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Higher Education is Not Associated with Greater Cortical Thickness in Brain Areas Related to Literacy or Intelligence in Normal Aging or Mild Cognitive Impairment

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Abstract

Education may reduce risk of dementia through passive reserve, by increasing neural substrate. We tested the hypotheses that education is associated with thicker cortex and reduced rates of atrophy in brain regions related to literacy and intellectual ability. Healthy older adults and those with mild cognitive impairment were categorized into High (≥18 yrs) and Low (≤13 yrs) education groups. Higher education was associated with thinner cortices in several areas, but one-year atrophy rates in these areas did not differ by education group. These results do not support a passive reserve model in which early life education protects against dementia by increasing cortical thickness. Connectivity and synaptic efficiency, or other lifestyle factors may more directly reflect cognitive reserve.

Keywords

Brain reserve; cortical thickness; education; hippocampal volume; literacy; Mild Cognitive Impairment (MCI); aging

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Disclosures

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Introduction

Many studies have noted preserved cognitive function in individuals whose brains harbor an appreciable burden of neuropathology (Katzman, et al., 1988; Knopman, et al., 2003; Riley, Snowdon, & Markesbery, 2002). This disjunction between the degree of neuropathology and cognitive performance has been attributed to active cognitive reserve and passive brain reserve (Satz, 1993; Stern, 2009). According to the active cognitive reserve model, effects of tissue damage are compensated by alternate cognitive strategies or by increased efficiency, capacity, or flexibility of the neural networks underlying cognitive task performance (Stern, 2009). In the passive reserve model, greater neural substrate provides a backup for loss from pathology (Satz, 1993), allowing for a greater degree of brain tissue damage before a critical threshold is reached that results in functional impairment. Larger numbers of pyramidal neurons (Katzman, et al., 1988), larger brain size estimated by intracranial volume (Wolf, Julin, Gertz, Winblad, & Wahlund, 2004), and larger head circumference (Mortimer, Snowdon, & Markesbery, 2008; Schofield, Logroscino, Andrews, Albert, & Stern, 1997) have all been investigated as potential markers of passive reserve.

While reserve may depend on genetic and developmental factors, there is evidence to support contributions from environmental factors and use-dependent plasticity. Epidemiological studies have noted various proxies for reserve that are associated with a delay in the onset of memory decline in the preclinical stages of dementia. These proxies include early life education, linguistic ability and IQ, participation in cognitively stimulating leisure activities later in life, exercise and social networks (Fritsch, McClendon, Smyth, & Ogrocki, 2002; Fritsch, et al., 2005; Riley, Snowdon, Desrosiers, & Markesbery, 2005; Snowdon, et al., 1996; Stern, et al., 2003; Verghese, et al., 2003; Whalley, et al., 2000).

Educational attainment may protect against deleterious effects of neuropathology through passive brain reserve, perhaps by stimulating neurogenesis or increasing synaptic density, resulting in an increased amount of neural substrate that can be quantified in structural MRI. Although studies of brain plasticity have reported increases in brain grey matter following education or acquisition of specific cognitive skills in normal adults (Bermudez, Lerch, Evans, & Zatorre, 2009; Carreiras, et al., 2009; Lazar, et al., 2005; Sluming, et al., 2002), the literature relating education to brain morphology is controversial. Some studies have found that education results in increased brain weight (Brayne, et al., 2010) or increases in regional cortical thickness (Liu, et al., 2012), whereas others have reported reduced brain volumes (Apostolova, et al., 2006; Querbes, et al., 2009) or increases in sulcal cerebrospinal fluid (a marker of atrophy) in individuals with higher education levels (Coffey, Saxton, Ratcliff, Bryan, & Lucke, 1999).

The effect of education, however, may be more specific; that is, education may increase neural substrate in a more regionally-specific manner. Education increases intellectual ability and literacy skills (e.g. Flynn, 2007), and variation in these abilities has been associated with variation in cortical thickness or volume in specific brain regions (Carreiras, et al., 2009; Castro-Caldas, Petersson, Reis, Stone-Elander, & Ingvar, 1998; P. Shaw, et al., 2006). For example, intellectual ability has been associated with cortical thickness in superior and mid frontal regions (Shaw, et al., 2006). Literacy has been associated with grey matter density in lateral occipital and parieto-temporal regions, and grey matter density in these areas has been noted to change following acquisition of reading skill in newly literate adults (Carreiras, et al., 2009; Castro-Caldas, et al., 1998). These findings suggest that individual differences in the relation of these areas to literacy may not arise solely from inborn or developmental differences in brain architecture, but may reflect experiential differences.

Here, we used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to test the hypothesis that a higher education level is associated with thicker cortex in brain regions responsive to specific (literacy) or general (IQ) cognitive experience in healthy older adults and those with mild cognitive impairment (MCI). We also tested the hypothesis that a higher level of education is associated with a slower one-year atrophy rate in healthy older individuals and those with MCI. Although our main focus was on brain areas related to literacy and intellectual ability, we secondarily examined whether education protects against loss in brain areas most vulnerable to the effects of early AD, including the entorhinal cortex and hippocampus. We additionally examined whether the American National Adult Reading Test (AMNART), a measure that may better reflect lifetime educational attainment relative to years of education, showed similar associations with cortical thickness; the AMNART was not used as our primary proxy for cognitive reserve as it may be influenced by neurodegeneration (Lowe & Rogers, 2011; Taylor, et al., 1996).

Materials and Methods

Data used in the preparation of this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (www.adni-info.org). The ADNI was launched in 2003 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies and non-profit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials. Subjects have been recruited from over 50 sites across the U.S. and Canada. At the time of data access for this report, ADNI had recruited 230 cognitively normal healthy control subjects, 399 people with amnestic MCI, and 193 patients with mild AD (for-up-to-date information see www.adni-info.org). Details regarding the study cohort and MRI acquisition have been published previously (Jack, et al., 2008; Petersen, et al., 2010).

Participants

We analyzed data from ADNI's healthy control (HC) and MCI participants. ADNI eligibility criteria are described in the ADNI protocol, which can be found at http://www.adni-info.org/Pdfs/adni_protocol_9_19_08.pdf. Briefly, participants are 55–90 years of age, had an informant able to provide an independent evaluation of functioning, and spoke either English or Spanish. Participants had completed at least 6 years of education (or had a work history sufficient to exclude mental retardation). Participants had minimal cerebrovascular disease based on modified Hachinski score of 4 or less, and use of specific psychoactive medications was exclusionary. General inclusion/exclusion criteria are as follows:

1. Healthy control subjects (HC): Mini Mental State Exam (MMSE) scores between 24 and 30 (inclusive), a Clinical Dementia Rating (CDR) of 0, non-depressed, non-MCI, and non-demented.
2. MCI subjects: MMSE scores between 24 and 30 (inclusive; exceptions made on a case by case basis by neurologists at the center of follow up), a memory complaint, objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia.

Across the full HC and MCI sample, the range of education was 6-20 yrs. High education was defined as the highest quartile of education years in this sample, ≥ 18 yrs; low education was defined as the lowest quartile; ≤ 13 yrs.

After local quality control of all MRI data, there were 119 HC and 207 MCI participants included for baseline analysis; for the longitudinal MRI analyses data from 91 HC and 140 MCI subjects were included. The detailed demographics of the high and low education groups at baseline among the HC and MCI participants are shown in Table 1. As expected, due to its high correlation with education (Grober & Sliwinski, 1991), error scores on American National Adult Reading Test (AMNART) significantly differed between the high and low education groups amongst both HC and MCI participants. Among HCs, the high and low education groups did not differ in their mean scores on the Alzheimer's Dementia Assessment Scale, Cognitive-Subscale (ADAS cog) or Global depression scale (GDS) at baseline or at 1 year follow up; the high education group showed higher MMSE scores at both time points. Among MCI participants the high education group showed superior cognitive performance to the low education MCI group as reflected in their significantly lower ADAS cog scores and higher MMSE scores at baseline.

To examine the suitability of the AMNART error scores as a potential marker of cognitive reserve, in contrast to level of education, we assessed whether the AMNART scores were sensitive to cognitive impairment in MCI, which may reflect the prodromal phase of AD. AMNART error scores were significantly higher in the MCI group relative to the HC group (13.6 vs, 9.4, respectively, $F(1,565) = 22.9$; $p < .001$). After controlling for disease severity, as assessed with the ADAS cog, the difference in error scores between MCI and HCs was not significant ($F(1,563) = 1.6$; $p > .1$).

High and low education groups did not differ significantly in the proportion of subjects with CSF biomarkers of amyloid-beta pathology (CSF data were collected from half of all ADNI participants). Among HCs, 47% (16/34) of high education subjects and 32% (7/22) of low education subjects ($\chi^2 = 1.28$ $p = 0.26$) had CSF $A\beta_{1\text{-}42}$ levels indicative of AD, as determined using a previously established threshold ($A\beta_{1–42} \leq 192$ pg/ml) (Shaw et al, 2009). Among MCI participants 76% (48/63) of individuals in the high education group and 80% (32/40) in the low education group showed CSF $A\beta_{1\text{-}42}$ levels indicative of AD pathology ($\chi^2 = 0.21$ $p = 0.65$). Details regarding the CSF biomarker assay and CSF biomarker characteristics of the ADNI cohort have been published previously (Shaw et al, 2009, 2011).

Image Analysis

Raw DICOM MRI scans (including two T_1-weighted volumes per subject per visit were downloaded from the public ADNI web site (http://www.loni.ucla.edu/ADNI/Data/index.shtml). These data were collected across a variety of scanners with protocols individualized for each scanner (Jack, et al., 2008) see http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml). Locally, raw MRI data were reviewed for quality, automatically corrected for spatial distortion due to gradient nonlinearity (Jovicich, et al., 2006) and B_1 field inhomogeneity (Sled, Zijdenbos, & Evans, 1998), registered, and the two volumes per subject were averaged to improve the signal-to-noise ratio. Volumetric segmentation (Fischl, et al., 2002) and cortical surface reconstruction (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999; Fischl & Dale, 2000) and parcellation (Desikan, et al., 2006; Fischl, et al., 2004), produced by a locally optimized version of the FreeSurfer software package, were used to quantify baseline regional thickness and volumes as described in detail elsewhere (Fennema-Notestine, et al., 2009).

One year change in brain structural measures was quantified using Quarc (Quantitative anatomical regional change analysis) (Holland & Dale, 2011; Holland, McEvoy, & Dale, 2011). The one-year follow-up MRI scans for each subject were corrected for spatial distortion due to gradient nonlinearity, rigid-body aligned, and the two images obtained from that time point were averaged. The averaged follow-up image was registered to the subject's baseline image using a 12-parameter affine registration, then intensity-normalized to the baseline image using an iterative procedure. A deformation field was then calculated from nonlinear registration and used to align scans at the sub-voxel level resulting in a one-to-one correspondence between each vertex in the baseline and the follow-up images. Subcortical segmentation and cortical parcellation labels from the baseline image were used to extract average volume change for each region of interest. Visual quality control was performed on the volume change field to exclude cases with degradation in registration due to artifacts (eg. patient motion, scanner changes over time).

Statistical Analysis

Statistical analyses were performed using SPSS ™ (Chicago, IL) statistical software package. Differences between education groups at baseline were completed, comparing sex, APOE ε4 status, age, MMSE, AMNART error and GDS scores separately for HC and MCI participants. Chi square analysis was used for categorical variables and independent sample t-tests for continuous variables (see Table 1). In all analyses, a difference with a two-tailed probability of $p < 0.05$ was considered significant.

Baseline regional cortical thickness and volume analyses—Statistical analyses were performed to determine whether baseline cortical thickness or volumes of interest differed between high and low education groups for HC and MCI within select ROIs. Multivariate linear regression models included age, sex and estimated total intracranial volume (the latter for volumetric measures only) as covariates; education group as the independent variable; and cortical thickness or brain volume as the dependent measure. APOE e4 allele frequencies were similar in the high and low education groups of HC and MCI (Table 1) and were not included in statistical models. For the MCI group, an additional regression model was performed in which we examined potential confounding effects of disease severity by including performance on the ADAS-Cog as a covariate.

The primary ROIs examined included those that have been reported to relate to intellectual ability, including left and right caudal middle frontal, rostral middle frontal, superior frontal regions (Shaw, et al., 2006); and to literacy, including left and right inferior parietal, middle temporal, superior temporal and lateral occipital regions (Carreiras, et al., 2009; Castro-Caldas, et al., 1998). In secondary analyses, we examined whether education may protect against changes in brain areas sensitive to early AD, including hippocampal volumes and entorhinal cortical thickness. Due to their sensitivity to prodromal AD, we also investigated more global measures of atrophy, including whole brain and ventricular volumes.

Rate of change analyses—Using the same multivariate linear regression model described above, we examined whether 1-year atrophy rates differed between high and low education groups within ROIs that showed education-related differences at baseline. To determine whether baseline cortical thickness was predictive of atrophy rates over time, we also included baseline thickness in the multivariate model as an additional independent variable to predict rate of change in the same region. In secondary analyses, we also examined whether education affected atrophy rates in brain regions sensitive to AD-related neurodegeneration.

Interactions of education with diagnostic group, age, and CSF amyloid status —In addition to examining education-related differences on morphometric measures within HC and MCI separately, we also examined if there were significant interactions between education and diagnostic group (HC or MCI) by adding diagnostic group and education x diagnostic group as additional variables in the primary regression models. To determine whether any associations of education with morphometric measures varied as a function of age, participants were stratified into young (<75 years) and older (>75 years) groups, and age group by education was included as an interaction term in the models.

To determine whether the relationship between cortical thickness and cognitive reserve (as determined by education level) differed as a function of amyloid status, we included CSF amyloid status as an interaction term in the model for the subgroup with available data, collapsed across HC and MCI groups to provide sufficient power. Participants were categorized as positive (CSF $A\beta_{1–42} \leq 192$ pg/ml) or negative (CSF $A\beta_{1–42} > 192$ pg/ml) for amyloid pathology based on the previously established threshold (Shaw et al, 2009). Since CSF measures were available on half the participants only, we performed this analysis on the full study sample (HC and MCI subjects combined), controlling for disease severity with the ADAS cog.

Results

Baseline regional cortical thickness and volume

Healthy controls—Relative to the low education group, the high education group had significantly thinner baseline cortex in right lateral occipital and right middle temporal areas related to literacy but no significant differences in the frontal areas related to intellectual ability (Table 2). The higher education group demonstrated thinner left entorhinal cortex and smaller right hippocampal volume relative to the lower education group. Whole brain and ventricular volumes were not different between education groups (Table 2). In areas showing significant education-related differences, age was negatively associated with thickness or volume, although the age effect for the left entorhinal cortex was not significant ($p = .11$). However, there were no significant interactions between education and age group on regional thickness or volumes.

MCI—Relative to the low education group, the high education group had significantly thinner baseline cortex in the left inferior parietal area, related to literacy. There were no significant differences in frontal areas related to intellectual ability (see Table 2). After controlling for disease severity, the high education group had significantly thinner baseline cortex in two areas related to literacy, the left inferior parietal area and left middle temporal cortex [$F(1,202) = 10.45$; $p = .001$; $F(1,202) = 5.2$; $p = 0.024$, respectively]. No statistically significant differences between the high and low education groups were found for entorhinal cortex, hippocampus, whole brain or ventricular volumes. Age was not significantly associated with left inferior parietal thickness ($p = .15$), but was significantly negatively associated with left middle temporal thickness. There were no significant education by age group interactions.

Interactions with diagnostic group or CSF amyloid status

As expected, there was a significant effect of diagnostic group across all ROIs, with MCI participants showing thinner cortex, reduced hippocampal and whole brain volumes, and expanded ventricles relative to HCs. However, there were no significant diagnosis by education group interactions. Similarly, there were no significant interactions between educational level and CSF amyloid status on cortical thickness or volumes. Controlling for

amyloid status did not alter the findings that when significant effects of education were observed, those with lower education showed greater thickness or volumes.

Rate of change

Healthy controls—In cortical areas significantly different at baseline (right lateral occipital and right middle temporal areas), atrophy rate did not differ by education group, whether baseline measures were included in the model or not. The atrophy rates of entorhinal cortex, hippocampus, whole brain, and ventricles were not significantly different between the high and low education groups.

MCI—Neither the left inferior parietal nor the left middle temporal areas (both with significant education effects at baseline) showed education-related differences in 1-year rate of atrophy, whether baseline measures were in the model or not. The atrophy rates of entorhinal cortex, hippocampus, whole brain, and ventricles did not significantly differ between the high and low education groups.

Interaction between Education and Diagnostic group

There was a significant effect of diagnostic group on rates of atrophy, with MCI participants having greater 1-year atrophy rates than HCs, as expected. There were no significant interactions between education and diagnostic group in ROIs showing education-related effects at baseline, nor in the brain measures sensitive to AD-related atrophy.

AMNART as the Proxy for Reserve

When participants were separated into groups according to highest and lowest quartile AMNART error scores, no significant differences as a function of AMNART group were observed in any region for HC or MCI participants. However, mean thickness and volume differences between highest and lowest AMNART quartiles were in the same direction as found for education group differences. That is, individuals with the highest error scores showed thicker cortex or greater volumes than those with the lowest error scores.

Discussion

In this study we hypothesized that baseline cortical thickness would be greater, and atrophy rates slower, in participants with higher levels of education than in those with lower levels of education. The results, however, showed that when significant education-related differences were observed at baseline, those with lower levels of education showed thicker cortex or larger volumes than those with higher levels of education; and atrophy rates in these areas did not significantly differ between education groups.

These results do not support the notion that early life education is associated with greater neural substrate later in life within brain areas related to literacy or intellectual ability. The finding that higher education was associated with thinner regional cortex is counterintuitive, although consistent with another report from ADNI that more highly educated HC and MCI participants had a significantly thinner global cortical mantle as measured by an index of normalized whole brain cortical thickness compared to lower education subjects (Querbes, et al., 2009). Our findings are also consistent with a report on a separate population that higher education was associated with smaller hippocampal volumes in MCI and AD patients (Apostolova, et al., 2006). Conflicting findings, however, have also been reported. One study used a combined measure of education, occupational attainment and social engagement as a proxy for reserve, and found that among a very small group of healthy controls (n= 16) those with higher reserve had greater brain volume, whereas the reverse relationship was observed in the small samples of MCI (n=12) and AD (n=16) patients

examined (Sole-Padulles, et al., 2009). The small samples and lack of education information within the samples make these findings difficult to interpret. A more recent, larger study reported greater temporal cortex thickness with greater education among healthy older adults (Liu, et al., 2012). In this study, in which participants were recruited from multiple sites across Europe, the overall education level was lower. This was particularly true for the low education group, who had 6±2 years of education. It is possible that when individuals with such extreme low levels of education are compared to those with higher levels, education may be associated with thicker cortex. This would be consistent with findings that the association between smaller head circumference and increased risk of dementia is only apparent at the extreme (Coffey, et al., 1999; Mortimer, et al., 2008; Reynolds, Johnston, Dodge, DeKosky, & Ganguli, 1999; Schofield, et al., 1997).

Educational level, although commonly used, is a relatively crude estimate of reserve. Quality of education can vary widely, and it does not reflect cumulative life time experiences that may act to increase reserve. The AMNART score may better reflect such cumulative experience, and provide a more sensitive assessment of literacy. However, AMNART is influenced by progression of dementia (Lowe & Rogers, 2011; Taylor, et al., 1996), and our findings of a significant difference between HC and MCI participants suggest that it may be influenced by cognitive changes that occur in the prodromal stage, potentially making it a less suitable proxy than education level in individuals with MCI. When we substituted AMNART for education level as the proxy for reserve in cognitively healthy subjects (HC), we found no significant differences in cortical thickness or volumes between those scoring in the lowest and highest quartiles. Mean differences, however, were generally in the same direction as observed for education level: the group with the highest errors showed thicker cortex than the group with the lowest number of errors. This suggests that the counterintuitive findings did not result from the choice of cognitive reserve proxy.

One possible explanation of the finding of thinner cortex among more highly educated participants is that these participants are able to compensate while harboring a higher level of AD neuropathology, and thus may be experiencing some degree of AD-related atrophy. However, high and low education groups did not differ in CSF biomarkers of amyloid pathology using available data. Secondary analyses on the subset of subjects with CSF biomarker data showed that differences in cortical thickness or volume between high and low education groups did not vary as a function of CSF $A\beta_{1–42}$ status; and controlling for CSF $A\beta_{1–42}$ status did not change the pattern of results. Thus it is unlikely that differences in amyloid pathology in the full sample account for the findings. Similarly, it is unlikely that the high education group experienced greater atrophy related to AD neuropathology since the longitudinal MRI analyses showed that atrophy rates did not differ between low and high education groups.

In cross-sectional studies of MCI and AD patients, findings of smaller hippocampal or entorhinal cortex volumes among the more highly educated subjects relative to less educated subjects have been interpreted as supporting the cognitive reserve hypothesis (Apostolova, et al., 2006; Serra, et al., 2011). That is, even though high and low education groups display similar levels of cognitive function, the more highly educated individuals are thought to have undergone a longer period of AD-related atrophy, resulting in thinner cortex. However, our longitudinal findings, which showed a lack of education-related differences in entorhinal or hippocampal atrophy rates among healthy adults and those with MCI, do not support that view. Instead, our finding that a similar pattern of education-related differences (thinner cortex among the more highly educated) can be observed in healthy adults suggests that education-related differences in entorhinal thickness and hippocampal volume may exist independent of AD-related atrophy.

The current study, which examined brain morphological differences as a function of education, does not directly address the issue of cognitive reserve, which posits that individuals with higher levels of education can better resist cognitive consequences of neuropathology and brain atrophy. The finding that the higher education group performed better on cognitive tasks (e.g., MMSE and ADAS-Cog for MCI participants; MMSE for HCs) than the lower education group, despite reduced cortical thickness, is consistent with an active reserve model but does not provide direct support. This would require demonstration that education level modulates the relationship between atrophy and cognitive function (Christensen, et al., 2007). However, our findings are inconsistent with the view that education affects passive reserve by leading to an increase in neural tissue.

Although we hypothesized that greater educational attainment would increase passive reserve, i.e., greater cortical thickness, we found the opposite: greater educational attainment was associated with thinner cortex. Connectivity and synaptic efficiency, rather than brain structure (or brain reserve), may more directly reflect cognitive reserve, and may be more readily influenced by educational attainment than cortical thickness. Higher education, obtained during young adulthood, may result in greater pruning of the cortex, increasing neural efficiency; and this efficiency may provide the basis of cognitive reserve associated with education. However, it is also possible that other, unmeasured factors that occurred during the long interval between education and MRI assessment (30-50 years), such as cognitive stimulation, social engagement, physical activity, or health issues, may have contributed to the observed group differences.

Limitations

The relatively high level of education in the ADNI sample is a limitation. As previously noted, the association of education with cortical thickness may differ when individuals with much lower levels of education are included in the analyses. The choice of education as the proxy for reserve may also be considered a limitation. Education is a complex marker of reserve and is likely related to several factors, including lifestyle and medical care factors that may influence risk of impairment. Although the high and low education groups were comparable for some factors that influence cortical atrophy rate (Table 1), they may have differed in other possible confounding factors including presence and severity of metabolic and cardiovascular risk factors such as diabetes, hypertension and hypercholesterolemia. Type I error must also be considered as a possibility. However the consistency of the education effects on baseline thickness, in which greater education was associated with thinner cortex across multiple ROIs and in both HC and MCI suggests that these effects may not be due to chance. Finally, there is a long interval between the period of education and the late life acquisition of the MRIs, thus unmeasured factors related to intervening cognitive stimulation may affect the relation of early life education to late life brain morphology.

Summary

Our study examined whether education level related to cortical thickness in areas of the brain associated with literacy or intellectual ability, including bilateral regions of frontal, inferior parietal, temporal and lateral occipital cortex. In our highly educated sample, we found that education was associated with thinner cortex in lateral occipital bilaterally and in right middle temporal areas in healthy older adults. In MCI, education was associated with thinner cortex in left inferior parietal regions. We also found that, in healthy adults, education was associated with thinner cortex or smaller volumes in medial temporal areas vulnerable to AD, despite a lack of difference in AD-related CSF biomarkers between education groups. Education-related differences in these regions did not predict one year atrophy rates. These findings suggest that early life education does not provide a protective

buffer against cognitive decline through an increase in neural substrate as reflected in cortical thickness or volume measures.

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Table 1

Demographic and clinical characteristics of the low and high education groups for healthy control MCI participants.

	Baseline			1 Year Follow-Up		
	≤13yrs education	**≥18yrs education**	***p* value**	**≤13yrs education**	**≥18yrs education**	***p* value**
HC	**n=39**	**n=80**		**n=31**	**n=60**	
Age	75.6(4.9)	76.3(5.2)	ns	75.0 (4.7)	76.0 (5.4)	n.s
Sex (M/F)	10/29	53/27	p<0.001	7/24	38/22	p<.001
APOE e4	25.6%	25%	ns	29%	28.3%	n.s
Education	11.6 (1.9)	18.9 (0.9)	p<0.001	11.9 (1.6)	18.8 (0.9)	p<0.001
ADAS cog	6.0 (2.6)	6.0 (3.1)	ns	5.1 (2.5)	5.1 (3.0)	n.s
MMSE	28.7 (1.1)	29.3 (0.8)	p< 0.01	28.9 (1.3)	29.2 (1.1)	p<.01
AMNART	17.1	6.8	p<0.001	15.9 (9.3)	7.0 (8.9)	p<.001
GDS	1.6	1.7	ns	1.1 (1.4)	1.4 (1.1)	n.s

MCI	**n=85**	**n=122**		**n=52**	**n=88**	
Age	75(7.4)	73.6 (7.9)	ns	74.9 (7.0)	73.6 (7.6)	n.s
Sex (M/F)	51/34	79/43	ns	29/23	57/31	n.s
Education	11.5 (1.5)	18.8 (0.9)	p<0.001	11.4 (17)	18.8 (0.9)	p<0.001
APOE %	52.9%	52.8%	ns	57.7%	55.6%	n.s
ADAS cog	12.2 (4.0)	10.6 (4.2)	p<0.003	11.3 (3.8)	10.9 (4.4)	n.s
MMSE	26.7	27.4	p<0.006	26.0 (2.9)	27.0 (2.77)	n.s
AMNART	19.5	10	p<0.01	20.0 (10.1)	10.9 (10.3)	p<.001
GDS	2.7	2.7	ns	2.1 (2.0)	1.8 (2.1)	n.s

Values are mean (standard deviation) unless otherwise indicated. P values reflect independent sample t-tests or chi-square tests for continuous and categorical variables, respectively. MCI = mild cognitive impairment; APOE – indicates percentage of participants with at least one apolipoprotein episilon 4 allele; ADAS-Cog = Alzheimer's Disease Assessment Scale – Cognitive Subscale; MMSE = Mini Mental State Exam; GDS = Global Depression Inventory; AMNART = American National Adult Reading Test error scores

Table 2

Mean (standard error of the mean) cortical thickness or volume as a function of education level for healthy control and MCI participants.

	Healthy Control			MCI		
Region of interest	**Low Ed**	**High Ed**	**F statistic**	**Low Ed**	**High Ed**	**F statistic**
Healthy control	N=39	N=80		N=85	N=122	
Left caudal middle frontal	2.20 (0.2)	2.17 (0.2)	0.6	2.12 (0.2)	2.10 (0.2)	0.7
Left rostral middle frontal	2.01 (0.2)	1.97 (0.2)	0.2	1.93 (0.1)	1.92 (0.1)	0.3
Left superior frontal	2.39 (0.2)	2.34 (0.2)	0.6	2.29 0.2)	2.28 (0.2)	0.2
Right caudal middle frontal	2.14 (0.2)	2.16 (0.2)	0.1	2.09 (0.2)	2.07 (0.2)	0.5
Right rostral middle frontal	1.97 (0.2)	1.97 (0.2)	0.4	1.90 (0.1)	1.91 (0.1)	0.5
Right superior frontal	2.39 (0.2)	2.37 (0.2)	0.9	2.28 (0.2)	2.30 (0.2)	0.7
Left inferior parietal	2.09 (0.2)	2.02 (0.2)	3.5	2.01 (0.2)	1.94 (0.2)	**6.4***
Left lateral occipital	1.90 (0.2)	1.83 (0.2)	**5.0***	1.84 (0.1)	1.81 (0.2)	2.2
Left middle temporal	2.61 (0.2)	2.55 (0.2)	3.9	2.46 (0.2)	2.42 (0.2)	1.7
Left superior temporal	2.40 (0.2)	2.35 (0.2)	2.3	2.27 (0.2)	2.27 (0.2)	0.0
Left supramarginal	2.19 (0.2)	2.13(0.2)	2.5	2.10(0.2)	2.08(0.2)	0.5
Right inferior parietal	2.09 (0.2)	2.03 (0.2)	3.4	1.99 (0.2)	1.96 (0.2)	1.1
Right lateral occipital	1.92 (0.2)	1.83 (0.1)	**9.0****	1.83 (0.2)	1.82 (0.2)	0.1
Right middle temporal	2.66 (0.2)	2.57 (0.2)	**5.8***	2.51 (0.2)	2.49 (0.2)	0.4
Right superior temporal	2.41 (0.2)	2.37 (0.2)	0.9	2.30 (0.2)	2.33 (0.2)	1.1
Left entorhinal	3.3 (0.3)	3.1 (0.3)	**5.3***	3.0 (0.5)	2.9 (0.5)	0.7
Right entorhinal	3.4 (0.4)	3.2 (0.4)	3.2	3.0 (0.6)	3.0 (0.6)	0.1
Left hippocampus	3590 (368)	3515 (355)	1.0	3244 (445)	3161 (444)	1.8
Right hippocampus	3830 (406)	3597 (382)	**8.5****	3390 (508)	3365 (507)	0.1
Whole brain	983092 (60088)	968186 (58293)	1.5	969920 (62375)	962784 (62126)	0.7
Ventricles	36687 (14076)	37940 (13568)	0.2	43972 (15893)	44641 (15877)	0.1

Significance of two-tailed comparison is denoted in bold by

Ed = Education.

* p<.05

** p<.01.