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Decreased Cognition in Children with Risk Factors for Alzheimer's Disease

Cinnamon S. Bloss, Ph.D.[1,*], **Dean C. Delis, Ph.D.**[2], **David P. Salmon, Ph.D.**[3], and **Mark W. Bondi, Ph.D.**[2]

1 *San Diego State University and the University of California, San Diego Joint Doctoral Program in Clinical Psychology*

2 *VA San Diego Healthcare System and Department of Psychiatry, University of California, San Diego*

3 *Department of Neurosciences, University of California, San Diego and UCSD Shiley-Marcos Alzheimer's Disease Research Center*

Abstract

Background—The ε4 allele of the apolipoprotein E gene (APOE-ε4) and a family history (+FH) of Alzheimer's disease (AD) are both risk factors for the development of AD. While studies to identify a preclinical phase of AD have led to evidence of APOE-ε4- and +FH-related differences in brain and cognitive functioning in healthy adults, the relative influence of these factors in children is unknown.

Methods—To investigate this issue, school-aged children (n = 109) received standardized achievement tests, the Rey-Osterrieth Complex Figure Test (Copy Condition; RCFT-CC), assessment of family medical history, and buccal swab testing to determine their APOE genotype.

Results—Analyses revealed that, relative to children without these risk factors, children who possess both an APOE-ε4 allele and a +FH of AD and/or significant memory problems (MP) obtained lower scores on nearly every cognitive test administered.

Conclusions—Findings suggest that when both AD risk factors are present, cognition may be adversely impacted as early as childhood. Thus, risk factors for a disorder of pathological aging (i.e., AD) may have implications for the etiology of certain types of learning difficulties in children.

Keywords

Alzheimer's disease; apolipoprotein E; cognition; children; learning disorders; cognitive reserve

Correspondence to: Cinnamon S. Bloss.

Current Affiliation/Address: Scripps Genomic Medicine, Scripps Health and The Scripps Research Institute, 3344 North Torrey Pines Court, Suite 300, La Jolla, CA 92037, U.S.A.,(858) 554-5737 (phone), (858) 546-9281 (fax), cbloss@scripps.edu (email)

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Introduction

The ε4 allele of the apolipoprotein E gene (APOE-ε4) and the presence of a first-degree relative with Alzheimer's disease (AD) are two known risk factors for the development of AD (1). The discovery of these risk factors, coupled with interest in identifying and characterizing a preclinical phase of AD, has led to several studies that have found an adverse relationship between each risk factor and brain and cognitive function in healthy adult populations (2). Furthermore, subsequent studies of the combined influence of both risk factors in adults have suggested that, together, they may have a greater negative influence than either one alone (3, 4). There are, however, no studies of which we are aware that have assessed the combined effect of these AD risk factors on cognitive functioning in children.

While studies in adolescents, thus far limited to examination of general cognitive ability, have generally failed to find APOE-related differences (5–7), investigations of the APOE-ε4 allele in human prenatal, perinatal, and infancy periods of life provide evidence of antagonistic pleiotropy. Antagonistic pleiotropy is a somewhat counter-intuitive effect in which the ε4 allele appears to have protective effects early in development (e.g., on survival and cognition), but well-known detrimental effects during the post-reproductive years (8–10). In light of these findings, we predicted that in a sample of school-aged children, the ε4 allele might be associated with better test performance in specific cognitive domains, rather than no association or the poorer performance that might be expected if its effects were constant across the lifespan. The lack of studies on the relationship between a positive family history (+FH) of AD and cognitive functions in children, however, made it difficult to predict what independent effect this risk factor may have on test performance, or how it might interact with the presence of the APOE-ε4 allele during childhood.

Methods and Materials

The study was approved by the Institutional Review Boards of the University of California, San Diego and San Diego State University, and informed consent was obtained from a parent of each participant.

Participants

Children between 11 and 16 years of age were recruited from a group of public charter schools and genotyped for APOE. Subjects were screened and DNA was collected using a buccal swab technique. Exclusion criteria consisted of the following: First language learned was not English, color blindness, uncorrected visual impairment, upper extremity motor disability, genetic disorder known to affect central nervous system functioning, history of head injury with loss of consciousness for greater than 10 minutes, and a diagnosed seizure disorder.

Procedures

Each child's results from four verbal subtests of the California Achievement Test (CAT-6) (11) were obtained, and each child was administered a test of visuospatial and constructional skills in their classroom setting (i.e., the Rey-Osterrieth Complex Figure Test Copy Condition; RCFT-CC) (12,13). The CAT-6 has been used in previous neurocognitive research (14), and standardized Normal Curve Equivalent (NCE) scores provided for each subtest are reported here. NCE scores have a mean of 50 and a standard deviation of 21. The RCFT-CC was scored using the Taylor Scoring Criteria and normative data (15,16), and a Z-score was calculated for each child, which was then transformed to a NCE score in order to facilitate direct comparisons with CAT-6 subtest scores.

Parents of participants were asked to complete an online demographic questionnaire that included several questions pertaining to their child's family medical history (see Supplemental Data), including whether the child's biological family history (FH) was significant for AD and/or significant memory problems (MP). For each instance in which the parent endorsed a +FH, he or she was asked to indicate how the affected individual(s) is/was related to the child. Children were grouped on the basis of APOE genotype and the presence or absence of a +FH of AD and/or MP for our primary analyses.

Sample Characteristics and Statistical Analyses

All ε2/4 heterozygotes ($n = 4$) were removed from the analysis. In total, there were 109 children for whom genotype, FH, and RCFT-CC data were available, and a subset of 102 children for whom CAT-6 subtest data were additionally available. There was one subject who had an RCFT-CC score that fell more than 3 standard deviations below the mean and was thus removed from all subsequent analyses of RCFT-CC scores. Statistical analyses (see Table 2 legend) were conducted using SPSS statistical software. An alpha level of 0.05 was used in the interpretation of all results.

Results

Demographic data are presented in Table 1. Twenty-two percent of subjects were ε4-positive and 78.0% were ε4-negative. With respect to the sample as a whole, there were 32 children (29.1%) for whom a family history of AD was endorsed. The breakdown with regard to the relation of the reportedly affected relative(s) was as follows: grandparent, $n = 18$; great-grandparent, $n = 10$; great-aunt, $n = 1$; uncle, $n = 1$; and two or more relatives, $n = 2$. In addition, there were 22 children (20.0%) for whom a family history of significant MP was endorsed. The breakdown with regard to the relation of the reportedly affected relative(s) was as follows: grandparent, $n = 15$; great-grandparent, $n = 4$; and parent, $n = 3$. Furthermore, considering cases of overlap, there were 43 children (39.1%) for whom a +FH of AD and/or MP was endorsed. When examining the combined effect of APOE genotype and FH status, analyses were initially completed with a +FH defined as the presence of a relative with AD, and then again with a +FH defined as the presence of a relative with AD, MP, or both. The results of these two sets of analyses were similar; thus, because there was increased statistical power in the latter case (i.e., due to a slightly higher number of children in the +FH groups), those results are presented here.

There were no significant main effects of APOE-ε4 status or FH status for any of the CAT-6 subtests or the RCFT-CC (Table 2). There were, however, significant interaction effects between APOE-ε4 status and FH status with respect to the Reading subtest ($F(1, 98) = 4.726$, $p = .032$; $\eta_p^2 = .046$), Language subtest ($F(1, 98) = 4.151$, $p = .044$; $\eta_p^2 = .041$), and the RCFT-CC ($F(1, 104) = 6.181$, $p = .015$; $\eta_p^2 = .056$). Table 2 depicts the mean scores for each group, and, as shown, children with both an APOE-ε4 allele and a +FH of AD/MP obtained lower scores on each measure relative to children in the other three groups. To further explore this finding, follow-up simple effects testing was performed, and among APOE-ε4 allele carriers, results revealed significantly lower reading and RCFT-CC scores among +FH children relative to −FH children (Table 2); among children without an APOE-ε4 allele, there were no significant differences in scores as a function of FH status. Analyses were also completed with a subset of the other FH conditions assessed (see Supplemental Data), and no other FH condition (e.g., stroke) showed a significant interaction with APOE-ε4 status for any of the cognitive measures.

Discussion

Here we present the first evidence of which we are aware that the combined presence of two risk factors for AD, the APOE-ε4 allele and a +FH of AD/MP, may be associated with lower

cognitive test performance in school-aged children. Although children with both risk factors obtained test scores within the average range, their lowered performance suggests that there may be a subtle synergistic effect of these AD risk factors that could lead to the development of less cognitive reserve early in life. These results also invite the hypothesis that factors still unknown at this time (e.g., other genetic factors, environmental factors) that are embodied in a +FH of AD/MP may interact with APOE during early development to adversely impact cognition in childhood. Thus, risk factors for a disorder of pathological aging (i.e., AD) may have implications for the etiology of certain types of learning difficulties in children, which is consistent with retrospective work in this area (17). Furthermore, our results are generally consistent with neuroimaging findings of APOE-ε4-related differences in young adults (e.g., see 18).

As this is a preliminary study, findings should be viewed with some caution in light of the relatively small sample sizes studied, as well as the fact that FH status was based primarily on second-degree relatives and assessed via parent-report. Results also suggest a number of areas for further study. Most notably, future studies that examine additional cognitive domains, in particular memory, would be critical given that most studies that have found differences between individuals with and without a family history of AD have primarily observed these differences with respect to learning and memory (19,20). In addition, more detailed assessment of family history status (e.g., confirmed by medical records), as well as assessment of additional early-life variables (e.g., perinatal complications) and genetic factors that have been implicated in AD pathogenesis may help elucidate the complex relationship between environmental and genetic risk factors for AD and their impact on cognitive functioning in early life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Basic Demographic Information by APOE-ε4 Status

	ε4− ***n*** **= 85**	**ε4+** ***n*** **= 24**	***p***
Percentage in Allele Category	78.0	22.0	n/a
Age at Exam[a]	13.42 (1.22)	13.42 (1.40)	.979[b]
Male/Female	37/48	12/12	.574[c]
Ethnicity			.127[c]
Asian	5	0	
African American	3	4	
Caucasian	63	16	
Filipino	4	0	
Hispanic	9	4	
Other	1	0	
Handedness (R/L)	74/11	22/2	.539[c]
Parent Education in Years[a]			
Mother	16.35 (2.09)	16.46 (2.17)	.829[b]
Father[d]	16.26 (2.41)	16.21 (2.60)	.925[b]
AD/MP Family History (Yes/No)	32/53	11/13	.469[c]

[a] Data are presented as mean (standard deviation).

[b] One-way ANOVA used to test group differences.

[c] Chi-square used to test group differences.

[d] Based on $n = 108$.

Table 2

Cognitive Test Performance by APOE-ε4 Status and Family History of AD and/or Memory Problems[a]

	ε4−		ε4+		ε4	FH	Interaction	Simple Effect
	−FH	+FH	−FH	+FH				−FH vs. +FH Within ε4+
	n = 52	*n* = 28	*n* = 12	*n* = 10	*p*[b]	*p*[c]	*p*[d]	*p*[e]
Reading	67.94 (19.32)	71.14 (15.69)	72.83 (10.95)	57.60 (16.91)	.310	.159	.032*	.027*
Language	69.79 (20.19)	71.21 (16.29)	74.17 (12.98)	56.50 (26.47)	.273	.086	.044*	.077
Spelling	64.69 (18.25)	66.21 (16.30)	69.58 (22.78)	62.00 (31.98)	.945	.535	.352	N/A
Math	62.77 (19.26)	68.39 (18.51)	64.83 (13.60)	56.30 (19.34)	.270	.748	.120	N/A
RCFT-CC[f]	50.67 (13.61)	55.48 (11.40)	57.51 (7.42)	48.32 (9.19)	.956	.439	.015*	.015*

[a] Examined with univariate ANOVA. The following are depicted here: main effects of

[b] APOE-ε4 status,

[c] AD/MP FH status, and the

[d] interaction effect.

[e] Results of follow-up simple effects testing are also presented.

[f] Sample sizes for the Rey Complex Figure Test Copy Condition (RCFT-CC) analysis were slightly higher (i.e., ε4−/+FH, n = 31; ε4−/−FH, n = 53; ε4+/+FH, n = 11; ε4+/−FH, n = 13) than for the California Achievement Test (CAT-6) subtests; furthermore, the overall lower mean scores observed on the RCFT-CC relative to the achievement subtests likely reflect the fact that the two types of tests utilize different normative comparison groups. Data are standardized Normal Curve Equivalent (NCE) scores, which have a mean of 50 and a standard deviation of 21. NCE scores are presented as mean (standard deviation).

* Denotes $p < 0.05$.