

Tract Based Spatial Statistic reveals no differences in white matter microstructural organisation between carriers and non-carriers of the ApoE ϵ 4 and ϵ 2 alleles in young healthy adolescents

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Purpose:

Alleles of the Apolipoprotein E (ApoE) gene are known to modulate the genetic risk for developing late-onset Alzheimer's disease (AD) and have been associated with hippocampal volume differences in AD. While the presence of ApoE ϵ 4 allele is a major genetic risk factor for the development of late onset AD [1-2], the possession of the ϵ 2 allele has been suggested to confer a protective effect against the disease [3-5]. However, it has not been established whether it is possible to detect the effect of these alleles already in the white matter of young adolescents. Using a large cohort of more than 500 adolescents [6], diffusion tensor imaging data was analyzed using tract based spatial statistics (TBSS) [7] to investigate group differences between carriers and non-carriers of the ϵ 4 and ϵ 2 alleles and for dose-dependent effects.

Methods:

Healthy adolescents were studied from the European multi-centre neuroimaging-genetics IMAGEN project [6]. From this study 575 subjects (mean age 14.43 ± 0.47 years) from 5 imaging centers with compatible DTI acquisition protocols and with ApoE genotype information available were selected. MR Diffusion data was acquired on 3T systems using, 32 DW directions, 4 non-DW volumes, b-value = 1300 s/mm^2 and isotropic resolution of $2.4 \times 2.4 \times 2.4$. For each subject, blood samples were collected for DNA analysis and extraction. Samples were subsequently genotyped using the Illumina Quad 610 and 660 arrays (Illumina, San Diego, CA, USA) [20]. Two ApoE single nucleotide polymorphisms, rs429358 (T, C) and rs7412 (C, T) were used to identify 3 allelic variants of ApoE (ϵ 2, ϵ 3, and ϵ 4) in order to define a subject's genotype. After diffusion MR data was corrected for motion and eddy current distortions, diffusion tensor was estimated using a non linear least square fitting procedure using ExploreDTI [8]. Data quality was assessed by automatically identifying outliers using residual maps of the tensor fitting and by visually inspecting each subject for major anatomical abnormalities (21 subjects were excluded from analysis). TBSS analysis was performed on the remaining 554 subjects comparing FA, MD, axial and radial Diffusivity across the different genotypes and correcting for the imaging center, gender and IQ. A customized template was generated from 50 randomly selected subjects.

Results:

In healthy adolescents no statistical significant differences were found in FA, MD, radial diffusivity or axial diffusivity when comparing ϵ 4 vs non- ϵ 4, ϵ 4 vs ϵ 3, ϵ 4 vs ϵ 2 and ϵ 2 vs ϵ 3 carriers. No statistical significant dose-dependent effect of ApoE ϵ 4 or ϵ 2 alleles was detected on the diffusion indices used in this study.

Discussion and Conclusions:

Contrary to previous findings suggesting an altered brain white matter integrity in healthy adults, this study found no significant differences in the microstructural organization of white matter in healthy adolescent carriers of the ApoE ϵ 4 and ApoE ϵ 2 alleles [7,8]. These results suggest that the underlying neurobiological vulnerability of white matter tracts in ApoE ϵ 4 and ϵ 2 carriers may only become apparent later in life. However, a possible limitation of this study could be a decrease statistical sensitivity due to the intrinsic larger variability of diffusion microstructural properties during adolescence compared to adulthood.

References: [1]Poirier J, *Lancet* 342, 697–699, 1993. [2]Saunders a. M *Neurology* 43, 1467–1472, 1993. [3]Lehtovirta M, *Neuroscience* 67, 65–72, 1995. [4]West HL, *Neurosci Lett* 175, 46–48, 1994. [5]Qiu C, *J Neurol Neurosurg Psychiatry* 75, 828–833, 2004. [6] Schumann G, *Mol Psychiatry* 15, 1128–39, 2010, [7] Persson J et al *Neurology* 66, 1029–1033, 2006. [8] Heise V et al. *Mol Psychiatry* 1–9, 2010. [7]Leemans A et al. *17th Proc ISMRM Hawaii, USA*, p3537, 2009 [8] SM Smith, *NeuroImage*, 31:1487-1505, 2006.