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Neurobiology of Aging 31 (2010) 787–795

NEUROBIOLOGY OF AGING

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APOE genotype is associated with left-handedness and visuospatial skills in children

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Received 26 January 2008; received in revised form 12 May 2008; accepted 25 May 2008
Available online 7 July 2008

Abstract

We sought to investigate whether apolipoprotein E (APOE) genotype is associated with unique profiles of cognitive functioning during early-life. School-aged children ($N = 147$) received standardized achievement tests, the Rey–Osterrieth Complex Figure Test (Copy Condition; RCFT-CC), assessment of hand dominance for writing, and buccal swab testing to determine their APOE genotype. Significant differences were found on the RCFT-CC, with ε2-positive children performing worse on this measure relative to both ε3/3 ($p = 0.032$) and ε4-positive children ($p = 0.018$). Further, a higher prevalence of left-hand dominance for writing was observed among ε2-positive children (29.2%) relative to ε3/3 (8.9%) and ε4-positive children (6.1%; $p = 0.012$), although this finding did not account for the observed group differences on the RCFT-CC. Findings raise the possibility that in childhood, the ε2 allele may be associated with: (a) decreased functioning in certain cognitive domains; (b) factors associated with atypical hemispheric dominance. Results may be consistent with the theory of antagonistic pleiotropy, which suggests that APOE may have different protective effects at different developmental stages.
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Keywords: Cognitive aging; Neurodevelopment; Apolipoprotein E; Developmental neuropsychology; Dementia; Alzheimer's disease

1. Introduction

Alzheimer's disease (AD) is associated with a number of risk factors, with the most prominent being possession of one or more ε4 alleles of the apolipoprotein E (APOE) gene (Corder et al., 1993). In addition to this established genetic risk factor, there is also evidence that the development of AD may be associated with a number of early-life risk factors, including poor perinatal conditions, sub-optimal early-life brain development and body growth, poor early-life socioeconomic conditions, and decreased cognitive reserve, including lower educational attainment (for review see Borenstein et al., 2006). The fact that these two sets of risk factors have in common an association with the development of AD raises the possibility that APOE-ε4 itself could be associated with the presence or absence of one or more of these early-life variables (Richards and Sacker, 2003). In other words, are individuals with the APOE-ε4 genotype at risk for both early-life and late-life cognitive compromise?

Efforts to address this question in children have produced intriguing and somewhat counterintuitive results. A small number of developmental studies have found evidence for protective effects of the ε4 allele during human prenatal, perinatal, and infancy periods of life, characterized by higher survival rates and better cognitive functioning in the face of illness and toxic exposure (Oria et al., 2005; Wright et al., 2003; Zetterberg et al., 2002). Furthermore, one study found

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0197-4580/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.neurobiolaging.2008.05.021

evidence for a detrimental effect of the ε2 allele, characterized by its over-representation in a Scottish cohort of perinatal deaths (Becher et al., 2006). This finding seems contrary to expectations given that the ε2 allele has been shown to have protective properties against the development of AD later in life (Farrer et al., 1997). On the basis of these findings, it has been proposed that APOE may be an example of a gene that exhibits antagonistic pleiotropy (Wright et al., 2003), which is a theory that suggests, in part, that some genes may have different effects at different life stages (Albin, 1993; Williams, 1957).

In contrast to these findings, several studies have failed to find APOE-related differences in brain and cognitive functioning among children beyond infancy (Deary et al., 2002; Plomin et al., 1995; Turic et al., 2001). However, these analyses were generally restricted to investigation of general intellectual ability (i.e., IQ), with specific domains of cognition not examined. Therefore, especially in light of evidence of early-life APOE-related differences in pre- and peri-natal survival rates (Becher et al., 2006; Zetterberg et al., 2002), susceptibility to the adverse effects of illness and toxic exposure on cognition (Oria et al., 2005; Wright et al., 2003), brain functional differences using EEG (Alexander et al., 2007), and region-specific cortical morphology (Shaw et al., 2007), the question remains as to whether or not APOE genotype influences development of cognitive functions in children.

The aim of the current study was to further explore this question by examining achievement and visuospatial test performances in a sample of school-aged children and adolescents genotyped for APOE. In addition, APOE-related differences in hand dominance, which is often considered an indicator of early atypical brain and/or cognitive development (Satz, 1973), were assessed. Based on several studies that have found decreased cognitive functioning among ε4-positive adults (for review see Small et al., 2004) and the relative absence of cognitive decline among ε2-positive adults, we would predict that a similar pattern would be observed among our sample of school-aged children (i.e., worse performance among ε4-positive children relative to ε2-positive children). However, the studies reviewed above reporting an advantageous effect of the ε4 allele very early in human development and possibly a detrimental effect of the ε2 allele, suggest that the opposite hypothesis was also plausible (i.e., better performance among ε4-positive children relative to ε2-positive children).

2. Methods

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

2.1. Subjects

2.1.1. Recruitment

Participants were recruited from a group of San Diego area charter middle schools and high schools. An email message was sent to parents of prospective children, and classroom presentations were made by the first author to explain the study. An "informational booth" was then set up outside the school during after-school hours. During this time, parents and students could obtain additional information about the study and sign an informed consent agreement to participate if they chose to do so, which included a release of information providing access to the child's standardized group achievement test records.

2.1.2. Screening

Typically developing children between the ages of 11 and 16 years were included in the study. Parents of participants were asked to complete an online demographic questionnaire pertaining to their child's developmental, medical, educational, psychiatric, and family medical history. Exclusion criteria consisted of the following: first language learned was not English, color blindness, uncorrected visual impairment, upper extremity motor disability that may affect test performance on visual-motor tasks, genetic disorder known to affect central nervous system functioning (e.g., Fragile X), history of head injury with loss of consciousness for greater than 10 minutes, and a diagnosed seizure disorder. A history of learning and/or attentional problems was not exclusionary. In addition, due to the fact that the children were tested in their classroom groups (see Section 2.2 below), it often occurred that a child was tested prior to their parent(s) completing the screening questionnaire. If, however, it was determined after a child was tested that he or she did not meet inclusion criteria, their case was removed from further analyses. Overall, screening questionnaires were completed for approximately 80% of the sample. In the case where two or more siblings enrolled in the study, if applicable, either the male sibling and/or the sibling with achievement test data available were included.

2.2. Procedures

Once a number of students from a particular class had signed up to participate in the study, a lunchtime testing session was arranged with the teacher of that particular class. On the specified date, children participating in the study remained in their classroom during lunch and were administered the RCFT-CC (Osterrieth, 1944) in the group setting. Following administration of this measure, DNA samples were obtained from each child using a buccal swab technique (i.e., a mild brushing of the inside of the cheek). Then, as a group, the children received a complimentary pizza lunch for their participation (e.g., see Brown et al., 2005). Finally, standardized group achievement test records were requested from the school for each participant. This procedure was repeated sev-

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