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ORIGINAL ARTICLE

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

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Alzheimer's;
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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