svMCI, and SVaD groups. These results were consistent with the statistical maps of differences in cortical thickness between the groups.

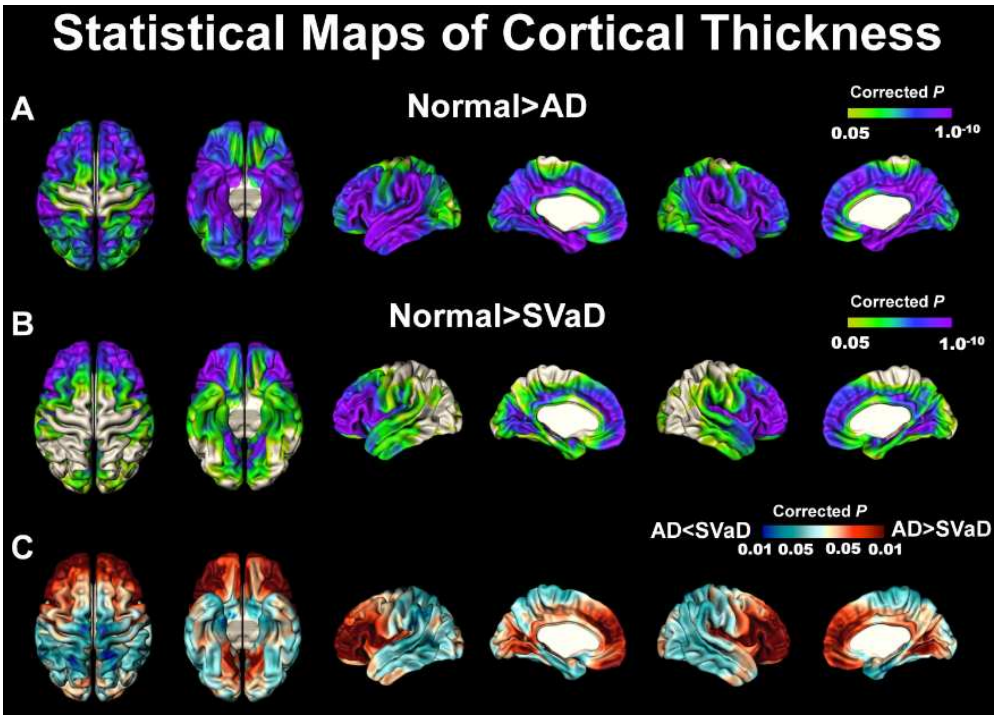

Figure 5. Cortical thickness statistical maps in the NC, AD, and SVaD groups. Relative to the NC group, AD patients showed cortical thinning in the entire cortex except for the sensorimotor cortices (A). The difference was greatest in the medial temporal lobe, temporoparietal association cortex, posterior parietal medial lobule, and prefrontal cortex. Relative to the NC group, SVaD patients showed cortical thinning in prefrontal gyrus, orbitofrontal gyrus, medial frontal gyrus, cingulate gyrus, insula, the anterior portion of lateral temporal gyrus, parahippocampal and fusiform gyrus, cuneus, and lingual gyrus (B). Direct comparison of the AD and SVaD groups revealed that SVaD patients showed cortical thinning in the inferior portion of prefrontal cortex, lateral orbitofrontal gyrus, and anterior cingulate gyrus (C). Relative to SVaD, AD patients showed cortical thinning in the superior parietal lobule, left temporal and parietal association cortex, and left medial temporal lobe (C).

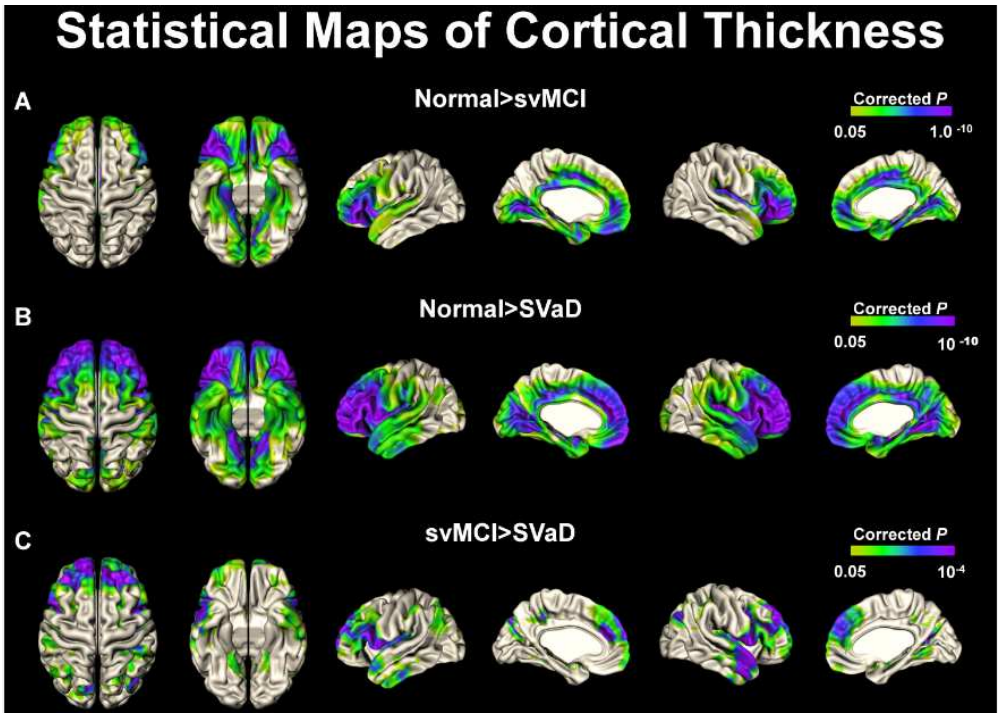

Figure 6. Cortical thickness statistical maps in the NC, svMCI, and SVaD groups. Relative to the NC group, svMCI patients showed cortical thinning in the inferior portion of prefrontal cortex, orbitofrontal gyrus, anterior cingulate, insula, superior temporal gyrus, parahippocampal gyrus, cuneus, and lingual gyrus (A). Relative to the NC group, SVaD patients showed cortical thinning in prefrontal gyrus, orbitofrontal gyrus, medial frontal gyrus, cingulate gyrus, insular, the anterior portion of lateral temporal gyrus, parahippocampal and fusiform gyrus, cuneus, and lingual gyrus (B). Comparison of svMCI with SVaD revealed that SVaD patients showed cortical thinning in prefrontal gyrus, anterior cingulate, insula, superior temporal gyrus, temporoparietal association cortex, lingual gyrus, and cuneus (C).

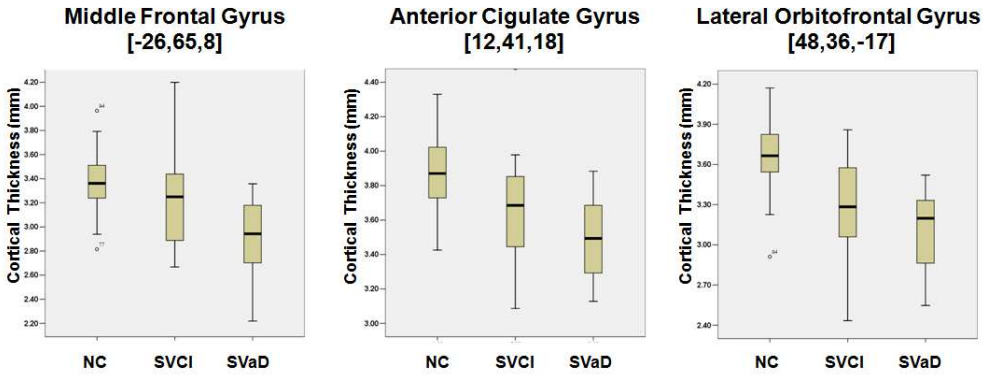

Figure 7. Cortical thickness in representative vertices from middle frontal gyrus, anterior cingulate gyrus, and lateral orbitofrontal gyrus for the NC, svMCI, and SVaD groups. These results are consistent with the statistical maps of differences in cortical thickness between the groups.

IV. DISCUSSION

To my knowledge, this is the first study to analyze the cortical thickness in SVaD using a vertex-based method. There has been a study that performed MRI-based volumetry in patients with SVaD, showing that the volume of gray matter (total intracranial volume, amygdala-hippocampus, and gray matter) is decreased in SVaD.[34] However, one of limitations of volumetry is that it can only estimate the mean gray matter volume of each lobe rather than the distribution of cortical atrophy in the entire cortex.[34] They showed that the reduction in the gray matter volume was very similar in AD and SVaD. This study also replicated that AD and VaD did not differ in the mean cortical thickness in each lobe except for the frontal lobe. However, the use of vertex-based analysis in the present study allowed us to compare the topography of cortical thinning between SVaD and AD, with patients with AD serving as controls. Relative to healthy subjects, AD patients showed

cortical thinning distributed in temporoparietal association cortices including the medial temporal lobe. These findings are consistent with those of previous surface-based cortical analyses in AD.[29, 35] and also those of pathology investigations.[36] In contrast, patients with SVaD showed cortical thinning distributed in all frontal areas, with this being most pronounced in prefrontal cortices followed by premotor and motor cortices.

In addition to the frontal atrophy, these SVaD patients showed cortical thinning in the anterior parts of temporal lobe, superior temporal gyrus, insula, and visual cortices (cuneus and lingual gyrus). First, regarding the cortical thinning of the temporal areas, recent studies suggest that the temporal lobe (especially the right temporal pole and inferior frontal/striatal regions) are important in regulating complex social interactions,[37, 38] and that the superior temporal sulcus subserves as an important component of the social perception system.[39] Therefore, these lesions may explain the impaired social behaviors and loss of empathy that are frequently observed in patients with SVaD. Second, the insular lobe has important behavioral roles, such as in evaluating the motivational or emotional content of internal and external stimuli, error detection, response selection, decision making, regulation of context-dependent behaviors, and a multiple sensory modality.[40] Thus, lesions of the insular lobe might be associated with maladaptive behavior such as disinhibition, apathy, and obsessive-compulsive behaviors in patients with SVaD. As mentioned in the Introduction, one possible mechanism of cognitive decline in patients with SVaD is disruption of cholinergic fibers by ischemic lesions. The

perisylvian division of the lateral cholinergic pathway is known to originate from the basal forebrain and travel via the claustrum, projecting to opercular areas including superior temporal gyrus and insula cortex.[41] Thus, cortical thinning of the temporal opercular and insular areas in these patients with SVaD might be related to disruption of the perisylvian division of the lateral cholinergic pathway. Third, this study also found cortical thinning in visual cortices, especially the temporal part of lingual gyrus. Most studies involving neuropsychological evaluations of VaD have focused on frontal/executive functions. However, one study that considered visuoperceptual tasks showed that visuospatial and perceptual skills were more impaired in VaD patients than in AD patients.[42]

The results from previous MRI-based volumetry studies have suggested that one of the cortical mechanisms of SVaD is concomitant AD pathology.[43] Unlike previous studies, however, this study was able to investigate the distribution of cortical gray matter loss, and found that frontal atrophy was predominant in SVaD patients whereas AD patients exhibited atrophy mainly in the medial temporal lobe, superior parietal lobule, and temporoparietal areas. Thus, these results suggest that cortical thinning in SVaD cannot be explained entirely by concomitant AD pathology. These findings may also be inconsistent with previous autopsy findings that pure vascular pathology is present on only 17% of patients with SVaD, and the AD pathology predominates in most cases.[7] If the main pathology in these patients had been that of AD, the distribution of cortical atrophy would have been almost identical in the AD and SVaD groups. These patients had mild-to-moderate

dementia (mean MMSE score of around 18) and presented even in earlier stages with focal neurological signs (e.g., dysarthria, dysphagia, asymmetric deep tendon reflexes, and extensor plantar responses) and vascular parkinsonism (gait disturbance, rigidity, and bradykinesia). Thus, these SVaD patients may differ from a subset of patients who present with symptoms consistent with AD (i.e., gradual memory decline followed by other cognitive deficits without focal neurologic signs) and unexpectedly show marked ischemia on neuroimaging. It can therefore be concluded that the pathomechanisms underlying mild-to-moderate dementia fulfilling the clinical and imaging criteria of Erkinjuntti et al.[18] may differ from those of AD, even if there might be some overlap in the advanced stages of the disease.

In addition to the concomitant AD pathology hypothesis, an imaging study suggested that mechanisms underpinning cortical gray matter loss in SVaD are cortical microinfarcts or secondary axonal and transsynaptic degeneration following subcortical injury.[43] These findings might not support the cortical microinfarct hypothesis because there is no evidence that cortical microinfarcts in SVaD predominantly affect frontal areas. A study of the pathology of VaD showed that cortical microinfarcts were primarily located in the parieto-occipital regions,[44] which is inconsistent with the distribution of cortical thinning in these SVaD patients. Rather, these findings may support the secondary-degeneration hypothesis. Cerebral white matter contains both afferent and efferent fibers that serve as corticocortical and corticosubcortical connections. Experimental and clinical studies

suggest that when an axon in the brain is damaged, degeneration of the neuron occurs both proximally (dying back) and distally (Wallerian degeneration).[45-47] Distal to the damage, deafferented neurons also undergo transneuronal or transsynaptic degeneration, such that neurons that have received input from the damaged axon suffer sustained neuronal atrophy or transsynaptic apoptosis.[45] These mechanisms would result in atrophy in gray matter or cortical regions that are connected via damaged tracts. Recent studies using diffusion-tensor imaging (DTI) have demonstrated that ischemic changes in the white matter disrupt major white matter tracts such as superior and inferior longitudinal fasciculus, and superior and inferior occipitofrontal fasciculus.[48] Cortical apoptosis was also involved in cortical atrophy in Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), which is considered a model of pure SVaD and might be associated with the intensity of axonal damage in the subcortical white matter.[49] Therefore, cortical thinning in cuneus and lingual gyrus in these SVaD patients may be partly related to ischemic injury to superior occipitofrontal and inferior occipitofrontal fasciculus since the occipital area is the main origin and destination of these fasciculi. However, a possibility cannot be excluded that ischemic disruption of the white matter tract and cortical atrophy are independent processes. Future pathology or DTI studies may be needed to prove this hypothesis.

One of the main purposes of this study was to compare the cortical thickness between svMCI and SVaD patients. The present study found that the vertices with cortical thinning largely overlapped between SVaD and svMCI, but their extent and

severity were greater in SVaD than in svMCI. That is, the vertices with atrophy in SVaD relative to svMCI (svMCI>SVaD) extended to middle and superior frontal gyri, anterior cingulate gyrus, anterior temporal areas, and insula, although the opposite analysis (SVaD>svMCI) revealed no significant cortical thinning. These findings may have several clinical implications. First, a hierarchy might exist between svMCI and SVaD. The overall mean thickness reduced linearly as the subject group transited from normal to dementia, and the atrophied regions in SVaD encompassed all of those in svMCI. Further, the neuropsychological performances of svMCI patients were between those of healthy controls and SVaD patients. Thus, these findings support this hypothesis that svMCI is on the continuum from NC to VaD. Second, these results suggest that svMCI is a relatively homogeneous syndrome that is distinct from degenerative types of MCI, especially amnestic MCI, which is considered a prodromal stage for AD. Previous study reported that relative to controls, patients with single amnestic MCI showed cortical thinning in the medial temporal lobe, whereas the cortical thinning of multiple amnestic MCI patients occurred not only in the left medial temporal lobe but also in other areas such as precuneus, and anterior and inferior basal temporal, insular, and temporal association cortices.[50] Therefore, disease processes in svMCI involve largely frontal areas, while those of amnestic MCI involve posterior cortical areas. Third, these comparisons between the svMCI and SVaD groups suggest that vascular cognitive disorders associated with small vessel disease begin with cortical changes in orbitofrontal gyrus and inferior frontal gyrus, and then spread to middle and

superior frontal gyri and the anterior temporal area. Thus, cognitive and behavioral changes due to small vessel disease might begin with orbitofrontal syndromes such as disinhibition and decreased social behavior, followed by executive dysfunctions subserved by dorsolateral prefrontal cortices. Thus, questionnaires for neuropsychiatric symptoms rather than neuropsychological tests for executive functions may be more sensitive to the very early stages of SVaD. Future studies should test this hypothesis.

This study was subjected to limitations. Although the clinical findings of these patients (e.g., short-step gait, pseudobulbar, or other focal signs with executive dysfunctions) were entirely different from those of AD, and their MRI findings had to be indicative of remarkable ischemia to meet the imaging criteria of Erkinjuntti et al.,[18] the possibility that AD pathology was present in these svMCI and SVaD patients cannot be excluded. Also, differences in cortical thinning between svMCI and SVaD patients were examined cross-sectionally. Therefore, future studies should examine the changes in cortical thickness in svMCI subgroups longitudinally.

V. CONCLUSION

This study analyzed the cortical thickness in SVaD using a vertex-based method, which showed that the distribution of cortical thinning of SVaD is distinct from that of AD. Thus, this topographical pattern of cortical changes in SVaD may represent secondary axonal and transsynaptic degeneration following subcortical

injury rather than concomitant AD pathology. Patterns of cortical thinning in addition to the ischemia rating on MRI may further elucidate the clinical characteristics and pathogenesis of SVaD.

When svMCI was compared with SVaD, the vertices with cortical thinning largely overlapped between the two groups, but their extent and severity were greater in SVaD than in svMCI. These findings may have several clinical implications. First, a hierarchy might exist between svMCI and SVaD. Second, these results suggest that svMCI is a relatively homogeneous syndrome that is distinct from amnestic MCI, which is considered a prodromal stage for AD. Third, these comparisons between the svMCI and SVaD groups suggest that vascular cognitive disorders associated with small vessel disease begin with cortical changes in orbitofrontal gyrus and inferior frontal gyrus, and then spread to middle and superior frontal gyri and the anterior temporal area. Thus, questionnaires for neuropsychiatric symptoms rather than neuropsychological tests for executive functions may be more sensitive indicating the very early stages of SVaD. Future studies should test this hypothesis.

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<ABSTRACT(IN KOREAN)>

피질하혈관성 경도인지장애와 피질하혈관성 치매에서의 공간적 피질의 감소

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배경: 기억성 경도인지장애는 알쯔하이머병의 전단계로 알려져 왔다. 이와 마찬가지로 소혈관과 관련된 경도인지장애(피질하혈관성 경도인지장애)는 피질하혈관성 치매의 전단계일 가능성이 있다. 피질하혈관성 경도인지장애 또는 피질하혈관성 치매 환자의 임상적 특성에 영향을 줄 수 있는 인자인 백색질 허혈성 변화뿐만 아니라 또 다른 중요한 요인인 피질 감소를 이들 질환에서 조사한 연구는 거의 없었다. ***목적:*** 피질하혈관성 치매와 알쯔하이머병에서의 피질 감소 부위의 차이를 확인하고자 하였다. 또한, 피질하혈관성 경도인지장애와 피질하혈관성 치매를 피질 감소의 분포에서 어떤 차이가 있는지를 파악해 피질하혈관성 경도인지장애와 피질하혈관성 치매의 계층차이와 피질하혈관성 경도인지장애가 피질하혈관성 치매로 진행하는데 어떤 변화를 거치는지를 파악하고자 하였다. ***방법:*** 20명의 피질하혈관성 치매, 34명의 피질하혈관성 경도인지장애, 115명의 알쯔하이머병, 96명의 건강한 피험자를 대상으로 피질의 두께를 측정하기 위해 뇌자기공명영상을 촬영하였다. 피질하혈관성 치매와 피질하혈관성 경도인지장애 피질감소 분포의 차이는 공분산분석을 이용해 분석하였다. ***결과:*** 정상인에 비해 알쯔하이머병 환자는 내측 측두엽을 포함한 측두두정엽 부위의 피질의 감소를 보였고, 피질하혈관성치매는 주로 전두엽 부위의 피질의 감소를 보였다. 피질하혈관성 경도인지장애는 아래이마엽, 안와이마엽, 앞띠이랑, 위측두이랑, 섬엽, 곁해마이랑, 쐐기엽, 혀이랑에서 피질의 감소가 관찰되었으며, 이러한 부위는 피질하혈관성 치매가 보인 피질 감소의 부위에 포함되었다. ***결론:*** 본 결과는 피질하혈관성치매의 피질 감소의 부위가 알쯔하이머병의 피질 감소 부위와 차이가 있음을 제시했는데, 이러한 결과는 이들 두 질환의 기전이 다름을 시사해주는 결과이다. 또한 피질하혈관성 경도인지장애와 피질하혈관성 치매간에 계층 차이가 있으며, 본 연구에서 설정한 피질하혈관성

경도인지장애가 정상인과 피질하혈관성 치매의 중간단계임을 시사해주는 결과였다.

핵심되는 말: 소혈관, 치매, 경도인지장애, 피질하, 피질 감소, 피질 위축

PUBLICATION LIST

None