ASSESSMENT OF STRUCTURAL DIFFERENCES IN HEALTHY ELDERLY IN RELATION TO APOLIPOPROTEIN E POLYMORPHISM AND A COMPARISON TO YOUNG ADULTS

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Background

A variety of anatomical findings are associated with Alzheimer's disease (AD), with hippocampal and diffuse brain atrophy among the strongest identified. The ε4 allele of the Apolipoprotein E (APOE) gene is associated with an increased risk of developing AD and a lowered age of onset [1]. Furthermore, the presence of the ε4 allele has been implicated in major AD-related biochemical disturbances [2]. Association of cerebral atrophy with APOE status in normal aging remains controversial despite the increasing number of investigations. Therefore, the aim of this study was to investigate hippocampal and whole brain volumes that allow the assessment of cerebral atrophy in normally aging elderly ε4 allele carriers, non-carriers, and young adults. We hypothesized that elderly ε4 allele carriers compared to non-carriers would have smaller hippocampal volumes but would have no greater cerebral brain atrophy. In addition, we expected that the elderly would show greater hippocampal and cerebral brain atrophy when compared to young adults.

Methods

Participants. Sixteen elderly ε3/ε4 heterozygots (ε4+; 7 males) and 16 closely matched ε3 homozygots (ε4-; 8 males) were recruited from the New Mexico Aging Process Study (NMAPS) [3], a large ongoing study of nutrition, genetics, and health. Exclusion criteria included a history of major medical, psychiatric, and/or neurologic disorders. Each participant was free of dementia, depression, and any overt health conditions (NMAPS screened for coronary heart disease, significant peripheral vascular disease, insulin-dependent diabetes, hepatic disease, history of internal cancer requiring surgery, x-ray, or chemotherapy in the past 10 years, hepatitis, untreated hypertension, and medication except for thyroid and estrogen replacement, and/or minor hypertension). The Hixson and Vernier [4] procedure was used for restriction enzyme isoform genotyping. NMAPS provided the Modified Mini Mental State Exam (3MS), Activities of Daily Living, and Fuld Object Memory (FULD) scores for each participant. Young participants were undergraduate students.

Magnetic Resonance Imaging & Analysis. All studies were completed on a 1.5 Tesla clinical scanner (Signa 5.4, GE Medical Systems, Waukesha, WI). The protocol included a T_1-weighted whole brain axial series (fast-3D-SPGR, TE/TR = 6.9/17.7 ms, flip angle=25°, 1.5 mm thickness, 256x192 matrix) and coronal series (fast-3D-SPGR, TE/TR = 6.9/17.7 ms, flip angle=25°, 3.0 mm thickness, 256x192 matrix) oblique to the longitudinal axis of the hippocampus. Total parenchyma was calculated from the axial images using the BET program (FMRIB Image Analysis Group, Oxford University). Automated k-means based segmentation of the cerebrum (excluding cerebellum) was used to determine gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and partial volume (PV). Intracranial volume (ICV) was calculated by summing WM, GM, PV, and CSF. Hippocampal volumetric analysis was performed following segmentation of the coronal images. Hippocampal measurements were taken from each side and included the hippocampus proper, subiculum, and dentate gyrus. Volumetric procedures are described in detail elsewhere [5]. Absolute and normalized to ICV volumes were both assessed.

Results

There were no significant differences between the ε4+ and ε4- groups in bilateral, right, left, or the posterior hippocampi for both absolute and normalized to ICV volumes ($p > 0.4$). However, the anterior hippocampal volume, both absolute (F (1,30) = 5.01; $p = 0.03$) and normalized (F (1,30) = 4.17; $p < 0.05$), was significantly smaller in the ε4+ group when compared to the a4- group. We found no significant differences between elderly ε4+ and ε4- in ICV ($p > 0.8$), or in absolute WM, GM, and CSF ($p > 0.1$) volumes. With normalized values, however, the ε4+ group had greater WM (F (1, 30) = 6.01; p =0 .02) and less CSF (F (1, 30) = 4.5; $p = 0.04$), but no significant difference in GM. In comparison to young adults, elderly ε4 allele non-carriers had less WM, GM, and more CSF compared to young adults for both absolute and normalized volumes (p's < 0.027), but no significant difference in ICV ($p = 0.15$). We found significant differences between young and ε4- elderly in absolute and normalized bilateral, right, left, and posterior hippocampi ($p = 0.001$), and a trend for the anterior hippocampi ($p > 0.05$).

Discussion

As expected, results revealed pronounced brain volume differences between the young and the elderly (combined ε4- and ε4+). These differences were evident in all of the absolute and normalized brain measures except for the anterior hippocampus, which has been suggested to be resilient to normal aging. However, the major findings of this study suggest subtle brain volume differences in ε4 allele- carriers and non-carriers. Specifically, there was a significant difference in normalized CSF and WM volumes between the ε4- and ε4+, but the direction was unexpected. The ε4+ individuals showed lower overall cerebral atrophy when compared to their ε4- counterparts. Interestingly, the ε4+ group had smaller anterior hippocampi when compared to the ε4- group. One possible explanation for these unexpected findings is that the elderly ε4+ participants, who have entered late senescence successfully without developing any age-related pathology (i.e. AD) despite their genetic predisposition and older age, may have a protective factor working to their advantage. Future research employing larger number of participants is necessary to elucidate the discriminatory power of anterior hippocampus as a diagnostic tool in pathology. Furthermore, prospective longitudinal investigations are necessary to disentangle the differences that may exist between those ε4+ individuals that eventually develop Alzheimer's disease and those that do not. It is possible that such studies will reveal possible protective effects that may have helped certain ε4 allele carriers escape the ill effects of aging.

References

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