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ORIGINAL ARTICLE

Educational attainment and hippocampal atrophy in the Alzheimer's disease neuroimaging initiative cohort

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KEYWORDS
Alzheimer's;
Hippocampal volume;
Education;
Cognitive reserve

Summary
Introduction: Subjects with higher cognitive reserve (CR) may be at a lower risk for Alzheimer's disease (AD), but the neural mechanisms underlying this are not known. Hippocampal volume loss is an early event in AD that triggers cognitive decline.
Materials and methods: Regression analyses of the effects of education on MRI-measured baseline HV in 675 subjects (201 normal, 329 with mild cognitive impairment (MCI), and 146 subjects with mild AD), adjusting for age, gender, APOE $\varepsilon 4$ status and intracranial volume (ICV). Subjects were derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI), a large US national biomarker study.
Results: The association between higher education and larger HV was significant in AD ($P = 0.014$) but not in cognitively normal or MCI subjects. In AD, HV was about 8% larger in a person with 20 years of education relative to someone with 6 years of education. There was also a trend for the interaction between education and APOE $\varepsilon 4$ to be significant in AD ($P = 0.056$).

Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's disease neuroimaging initiative; APOE, Apolipoprotein E; CDR, Clinical dementia rating; CR, Cognitive reserve; HV, Hippocampal volume; ICV, Intracranial volume; MMSE, Mini-mental state examination; MRI, Magnetic resonance imaging; PET, Positron emission tomography; THV, Total hippocampal volume.

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[1] Data used in preparation of this article were obtained from the Alzheimer's disease neuroimaging initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.ucla.edu/wpcontent/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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Conclusion: A potential protective association between higher education and lower hippocampal atrophy in patients with AD appears consistent with prior epidemiologic data linking higher education levels with lower rates of incident dementia. Longitudinal studies are warranted to confirm these findings.

Introduction

The search for lifestyle factors that may prevent or delay the onset of Alzheimer's disease has sparked interest in understanding the influence of education and cognitive reserve [1—28]. Epidemiologic studies nearly three decades ago first noted a greater risk for dementia in individuals with very low levels of education; though detection bias may have played a role, these results were replicated [1,4—6]. Similarly, studies have also linked higher IQ, larger head size, greater socio-occupational status or higher levels of mental activity with lower prevalence of dementia [1—7]. More recently, a review of 22 epidemiologic studies of effects of education or higher levels of brain-stimulating activities found a 46%-absolute-decrease in incident dementia risk [6].

The mechanisms underlying cognitive reserve and the effects of education on dementia risk remain uncertain. One theory is that education has a direct neuroprotective effect on brain structure (e.g. slowing hippocampal atrophy) or pathology (e.g. less beta-amyloid deposition). This is supported by animal studies that show that environmental enrichment can directly stimulate hippocampal neurogenesis [8]. The adult human hippocampus is also capable of neuroplasticity, and imaging studies before and after intense brain training (e.g. juggling, playing video games, cramming for medical exams) have documented changes in volumes of specific brain regions in healthy volunteers [9,10]. These data raise the possibility that some portion of education-related CR in humans might be localized to the hippocampus. However, neuropathological and imaging studies of hippocampal changes in cognitively normal subjects have yielded conflicting results with some studies finding a direct relationship between education or socioeconomic status and hippocampal volume [11,22] and others not finding any links [19].

The alternate theory suggests that education only has a compensatory effect. This theory emerged from autopsy studies that found that some highly educated individuals with abundant AD neuropathology remain non-demented (or cognitively spared) [3,7,13—15]. Such cognitive sparing was subsequently noticed in imaging studies and gave rise to the theory that education-related CR might serve as a compensatory mechanism [3]. However, this theory is not supported by some prior studies in normal subjects that reported a direct positive correlation between hippocampal volume and educational attainment status [11,22]. In summary, the concept of ''cognitive reserve'' and the effect of education on AD biomarkers remain incompletely understood [1].

Hippocampal damage (atrophy) is a key event in AD and has been reported to potentially have diagnostic value [29—33]. Moreover, MRI-measured hippocampal volumes are predictive of future cognitive loss in mildly impaired subjects [29—33]. The aim of this study was to use data from a national biomarker study to test the effect of education on HV at study entry across all three diagnostic stages of cognitive functioning (from cognitively normal to MCI to AD). Secondarily, we also examined whether the effect of education differed by APOE ε4 genotype.

Materials and methods

ADNI design and database

ADNI is a large-scale collaborative effort aimed at understanding, treatment, and prevention of AD. Additionally, up-to-date information can be found at www.adni-info.org. ADNI stems from the collaboration and participation of over 50 sites within the US and Canada. Each site's institutional review board approved all ADNI protocols. Prior to any testing, written, informed consent was obtained from all subjects and their legal representatives, when necessary.

Subject characteristics

Those subjects in the ADNI-1 classified as normal controls were required to have normal memory function, an MMSE score between 24 and 30, and a CDR of 0. MCI subjects were required to have abnormal memory function, an MMSE score from 24 to 30, and a CDR of 0.5. AD subjects met the ''probable AD'' criteria of the NINCDS/ADRDA, had a CDR of 1.0 or 0.5, and had an MMSE score between 20 and 26 (with some exceptions if the subject had less than 8 years of education). All subjects were between the ages of 55 and 90 and were not depressed, with a geriatric depression scale score of less than 6 required for inclusion. Additional inclusion and exclusion criteria for the ADNI-1 can be found at http://www.adni-info.org/scientists/proceduresmanuals.aspx#.

Inclusion criteria for this analysis

All subjects included in our analyses were required to have a diagnosis (according to the criteria listed above) and have baseline demographic information (gender, race, education, and age), APOE genotype, a baseline MMSE score, analysis of a 1.5 T MRI scan via FreeSurfer v. 4.4, and an estimated intracranial volume derived from the 1.5 T MRI scan. A total of 201 normal control, 329 MCI, and 146 AD subjects were included.

Educational achievement

Education was a self-reported measure collected from subjects themselves and verified by a caregiver (for dementia subjects) as appropriate. We analyzed education both as a continuous and categorical (12 years or less, 13 to 16 years, 17 to 20 years) variable. We report here only the results

of models testing education as a continuous measure, since it offered greater power and models testing education as a categorical measure showed essentially similar findings.

MR imaging acquisition

The ADNI used 1.5 T MP-RAGE T1-weighted MR images. All scans were performed using a standardized protocol specifically developed for ADNI, and which was tailored for use with each make and model of scanner used at the different data collection sites. More detailed information for the specific MR acquisition protocols and quality control methods for each type of scanner used can be found at http://adni.loni.ucla.edu.

MR volumetric methods

Hippocampal volumes were derived from volumetric segmentation of subject MR scans, performed with the Freesurfer image analysis suit. Total hippocampal volumes were computed as the sum of the right and left sides. Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strength [34,35]. Intracranial volumes were derived using standard methods from MRI scans (see adni.loni.ucla.edu and refer to the detailed ADNI-1 MRI Protocols for sequences and processing steps).

Statistical analysis

All statistical analysis was set two-tailed, $P < 0.05$ a priori for terms in the multivariate model. We first examined the effect of education on ICV after adjusting for effects of age, gender and APOE $\varepsilon 4$ (similar to model (0.0)). We then examined education effects on baseline HV in all three groups. No statistical comparisons between diagnoses were done since the intent of the paper was to look at education effects within diagnosis.

The data consists of hippocampal volume measurements y_i, measured on the i-th subject, $i = 1 \ldots 678$, from three groups, control, MCI, and AD.

$$\begin{aligned} y_i = {} & \alpha_0 + \alpha_{MCIi} + \alpha_{ADIi} + \beta_I ICV + \alpha_{g4i} + \alpha_{Mi} + \beta_a Age_i \\ & + \beta_e Educ_i + \alpha_{MCI:g4i} + \alpha_{AD:g4i} + \beta_{MCI:I} ICV_i + \beta_{AD:I} ICV_i \\ & + \beta_{MCI:a} Age_i + \beta_{AD:a} Age_i + \beta_{MCI:e} Educ_i \\ & + \alpha_{MCI:Mi} + \alpha_{AD:Mi} + \varepsilon_i \end{aligned} \tag{0.0}$$

In model (0.0), α_0 (intercept) denotes the baseline level of thickness/volume for a female subject in the control group of age 75 with 6 years of education and having the 3/3 APOE allele. The terms α_{MCIi} and α_{ADi} denote the average difference by diagnostic group, a_{g4i} denote the baseline effect of allele $\varepsilon 4$ of the *APOE* gene when it is present in subject i. The term α_{Mi} denotes the additional effect of gender (Male) in the control group. The terms β_a, β_e and β_I denote the effects of age, years of education and ICV on baseline hippocampal volume. The terms $\beta_{MCI:I}$ and $\beta_{AD:I}$ denote the additional effects of ICV in the MCI and AD groups, while the terms $\beta_{MCI:a}$ and $\beta_{AD:a}$ denote the additional effects of age in the MCI and AD groups, the terms $\beta_{MCI:e}$ and $\beta_{AD:e}$ denote the additional effects of education in the MCI and AD groups and the terms $\alpha_{MCI:M}$ and $\alpha_{AD:M}$ denote the additional effects of gender (Male) in the MCI and AD groups.

Finally ε_i is measurement error, assumed to be independent with a zero mean Gaussian distribution. The model fits the data moderately ($R^2 = 0.47$). We also examined the interaction between APOE $\varepsilon 4$ and education in each diagnostic group in an extended model (model not shown). To examine the appropriateness of the linearity assumptions inherent in model (0.0), we also fitted a more general additive model of the form:

$$y_i = \alpha_0 + \alpha_{g4i} + \alpha_{Mi} + f_A(Age_i) + f_E(Educ) + f_I(ICV) + \varepsilon_i \tag{0.1}$$

The coefficients α_0 (intercept, α_{g4i} and α_{Mi}) in model (0.1) are the same as in model (0.0). The functions f_A, f_E, and f_I denote arbitrary (but smooth) functions of age, education and ICV. These functions are estimated (under smoothness constraints) to minimize the least squares fit of model to hippocampal volume measurements y_i. Fitting was done using an iterative backfitting algorithm implemented in the mgcv package in the R platform (*Wood, S.N. (2006) Generalized Additive Models: An Introduction with R. Chapman and Hall/CRC*). For ease of interpretation, model (0.1) was fitted separately for each diagnostic group.

Results

Subject demographics and characteristics

Subject demographics by diagnoses are depicted in Table 1. The mean age for all three groups was in the seventies, reflecting the overall ADNI sample. The percent of $\varepsilon 4$ carriers was highest in AD group and lowest in controls, as expected. Likewise HV and MMSE scores were lowest in AD and highest in controls. The AD group was less well educated than the other groups with the lowest proportion of those with less than high school educational attainment.

Effect of education level on ICV

The effect of education on ICV was not significant in controls ($P = 0.24$), MCI ($P = 0.22$) or AD ($P = 0.34$). APOE $\varepsilon 4$ genotype also did not have an effect on ICV in any group ($P > 0.60$). The effect of gender was significant in all groups ($P < 0.05$) with males having bigger ICV.

Effect of education level on HV

As shown in Table 2, the effect of education on HV was not significant in the Control or MCI groups, but there was a significant association between higher HV and higher educational level in AD ($P = 0.014$), relative to the effect in controls. This amounts to about an 8% increase for someone with 20 years of education relative to someone with 6 years of education, in the AD group. Estimated regression functions from additive model (Figs. 1—3b) suggest that the dependence of HV on education is indeed approximately linear. The direction of the effects from additive modelling is similar to those estimated by the linear model. There was

Table 1 ADNI subject characteristics by diagnostic group.

Variable	Control	MCI	AD
n	201	329	146
Male proportion	54%	64%	51%
APOE ε4+ proportion	27%	54%	66%
Age	76.01 (5.04)	74.85 (7.23)	75.23 (7.54)
Education	16.10 (2.77)	15.76 (2.95)	14.82 (3.08)
Education < 13 (%)	10%	18%	28%
Education > 16 (%)	42%	38%	26%
MMSE	29.15 (0.99)	27.05 (1.76)	23.48 (1.94)
Hippocampal volume (mm^3)	6553.99 (826.05)	5806.23 (1027.52)	5178.83 (1003.86)
ICV (mm^3)	1,465,025 (132,345)	1,477,082 (150,694)	1,439,452 (159,338)

Mean (SD) values are shown for control, MCI, and AD subjects.

a trend to a significant interaction between education and APOE ε4 in the AD group ($P = 0.059$) but this was not seen in MCI or normal group.

Table 2 also shows that, as expected, MCI and AD subjects had significantly smaller HV than controls ($P < 0.0001$) and this effect was substantially larger than the effect of education. Increasing age causes a highly significant reduction (about 0.7%/year) in HV ($P < 0.0001$) and this effect is similar in all diagnostic groups. Additive modelling suggests that in the control group, the decrease appears to level off at age 80 and higher (Fig. 1a) but the rate of decrease appears to be maintained at higher ages in the MCI and AD groups (Figs. 2 and 3a). Conversely, increasing ICV has a significant positive effect on HV ($P < 0.0001$) and the effect is similar in all three groups. There are no significant differences due to gender ($P < 0.81$).

Discussion

While the mechanisms of cognitive reserve are still not well understood, educational attainment is viewed as an important surrogate marker of CR. Higher early life education usually leads to lifelong higher occupational attainment and a greater likelihood of pursuing mentally stimulating activities and a healthier lifestyle throughout life [1,11,12]. Likewise, lower educational attainment is predictive of higher childhood social stress and lower socioeconomic attainment in life [11,12]. Thus, early life education is accepted as one of the surrogate markers for CR and socioeconomic attainment [1,5—7,18,20]. Although the positive influence of CR (such as higher education) on lowering AD risk and on postponing cognitive decline is relatively consistent in the epidemiologic literature [1—6], there is

Table 2 Effect of education on HV in AD, MCI and controls.

	Estimate	Std. error	*t* value	Pr (> |t|)
Baseline	7129.6730	229.0073	31.13	< 0.0001
AD	—2021.2266	336.3117	—6.01	< 0.0001
MCI	—972.3168	286.3019	—3.40	0.0007
APOE ε4+	—102.4151	126.3811	—0.81	0.4180
ICV	0.0028	0.0005	5.25	< 0.0001
Age	—56.0511	11.3999	—4.92	< 0.0001
CN: education	—38.1314	21.8003	—1.75	0.0807
Male	—34.7337	144.3540	—0.24	0.8099
AD: APOE ε4+	—176.4713	191.6569	—0.92	0.3575
MCI: APOE ε4+	—310.8509	155.3819	—2.00	0.0459
AD: ICV	—0.0001	0.0008	—0.11	0.9155
MCI: ICV	—0.0005	0.0007	—0.83	0.4085
AD: age	9.5969	14.5368	0.66	0.5094
MCI: age	8.4721	13.1547	0.64	0.5198
AD: education	77.0546	31.4433	2.45	0.0145
MCI: education	12.6967	26.6395	0.48	0.6338
AD: male	—6.1461	228.3077	—0.03	0.9785
MCI: male	146.8606	187.1522	0.78	0.4329

P values and *t* values from the model examining effects of education on HV in each diagnostic group, adjusting for age, gender, ICV and APOE ε4 effects. Please see Methods for details of model. The comparison is against a female subject in the control group, of age 75, with 6 years of education and having the APOE ε3/3 genotype. The effect of education on HV was significant in the AD group ($P < 0.015$) but not in controls ($P < 0.081$) or MCI ($P < 0.64$). The effects of diagnosis, age and ICV on HV were significant.

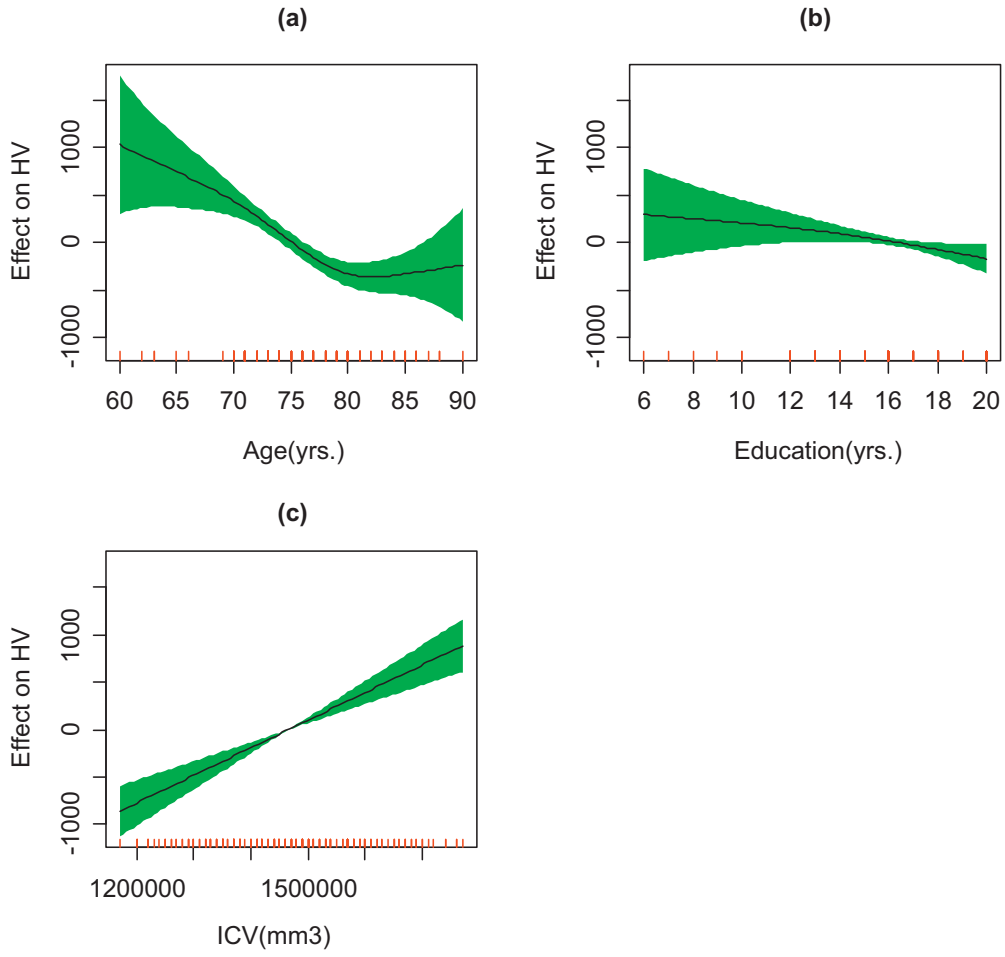

Figure 1 Estimated effects of continuous predictors from additive regression modelling for control group. The solid black line denotes the estimated effect function corresponding to each continuous predictor in model 0.1. The green shaded show a 95%-confidence-band for the estimated effect. The red ticks on the x-axis show the distribution of the predictor.

a discrepancy in literature over whether education has a direct effect on hippocampal atrophy in both normal aging and in AD [1]. Two lines of findings from autopsy and imaging studies have emerged — one suggesting education has a direct neuroprotective effect and the other suggesting that education allows people to compensate (i.e. for a given level of pathology performance is higher). Our study attempted to shed further light on the first question.

We used a large national sample to test the association between education and baseline HV in three groups — cognitively normal elders, MCI subjects at risk for AD, and those with mild AD. We found a significant positive association between education and HV in AD after stringently controlling for common factors known to affect HV. Speculatively, this could be interpreted as supporting a neuroprotective effect of education, consistent with experimental studies of the effects of environmental enrichment on neurogenesis [8—10]. The linearity of the effect potentially implies that the protective effect of an additional year of education may apply throughout the education range. Further, we also find a potential weak (non-significant) interaction effect between education and APOE genotype on HV in AD. This is also of interest since some prior data suggests that the effects of lifestyle variables on dementia risk may vary by genotype [36]. There are no prior imaging or autopsy studies to our knowledge, that have tested an education and APOE $\varepsilon 4$ interaction effect on HV in AD subjects; hence, we cannot directly compare this to prior studies. The weak effect would suggest caution in interpretation until further replication.

The lack of an association between education and HV in cognitively normal and MCI subjects does not seem consistent with the neurogenesis literature but is consistent with prior autopsy studies. Speculatively, the lack of an effect of education on HV in our sample of cognitively healthy or mildly impaired subjects, could be due to three possibilities — a true lack of an effect, a limited power for detecting slower or more heterogeneous rates of atrophy in such subjects, or a different mechanism such as education providing a compensatory rather than direct neuroprotective effect. Controls had a more limited MMSE range, a lower prevalence of APOE $\varepsilon 4$, and were three times as likely to have greater than high school education, compared to AD subjects.

However, our findings in non-demented subjects are consistent with prior autopsy studies. For example, Brayne et al.

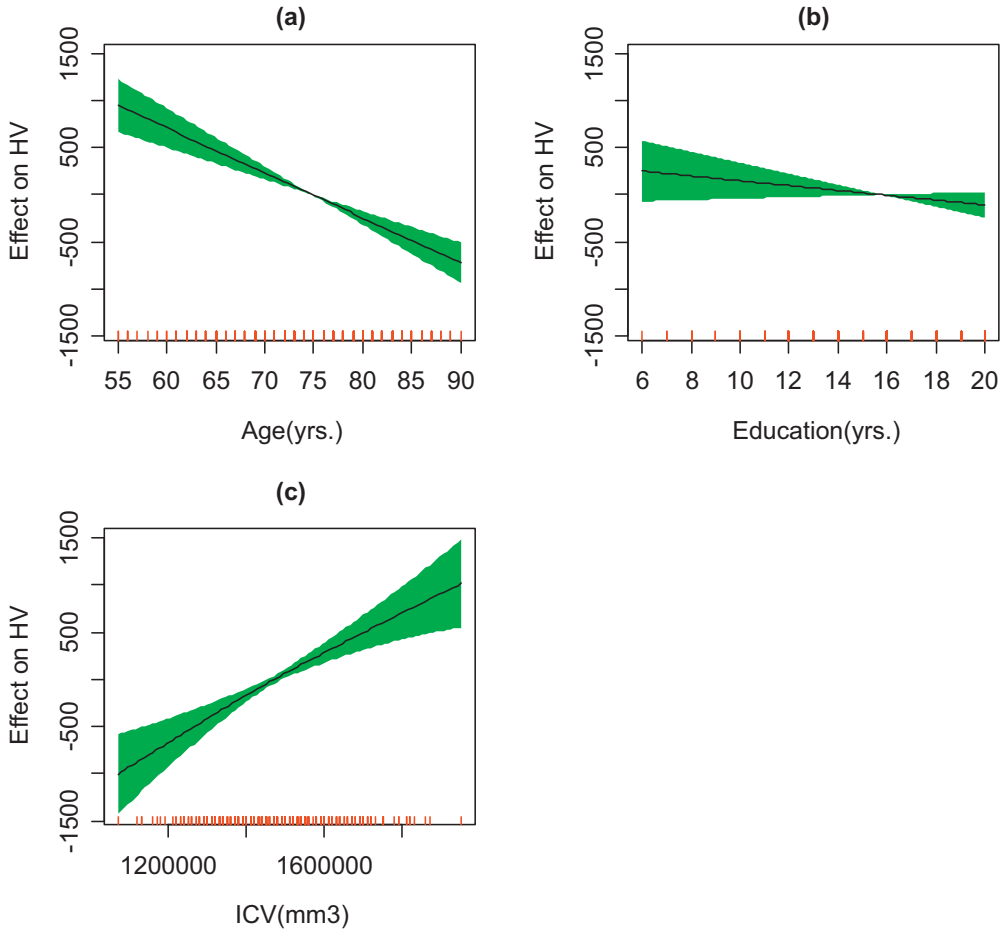

Figure 2 Estimated effects of continuous predictors from additive regression modelling for MCI group. The solid black line denotes the estimated effect function corresponding to each continuous predictor in model 0.1. The green shaded show a 95%-confidence-band for the estimated effect. The red ticks on the x-axis show the distribution of the predictor.

found that neurodegenerative pathologies did not vary by education in a sample of 872 people who came to autopsy in a large epidemiologic study although dementia onset was delayed by higher education [24]. In a study of 13,004 elderly individuals followed for 14 years, Valenzuela et al. noted no relationship between a cognitively active lifestyle and hippocampal neuronal density among the subset of 329 subjects who came to autopsy [19].

Prior MRI studies of non-demented subjects have also mostly been consistent with our findings. Liu et al. [20], after adjusting for age, gender, cognitive status and intracranial volume, found no correlation between years of education and HV in controls or MCI. They found an inverse effect in AD but did not adjust for ε4 status. Noble et al. [26] studied 275 cognitively healthy subjects between the ages of 17—87 years and found that the main effects of education on HV did not reach significance after adjusting for age, gender and brain volume. Piras et al. [27], in a study of 150 normal subjects, noted no effect of education on HV. Although one study by Staff et al. [25] found a positive correlation between education and HV, they did not adjust for any confounding variables so it is unclear if their effect would have survived such corrections. Thus, our findings taken together with much of the prior literature suggests that education is unlikely to have an effect on HV in normal elderly, though findings might be analyses specific depending on what confounding factors are co-varied for.

There are some strengths and limitations of our study. The use of a carefully selected national sample and control for multiple common confounding factors are relative strengths over prior studies. We employed a cross-sectional design since we wanted to examine the baseline effect, which captures lifelong nature-nurture changes prior to study entry. However, such a design has other biases and cannot study within subject changes over time, explore effects of MCI converters versus non-converters, or make inferences about causality. Early life education is simply one measure of CR and events happening later in life, which we did not control for, can also influence HV. Likewise, there are many genes beyond *APOE* ε*4* that might have an effect on HV, and to our knowledge no prior study has reported on any other genes (e.g. *BDNF*) that interact with education effects on HV in the setting of AD. We did not examine other pathologic markers such as plaques or tangles. Although ADNI is a national study, it's entry criteria may have selected for older subjects interested in memory research at academic settings. Hence, our findings should be viewed as hypothesis generating and may not be generalizable to the population.

Longitudinal studies combining functional MRI, molecular PET imaging, structural MR imaging and genomics data might

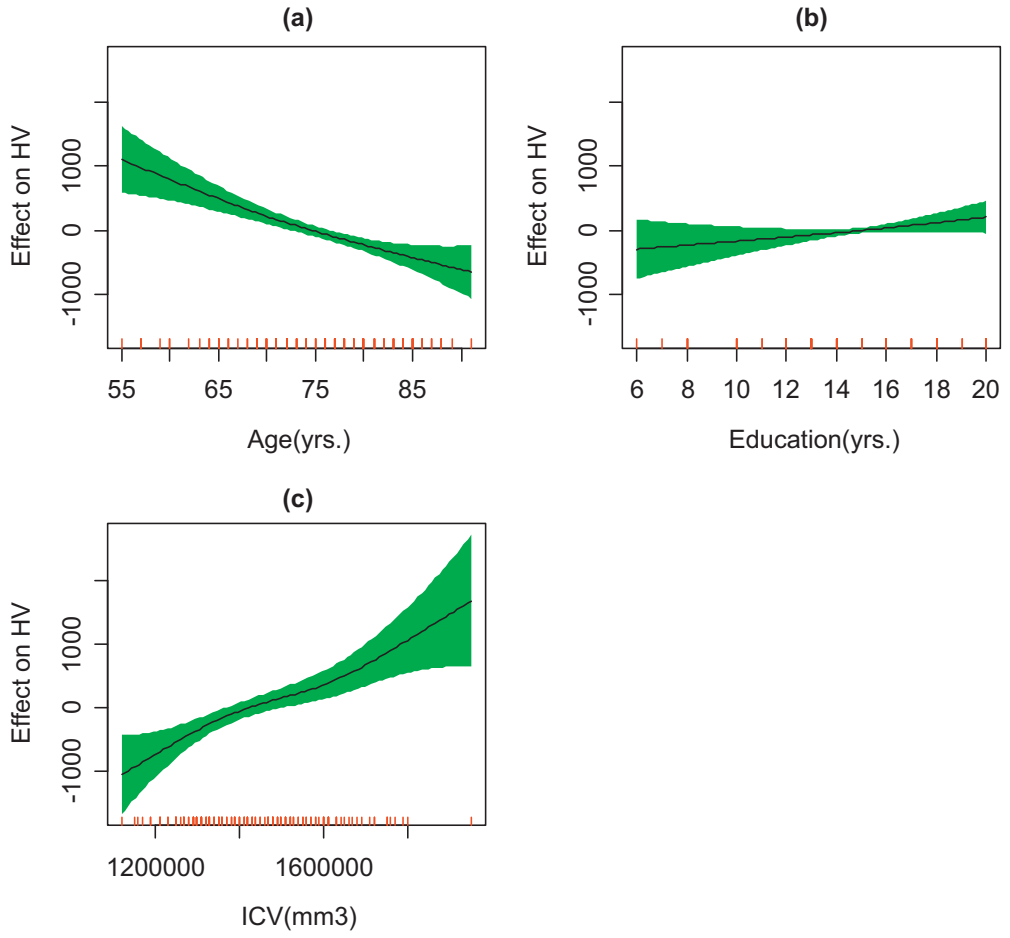

Figure 3 Estimated effects of continuous predictors from additive regression modelling for AD group. The solid black line denotes the estimated effect function corresponding to each continuous predictor in model 0.1. The green shaded show a 95%-confidence-band for the estimated effect. The red ticks on the x-axis show the distribution of the predictor.

help us better elucidate the neural basis of CR and potential effects of educational attainment on the aging brain.

Conclusion

Our study of a national sample finds a significant positive correlation between education and HV in AD subjects as well as a potential interaction effect of education and APOE $\varepsilon 4$ on HV. These data may support a protective effect of cognitive reserve on HV but longitudinal studies are needed to provide additional insights into the mechanisms.

Disclosure of interests

Katie Shpanskaya is a Wrenn clinical research scholar. Kingshuk Roy Choudhury and Christopher Hostage report no competing interests. Jeffrey Petrella is on the neuroradiology advisory board of Janssen Alzheimer Immunotherapy. P. Murali Doraiswamy received a grant from ADNI for clinical and imaging data collection. He has also received research grants and/or advisory/speaking fees from Alzheimer's Association, Alzheimer's Foundation of America, Alzheimer's Drug Discovery Foundation and several imaging and pharmaceutical companies for other studies. He owns stock in Sonexa, Daily Feats and Clarimedix, whose products are not discussed here.

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References

[1] Doraiswamy PM. Is the idle mind a devil's workshop? Biol Psychiatry 2012;71:765—6.
[2] Selkoe DJ. Preventing Alzheimer's disease. Science 2012;337(6101):1488—92.
[3] Stern Y. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord 2006;20(3 Suppl. 2):S69—74.
[4] Mortimer JA, Snowdon DA, Markesbery WR. Head circumference, education and risk of dementia: findings from the Nun Study. J Clin Exp Neuropsychol 2003;25(5):671—9.
[5] Evans DA, et al. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. Arch Neurol 1997;54(11):1399—405.
[6] Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychol Med 2006;36(4):441—54.
[7] Stern Y. Cognitive reserve in ageing and Alzheimer's disease. Lancet Neurol 2012;11(11):1006—12.
[8] Brown J, et al. Enriched environment and physical activity stimulate hippocampal but not olfactory bulb neurogenesis. Eur J Neurosci 2003;17(10):2042—6.
[9] Draganski B, et al. Neuroplasticity: changes in grey matter induced by training. Nature 2004;427(6972):311—2.
[10] Holzel BK, et al. Mindfulness practice leads to increases in regional brain gray matter density. Psychiatry Res 2011;191(1):36—43.
[11] Piha K, et al. Interrelationships between education, occupational class, income and sickness absence. Eur J Public Health 2010;20(3):276—80.
[12] McLeod JD, Kaiser K. Childhood emotional and behavioral problems and educational attainment. Am Soc Rev 2004;69(5):636—58.
[13] Jones RN, et al. Conceptual and measurement challenges in research on cognitive reserve. J Int Neuropsychol Soc 2011;17(4):593—601.
[14] Murray AD, et al. The balance between cognitive reserve and brain imaging biomarkers of cerebrovascular and Alzheimer's diseases. Brain 2011;134(Pt 12):3687—96.
[15] Charroud C, et al. Influence de la réserve cognitive sur le réseau du mode par défaut chez les sujets normaux, MCI et déments : une étude d'IRM fonctionnelle de l'état de repos. J Neuroradiol 2012;39(1):18.
[16] Ngandu T, et al. Education and dementia: what lies behind the association? Neurology 2007;69(14):1442—50.
[17] Paradise M, Cooper C, Livingston G. Systematic review of the effect of education on survival in Alzheimer's disease. Int Psychogeriatr 2009;21(1):25—32.
[18] Roe CM, et al. Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. Neurology 2007;68(3):223—8.
[19] Valenzuela MJ, et al. Multiple biological pathways link cognitive lifestyle to protection from dementia. Biol Psychiatry 2012;71(9):783—91.
[20] Liu Y, et al. Education increases reserve against Alzheimer's disease—evidence from structural MRI analysis. Neuroradiology 2012;54(9):929—38.
[21] Brickman AM, et al. White matter hyperintensities and cognition: testing the reserve hypothesis. Neurobiol Aging 2011;32(9):1588—98.
[22] Suo C, et al. Supervisory experience at work is linked to low rate of hippocampal atrophy in late life. Neuroimage 2012;63(3):1542—51.
[23] Ewers M, et al. Cognitive reserve associated with FDG-PET in preclinical Alzheimer disease. Neurology 2013;80(13):1194—201.
[24] Brayne C, et al. Education, the brain and dementia: neuroprotection or compensation? Brain 2010;133(Pt 8):2210—6.
[25] Staff RT, et al. Childhood socioeconomic status and adult brain size: childhood socioeconomic status influences adult hippocampal size. Ann Neurol 2012;71(5):653—60.
[26] Noble KG, et al. Hippocampal volume varies with educational attainment across the life-span. Front Hum Neurosci 2012;6:p307.
[27] Piras F, et al. Education mediates microstructural changes in bilateral hippocampus. Hum Brain Mapp 2011;32(2):282—9.
[28] Perneczky R, et al. Education attenuates the effect of medial temporal lobe atrophy on cognitive function in Alzheimer's disease: the MIRAGE study. J Alzheimers Dis 2009;17(4):855—62.
[29] Convit A, et al. Specific hippocampal volume reductions in individuals at risk for Alzheimer's disease. Neurobiol Aging 1997;18(2):131—8.
[30] Jack Jr CR, et al. MR-based hippocampal volumetry in the diagnosis of Alzheimer's disease. Neurology 1992;42(1):183—8.
[31] Apostolova LG, et al. 3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease. Brain 2006;129(Pt 11):2867—73.
[32] Frisoni GB. Structural imaging in the clinical diagnosis of Alzheimer's disease: problems and tools. J Neurol Neurosurg Psychiatry 2001;70(6):711—8.
[33] Henry-Feugeas MC. MRI of the 'Alzheimer syndrome'. J Neuroradiol 2007;34(4):220—7.
[34] Han X, et al. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage 2006;32:180—94.
[35] Reuter M, et al. Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 2012;61(4):1402—18.
[36] Kivipelto M, et al. Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study. J Cell Mol Med 2008;12(6B):2762—71.