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The impact of education on cortical thickness in amyloid-negative subcortical vascular dementia: cognitive reserve hypothesis

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Abstract

Background: The protective effect of education has been well established in Alzheimer's disease, whereas its role in patients with isolated cerebrovascular diseases remains unclear. We examined the correlation of education with cortical thickness and cerebral small vessel disease markers in patients with pure subcortical vascular mild cognitive impairment (svMCI) and patients with pure subcortical vascular dementia (SVaD).

Methods: We analyzed 45 patients with svMCI and 47 patients with SVaD with negative results on Pittsburgh compound B positron emission tomographic imaging who underwent structural brain magnetic resonance imaging. The main outcome was cortical thickness measured using surface-based morphometric analysis. We also assessed the volumes of white matter hyperintensities (WMH) and numbers of lacunes as other outcomes. To investigate the correlation of education with cortical thickness, WMH volume, and number of lacunes, multiple linear regression analyses were performed after controlling for covariates, including Mini Mental State Examination, in the svMCI and SVaD groups.

Results: In the SVaD group, higher education was correlated with more severe cortical thinning in the bilateral dorsolateral frontal, left medial frontal, and parahippocampal areas, whereas there was no correlation of education with cortical thickness in the svMCI group. There was no correlation between education and cerebral small vessel disease, including WMH and lacunes, in both patients with svMCI and patients with SVaD.

Conclusions: Our findings suggest that the compensatory effects of education on cortical thinning apply to patients with SVaD, which might be explained by the cognitive reserve hypothesis.

Keywords: Cognitive reserve, Gray matter atrophy, Education, Subcortical vascular dementia

Background

Subcortical vascular dementia (SVaD) is the most common type of vascular dementia in the memory clinic setting. Unlike other types of vascular dementia showing a stepwise deterioration and fluctuating course, patients

with SVaD have insidious onset and gradual progression of disease, similarly to neurodegenerative dementia [1]. SVaD is characterized by extensive cerebral small vessel disease (CSVD), such as white matter hyperintensities (WMH) and lacunes, on magnetic resonance imaging (MRI) [2]. Previous studies showed that about 30% of patients with SVaD had increased uptake of amyloid- β (A β) measured by carbon-11-labeled Pittsburgh compound B ([¹¹C]PiB) positron emission tomography (PET) [3]. A β -negative patients with SVaD and those with its prodromal stage, subcortical vascular mild cognitive

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impairment (svMCI), showed cortical thinning prominently in the frontal and perisylvian regions, although CSVD was located predominantly in the subcortical regions [4]. In fact, cortical thinning might be considered as an important biomarker in patients with SVaD and patients with svMCI because it has been reported that CSVD was independently associated with cortical thinning, regardless of increased uptake of A β [5].

In previous studies, the protective effects of education reducing the risk of dementia have been shown in neurodegenerative diseases, including Alzheimer's disease (AD) and frontotemporal dementia (FTD) [6–9]. Neuroimaging studies showed higher levels of education to be correlated with more severe neurodegeneration as measured by cortical atrophy, hypometabolism, or hypoperfusion in patients with AD dementia [10, 11], mild cognitive impairment (MCI) [12], preclinical AD [13], or FTD [14] when controlled for cognitive performance. Results from these studies have been explained by the theory of cognitive reserve [15]. Cognitive reserve refers to the ability to make efficient and flexible use of the brain for task performance, and it is estimated using education, IQ, and leisure activities [16]. In the cognitive reserve concept, individuals with higher education can cope with a larger extent of neurodegeneration before showing a level of cognitive impairment similar to that of someone with a lower level of education. Higher network efficiency and capacity (neural reserve) or compensatory functional brain differences (neural compensation) may account for such a higher reserve ability [16, 17]. Thus, according to the cognitive reserve hypothesis, protective life factors such as education mitigate the impact of brain pathology in cognition.

Beyond AD, cognitive reserve theory has not been well studied in vascular dementia. Previous studies reported that lower education levels predicted an increased risk of developing of poststroke cognitive impairment [18, 19]. In support of the hypothesis that education is related to reserve capacity in vascular dementia, it was previously shown that patients with higher education had a higher cognitive status than those with lower education despite similar degrees of subcortical hyperintensities [20]. However, these studies did not assess the influence of education on possible comorbidities such as AD pathology or on the level of brain integrity, including gray matter atrophy.

Previous studies by our group [10, 21, 22] suggested there were differences in the relationships between levels of education and cortical thickness among levels of cognition. That is, healthy control subjects showed a positive correlation between level of education and cortical thickness, whereas patients with dementia showed a negative correlation between level of education and cortical thickness. Another study by our group [23]

suggested that there might be an inflection point in MCI stage. That is, the protective effects of education against cognitive decline remain in early-stage amnesic MCI and disappear in late-stage amnesic MCI. It would therefore be reasonable to expect that the correlation of education with cortical thinning might be more prominent in dementia stage rather than in MCI stage.

In the present study, we examined the correlation of education with cortical thickness and CSVD markers in patients with PiB(-) svMCI and patients with PiB(-) SVaD. We divided these patients into svMCI and SVaD groups because the cortical thinning patterns and the severity of cortical thinning and CSVD markers are different between these two groups [4]. The correlation of education might be distinct according to different vulnerable areas. On the basis of the cognitive reserve hypothesis, we predicted that both patients with SVaD and patients with svMCI would show a negative correlation between education and cortical thickness or a positive correlation between education and CSVD MRI markers when controlling for cognitive status in each group. In addition, we supposed that the correlation of education would be maximized in the SVaD group.

Methods

Participants

We prospectively recruited 67 patients with svMCI and 70 patients with SVaD, all of whom had been clinically diagnosed at Samsung Medical Center between September 2007 and August 2011. Patients with SVaD met the diagnostic criteria for vascular dementia as determined using criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [24]. All patients with SVaD exhibited significant ischemia as determined by MRI scans, defined as a cap or band ≥ 10 mm as well as a deep white matter lesion ≥ 25 mm (a modification of the Fazekas ischemia criteria) [25]. Patients with svMCI were diagnosed using the Petersen criteria [26] with inclusion of the following modifications: (1) subjective cognitive complaints by the patient or his/her caregiver, (2) normal activities of daily living, (3) objective memory decline assessment below the 16th percentile on neuropsychological tests, (4) absence of dementia, and (5) presence of a subcortical vascular feature defined as both a focal neurological symptom/sign and significant ischemia on MRI, as for SVaD. We excluded patients with focal cortical cerebrovascular lesions, intracranial hemorrhage, territory infarctions, and hydrocephalus and those with high signal abnormalities on MRI owing to radiation injury, multiple sclerosis, vasculitis, or leukodystrophy.

In our previous studies, 32.8% (22 of 67) of patients with svMCI and 32.9% (23 of 70) of patients with SVaD were PiB-PET-positive [3, 4, 27]. We excluded

PiB-positive patients with svMCI and PiB-positive patients with SVaD in the present study because we wanted to exclude the possibility that the effects of education were driven by AD. As a result, a total of 45 PiB(-) patients with svMCI and 47 PiB(-) patients with SVaD were included. We obtained written consent from each patient, and the institutional review board of Samsung Medical Center approved the study protocol.

Neuropsychological tests

All participants underwent neuropsychological tests using a standardized neuropsychological battery, the Seoul Neuropsychological Screening Battery, for diagnostic purposes [28]. The battery comprised tests for attention, language, calculation, praxis, visuospatial/constructive function, verbal/visual memory, and frontal/executive function as previously described [29]. One patient with PiB(-) SVaD did not complete the battery, owing to severe cognitive impairment.

Education

To thoroughly evaluate the level of education achieved by the participants, we gathered information about the number of years of formal education that they had completed. The South Korean education system is composed of elementary school (6 years), middle school (3 years), high school (3 years), and university (4 years). We confirmed the patients' education history with their caregivers.

[¹¹C]PiB PET imaging

All patients had an [¹¹C]PiB-PET scan at Samsung Medical Center or Asan Medical Center. All participants completed the same type of PET scan with a Discovery STe PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA). The detailed radiochemistry profiles and scanning protocol were described in a previous study [3]. Data processing was performed using SPM version 5 in MATLAB 6.5 (MathWorks, Natick, MA, USA). To measure PiB retention, we used the cerebral cortical region/cerebellum uptake ratio, which is identical to the standardized uptake value ratios. Patients were considered PiB-positive if their global PiB retention ratio was > 2 SD greater than the mean of the normal control subjects [3].

Acquisition of three-dimensional MRI images

Using the same 3.0-T MRI scanner (Philips 3.0 T Achieva; Philips Healthcare, Andover, MA, USA), we acquired 3D T1 turbo field echo MRI and fluid-attenuated inversion recovery (FLAIR) images from all participants as previously described [30]. Imaging parameters were as follows: T1-weighted—slice thickness, 1 mm; repetition time (TR)/echo time (TE), 4.6/9.9 ms; flip angle, 88

degrees; field of view, 24 × 24 cm; and matrix size, 240 × 240 pixels; and FLAIR—axial slice thickness, 2 mm; no gap; TR/inversion time/TE, 11,000/2800/125 ms, respectively; field of view, 24 × 24 cm; and matrix size, 256 × 256 pixels.

Measurement of CSVD markers

We quantified WMH volume (in milliliters) on FLAIR images using an automated method as previously described [31]. WMH candidate region mask was generated on T1 images. FLAIR images were subjected to nonuniformity correction, intensity normalization, and coregistration of FLAIR and T1 images of each subject. WMH was segmented using the FMRI Automatic Segmentation Tool (FAST) algorithm with WMH candidate region mask on FLAIR images. By using an intensity substitution method, T1 images could be classified into white matter and gray matter and localized into lobes properly. After regional parcellation, local WMH volume in four lobes was quantified. We used the total volume as a dependent variable. Lacunes were defined as lesions (≥ 3 mm and ≤ 15 mm in diameter) with low signal on T1-weighted images, high signal on T2-weighted images, and a perilesional halo on 80 axial sections of FLAIR images. The detailed measurement methods for lacunes are described in a previous paper [27]. We used the number of lacunes as a dependent variable.

Image processing for cortical thickness measurements

Images were processed using the standard Montreal Neurological Institute anatomic pipeline. Native MRI images were registered into a standardized stereotaxic space using a linear transformation. After nonuniformities were corrected, the images were classified into white matter or gray matter using a 3D stereotaxic brain mask and the Intensity-Normalized Stereotaxic Environment for Classification of Tissues (INSECT) algorithm. The surfaces of the inner and outer cortices were automatically extracted using the Constrained Laplacian-Based Automated Segmentation with Proximities (CLASP) algorithm. Cortical thickness was defined as the Euclidean distance between the linked vertices of the inner and outer surfaces [32]. For cortical thickness analysis, diffusion smoothing with a FWHM of 20 mm was used to pixelate each map of cortical thickness, which simultaneously increased both the signal-to-noise ratio and the statistical power [33]. For global and lobar regional analyses, data of 30 normal subjects that had previously been manually categorized to lobes, and which showed high interrater reliability [34], 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 pre-categorized 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 our analysis. The more detailed image-processing methods are described in previous studies [30].

Statistical analysis

The demographic and clinical differences between svMCI and SVaD were investigated using the *t* test and chi-square test. We transformed the WMH volume and the number of lacunes using square root transformations (sqrtWMH and sqrtLacune) because these variables were not normally distributed.

To investigate the correlation of education with cortical thickness and CSVD markers at the same clinical severity, multiple linear regression analyses were performed after controlling for age, sex, intracranial volume (ICV), and Mini Mental State Examination (MMSE) in both the svMCI and SVaD groups (model 1). MMSE was used as an index of the clinical severity. Because vascular risk factors affect cortical thinning [35–37], we also added hypertension, diabetes mellitus, hyperlipidemia, and smoking to the covariates of model 1 (model 2). Because WMH volume and the number of lacunes are associated with cortical thinning [5, 38], we further

controlled for global cortical thickness with the covariates of model 2 in the relationship between education and CSVD markers (model 3 of Table 2). For the same reason, we further controlled for WMH and lacunes with covariates of model 2 in the relationship between education and cortical thickness (model 3 of Table 3).

Results

Demographics and clinical characteristics

There were no differences in the age, sex, and years of education between patients with svMCI and patients with SVaD. The prevalence of cardiovascular risk factors and the APOE $\epsilon 4$ allele also did not differ between patients with svMCI and patients with SVaD. However, patients with SVaD exhibited larger WMH volumes and more lacunes than patients with svMCI. Cortical thickness was thinner in patients with SVaD than in patients with svMCI (Table 1).

Relationship between education and CSVD

In the multiple linear regression model for CSVD, after controlling for age, sex, ICV, and MMSE, there was no correlation between education level and WMH or lacunes in both the svMCI and SVaD groups (Table 2).

Table 1 Demographics and clinical characteristics

	PiB(–) svMCI (n = 45)	PiB(–) SVaD (n = 47)	<i>p</i> Value
Demographics			
Age, years	72.1 ± 6.6	71.9 ± 7.2	0.892
Sex, female, <i>n</i> (%)	29 (64.4)	24 (51.1)	0.194
Education, years	8.9 ± 5.3	8.5 ± 4.9	0.676
Cardiovascular risk factors, <i>n</i> (%)			
Hypertension	38 (84.4)	37 (78.7)	0.480
Diabetes mellitus	12 (26.7)	12 (25.5)	0.901
Hyperlipidemia	14 (31.1)	21 (44.7)	0.180
Smoker (current/previous/total)	0/11/40	5/12/45	0.112
APOE genotype ^a , <i>n</i> (%)			
$\epsilon 2$ allele carrier	6/45 (13.3)	5/44 (11.4)	0.778
$\epsilon 4$ allele carrier	5/45 (11.1)	10/44 (22.7)	0.143
Small vessel MRI markers			
WMH volume, ml	33.8 ± 17.6	41.7 ± 15.4	0.027
Lacunes, <i>n</i>	8.4 ± 8.6	20.1 ± 18.1	< 0.001
Global PiB retention ratio	1.3 ± 0.1	1.2 ± 0.1	0.085
Intracranial volume, ml	1353.7 ± 102.7	1378.1 ± 132.3	0.329
Mean cortical thickness, mm	2.8 ± 0.1	2.7 ± 0.2	< 0.001
MMSE	26.6 ± 2.4	21.5 ± 4.6	< 0.001
CDR-SOB	1.3 ± 1.0	6.0 ± 3.7	< 0.001

Abbreviations: APOE Apolipoprotein E, CDR-SOB Clinical Dementia Rating Sum of Boxes, MMSE Mini Mental State Examination, MRI Magnetic resonance imaging PiB Pittsburgh compound-B, svMCI Subcortical vascular mild cognitive impairment, SVaD Subcortical vascular dementia, WMH White matter hyperintensity

^aAPOE genotyping was performed in 89 of 92 participants. Values are expressed as the mean ± SD or number (%)

Table 2 Multivariate analysis for the correlation of education with cerebrovascular disease markers

	sqrtWMH volume		sqrtLacunes	
	B	p Value	B	p Value
PiB(-) svMCI (n = 45)				
Model 1	1.590	0.251	0.053	0.249
Model 2	0.399	0.769	0.088	0.100
Model 3	0.035	0.979	0.066	0.172
PiB(-) SVaD (n = 47)				
Model 1	-1.114	0.393	-0.058	0.322
Model 2	-1.912	0.537	-0.051	0.430
Model 3	-1.243	0.440	-0.053	0.456

Abbreviations: PiB Pittsburgh Compound B, sqrt Square root, svMCI Subcortical vascular mild cognitive impairment, SVaD Subcortical vascular dementia, WMH White matter hyperintensity

Multiple linear regression was performed after controlling for the covariates as follows:

Model 1: age, sex, ICV, and MMSE control

Model 2: age, sex, ICV, MMSE, hypertension, diabetes, hyperlipidemia, and smoking control

Model 3: age, sex, ICV, MMSE, hypertension, diabetes, hyperlipidemia, smoking, and global cortical thickness control

This result was not changed after additional controlling for vascular risk factors and global cortical thickness.

Relationship between education and cortical thickness

In the multiple linear regression model for cortical thickness after controlling for age, sex, ICV, and MMSE, there was no significant relationship between education and cortical thickness in patients with svMCI (Table 3). However, there was a negative correlation of education with cortical thickness in patients with SVaD. Even when controlling for vascular risk factors, WMH (square root transformation) and number of lacunes (square root transformation), the result was not changed. The correlation between education and cortical thinning had

regional specificity for the bilateral dorsolateral frontal, left medial frontal, and parahippocampal areas (Fig. 1).

Discussion

In the present study, we investigated the correlation of education with cortical thinning and CSVD in patients with svMCI and patients with SVaD. Our main findings were as follows. First, in the SVaD group, higher education was correlated with more severe cortical thinning, whereas in the svMCI group, there was no correlation of education with cortical thickness. Second, the correlation between education and cortical thinning in patients with SVaD had regional specificity for the bilateral dorsolateral frontal, left medial frontal, and parahippocampal areas. In contrast, we did not find any correlation between education and CSVD, including WMH and lacunes, in patients with svMCI and patients with SVaD. Taken together, our findings suggested that education gives an ability to endure cortical thinning in patients with SVaD, which might be explained by the cognitive reserve hypothesis.

Our major finding was that a higher level of education was correlated with more severe cortical thinning in patients with SVaD. Our findings are consistent with a previous study based on cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is a genetic variant of pure vascular cognitive impairment with severe CSVD. That study demonstrated that education had a protective effect on cognitive performance in patients with vascular pathology [39]. However, there was no correlation between education and cortical thickness in patients with svMCI in our study. The results are also consistent with studies in patients with AD dementia, showing higher education levels to be associated with more cortical thinning [10], whereas these effects were not prominent in

Table 3 Multivariate analysis for the correlation of education with cortical thickness

	Cth_Global		Cth_Frontal		Cth_Temporal		Cth_Parietal		Cth_Occipital	
	B	p Value	B	p Value	B	p Value	B	p Value	B	p Value
PiB(-) svMCI										
Model 1	-0.004	0.352	-0.005	0.278	-0.005	0.283	-0.004	0.310	-0.001	0.800
Model 2	-0.004	0.375	-0.004	0.438	-0.004	0.398	-0.007	0.146	-0.001	0.880
Model 3	-0.001	0.823	0.001	0.859	-0.002	0.717	-0.004	0.359	0.001	0.758
PiB(-) SVaD										
Model 1	-0.016	0.028*	-0.020	0.019*	-0.014	0.115	-0.017	0.014*	-0.013	0.047*
Model 2	-0.020	0.024*	-0.023	0.024*	-0.019	0.078	-0.021	0.012*	-0.016	0.035*
Model 3	-0.020	0.029*	-0.023	0.032*	-0.020	0.065	-0.021	0.017*	-0.016	0.046*

Abbreviations: Cth cortical thickness, PiB Pittsburgh Compound B, svMCI Subcortical vascular mild cognitive impairment, SVaD Subcortical vascular dementia

* p < 0.05

Multiple linear regression was performed after controlling for the covariates as follows:

Model 1: age, sex, ICV, and MMSE control

Model 2: age, sex, ICV, MMSE, hypertension, diabetes, hyperlipidemia, and smoking control

Model 3: age, sex, ICV, MMSE, hypertension, diabetes, hyperlipidemia, smoking, sqrtWMH, and sqrtLacune control

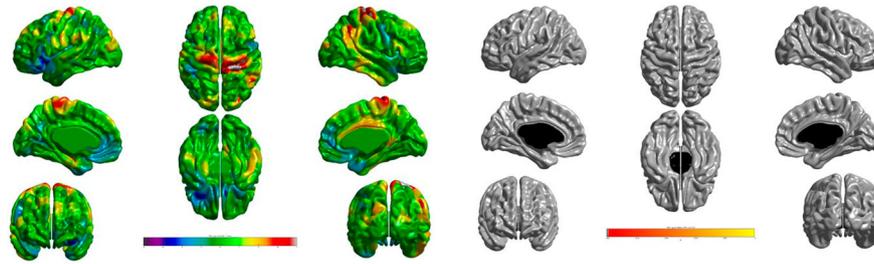
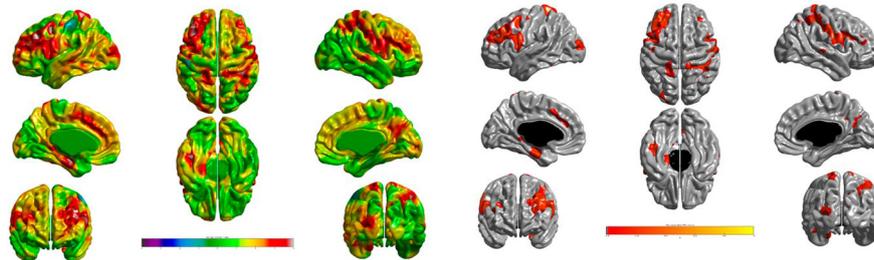
A PiB (-) svMCI group**B PiB (-) SVaD group**

Fig. 1 The topography of cortical thinning related to education in (a) PiB(-) svMCI and (b) PiB(-) SVaD. A negative relationship between education and cortical thickness was found in the bilateral dorsolateral frontal, left medial frontal, and parahippocampal areas in the PiB(-) SVaD group. $q < 0.05$ after false discovery rate correction. Adjusted for age, sex, intracranial volume, MMSE, hypertension, diabetes, hyperlipidemia, smoking, sqrtWMH, and sqrtLacune (model 3). MMSE Mini Mental State Examination, PiB Pittsburgh Compound B, svMCI Subcortical vascular mild cognitive impairment, sqrt Square root transformation, SVaD Subcortical vascular dementia, WMH White matter hyperintensities

MCI stage [40, 41]. In terms of MCI, not subcortical vascular type, there are several studies with inconsistent results regarding cognitive reserve. Cognitive reserve proxies, including education, are not associated with cortical atrophy [40, 41] or functional activity [12], but cognitive reserve has a negative association with brain volumes [12]. Researchers in one study reported that higher cognitive reserve, including education, is related to more severe hypometabolism in MCI [42].

Although the correlation of education with gray matter thinning in AD but not in MCI seems perplexing, the results may be reconciled when considering the dynamic evolution of reserve effects during the course of AD. We previously observed in a longitudinal study that better-educated participants with early-stage MCI had a slower decline in cognition, whereas better-educated participants with late-stage MCI had faster rates of cognitive decline than less well-educated participants with MCI [23]. Better-educated participants with late-stage MCI were more likely to convert to AD dementia within the next 1.4 years [23]. Consistent with those results, previous longitudinal studies showed higher education to be associated with steeper cognitive decline shortly before conversion to AD [43, 44]. These results suggest that individuals with higher education may dynamically exhaust the reserve capacity until a threshold where an even steeper cognitive decline follows owing to the

relatively high degree of accumulated pathology. Thus, better-educated individuals should have accrued, especially at the dementia level, much more neurodegeneration than individuals with lower education levels, whereas at the MCI level, the accrued neurodegeneration will be more subtle. Although reserve effects in prodromal AD have been demonstrated across different studies [45, 46], the neurodegeneration in svMCI may be more subtle, and thus any reserve effects may be more difficult to detect.

Unexpectedly, we did not find any correlation between the level of education and CSVD MRI markers in patients with svMCI and patients with SVaD, suggesting that high education level had no role in buffering against vascular pathology. In a previous study, higher cognitive reserve (e.g., education) was associated with more severe WMH [47]. In healthy elderly people, higher cognitive reserve protects against the cognitive deterioration related to WMH [47–49]. One study in which researchers investigated patients with CADASIL showed that education significantly influenced cognitive function in patients with mild to moderate brain pathology, including lacunes, whereas there was no effect of education on cognition in patients with severe pathology [39]. We supposed that cognitive reserve mitigates the impact of cortical thinning but not CSVD in patients with already substantial vascular pathology such as our participants.

In svMCI and SVaD, CSVD burden may exceed a threshold beyond which the attenuating effect of education on cognitive function may disappear.

Our final finding was that the association between education and cortical thinning in SVaD had regional specificity for the frontal region, which is partially different from the distribution of the association in AD. There have been no studies investigating the specific brain regions related to education in patients with SVaD. Considering that patients with PiB(-) SVaD had cortical thinning prominently in the frontal and perisylvian regions, our findings suggested that the regions related to education in PiB(-) SVaD seemed to overlap with prominently involved regions in PiB(-) SVaD. In fact, a previous study based on patients with AD showed that higher education levels were found to correlate with cortical thinning prominently in the temporoparietal association region where patients with AD had characteristic cortical thinning [10]. Our findings therefore suggest that the correlation of education with cortical thickness occurs in the vulnerable regions where each type of dementia showed cortical thinning [4]. The compensatory mechanism related to specific areas has not been extensively established. Further investigation is needed. However, our findings suggested that the cognitive hypothesis might be applicable to patients with PiB(-) SVaD.

The strengths of our study are that we investigated the correlation of education with cortical thickness in patients with vascular pathologies without AD pathologies using multimodal imaging analyses. However, there are some limitations of the current study. First, we did not obtain more information on sociodemographic variables, such as occupation and leisure activities, other than the duration of education to confirm cognitive reserve. Second, we did not consider the effects of other pathologies, including other AD pathologies (soluble A β and neurofibrillary tangles), microinfarcts, or possible combined degenerative dementia (dementia with Lewy bodies and FTD) pathologies, which are also associated with cortical thinning. Third, the education level (mean 8.7 years) of our participants was lower than that of other cohorts (mean 15–17 years), such as the Alzheimer's Disease Neuroimaging Initiative [41, 50]. Elderly Koreans had less opportunities for educational attainment owing to the Korean War and an increased dropout rate owing to financial reasons following the war. Finally, our study population included a large proportion of patients with significant vascular burden, which may limit the generalizability of our data to other populations.

Conclusions

We investigated the correlation of education with cortical thickness in patients with vascular pathologies

without AD pathologies using multimodal imaging analyses. Our findings suggest that the protective effect of education apply to patients with SVaD, which might be accounted for by the cognitive reserve hypothesis. It will be important to identify those functional and structural brain mechanisms that may support cognitive reserve in AD [45] and cerebrovascular disease.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NYJ, HC, and SWS contributed to the conceptualization of the study, analysis and interpretation of data, and drafting. JML and SP contributed to analyses of imaging data, prepared the figures, and provided technical support. YJK, HJK, STK, EJK, JSK, SHM, and JHL contributed to data collection and interpretation. ME and DLN contributed to analysis and interpretation of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Approval of the study design was obtained from the ethics committee of Samsung Medical Center, Seoul, Korea. This study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Written consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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