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Apolipoprotein E4 and Sex Affect Neurobehavioral Performance in Primary School Children

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ABSTRACT: Apolipoprotein E4 (apoE4) and female sex are risk factors for developing Alzheimer's disease. It is unclear whether apoE4 contributes to behavioral function at younger ages. Standard neuropsychological assessments [intelligence quotient (IQ), attention, and executive function] and a test developed in this laboratory (Memory Island test of spatial learning and memory) were used to determine whether E4 and sex affect neuropsychological performance in healthy primary school children (age 7–10). A medical history was also obtained from the mother to determine whether negative birth outcomes were associated with apoE4. Mothers of apoE4+ children were more likely to report that their newborn was placed in an intensive care unit. A sex difference in birth weight was noted among apoE4− (males > females), but not apoE4+, offspring. Conversely, among apoE4+, but not apoE4− children, there was a sex difference in the Wechsler Abbreviated Scale of Intelligence (WASI) vocabulary score favoring boys. ApoE4− girls had better visual recall than apoE4+ girls or apoE4− boys on the Family Pictures test. Finally, apoE4+, unlike apoE4−, children did not show spatial memory retention during the Memory Island probe trial. Thus, apoE4 may affect neurobehavioral performance, particularly spatial memory, and antenatal health decades before any clinical expression of neurodegenerative processes. **(*Pediatr Res* 67: 293–299, 2010)**

Apolipoprotein E (apoE), a lipid transport protein implicated in artherosclerosis and neurodegeneration (1,2), is widely distributed throughout the brain (3–5). ApoE is important for neuron migration, axon guidance, microtubule stability, dendritic spine density, synaptic plasticity, and regeneration after injury (1). The three major human apoE isoforms, apoE2, apoE3, and apoE4, differ in binding affinity to members of the LDL family of receptors (6). ApoE4-carrying individuals have a shorter lifespan and age less successfully (7,8). ApoE4 has been associated with an earlier onset of Alzheimer's disease (AD) (9,10) and interacts with female sex to increase AD risk (11). In addition to AD, apoE4 has been associated with age-related cognitive decline in the absence of dementia (12–14). A fundamental issue is whether apoE4 alters the neurobiology of the brain in ways that only become more evident during aging or after environmental challenges later in life.

The neurobehavioral consequences of apoE4 depend on the cognitive domain measured and at what age it is assessed (14–17). The apoE4 allele was more common among Czech university graduates relative to those that did not complete secondary school (18). Similarly, apoE4-carrying young adults showed better recall of a list of words (19). However, apoE4 did not modify California Achievement test performance among adolescents (20) and apoE4-carrying high school students with a family history of AD did exhibit reduced performance on the reading subtest of the California Achievement test and in visual-spatial memory (21). Relatively little is known about the potential effects of apoE4 on cognition in children. There were no effects of apoE4 on verbal and nonverbal reasoning in 11 y olds, but there were effects of apoE4 on this measure when the same study participants were retested as nondemented octogenarians (22). Similarly, overall intelligence quotient (IQ) was unaltered by apoE4 in children (23–25). However, Mental Development Index scores were higher among Mexican apoE4 carrying 2 y olds (26). The primary objective of this study was to examine whether apoE4 affects neuropsychological performance in 7- to 10-y-old children. As previous research has implicated apoE in fetal health (27–29), it was also determined if apoE4 was associated with adverse birth outcomes. On the basis of an earlier investigation (13), we hypothesized that reduced spatial memory would be observed among children with at least one apoE4 allele.

METHODS

Study participants. Flyers were posted at Oregon Health & Science University (OHSU) to recruit healthy 7- to 10-y-old boys and girls. This age range was selected because language skills are sufficiently developed to readily assess relatively complex functions and prepubescent children might be expected to show less evidence of sex differences than at older ages. Exclusion criteria were children with severe visual impairments, born >5 wk premature, epilepsy, cerebral palsy, congenital abnormalities,

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Abbreviations: AD, Alzheimer's disease; **apoE,** apolipoprotein E; **BRIEF,** behavior rating inventory of executive function; **WASI,** Wechsler abbreviated scale of intelligence

severe brain trauma, or any other medical condition that could interfere with cognitive assessments. The parent completed an informed consent and a disclosure form so that the OHSU medical record database was examined for each child to verify the exclusion criteria. For study participation, there was a $50 Toys-R-Us gift certificate. Saliva samples were collected at the beginning of the session using the Oragene self-collection methodology (DNA Genotek Inc., Ottawa, ON, Canada), and genotypes were determined at the General Clinical Research Center of OHSU as described (13). All procedures were approved by the Institutional Review Board of OHSU.

Behavioral assessments. The children completed a session that averaged about 1.5 h. The neurobehavioral assessments included several general domains (attention, intelligence, and executive function), spatial learning and memory, and instruments sensitive to effects of apoE4 in the elderly (13). The sequence of tests was 1) Dot Location (30); 2) Conner's Continuous Performance test (31); 3) Memory Island spatial navigation (13,32); 4) Family Pictures (30); 5) Wechsler Abbreviated Scale of Intelligence (WASI): Vocabulary and Block Design; 6) Forward and Backward Spatial Span. A single assessor (S.F.A.), blinded to the genotypes, administered all tests to the children. In addition, the mother filled out a questionnaire to determine demographics and pregnancy outcomes (*e.g.* use of an intensive care unit (ICU) after birth, whether the birth occurred vaginally or by cesarean), and the Behavior Rating Inventory of Executive Function (BRIEF) (33). Each of these assessments is described in further detail later.

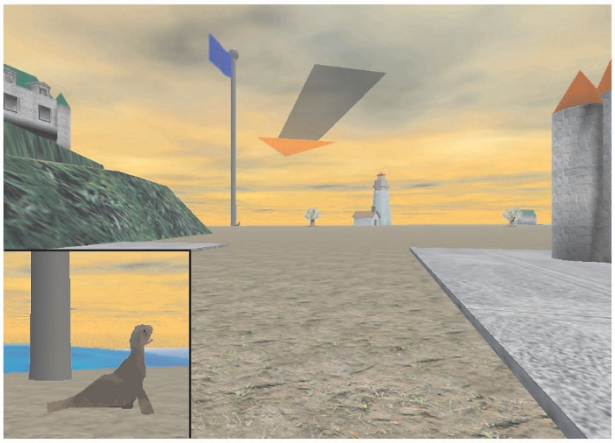

Figure 1. Screen shot of Memory Island during a visible trial. If the target (insert) is not reached in 2-min, an arrow appears (shown).

The Dot Location test is a spatial memory assessment and a component of the Children's Memory Scale. Dot Location includes age appropriate difficulty levels for children aged 4–8 and 9–17 y (30). The primary dependent measures were the learning, short delay, long delay, and total correct (expressed as age-corrected scaled scores). Further, the percent of the distracter items recalled was recorded.

The Conner's Continuous Performance test is a 14-min computerized assessment of attention, where respondents press the space bar whenever any letter except the target, an "X," is displayed. The interstimulus intervals were 1, 2, and 4 s. The primary measures are omission and commission errors, hit reaction time SE, detectability, and response style (31).

Memory Island is a human equivalent of the Morris water maze and has been used previously with healthy adults, the elderly, and children (13,32). This approach has also been validated in that hippocampal lesions disrupt spatial memory in a virtual reality paradigm (34). The children were first asked to navigate using a joystick to a target location visibly marked with a flag adjacent to the target (visible session). Unique targets in each of the four quadrants were used for visible target training in four trials. The starting orientation of the participant was varied for each trial, and these variations are kept consistent for all participants. After completing training to find the visible targets, the children were trained to navigate to a hidden target (*i.e.* no flag adjacent to the target) in four trials. The participants had to remember where the hidden target was and how to get there. The location of the hidden target, a sculpture, was constant for all children. In each trial of the visible or hidden session, if the subject was unable to locate the target within 2 min, a directional arrow appears to guide them to the target (Fig. 1). Approximately 15 min after the last hidden target trial, the participant received a 30-s probe trial with the target removed to assess spatial memory. In each trial, movement of the children was recorded in time-stamped coordinate files, which were used to calculate cumulative distance to the target and distance traveled (virtual units), velocity (virtual units/s), latency to reach the target, and percentage time spent in each quadrant.

The Family Pictures visual recognition test is part of the Children's Memory Scale (30). Children were shown pictures of people in a particular scene and asked to remember everything they could about each scene (four scenes total). Immediate recall was assessed by asking who was in the scene, where they were in the scene, based on a quadrant division of the scene, and a basic description of what they were doing in the scene (eating, gardening, etc.). After an interval of 30 min, participants were asked the same questions again. All intervals for multipart tests are approximations because of the variable time demands of children during assessments. For the immediate and delayed scores, one point was given for correctly identifying who was in the picture, one point for the location, and two points for the correct description of their actions. This assessment was selected because it was previously shown to be sensitive to the effects of apoE4 in nondemented elderly (13).

Table 1. *Child and maternal demographics by apoE4 and sex*

	ApoE4		Sex	
	E4−	E4+	Males	Females
Child				
Sex (% female)	41.5%	58.3%	NA	NA
Genotype (% E4+)	NA	NA	17.2%	29.2%
Race (% non-white)	19.5%	16.7%	17.2%	20.8%
Result of Cesarean delivery	8.1%	27.3%	14.8%	9.5%
Birth weight (g)	3553.8 (93.6)	3166.1 (133.7)*	3616.5 (113.1)	3292.0 (108.2)*
Placed in ICU (% yes)	2.7%	27.3†	3.7%	14.3%
Hospitalized <1 d (%)	24.3%	0.0%†	25.9%	9.5%
ADHD	4.9%	0.0%	6.9%	0.0%
Reading (below age)	7.3%	8.3	6.9%	8.3%
Overall school (below age)	2.4%	0.0%	3.4%	0.0%
Age at testing (y)	9.0 (0.2)	9.0 (0.3)	9.2 (0.2)	8.9 (0.2)
Maternal				
Age at pregnancy	29.2 (1.0)	31.2 (1.6)	29.2 (1.0)	30.2 (1.3)
Pregnancy weight gain (kg)	15.6 (1.2)	14.2 (1.4)	15.6 (1.3)	14.9 (1.5)
Smoking in pregnancy (% yes)	7.5%	8.3%	3.4%	12.5%
Alcohol in pregnancy (% yes)	12.2%	16.7%	10.3%	17.4%

* *t* test $p < 0.05$.

† Likelihood ratio $p < 0.05$.

ADHD, attention deficit hyperactivity disorder, NA, not applicable.

The WASI is an abbreviated version of the Wechsler Intelligence Scale for Children (Third Edition, WISC-III) that provides subtest and composite scores representing intellectual functioning. The Vocabulary and Block Design components were completed to assess performance relative to normative data.

The spatial span provides a measure of visual-spatial working memory and is also a subtest of the WISC-III. The child watches an examiner tap a sequence of numbered cubes on the spatial span board (numbered side faces examiner) and then is asked to tap out the same sequence. The spatial span is discontinued if a subjects scores 0 on each of two trials of the same item. In the first test, the child must repeat the same order (spatial span forward) and, in the second test, the order is reversed (spatial span backwards).

The BRIEF is an 86-item parental questionnaire of executive functioning in the context of the child's everyday activities. Behaviors are rated as never, sometimes, or often a problem (1–3 points, respectively) and expressed as a T_{50} score (33).

Statistical analysis. All analyses were conducted using SPSS, version 16.0 (SPSS Inc., Chicago, IL). A p value of <0.05 was considered statistically significant, although, because multiple tests were conducted, statistics that met more conservative thresholds (0.01 or 0.001) were also noted. Likelihood ratios were reported to determine whether apoE4 status (E4− *versus* E4+) was associated with nominal level outcomes. The age corrected (T_{50} or Scaled Scores) were used for all behavioral tests except where noted. As sex differences favoring males in spatial learning and memory have been observed previously in this research area (13,32), a two (apoE: E4− *versus* E4+) by two (sex: boy *versus* girl) ANOVA was completed for continuous neurobehavioral measures. For Memory Island, the visible, hidden, and probe trials were analyzed separately. The probe trial data were analyzed with a mixed (trial: target, left, right) × apoE × sex ANOVA. Note that the opposite quadrant could not be included because inclusion of all four quadrants in the model simultaneously violates the ANOVA data requirements. Paired t tests comparing the percent time in the target relative to each of the other quadrants were also conducted for each apoE4 group. As previous research in this laboratory with children identified a pronounced improvement in spatial memory on Memory Island between ages 9 and 10 (unpublished data), age was also entered into the ANOVA model for the probe trial analyses. A *posthoc* power analysis for the comparison of two groups with alpha = 0.05 was conducted with G*Power 3.1.0 (35).

Table 2. *Pregnancy complications by apoE4 and sex*

	ApoE4 (%)		Sex (%)	
	E4−	E4+	Males	Females
Cervical cerclage	0.0	16.7*	3.4	4.3
Vaginal bleeding	17.5	25.0	24.1	13.0
Urinary tract infection	7.5	0.0	10.3	0.0
High blood pressure	5.0	8.3	6.9	4.3
Placenta previa	0.0	8.3	0.0	4.3
Premature rupture of membranes	5.0	8.3	6.9	4.3

* Likelihood ratio $p < 0.05$.

RESULTS

ApoE genotype. Among males (n = 26), 19 were E3/E3, two were E2/E3, one was E4/E4, two were E3/E4, and two were E2/E4. Among females (n = 24), 12 were E3/E3, five were E2/E3, one was E4/E4, five were E3/E4, and one was E2/E4.

Demographics and birth history. There were no significant differences between apoE4− and apoE4+ children in terms of age at testing, sex, ethnicity, academic performance, or prenatal exposure to recreational drugs (Table 1). However, apoE4+ offspring were 10 times more likely to be placed in an ICU after birth [likelihood ratio (1) = 5.451, $p < 0.05$]. A 2 (sex) × 2 (apoE4) ANOVA on birth weight revealed a trend for a main effect of sex [F (1,47) = 3.933, p = 0.053] and an apoE4 × sex interaction (p = 0.096). ApoE4+ boys (3012.1 ± 233.2) and girls (3254.1 ± 166.5) were equivalent. In contrast, a pro-

Table 3. *Neuropsychological performance by apoE4 and sex*

	ApoE4		Sex		ANOVA		
	E4− (n = 38)	E4+ (n = 12)	Males (n = 26)	Females (n = 24)	ApoE4	Sex	ApoE4 × sex
WASI							
Vocabulary	54.5 (2.0)	54.8 (3.0)	53.4 (1.9)	55.8 (2.7)		0.097	0.051
Block design	56.5 (1.9)	62.2 (3.5)	57.1 (2.2)	58.7 (2.6)			
BRIEF							
Global executive composite	49.1 (1.5)	47.8 (2.1)	46.8 (1.8)	51.0 (1.6)		0.057	
Metacognition Index	49.7 (1.6)	48.4 (2.5)	47.0 (1.8)	52.0 (1.8)		0.079	
Initiate	50.5 (1.6)	48.3 (2.2)	47.9 (1.7)	52.3 (1.9)		0.061	
Working memory	49.6 (1.6)	47.9 (2.5)	48.5 (1.8)	50.0 (2.1)			
Planning	49.8 (1.5)	49.4 (2.9)	48.3 (2.0)	51.2 (1.8)			
Organize	51.8 (1.6)	53.0 (2.3)	49.0 (1.8)	55.4 (1.8)			
Monitor	47.6 (1.9)	45.0 (2.3)	43.4 (2.0)	50.7 (2.2)		<0.05	
Behavioral regulation index	47.8 (1.4)	47.0 (2.4)	46.3 (1.9)	49.0 (1.6)		0.071	
Inhibit	47.7 (1.3)	47.1 (1.7)	46.1 (1.7)	49.1 (1.3)		0.083	
Shift	48.8 (1.7)	48.4 (2.5)	48.3 (2.1)	49.2 (1.9)			
Emotional control	48.0 (1.5)	46.6 (2.7)	46.6 (2.0)	48.8 (1.7)			
Negativity	0.2 (0.1)	0.3 (0.2)	0.2 (0.1)	0.2 (0.1)			
Inconsistency	2.7 (0.2)	2.5 (0.3)	2.7 (0.3)	2.5 (0.2)			
Dot Location							
Total	11.1 (0.5)	12.7 (0.6)	12.3 (0.6)	10.7 (0.6)	0.089		
Learning	10.5 (0.6)	11.8 (0.7)	11.5 (0.6)	10.0 (0.7)			
Short delay	12.0 (0.4)	12.8 (0.3)	12.6 (0.3)	11.7 (0.5)			
Long delay	11.8 (0.3)	11.9 (0.6)	11.9 (0.4)	11.7 (0.4)			
Distracter (%)	72.5 (3.5)	82.3 (7.1)	81.7 (3.7)	67.4 (5.0)		<0.05	
Family Pictures							
Total	23.7 (1.1)	21.5 (1.5)	21.1 (1.1)	25.4 (1.3)			0.051
Immediate	11.7 (0.5)	10.8 (0.7)	10.4 (0.5)	12.7 (0.6)		0.098	0.081
Delayed	11.9 (0.6)	10.8 (0.8)	10.7 (0.6)	12.7 (0.7)			<0.05

nounced sex difference was evident in the apoE4− group [boys = 3717.3 ± 115.1, girls = 3038.6 ± 140.5, t (38) = 2.248, $p < 0.05$]. In terms of other pregnancy complications, mothers of apoE4+ offspring were more likely to report cervical cerclage (*i.e.* a surgical procedure in which a weak cervix is sewn closed to prevent miscarriage, Table 2).

Behavior. Performance on WASI Vocabulary (T_{50} = 54.6 ± 1.6) and Block Design (T_{50} = 57.7 ± 1.7) for the entire sample was above average. ANOVA revealed a trend for an apoE4 × sex interaction [F (1,45) = 4.013, p = 0.051] in the vocabulary subtest (Table 3). ApoE4+ boys (T_{50} = 63.0 ± 4.2) performed better than apoE4+ girls [49.0 ± 2.4, t (10) = 3.11, $p < 0.05$]. No sex difference was evident among the apoE4− group (boys = 54.0 ± 3.1, girls = 55.2 ± 2.4). There were no differences on the Block Design, Conner's Continuous Performance, Spatial Span tests, or BRIEF.

The Family Pictures total score (immediate + delayed) was analyzed with an apoE4 × sex ANOVA, which revealed a trend toward an apoE4 × sex interaction [F (1,46) = 3.99, p = 0.051, Table 3]. ApoE4− girls exhibited higher immediate recall relative to apoE4+ girls as well as apoE4− boys (Fig. 2, Top). Similarly, apoE4− girls showed greater delayed recall than apoE4+ girls or apoE4− boys (Fig. 2, Bottom).

There were no effects of apoE4 or sex on the total scores of Dot Location assessment (Table 3). However, the percentage of total correct items on the distracter trial was higher in boys (81.7 ± 3.7%) than girls [67.4 ± 5.0%, t (42.89) = 2.32, $p < 0.05$].

Memory Island performance was examined separately for the visible and hidden trials. The cumulative distance to the target during the visible trials was analyzed with a 4 (trial) × 2 (apoE4) × 2 (sex) ANOVA. There was an effect of trial [F (1.7,74.2) = 40.45, $p \leq 0.0005$] and an apoE4 × sex interaction [F (1,44) = 4.55, $p < 0.05$]. Further analyses of the sexes separately again revealed a significant effect of trial, and, for girls, a trend toward an effect of apoE4 (p = 0.09). The latency to find the target showed only an effect of trial [F (1.3,57.2) = 38.2, $p \leq 0.0005$]. Similarly, speed showed only a main effect of trial [F (2.3,100.7) = 27.4, $p < 0.005$].

During the hidden trials, there was an effect of trial on distance traveled [F (2.3,102.4) = 4.72, $p < 0.01$]. For latency during the hidden trials, there was an effect of trial [F (2.3,101.9) = 6.16, $p \leq 0.001$]. For velocity, there was an effect of trial [F (3,141) = 3.34, $p < 0.05$], sex [F (1,47) = 5.74, $p < 0.05$], and a trial × sex interaction [F (3,141) = 2.86, $p < 0.05$]. Figure 3 shows that boys moved significantly more quickly in the first and second hidden trials with a trend toward a difference observed in the third and fourth trials.

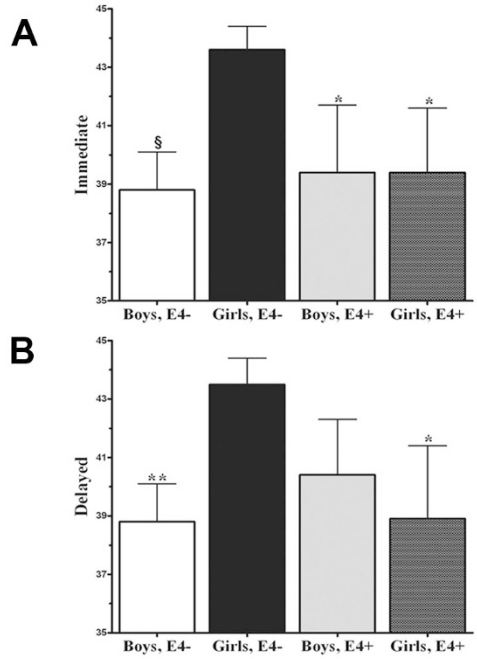

Figure 2. Performance of apoE4− and apoE4+ children on the immediate (*A*) and delayed (*B*) Family Pictures tests. *$p < 0.05$, **$p < 0.01$, or §$p < 0.001$ versus apoE4− females.

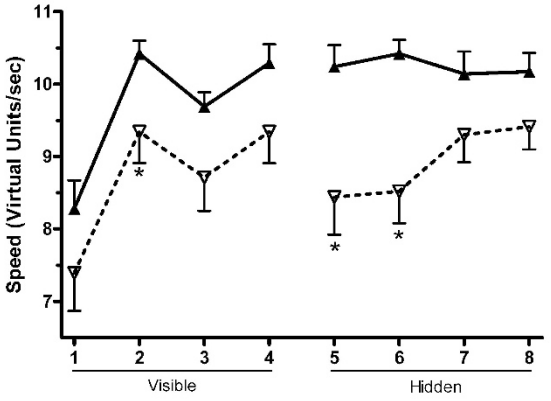

Figure 3. Speed (virtual units/s) on the visible and hidden trials of Memory Island. ▲ males; ▽ females. (*$p < 0.05$ *vs* males).

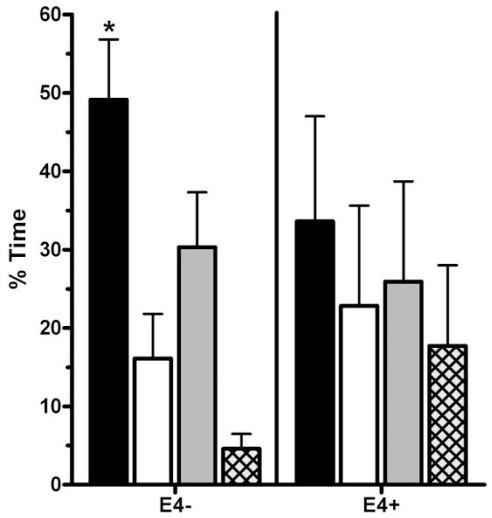

Figure 4. Spatial memory retention of apoE4− and apoE4+ children in the probe trial of Memory Island. *$p < 0.05$ *vs* other quadrants, ■ target, □ left, ▩ right, or ⊠ opposite quadrant (for additional details, see text).

The probe trials were first analyzed with a mixed quadrant × apoE4 × sex × age (above or below age 10) ANOVA. This analysis revealed an effect of age [F (1,47) = 5.95, $p < 0.05$], quadrant [F (1.4,94) = 46.0, $p \leq 0.0005$], and age × quadrant interaction [F (1.4,94) = 7.25, $p < 0.005$]. Examination of the percent-time spent in the target quadrant by age revealed that 10 y olds had significantly higher scores relative to younger children [10 y olds = 73.9 ± 6.2%, seven to nine = 45.5 ± 6.7%, t (33.6) = 3.1, $p < 0.005$]. Therefore, the quadrant data were further analyzed with the 10 y olds (four apoE4+ and seven apoE4−) removed. This analysis (quadrant × apoE4 × sex) revealed a main effect of apoE4 [F (1,31) = 5.20, $p < 0.05$], sex [F (1,31) = 9.38, $p \leq 0.005$], and an apoE4 × sex interaction [F (1,31) = 6.14, $p < 0.05$]. Figure 4 shows that although apoE4− children spent more time in the target relative to the right [t (26) = 2.78, $p \leq 0.01$] or opposite quadrants [t (26) = 5.91, $p \leq 0.0005$], apoE4+ children did not show a target preference ($p > 0.40$ for all comparisons).

DISCUSSION

This report determined that apoE4+ children, unlike apoE4−, do not show a target preference in the Memory Island paradigm. The hippocampus and adjacent entorhinal cortex are key structures in the neural network responsible for spatial function (36). ApoE is important for several neurodevelopmental processes (1), which may account for the finding of apoE4 carrying children having a thinner entorhinal cortex relative to apoE2 or apoE3 (24). The current results complement those from two other reports (Table 4) showing effects of apoE on spatial learning and memory in young people (17,20).

Geriatric women performed better than men on Family Pictures (13). Using the same paradigm, and unlike the elderly (13), there was an apoE4 by sex interaction among children. Girls without apoE4 performed better than those with apoE4 at both the immediate condition and after a short delay. Most investigations (23–25) have noted that overall IQ was unaffected by apoE4. However, the presence of apoE4 has been associated with improved WASI performance IQ (37). The effect of sex in mediating the susceptibility to apoE4-induced neuropsychological alterations is consistent with apoE4+ positive females exhibiting greater age-related declines then men on Wechsler Adult Intelligence Scale Performance IQ (12). In addition, during the visible learning trials of Memory Island, there was a genotype × sex interaction. With the heightened sensitivities of females to the consequences of apoE4 (11,38), these findings highlight the importance for future investigations to carefully monitor for apoE by sex interactions or to continue examining females separately (37,39). Sex differences, independent of apoE4, were also identified in the spatial learning trials of Memory Island with boys showing greater velocity and reaching the target sooner than girls, consistent with faster and more accurate performance by males than females in virtual water mazes across the lifespan (13,32,40,41).

ApoE4+ infants were more likely to require ICU and apoE4+ neonates weighed less at birth overall. In addition, a sex difference in birth weights favoring males was observed among the apoE4−, but not apoE4+, offspring. Epidemiologic data noted subtle (*i.e.* 100 g) sex differences favoring males in birth weight (J.A. Martin, personal communication), so the current finding of a large (400 g) sex difference was unanticipated. Although birth weight has been associated with cognition (42), these sequelae are most pronounced for babies that qualify as at least low birth weight (<2500 g). As only one apoE4+ subject met this criterion, albeit barely (2495 g), compared with two in the apoE4− group, it is unlikely that the present neurobehavioral findings are an indirect consequence of apoE4 acting simply on birth weight. However, because of the relatively low sample size, the present observations on birth outcomes, cognition, and apoE4 should be regarded as preliminary. The power for the apoE4 differences in body weight was only moderate (0.57), especially relative to other outcomes [Fig. 2 (Top), Power = 0.85]. Although the veracity of maternal recall over a decade, particularly for mothers that have given birth to several children, may be suspect, events like an ICU visit are unlikely to be forgotten. The body mass and medical resource utilization findings, if replicated based on the medical records, would extend on previous reports of

Table 4. *Neurobehavioral findings in infants, children, adolescents, and young adults comparing apoE4+ vs* apoE4−

Age, y	Outcome	References
2	apoE4+ > apoE4− on Bayley scale of infant development	26
6–15	apoE4+ = apoE4− on IQ	6
7–9	apoE4+ < apoE4− on spatial memory of Memory Island	Present study
8–20	apoE4+ < apoE4− on entorhinal cortical thickness	24
8–16	apoE4 × health interaction on visual memory	15
11	apoE4+ = apoE4− on verbal and nonverbal reasoning	22
11–16	apoE4 < apoE2 on Rey-Osterrieth complex figure test (ROCFT)	20
11–16	apoE4 × Alzheimer's family history interaction on and ROCFT	21
11–16	apoE4 × Alzheimer's family history interaction on reading and language	21
16–30	apoE4 < apoE3 on navigating through a computerized grid maze	17
19–21	apoE4+ > apoE4− on performance IQ	37
20–35	apoE4+ > apoE4− on hippocampal activity during memory encoding	47
22	apoE4+ > apoE4− on verbal delayed recall	19

>, better performance (higher percent correct, faster reaction time, fewer trials to criterion).
<, worse performance (lower percent correct, slower reaction time, more trials to criterion).

adverse gynecological and birth outcomes being influenced by apoE (27–29,43–45).

These results showing effects of apoE4 in children are in conjunction with several other investigations in children and young adults and indicate that apoE may modulate neurocognitive function. However, Table 4 indicates that the direction of the effects seems to depend on the domain and age assessed (16,22). Environmental challenges might also modulate the direction of the apoE4 effects in children (24). ApoE4-carrying children were more resistant to the detrimental effects of diarrhea on cognitive function (15). Similarly, among neonates that underwent cardiac corrective surgery, those with apoE2 scored lower on gross and fine motor function when assessed on the Bayley Scale of Infant Development (43). In addition, apoE2 infants, relative to apoE3 homozygotes, had lower Mental Development Index scores, a broad measure that includes memory, problem solving, early number concepts, language, and social skills, after heart surgery (45). Finally, the risk of developing cerebral palsy was strongly elevated by the presence of at least one apoE2 allele (44), although see (46).

In conclusion, second to fifth grade children exhibit sex- and apoE4-dependent behavioral differences, typically favoring apoE4− participants. ApoE4, acting either alone or in conjunction with sex-modified spatial learning and memory on Memory Island, the vocabulary score on the WASI, and immediate and delayed visual recall on the Family Pictures assessment. These early effects of apoE4 might contribute to the enhanced risk of apoE4 carriers to age-related cognitive decline and cognitive impairments after environmental challenges.

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