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Higher education affects accelerated cortical thinning in Alzheimer's disease: a 5-year preliminary longitudinal study

Hanna Cho,[1,2] Seun Jeon,[3] Changsoo Kim,[4] Byoung Seok Ye,[5] Geon Ha Kim,[6] Young Noh,[7] Hee Jin Kim,[1] Cindy W Yoon,[8] Yeo Jin Kim,[1] Jung-Hyun Kim,[1] Sang Eon Park,[1] Sung Tae Kim,[9] Jong-Min Lee,[3] Sue J. Kang,[1] Mee Kyung Suh,[1] Juhee Chin,[1] Duk L. Na,[1] Dae Ryong Kang[10] and Sang Won Seo[1]

[1]*Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*
[2]*Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea*
[3]*Department of Biomedical Engineering, Hanyang University, Seoul, South Korea*
[4]*Department of Preventive Medicine and the Institute for Environmental Research*
[5]*Department of Neurology, Yonsei University College of Medicine, Seoul, South Korea*
[6]*Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University School of Medicine, Seoul, South Korea*
[7]*Department of Neurology, Gachon University Gil Medical Center, Incheon, South Korea*
[8]*Department of Neurology, Inha University School of Medicine, Incheon, South Korea*
[9]*Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*
[10]*Biostatics of Collaboration Unit, Yonsei University College of Medicine, Seoul, South Korea*

ABSTRACT

Background: Epidemiological studies have reported that higher education (HE) is associated with a reduced risk of incident Alzheimer's disease (AD). However, after the clinical onset of AD, patients with HE levels show more rapid cognitive decline than patients with lower education (LE) levels. Although education level and cognition have been linked, there have been few longitudinal studies investigating the relationship between education level and cortical decline in patients with AD. The aim of this study was to compare the topography of cortical atrophy longitudinally between AD patients with HE (HE-AD) and AD patients with LE (LE-AD).

Methods: We prospectively recruited 36 patients with early-stage AD and 14 normal controls. The patients were classified into two groups according to educational level, 23 HE-AD (>9 years) and 13 LE-AD (≤9 years).

Results: As AD progressed over the 5-year longitudinal follow-ups, the HE-AD showed a significant group-by-time interaction in the right dorsolateral frontal and precuneus, and the left parahippocampal regions compared to the LE-AD.

Conclusion: Our study reveals that the preliminary longitudinal effect of HE accelerates cortical atrophy in AD patients over time, which underlines the importance of education level for predicting prognosis.

Key words: education, cortical thickness, Alzheimer's disease, cognitive reserve theory

Introduction

Epidemiological studies have reported that higher education (HE) is associated with a reduced risk of incident Alzheimer's disease (AD) (Letenneur *et al.*, 1994; Stern *et al.*, 1994; Evans *et al.*, 1997; Qiu *et al.*, 2001), suggesting that education may provide protection against the onset of the disease (Stern *et al.*, 1994). This protective effect of education is supported by the cognitive reserve (CR) hypothesis (Stern, 2002; Scarmeas and Stern, 2004). CR refers to the ability of the brain to compensate for damage by using pre-existing cognitive processing approaches or by recruiting compensatory approaches (Stern, 2002, 2009). Therefore, an individual with HE should cope better with an equivalent level of pathology than an individual with lower education (LE), which in turn, should delay the clinical expression of AD.

Once AD clinically manifests, brain pathology is already quite advanced in AD patients with HE (HE-AD), more so than those with LE (LE-AD)

Correspondence should be addressed to: Sang Won Seo, MD, PhD Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, South Korea. Phone: +82-2-3410-1233; Fax: +82-2-3410-0052. Email: sangwonseo@empal.com.
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(Wilson *et al.*, 2000; Stern *et al.*, 1999; Scarmeas *et al.*, 2006). Specifically, previous cross-sectional studies demonstrated that HE-AD exhibited higher amyloid burdens as measured by the Pittsburgh Compound B retention ratio (Kemppainen *et al.*, 2008), lower cerebral blood flow and glucose metabolism (Alexander *et al.*, 1997; Scarmeas *et al.*, 2003; Liao *et al.*, 2005; Kemppainen *et al.*, 2008), and more severe cortical atrophy (Seo *et al.*, 2011; Liu *et al.*, 2012). Moreover, after the clinical onset of AD, HE-AD experienced more rapid cognitive decline than LE-AD (Stern *et al.*, 1999; Andel *et al.*, 2006; Scarmeas *et al.*, 2006; Bruandet *et al.*, 2008). To our knowledge, however, the topography of structural changes according to education level has not been compared longitudinally.

Pathologic changes in AD occur predominantly in cortical gray matter, resulting in cortical atrophy (Mirra *et al.*, 1991). Cortical thickness analysis using surface-based morphometry analysis of magnetic resonance imaging (MRI) (Lerch and Evans, 2005) has been used in AD studies as a marker of disease progression (Querbes *et al.*, 2009; Julkunen *et al.*, 2010). In the present study, we hypothesized that education might influence brain structural changes in AD, specifically, cortical thinning. The aim of this study was to longitudinally investigate the topography of cortical thinning between the HE-AD and LE-AD.

Methods

Participants

This study was approved by the Institutional Review Board of Samsung Medical Center. We obtained informed consent from all patients and control participants.

Patients

We prospectively recruited 36 patients with AD to participate in the Alzheimer Disease and Positron Emission Tomography (ADAPET) study, which was described in detail previously (Cho *et al.*, 2013a; 2013b). The patients fit the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 1994), and they also fit the criteria for probable AD proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann *et al.*, 1984). For this longitudinal study, only the patients who had early-stage AD with a Clinical Dementia Rating (CDR) = 0.5 or 1 were enrolled. The patients were voluntary candidates for this study and had caregivers. None of the patients had a family history suggestive of an autosomal dominant disease. We excluded patients with other structural lesions found by brain MRI, such as territorial infarction, intracranial hemorrhage, brain tumor, hydrocephalus, or severe white matter hyperintensities.

At the initial visit, patients underwent clinical interviews, a neurological examination, a battery of neuropsychological tests called the Seoul Neuropsychological Screening Battery (SNSB), and conventional brain MRI scans. Potential secondary causes of cognitive deficit were ruled out by laboratory tests including complete blood count, blood chemistry, vitamin B12 levels, folate levels, syphilis serology, and thyroid function tests.

Controls

We recruited 14 healthy volunteers to serve as normal controls (NC). The NC was spouses of the AD patients, had no history of neurological or psychiatric illness, and had no abnormalities upon neurological examination. The NC exhibited normal cognition on the Mini-Mental State Examination (MMSE) and neuropsychological tests.

Education

To thoroughly evaluate the level of education achieved by participants, we gathered detailed information about their educational background, including whether or not they had completed each step of education (elementary school, middle school, high school, college, and graduate school). We confirmed the history of education with patient caregivers. We organized participants into two groups: those with more than 9 years of education and those with less. This 9-year cut-off criterion (HE-AD cut-off $>$ 9 years) was used because it corresponds to the duration of schooling that precedes the beginning of high school in South Korea. Overall, 23 AD patients were in the HE group (education $>$ 9 years) and 13 AD patients were in the LE group (education $\leq$ 9 years).

Neuropsychological tests

The AD patients and NC underwent a standardized neuropsychological battery of tests called the SNSB (Kang and Na, 2003; Ahn *et al.*, 2010). The battery contains tests for attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructive function, verbal and visual memory, frontal/executive function, and the MMSE.

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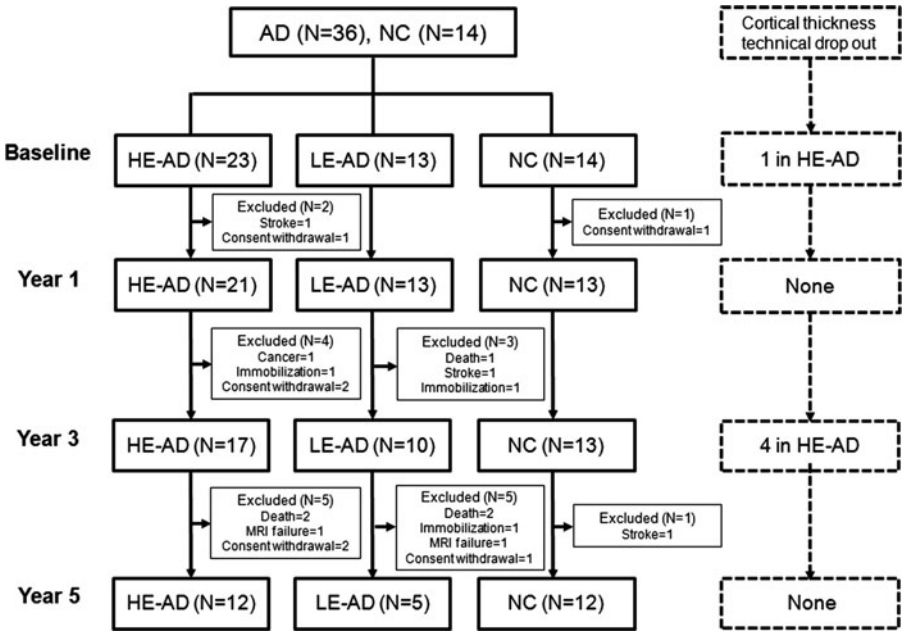


Figure 1. Study flow diagram. Abbreviations: AD = Alzheimer's disease; HE = higher education; LE = lower education; NC = normal controls.

Image acquisition and processing and cortical thickness measurement

We acquired 3D T1 turbo field echo MR images with the following imaging parameters: sagittal slice thickness, 1.0 mm, over contiguous slices with 50% overlap; no gap; repetition time (TR) of 9.9 msec; echo time (TE) of 4.6 msec; flip angle of 8°; and matrix size of 240 × 240 pixels, reconstructed to 480 × 480 over a field of view of 240 mm. The following parameters were used for the 3D FLAIR images: axial slice thickness of 2 mm; no gap; TR of 11000 msec; TE of 125 msec; flip angle of 90°; and matrix size of 512 × 512 pixels. A detailed description of the cortical thickness analysis is provided in Supplementary Method 1.

Follow-up evaluations with neuropsychological tests and neuroimaging

In the ADAPET study, patients were scheduled to undergo a high resolution T1-weighted volume MRI scan at baseline along with follow-up evaluations at Year 1, Year 3, and Year 5. Of the 36 AD patients, 34 completed the Year 1, 27 completed the Year 3, and 17 completed the Year 5. Nineteen patients were excluded, which included six due to withdrawal of consent, two due to stroke, one due to the detection of newly developed breast cancer, five due to death, three due to immobilization arising from progression of AD, and two due to MRI failures resulting from issues with cooperation. Of the 14 NC, 13 completed the Year 1 and Year 3, and 12 completed the Year 5. Two NC were excluded due to consent withdrawal and stroke. The total number of subjects (HE-AD, LE-AD, and NC) that participated in cortical thickness analysis is illustrated in Figure 1.

Statistical analysis

Demographic and neuropsychological data was analyzed using Mann–Whitney U test or Kruskal–Wallis test with Dunn's method for continuous variables and Fisher's exact tests with Bonferroni corrections for categorical variables.

In order to compare the baseline differences between groups, we performed an analysis using the General Linear Model. Each subject's native-space cortical thickness at every vertex or mean cortical thickness was a dependent variable. Variables, including age, gender, duration of disease, and intracranial volume were entered as independent variables. In order to assess the relationships between participants group and longitudinal changes in the cortical thickness over 5 years, we applied the Linear Mixed Models, which provides a flexible and powerful statistical framework for the analysis of longitudinal data (Verbeke and Molenberghs, 2000; Fitzmaurice *et al.*, 2012). The cortical thickness at each evaluation was a dependent variable. Variables, including age, gender, duration of disease, intracranial volume, participants groups (HE-AD, LE-AD, and NC), follow-up time (years) from baseline assessment, and the interaction between participants group and follow-up time (group-by-time) were entered as fixed effects (independent variable). The interaction

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Table 1. Demographic and clinical characteristics at baseline

	AD			
	TOTAL AD ($N = 36$)	HE-AD ($N = 23$)	LE-AD ($N = 13$)	NC ($N = 14$)
Baseline age: years[a]	70.2±8.0	70.5±7.0	69.7 ± 9.7	67.1 ± 7.6
Gender (female[b])	22/36 (61.1)	11/23 (47.8)[†]	11/13 (84.6)	7/14 (50.0)
Education (year)	11.0 ± 4.6	13.8 ± 2.2[†]	6.0 ± 2.8[*]	12.2 ± 4.7
Duration of disease (year)	3.8 ± 2.5	4.4 ± 2.8	2.8 ± 1.4	N/A
Hypertension	18/36 (50.0)	11/23 (47.8)	7/13 (53.8)	3/14 (21.4)
Diabetes	10/36 (27.8)	7/23 (30.4)	3/13 (23.1)	2/14 (14.3)
Hyperlipidemia	2/36 (5.6)	2/23 (8.7)	0/13 (0.0)	0/14 (0.0)
Heart disease	4/32 (11.1)	3/23 (13.0)	1/13 (7.7)	0/14
MMSE	20.9 ± 3.3	21.4 ± 3.3[*]	20.2 ± 3.1[*]	29.2 ± 0.9
CDR	0.8 ± 0.2	0.8 ± 0.3[*]	0.8 ± 0.2[*]	0.0 ± 0.0
CDR-SOB	4.7 ± 1.8	4.4 ± 1.8[*]	5.3 ± 1.7[*]	0.1 ± 0.2
ApoE4 genotype[c]	19/35 (54.3)	13/22 (59.1)[*]	6/13 (46.2)	2/14 (14.3)
Use of AchE inhibitor	34/36 (94.4)	22/23 (95.7)	12/13 (92.3)	N/A
Use of Memantine	7/36 (19.4)	5/23 (21.7)	2/13 (15.4)	N/A

[a]Values represent the mean ± SD or [b]numbers of cases with percentages in parentheses.
[c]APOE4 genotyping was performed in 49 participants; one AD patient refused the test.
[*]$p < 0.05$ between the NC and HE-AD or between the NC and LE-AD.
[†]$p < 0.05$ between the HE-AD and LE-AD.
Abbreviations: AchE inhibitor = acetylcholinesterase inhibitor; AD = Alzheimer's disease; APOE4 = apolipoprotein E4; CDR = Clinical Dementia Rating; CDR-SOB = Clinical Dementia Rating sum-of-boxes; HE = higher education; LE = lower education; MMSE = Mini-Mental State Examination; N/A = not applicable; NC = normal controls.

between participants group and follow-up time provided an estimate of whether there was a statistically significant difference in the cortical thickness in the group according to time. The cortical surface model contained 81,924 vertices; therefore, a correction for performing multiple comparisons was made using the false discovery rate (FDR) theory (Genovese *et al.*, 2002) at a q value of 0.05 after pooling the p values.

Demographic data and mean cortical thickness analyses were performed using Predictive Analysis Software (PASW) 18.0 (SPSS, Chicago, IL, USA). In order to compare the topography of cortical thickness, we used the Surfstat package created by Dr. Keith Worsley (http://www.math.mcgill.ca/keith/surfstat).

Results

Demographic and clinical characteristics

Demographic and clinical data are presented in Table 1. There were no differences between the HE-AD and LE-AD in any measure of dementia severity, including the MMSE, CDR, or Clinical Dementia Rating sum-of-boxes (CDR-SOB). There were fewer females in the HE-AD than LE-AD. Baseline and longitudinal comparisons from baseline to Year 5 of cognitive functions between the HE-AD and LE-AD were presented in Supplementary Tables S1 and S2.

Comparison of baseline difference in cortical thickness

At baseline, compared to the NC, the AD patients showed decreased cortical thickness in the bilateral prefrontal, medial and lateral temporal, precuneus, and temporo-parietal regions (Supplementary Figure S1). Compared to the NC, the HE-AD showed decreased cortical thickness in the bilateral prefrontal, medial and lateral temporal, precuneus, and fusiform regions. Compared to the NC, the LE-AD showed no significant regions of decreased cortical thickness. When the HE-AD and LE-AD were directly compared, there were no regions of significant difference in topography of the cortical thickness (Figure 2).

Comparison of longitudinal decline in cortical thickness from baseline to year 5

Compared to the NC, the AD patients showed significant group-by-time interaction throughout the cortex, sparing the primary motor and sensory, and cuneus regions (Supplementary Figure S1). Figure 3 provides statistical maps of vertices that showed significant group-by-time interactions in cortical thickness from baseline to Year 5. Compared to the NC, the HE-AD showed significant group-by-time interaction throughout the cortex, sparing the primary motor cortex. Compared to the NC, the LE-AD showed significant group-by-time interaction in the bilateral

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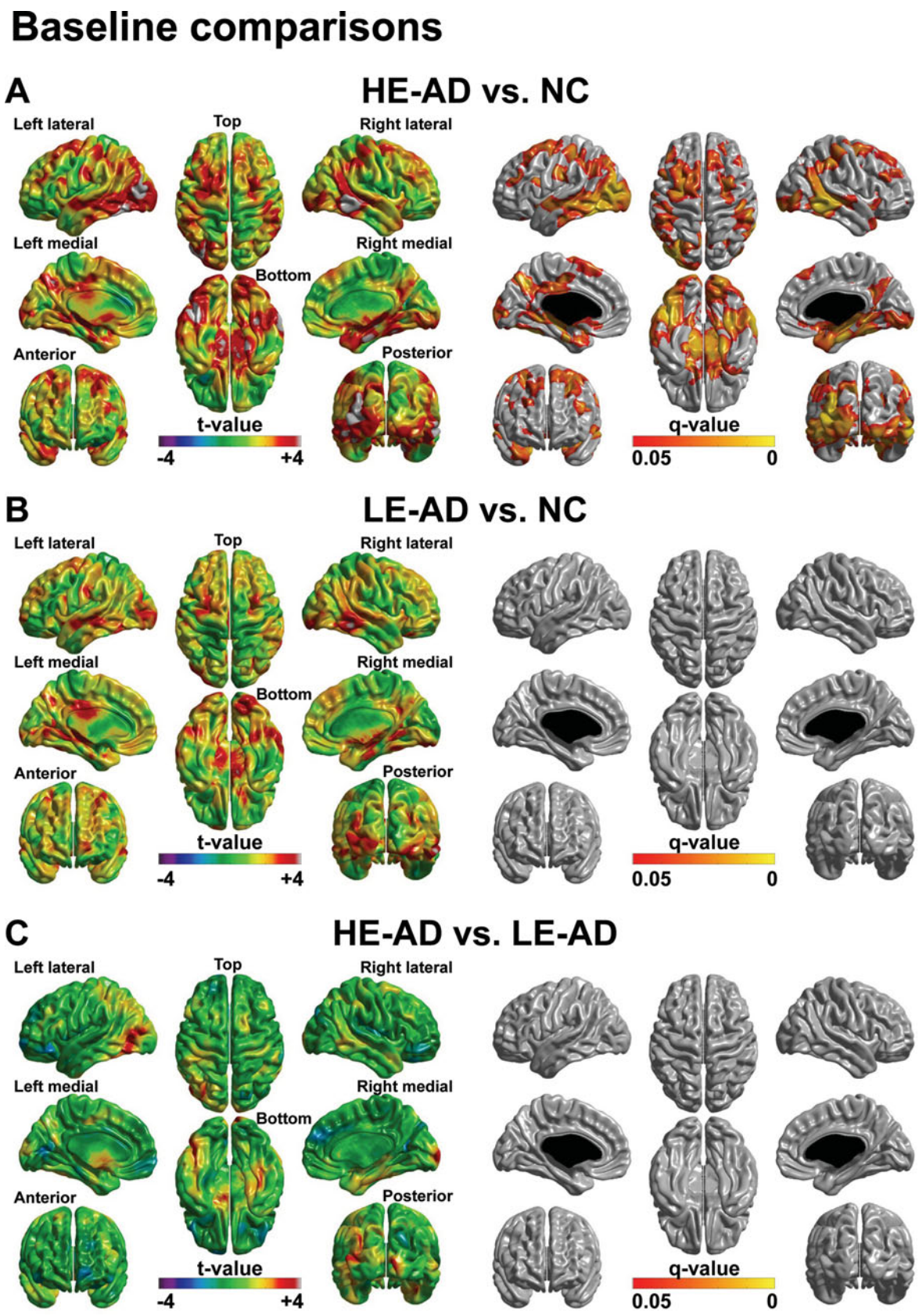


Figure 2. (Colour online) Statistical maps of baseline difference in regional cortical thickness (T-map, FDR corrected Q value < 0.05). Regional difference at baseline was analyzed by general linear model with adjusting for age, gender, duration of disease, and intracranial volume: (A) HE-AD vs. NC, (B) LE-AD vs. NC, and (C) HE-AD vs. LE-AD. Abbreviations: AD = Alzheimer's disease; FDR = false discovery rate; HE = high education; LE = low education; NC = normal controls.

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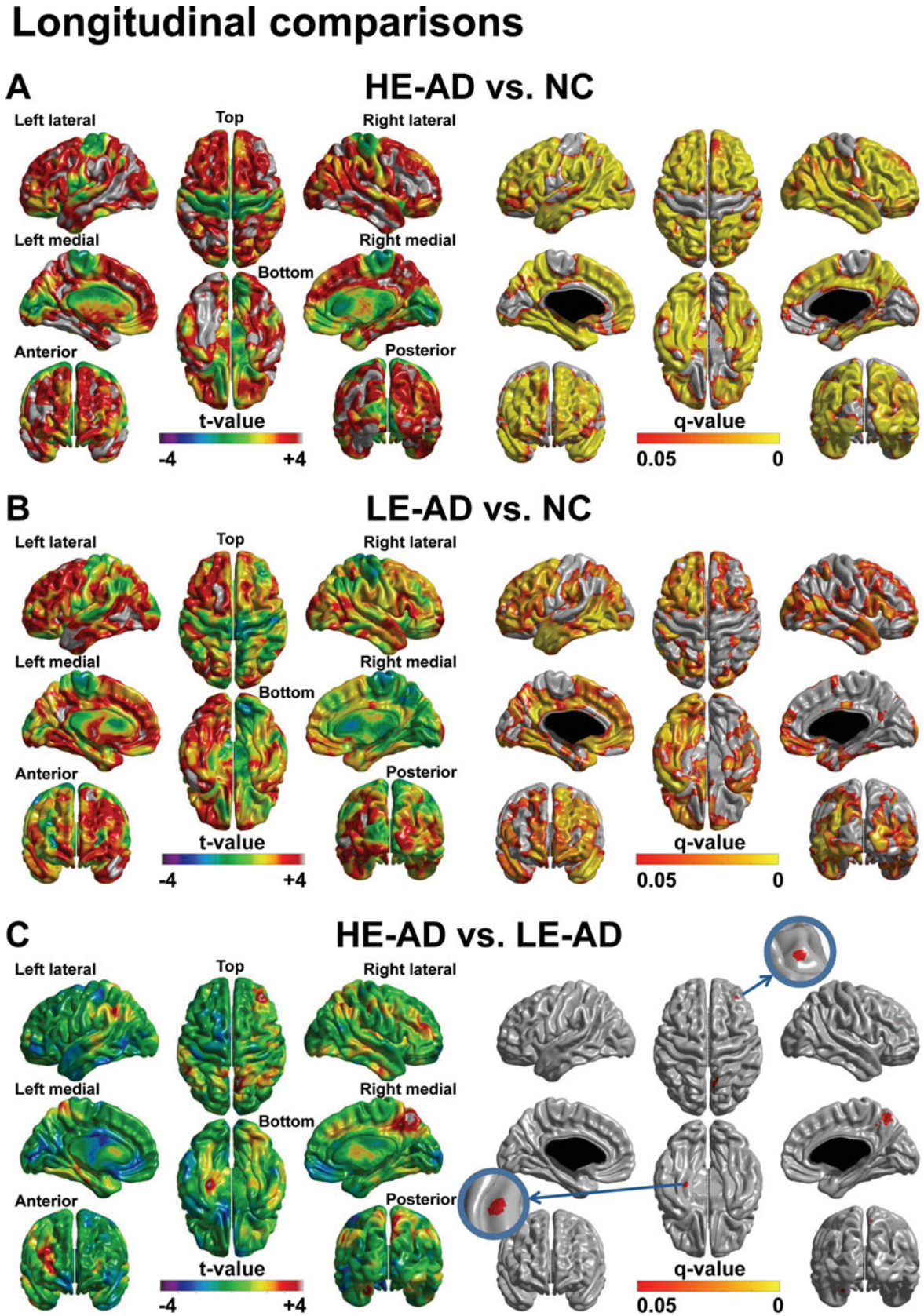


Figure 3. (Colour online) Statistical maps of longitudinal decrease (group-by-time interaction) in cortical thickness from baseline to Year 5 (T-map, FDR corrected Q value < 0.05). The group-by-time interaction was analyzed by linear mixed models after controlling for age, gender, duration of disease, and intracranial volume: (A) HE-AD vs. NC, (B) LE-AD vs. NC, and (C) HE-AD vs. LE-AD. Abbreviations: AD = Alzheimer's disease; FDR = false discovery rate; HE = high education; LE = low education; NC = normal controls.

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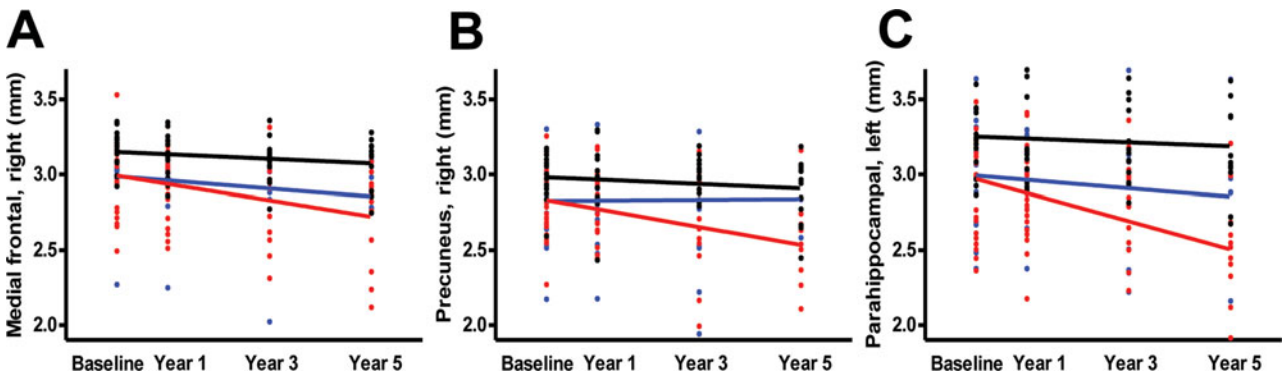


Figure 4. (Colour online) Cortical thickness data in representative vertex points from baseline to Year 5 follow-up in (A) the right dorsolateral prefrontal cortex, (B) the right precuneus, and (C) the left parahippocampal gyrus. HE-AD shows significantly accelerated cortical thinning in (A) the right dorsolateral prefrontal cortex, (B) the right precuneus, and (C) the left parahippocampal gyrus, when compared to LE-AD. (Black line = NC, Blue line = LE-AD, Red line = HE-AD). Abbreviations: AD = Alzheimer's disease; HE = high education; LE = low education; NC = normal controls.

prefrontal, medial and lateral temporal, fusiform, the left medial frontal, posterior cingulate, and precuneus regions. When the HE-AD and LE-AD were directly compared, the HE-AD showed significant group-by-time interaction in the right dorsolateral prefrontal and precuneus, and the left parahippocampal regions than did the LE-AD. The LE-AD did not show any regions with a significant group-by-time interaction compared to the HE-AD.

To further illustrate the magnitude of the cortical thinning rate that occurred from baseline to Year 5 follow-up, cortical thickness data as representative vertex points from the right dorsolateral prefrontal cortex, the right precuneus, and the left parahippocampal gyrus are presented in Figure 4. The HE-AD shows significantly accelerated cortical thinning in the right dorsolateral prefrontal cortex (group-by-time interaction $p = 0.013$), the right precuneus (group-by-time interaction $p = 0.001$), and the left parahippocampal gyrus (group-by-time interaction $p = 0.036$) compared to the LE-AD.

To address an arbitrary cut-off level of education of 9 years, we conducted the same analysis in the AD group using educational years as a continuous variable instead of a group comparison. As shown in Supplementary Figure 2(A), the AD group revealed that a higher level of education was associated with rapid cortical thinning in the right dorsolateral prefrontal and precuneus, and the left parahippocampal regions at an uncorrected level of significance with $P < 0.01$, which is generally consistent with the previous findings (using a cut-off of 9 years). However, the statistical significance disappeared after correction for multiple comparisons, which might be related to the small number of subjects enrolled. We also performed longitudinal analysis between the HE-AD and LE-AD groups using higher educational cut-off values of eight and 10 years. As shown in Supplementary Figure 2(B), relative to LE-AD ($N = 11$), HE-AD ($N = 25$) using a cut-off > 8 years showed a significant group-by-time interaction in the bilateral dorsolateral prefrontal and medial frontal, the right posterior cingulate and precuneus, and the left parahippocampal regions after FDR correction. In addition, in Supplementary Figure 2(C) relative to LE-AD ($N = 14$), HE-AD ($N = 22$) using a cut-off > 10 years showed a significant group-by-time interaction in the right dorsolateral prefrontal area and precuneus, and the left parahippocampal regions at an uncorrected level of significance with $P < 0.005$, which is generally consistent with our original findings.

Pairwise comparisons of the HE-AD and LE-AD were conducted at each time point (baseline – Year 1, Year 1 – Year 3, and Year 3 – Year 5) (Supplementary Figure S3). Significant findings were observed at Year 3 – Year 5 in terms of change in cortical thickness between the HE-AD and LE-AD in the bilateral parahippocampal and precuneus, the left temporo-parietal, and the right prefrontal regions after FDR correction.

Discussion

We reported novel findings about the longitudinal effects of education on cortical thinning over 5 years. The major finding of this 5-year prospective study was that as AD progressed, the HE-AD showed accelerated cortical thinning in the right dorsolateral prefrontal and precuneus, and the left parahippocampal regions than did the LE-AD, which may be related to the CR theory.

Recent cross-sectional studies reported that HE-AD had widespread cortical thinning in the frontal, temporo-parietal, precuneus, and occipital cortices

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compared to LE-AD (Seo *et al.*, 2011; Liu *et al.*, 2012). They explained these results by the CR theory. Since HE-AD have more CR than LE-AD, by the time AD clinically manifests in HE-AD, brain pathology is already quite advanced. Thus, more widespread atrophy in the brain must occur in HE-AD before AD is clinically manifested. However, we did not find that, at baseline, there were differences in the topography between the HE-AD and LE-AD.

Our major finding was that the HE-AD exhibited more accelerated cortical thinning than did the LE-AD. The present study is the first to investigate the longitudinal effect of education level on cortical degeneration in patients with AD. Our findings are consistent with one longitudinal study that used functional imaging with single photon emission computed tomography (SPECT) to show that HE-AD had a more rapid reduction in regional cerebral blood flow than LE-AD (Hanyu *et al.*, 2008). Like the functional study, our longitudinal findings might be explained by the CR hypothesis. That is, since pathology in HE-AD is more severe than in LE-AD after AD has developed, there is much less substrate remaining to function as a reserve (Stern, 2009; 2012). Therefore, the insufficient reserve in HE-AD contributes towards accelerated deterioration of AD (Stern *et al.*, 1999; Wilson *et al.*, 2000; Scarmeas *et al.*, 2006). Indeed, the topography of longitudinal cortical thinning observed in HE-AD in the current study was similar to that observed in several cross-sectional studies (Seo *et al.*, 2011; Liu *et al.*, 2012), although in the present study there were no differences between the two groups (HE-AD versus LE-AD) at baseline.

Accelerated cortical thinning was seen in the right dorsolateral prefrontal and precuneus, and the left parahippocampal regions in the HE-AD compared to the LE-AD. These findings are consistent with the longitudinal SPECT findings, which showed a significant regional cerebral blood flow reduction in the frontal, parietal, temporal, and limbic lobes of HE-AD group (Hanyu *et al.*, 2008). Also, our findings may be supported by previous neuropsychological studies. Frontal thinning was accelerated in HE-AD compared to LE-AD, which corresponds to quicker progression of AD in terms of executive function (Scarmeas *et al.*, 2006). Similarly, cortical thinning in the parahippocampal gyrus and precuneus is consistent with the reports of memory impairment shown in previous longitudinal studies (Stern *et al.*, 1999; Scarmeas *et al.*, 2006).

This study has some limitations. First, our patients were selected from a single center, and since this was a longitudinal study, there was attrition during the 5-year study period, resulting in a relatively small number of patients. Therefore, there may be limitations in the ability to generalize these findings. Second, when recruiting AD patients, we did not use any specific biomarkers for amyloid deposition such as cerebrospinal fluid amyloid beta levels or amyloid positron emission topography, although we did measure hippocampal atrophy and temporo-parietal hypometabolism. Moreover, at baseline and 5 years later, none of our subjects met the revised consensus criteria for dementia with lewy bodies (McKeith *et al.*, 2005), none had frontotemporal dementia (Neary *et al.*, 1998) and none had vascular dementia (Roman *et al.*, 1993). Finally, we could not obtain patient's information on the socio-demographic variables such as occupation or premorbid intelligence quotients that were frequently used proxies reflecting CR.

In conclusion, our study reveals that the preliminary longitudinal effect of HE accelerates cortical atrophy in AD patients over time, which underlines the importance of education level for predicting prognosis. This is noteworthy for a more comprehensive prognosis of AD patients, which is essential for the design of disease-modification strategies and the development of new AD treatments.

Conflict of interest

None.

Description of authors' roles

HC and SWS designed the study; all authors contributed to the acquisition of data and carrying out of the study; statistical analyses and interpretation of data were performed by DRK, SJ, CK, J-HK, J-ML, HC, and SWS. HC and SWS prepared the first draft; all authors revised the content critically for important intellectual content and approved the final version.

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Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1041610214001483

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