ALZHEIMER DISEASE

Effects of the *APOE* ϵ 4 allele on brain development

The ϵ 4 allele of apolipoprotein E (*APOE** ϵ 4) confers risk for late-onset Alzheimer disease (AD), but its effects on brain structure and development might be evident from infancy, according to a new study.

Sean Deoni and co-workers used a quiet (65 dB) MRI technique that enabled brain scanning in naturally sleeping infants aged 2–25 months. Data from 59 infants (23 carrying at least one copy of *APOE** ϵ 4 and 36 noncarriers) suggested that ϵ 4 carriers have decreased cortical grey matter volume in the precuneus, posterior–middle cingulate, lateral temporal and medial occipitotemporal regions—areas affected by AD.

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“*APOE* is believed to have a role in the maintenance of lipids and cholesterol—the principal components of brain myelin—so we thought the best opportunity to examine the role of *APOE* in myelination was to scan infants, because their brains are still myelinating,” explains Deoni. White matter myelin water fraction—a measure of myelin content—estimates based on brain scans of 162 infants (60 ϵ 4 carriers and 102 noncarriers) indicated different myelin distribution between the groups, with ϵ 4 carriers showing lower posterior and greater frontal myelination than noncarriers.

The results also showed different patterns of age-dependent myelination in ϵ 4 carriers versus noncarriers: in many regions, the youngest ϵ 4 carriers showed increased myelination compared with age-matched noncarriers, but

noncarriers had ‘caught up’ by 12–16 months and had significantly more white matter myelin than did ϵ 4 carriers by 2.5 years.

White matter volume has previously been linked with improved cognitive processing, but the investigators are not yet certain what effect—if any—the *APOE** ϵ 4-associated alterations in grey matter volume, white matter distribution and myelin development have for cognitive function in early life. “Perhaps surprisingly, we found no cognitive or behavioural differences between the groups,” says Deoni. Other groups have also looked at the role of *APOE* alleles in cognitive performance, but the results remain inconclusive.

The authors acknowledge the limitations of their study, particularly its cross-sectional nature. Deoni says that the team is following a cohort of 400 infants over several years, collecting regular, consecutive brain scans together with cognitive and behavioural assessments, and will eventually link the results with genotypic data.

Even though the results are preliminary, they raise important questions about the role of *APOE* in neurodevelopment. “If the results are true, *APOE* is affecting brain structure and development right from the start,” Deoni contends. “We need to be looking at infants and children to understand what this gene is doing, why it is conferring AD risk, and—most importantly—what can be done about it.”

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