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Apolipoprotein E-e4, Processing Speed, and White Matter Volume in a Genetically Enriched Sample of Midlife Adults

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Abstract

Healthy midlife children of a parent with Alzheimer's disease ([AD] N = 23; 9 male) participated in neuropsychological testing, and magnetic resonance imaging (MRI) of brain volumetrics were obtained. In all, 35% of the sample were apolipoprotein E (ApoE)-e4 positive (n = 8; 5 male). The ApoE-e4 group exhibited significantly slower performances on an executive function and processing speed measure and had less white matter volume than the non-ApoE-e4 group. Lesser white matter volume was significantly correlated with slower processing speed. Processing speed and changes in white matter volume might be indicators of preclinical decline in AD.

Keywords

ApoE, MRI, processing speed, white matter

Introduction

The apolipoprotein E (*ApoE*) gene on chromosome 19 is a primary transporter of endogenously produced lipids and has 3 allelic variants (ie, e2, e3, and e4).[1] The ApoE-e4 allele is associated with a 3- to 4-fold increase in the risk of Alzheimer's disease (AD).[2,3] In healthy persons without dementia, ApoE-e4 is associated with subtle cognitive impairments that are most commonly found on tests of memory, executive functions, attention, and processing speed.[4-6] In nondemented samples, ApoE-e4 is also associated with reduced cerebral metabolism in posterior cingulate, parietal, temporal, and prefrontal regions,[7] whole brain atrophy rates,[8] reduced hippocampal volume,[9] and myelin breakdown.[5,10] These changes mirror the changes in cognition, brain structure, and brain function that are evident in probable AD.[11]

The vast majority of research on the effects of ApoE-e4 on cognition and brain volume has been conducted on healthy, nondemented samples of older adults. The current study sought to extend this line of research to a genetically enriched, healthy sample of midlife adults. Mood, personality, and stress were measured to assess group differences that might be relevant for understanding cognition and brain volume in midlife.

We sought to study a genetically enriched sample and thus recruited healthy midlife adults who are the biological child of a parent with possible AD. In the general population, the respective prevalence of the 3 isoforms of ApoE (ie, e2, e3, and e4) is about 8% to 15%, 78% to 94%, and 14% to 25%, respectively.[12,13] However, in persons at genetic risk of AD, the prevalence of the ApoE-e4 allele is increased. In one study, 45% of adult children of a parent with AD had one or more ApoE-e4 alleles.[14]

Methods

Sample

Participants (N = 23, 9 male) had an average age of 55.8 years (standard deviation [SD] = 5.4; range 46-66); mean education was 17.3 years (SD = 1.8; range 13-20); income averaged 6.3 (SD = 1.7; range 3-8) on an 8-point scale (3 = $15 000-30 000; 6 = $60 000-70 000; 8 = $100 000+); and estimated Verbal IQ T - score averaged 52.0 on the Adult North American Reading Test (ANART), which is in the average range (SD = 2.5; range 46.5-56.8).

Procedure

Participants were recruited from the community, caregiver support groups, letters to directors of memory disorder clinics,

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and local neurologists who serve the population with AD. Participants were screened on the telephone to be free from major self-reported medical, psychiatric, and neurologic disorders; persons were screened for contraindications for the magnetic resonance imaging ([MRI] eg, pacemaker, metal in joints, and claustrophobia). Persons taking prescription medications that might affect cortisol and current smokers were excluded. Participants were biological children of a parent with AD; AD diagnosis was not confirmed but was screened via participant report on the phone. Persons who reported parental dementia diagnoses of unknown origin, atypical presentation of AD, or dementia due to vascular factors were excluded.

Participants attended 2 sessions. In the first session (2-2.5 hours), participants provided written informed consent, engaged in cognitive testing, and were instructed as to home-based collection of cortisol samples over the following 2 days. Sampling occurred via the whole saliva swab placed under the tongue for 1 minute. Sampling times were at the time of awakening, 30 minutes after waking, noon, 4 PM, and 9 PM. Samples were stored in each participant's residence in the freezer until they were collected by a research assistant for transport to University of Massachusetts Amherst, where they were stored in a freezer at −20° until they were shipped with dry ice for assay. The second session (less than 1 hour) was for MRI volumetric analysis; this session was scheduled within a few weeks after the first session.

Measures

Cognitive Measures. Three subtests from the Delis-Kaplan Executive Function System (DKEFS)[15] were administered. The Trail Making Test (TMT) is a set of 5 tasks that measure processing speed, switching quickly between conceptual sets, motor–visual coordination, and sequencing. Color–word assesses processing speed, inhibition of a prepotent response, and visual scanning. Verbal fluency (letter and category) assesses retrieval, working memory, long-term storage, and processing speed. Three tests of learning and memory were administered, 2 verbal and 1 nonverbal. The verbal tasks were the Wechsler Memory scales, Fourth Edition (WMS-4)[16], Logical Memory subtest, and the California Verbal Learning Test, Second Edition,[17] which assess story memory and list-learning memory, respectively. The nonverbal task was WMS-4 Visual Reproduction. All learning memory tasks had a long-delay free recall component (approximately 20 minutes); delayed recall scores are most strongly associated with ApoE-e4 status among memory measures.[18]

Self-report Measures. Baseline mood was assessed with the 20-item Positive and Negative Affect Schedule (PANAS).[19] Personality traits of neuroticism and extraversion were assessed with the Big Five Inventory (BFI).[20] Life events over the past year were assessed with the Life Events Questionnaire (LEQ), an 82-item questionnaire on which the participants indicate whether certain events occurred and whether the events were positive or negative.[21]

Magnetic Resonance Imaging. Magnetic resonance imaging scanning for all participants was performed with a 1.5-T Siemens scanner. Whole brain T1-weighted scans were obtained using magnetization-prepared rapid gradient echo (MPRAGE) acquisition (repetition time [TR] = 2400 ms, echo time [TE] = 3.84 ms, inversion time [TI] = 1000 ms, flip angle = 8°, slice thickness = 1 mm, and matrix size = 256 × 256). Cortical reconstruction and volumetric segmentation was performed automatically with Freesurfer v4.5 (http://surfer.nmr.mgh.harvard.edu) installed on an iMac workstation. Technical details of the processing steps are described elsewhere.[22,23]

Cortisol. Cortisol was assayed from whole saliva by Salimetrics (State College, Pennsylvania) and is reported in μg/dL units.

Statistical Analyses

Primary analyses involved comparisons between ApoE-e4 groups on cognitive, brain volumetric, and cortisol measures. Comparisons were conducted with univariate general linear models and were calculated in SPSS/PASW version 18.[24] Pearson correlations between cognition, brain volume, and cortisol were also calculated to illuminate significant group differences.

Results

Genotyping revealed that 8 participants were e3/e4 (5 males). One participant was e2/e3 and the remaining (n = 14) were e3/e3. Participants were grouped in ApoE-e4 (n = 8) and non-ApoE-e4 groups for analyses (n = 15) because our focus was on associations between ApoE-e4 and cognitive, brain volume, and stress outcomes; furthermore, there were too few ApoE-e2 to investigate the potential protective effects of this allele. There was a trend for the ApoE-e4 group to be younger than the non-ApoE-e4 group (M age = 52.9 [SD = 4.9] and 57.3 [SD = 5.1], respectively; $t[21] = -2.0$, $P = .06$); thus, age was controlled in all analyses comparing ApoE subgroups on dependent variables. Education was not significantly different between ApoE groups ($P > .15$) nor was estimated premorbid verbal IQ ($P > .90$). Chi-square tests reveal no significant group differences for employment, marital/partner status, number of children, number of persons who consume alcohol, or number of persons who exercise. There were also no significant differences for baseline mood, stress, neuroticism or extraversion, or for reporting of good and bad life events over past year (while controlling and not controlling for age).

Cognition and ApoE-e4 Status

Cognitive measures that tapped similar domains were standardized and aggregated to reduce the number of variables in analyses. A Trails composite was derived from performances across the 5 Trail Making Test subtests, which were intercorrelated, 0.33 to 0.79 (median = 0.54; 10 of 11 intercorrelations significant at $P < .05$). A Color–word composite was derived

Table 1. Descriptive Statistics for ApoE-e4 and Non-ApoE-e4 Groups on Demographic, Cognitive, Brain Volume, and Stress Measures[a]

	ApoE-e4 *M* (SD)	Non-ApoE-e4 *M* (SD)	*F*(1,20)
Trials composite	2.22 (4.75)	−1.19 (3.18)	5.52[b]
Color–word composite	0.74 (4.66)	−0.39 (2.54)	2.24
Verbal fluency composite	0.09 (2.01)	−0.05 (1.82)	0.03
Memory composite	0.72 (2.87)	−0.39 (2.03)	0.35
Total hippocampal volume	0.51^{-2} (0.41^{-3})	0.50^{-2} ($0.48^{-3)}$	0.05
Total white matter volume	0.15 (0.01)	0.16 (0.01)	6.41[b]
Total cortical volume	0.30 (0.03)	0.29 (0.02)	0.84
Cortisol mean slope	0.66 (0.30)	0.39 (0.25)	6.00[b]
Cortisol mean AUC	3.33 (1.12)	3.24 (1.85)	0.14

Abbreviations: ApoE-e4, apolipoprotein E-e4; AUC, area under the curve; SD, standard deviation.
[a] Age was controlled in all group comparisons because the ApoE-e4 group was younger than the non-ApoE-e4 group ($P < .10$).
[b] $P < .05$.

from the 4 subtests on this task (rs = .43-.83; median = 0.58; all Ps < .05). Verbal fluency composite was an aggregate of letter and category fluency ($r = .71$; $P < .01$). A memory composite was derived from long-delayed (approximately 20 minute) free recall scores on Logical Memory, Visual Reproduction, and the California Verbal Learning Test-2 (rs = .38-.42; median = 0.41; all Ps < .08). Controlling for age, persons with an ApoE-e4 allele were significantly slower on Trials than the non-ApoE-e4 group (Table 1).

Brain Volume and ApoE-e4 Status

Groups were compared for hippocampal, cortical, and white matter volume because these regions have been most consistently linked with ApoE status in prior research.[8-10] Although it would be valuable to study group differences in more cortical regions (eg, parahippocamal gyrus), our study did not have sufficient power. To normalize individual variation in head size, all brain volume measures were divided by the participant's total intracranial volume.[25] After controlling for age, persons with an ApoE-e4 allele had lesser white matter volume than the non-ApoE-e4 group (Table 1).

Cortisol and ApoE-e4 Status

Two participants (one in the ApoE-e4 group and the other in the non-ApoE-e4 group) had cortisol values that were outliers on one of the 2 days of sampling; thus, the cortisol data for only 1 day were analyzed for these participants. Groups were compared for the morning rise in cortisol, which occurred between the sample at the time of awakening and then again 30 minutes later, averaged over 2 days for all but 2 participants. Groups were also compared for total cortisol area under the curve (AUC), averaged for the 2 days for all but 2 participants. The ApoE-e4 group had significantly greater rise in cortisol than the non-ApoE-e4 group (Table 1).

Correlations Among Cognition, Brain Volume, and Cortisol

Persons with an ApoE-e4 allele had slower processing speed on the Trials composite and lesser white matter volume than persons without an ApoE-e4 allele; these 2 factors were significantly correlated (Table 2). Better processing speed (ie, lower Trials score) was correlated with greater white matter volume. Faster processing on the Color–word composite also was associated with greater white matter volume. Rise in morning cortisol was not associated with cognitive or brain volume measures; total cortisol over the day was positively associated with verbal fluency.

Discussion

Alzheimer's disease is a progressive neurodegenerative disease. Neuropathology begins to accumulate decades before clinical symptoms of AD are manifest.[26-28] Identification of early markers of AD is crucial for treatment and preventative interventions to have maximal effect. The current study determined how ApoE genetic risk for AD was associated with cognition and brain volume in midlife. Participants were midlife adult children of a biological parent with AD, a population that is at increased risk of AD in later life. Indeed, about 35% of the sample had an ApoE-e4 allele, which is greater than population estimates of 14% to 25%.[12,13] The ApoE-e4 allele is associated with a 3- to 4-fold increased risk of AD.[2,3]

Studies with healthy, nondemented older adults indicate that the presence of 1 or 2 ApoE-e4 alleles is associated with preclinical decline in cognition[4-6] and changes in brain structure[9] and function[7] that are similar to changes seen in AD. Our study confirms these results and extends them to healthy midlife adults. Participants with an ApoE-e4 allele had reduced performance on an executive function and visuospatial processing speed task (TMT), relative to peers without an ApoE-e4 allele. Executive functions and processing speed have not been a focus in most previous studies of genetically enriched samples for AD;[14,29-31] but similar to the current study, ApoE-e4 was associated with poorer Trails performance in older women.[32] Apolipoprotein E-e4 is also linked to deficits in middle-aged adults on tests of attention shifting, attention scaling, and vigilance.[4] In fact, Parasuraman et al[4] present a compelling synthesis of the literature indicating that middle-aged adults without dementia but who have the ApoE-e4 allele have qualitatively similar deficits in visuospatial attention as persons with AD. They postulate that ApoE-related effects on cholinergic transmission might mediate attention impairments in persons with an ApoE-e4 allele and further observe that attention impairments are likely due to hypometabolism in the posterior parietal cortex, which is observed in ApoE-e4 carriers.

In our study, in addition to processing speed, persons with an ApoE-e4 allele had lesser white matter brain volume than

Table 2. Correlations Between Cognitive Scores, Brain Volume, and Cortisol Measures

	2	3	4	5	6	7	8	9
1. Trials composite	.54[a]	−.36	−.12	.24	−.47[a]	.40	.28	.07
2. Color–word composite		−.45[a]	−.16	.16	−.50[a]	.23	−.22	−.17
3. Verbal fluency composite			.38	.04	.11	−.31	.18	.43[a]
4. Memory composite				−.02	.28	−.16	.23	.29
5. Total hippocampal volume					−.02	.62[b]	−.14	−.09
6. Total white matter volume						−.15	−.30	−.14
7. Total cortical volume							−.03	.08
8. Cortisol mean slope								.16
9. Cortisol mean AUC								

Abbreviation: AUC, area under the curve.
[a] $P < .05$.
[b] $P < .01$.

persons without an ApoE-e4 allele. Processing speed is linked to white matter volume[33] and, in fact, these 2 factors were significantly correlated in our sample. Differences in white matter volume based on ApoE-e4 status have not been reported in other studies, but Bartzokis et al[5,10] found that ApoE-e4 was associated with myelin breakdown and slower processing speed scores. Although previous research indicated mixed results for white matter change in AD, more recent data point to distinct changes in white matter volume in AD. Changes in white matter volume appear to be a consequence of normal aging and additional volume reduction is found in AD.[34]

Early ApoE research in AD focused on the hippocampus and learning and memory, but more recent work is consistent with our results that a broader focus on early, preclinical markers for AD is needed. Differences or changes in executive functions, processing speed, and white matter volume may also signal early change. Indeed, processing speed deficits are evident in early AD[35] and in mild cognitive impairment (MCI),[36,37] and this work supports a broader conceptualization of cognitive impairment in preclinical dementia. Our data suggest that investigators consider the possibility of subtle changes in processing speed even before clinical symptoms of MCI or AD are manifested.

Persons with an ApoE-e4 allele had greater rise in morning cortisol than persons without an ApoE-e4 allele. Investigators have raised questions about links between vulnerability to stress and cognitive impairment,[38,39] but the significance and replicability of this finding is not known. Rise in morning cortisol was not associated with cognition and brain volume, which was surprising, because elevated cortisol can be associated with poorer cognition and reduced hippocampal volume.[40] However, cortisol measures over the entire day did not differ between ApoE groups. Given the significance of cortisol for brain structure and function,[41] more research into associations between ApoE and cortisol is needed.

Limitations

Our sample was small and may not be broadly representative of biological children of a parent with AD. Parental diagnosis of AD was not confirmed. However, parental diagnosis of AD was used as a means to recruit a genetically enriched sample for ApoE-e4 and that mission was accomplished due to the 35% rate of ApoE-e4 in the study sample. Furthermore, the study was cross-sectional and relied on correlational analyses and group comparisons to surmise potential risks of a future neurodevelopmental disorder.

Future Directions

Studies of midlife adult children of a parent with AD would be well served to include broad measures of neuropsychological function that include processing speed as well as broad measures of brain volume that include white matter volume. The most valuable data about early, preclinical AD will come from longitudinal studies of high-risk samples, and we hope to expand our current sample and follow them overtime to determine which neuropsychological and brain volume measures are related to future cognitive decline.

Declaration of Conflicting Interests

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