

Multi modal MRI reveals early life brain changes in human ApoE-ε4 carriers

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Introduction

The APOE gene and its protein product play a crucial role in lipid metabolism. The APOE gene APOE-ε4 allele prevalence is increased in Alzheimer's disease (AD) and several other neurodegenerative diseases. Compared to non APOE-ε4 carriers, the carriers of one APOE-ε4 allele have a 2-3 fold risk of developing AD. The effect and timeline in which APOE-ε4 influence the neurodegenerative diseases is not known, but previous studies showed significant brain differences in non affected individuals. Brain structural differences were found in as early as 50 year-old carriers. PET studies showed differences in the level of glucose metabolism in the brain even in young 20 year-old normal subjects.

Methods

In our study 52 young healthy Ashkenazi Jews (ages 20-35), underwent a battery of cognitive tests, and an MRI protocol on a 3T (GE) MRI system equipped with 8 channel array coil and parallel imaging hardware. The protocol included DTI-EPI (3 repetitions of diffusion weighted spin-echo EPI, 19 gradient directions, b value of 1000 s/mm², and an additional image with no diffusion weighting (b₀), resolution of 2.1 mm³, in 70 slices covering the whole brain). Structural T1 (whole brain 3D SPGR at 1mm³) and T2 map (calculated from fast spin echo sequence, TR=6500, with 5 repetitions at TEs of 30/60/90/120/150ms). In addition the subjects gave either blood sample or saliva sample using Oragene[®] OG-500 kit for genotyping.

DTI indices (FA, ADC, λ_1 , λ_2 , λ_3) were calculated using an in-house software. The T2 data was fitted to a mono exponential decay function to calculate the T2 value on a voxel by voxel basis. Statistical analysis was done using the SPM software (version 2, UCL, London, UK). T1 data was processed using the VBM toolbox (University of Jena, Department of Psychiatry). The T2 maps were coregistered to the T1 of each individual and then normalized according to the T1 normalization parameters. An FA atlas was created using normalized FA images based on normalization of the b0 images to the EPI-mni template. The DTI scans were then normalized according to the custom created FA atlas.

DNA was purified from the blood/saliva samples and then amplified by PCR using primers around the APOE gene. Each individual sample was sequenced to identify the APOE genotype.

Results

Out of the 52 subjects, 29 were APOE-33, 11 were APOE-34, 8 were APOE-23, 2 were APOE-24 and 2 were APOE-44.

We compared APOE-33 and APOE-23 subjects against APOE-34 using ANOVA in the SPM. All results are of $p < 0.005$ and cluster size > 20 . T1 VBM (figure 1) showed mainly significant differences in the parahippocampal gyrus, the hippocampus, primary visual cortex, and the frontal cortex (including orbitofrontal and dorsolateral prefrontal cortex) (APOE-33/APO23 $>$ APOE-34). VBA of the T2 maps (figure 2) showed significant differences in the parahippocampal gyrus and orbito-frontal gyrus. VBA analysis of the DTI (figure 3) showed mainly significant differences in the parahippocampal gyrus, the hippocampus, the globus pallidus and the orbito-frontal gyrus. For the reported areas, ADC was lower, and FA was higher in APOE-34 compared to APOE-33 and APOE-23 subjects.

Discussion

The extent of brain differences that were found in this study are known to exist in older (50 years and above) APOE4 carriers. Frontal Cortical areas are known to be affected in late stages of AD. In our study we found such changes in young ApoE4 carriers. By minimizing the genetic variance in our sample (only Ashkenazi Jews), and as a result of new and improved methodologies and the micro-structural sensitivity of DTI we showed that these differences exist from early life stages. The existence of such findings at ages just after final developmental stages of the brain raises the question if APOE4 increased risk is already determined in developmental stages.

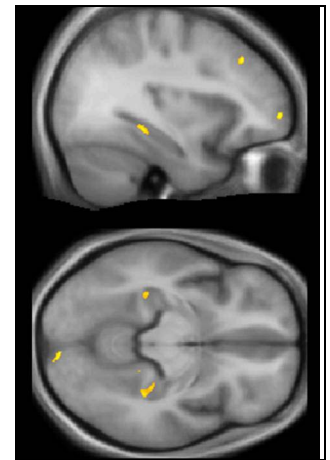


figure 1: VBM results overlaid on averaged T1

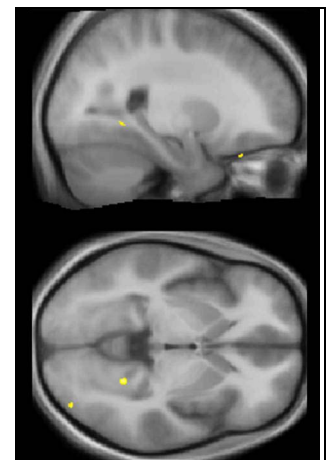


figure 2: T2 map results overlaid on averaged T1

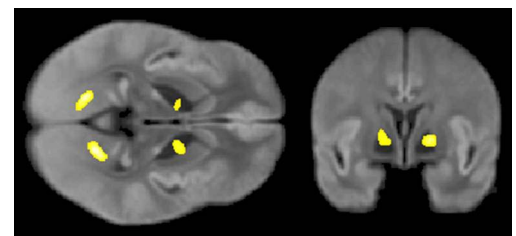


figure 3: FA results overlaid on averaged DWI