APOE ε4 Allele Status Influences Early Neurodevelopment

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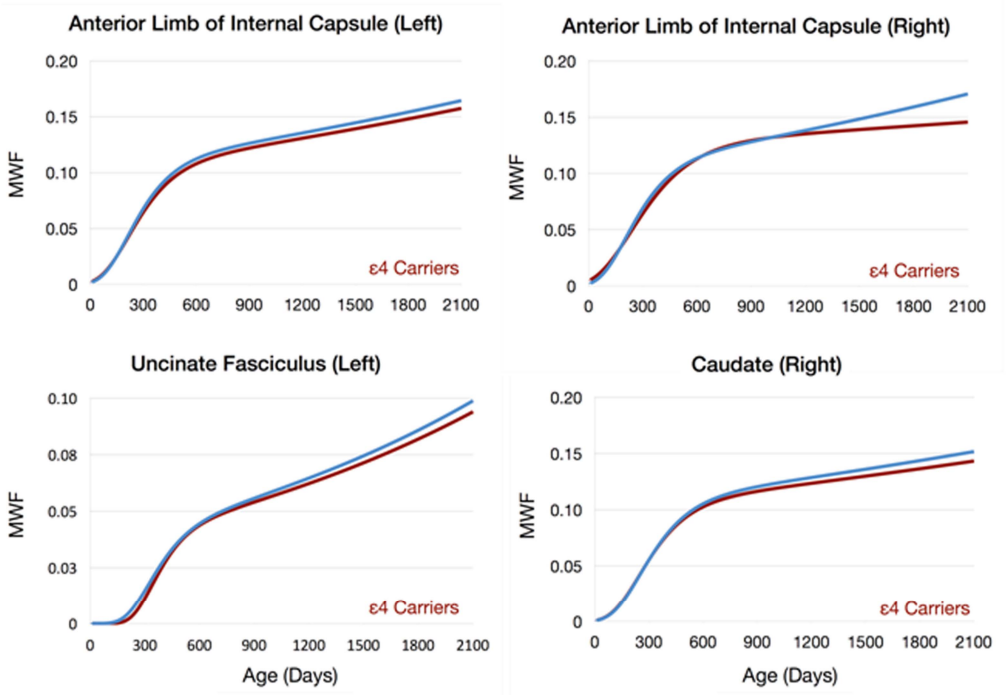
Introduction: Despite numerous investigations into the origin and etiology of neurodevelopmental and neurological disorders, significant information on the earliest manifestations of the brain differences in these diseases are still unclear. The apolipoprotein (APOE) ε4 allele has been implicated as a risk factor for numerous neurological disorders, the most prolific being the development and progression of late onset AD[1-3]. We have previously shown in a cross-sectional study that infants with at least one copy of the APOE ε4 allele (ε4 carriers) display both local gray matter volume variations along with differential white matter development at as early as 2 months of age[4]. These prior results cast important new light on the early developmental influences of the APOE ε4 allele, but longitudinal analysis is essential to consider individual differences, causative relationships between APOE genotype and neurodevelopment, and substantiate cross sectional results.

Purpose: In this work, we performed the first longitudinal analysis of differential brain development in healthy, infants and young children (2 months to 5.7 years of age) stratified by APOE genotype. Using mixed effects modeling, we examined white matter (WM) maturation profiles, and cognitive ability trends, in ε4 carriers and non-carriers. We show that both myelin development and cognition differ in children over the first five years of life with respect to APOE genotype.

Materials/Methods: Longitudinal mcDESPOT data was successfully obtained from 223 infants (total of 403 imaging datasets) grouped according to APOE genotype. Subjects recruited were between the ages of 3 months to 5.5 years and all data was acquired on a Siemens Tim Trio scanner during non-sedated sleep or while watching a movie. McDESPOT 3 pool post processing was used to calculate quantitative myelin water fraction (MWF) maps, which were subsequently aligned to a study-specific template using a longitudinal image registration protocol. Initial analysis consisted of generating mixed effects models of MWF development based on regions previously shown to exhibit cross sectional differences[3,5]. Next, we investigated differential neurodevelopment in specific white matter tracts associated with Alzhemeir's Disease pathophysiology[6]. Relationships between APOE genotype and cognition (data obtained from Mullens Scales for Early Learning scores) were also considered through linear mixed effects modeling and group comparisons.

Results: Our sample comprised 74 APOE ε4 carriers and 149 noncarriers. Myelin growth curves for carriers showed developmental difference in the anterior limb of the left internal capsule ($p << 0.001$), anterior limb of the right internal capsule (right) ($p = 0.02$), left external capsule ($p = 0.05$), left uncinate fasciculus ($p = 0.05$), right caudate ($p = 0.049$). Group cognitive differences were observed between ε4 carriers and noncarriers as well with respect to early learning composite (ELC), a surrogate measure of IQ ($p = 0.019$) and nonverbal developmental quotient (NVDQ) ($p << 0.001$).

Discussion: The longitudinal findings presented here align with, and confirm, prior cross sectional results with respect to the internal capsule providing further evidence of early differential brain development. Results from this study differ from prior analysis in that differential longitudinal white matter maturation was not observed in the splenium of the corpus callossum, cingulum, or the temporal lobe. The reasons for these discrepancies are unclear, but our results suggest that the APOE genotype impacts longitudinal myelin development. Variation in ELC and NVDQ between ε4 carriers and noncarriers is of interest because these values are overall measures of cognition and are both age independent, indicating that APOE genotype may be associated with differential overall cognitive ability.



Conclusions: In this study we have sought to identify differential longitudinal myelin development between ε4 carriers and noncarriers in white matter tracts that have shown differential development cross sectionally. We have shown that trajectories of myelin growth are significantly different between ε4 carriers and noncarriers over the first 5.7 years of life and ε4 carriers show lower overall cognition. While the relationship between these findings and AD pathology remains unclear, APOE allelic variation plays an important role in the inherent relationships of early neurodevelopment,

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