

Longitudinal imaging of the influence of ApoE isoforms on brain structure and function

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Introduction

Inheriting the apolipoprotein (Apo) E4 allele has been shown to increase the risk and accelerate memory decline in ageing and Alzheimer's disease (AD). Imaging study revealed selective anatomical and functional changes in the hippocampus of young and aged non-AD ApoE4-carriers (Honea et al, 2009). However, little is known about the underlining mechanisms leading to reduced cognitive performance and greater synaptic deficits detected. To understand the genetic influence of Apo isoforms on the brain in the ageing process, we conducted longitudinal structural and perfusion MRI on transgenic mice with human Apo E3 (hApoE3) or hApoE4 genes.

Method

The study was approved by the IACUC of Biomedical Sciences Institutes, Singapore. Female mice carrying hApoE3 (n=10) and hApoE4 (n=11) genes were scanned at 6 and 9 months old. Imaging was conducted on a 7T MRI (ClinScan, Bruker BioSpin, Germany) using 4 channel array coils. The structure image was acquired by Fast-Spin-Echo T2-weighted MRI with TR=2760ms, TE=43ms, and 100x100x300 micron resolution. Perfusion imaging was obtained by pseudo-continuous arterial spin labeling (pCASL) with labeling duration of 1600ms, series of post-labeling delays of 0, 25, 50, 75, 100, 150, 200, 250, 300 and 400ms. A spin-echo EPI and TR=4000ms, TE=20ms, and 280x280x1000 micron resolution was used for acquiring pCASL images.

FSE images were normalized to a mouse brain template (<http://lbam.med.jhmi.edu/>; Johns Hopkins University) using SPM8. The brain was segmented to separate gray matter, white matter, and CSF using a modified template based on SPMmouse (Sawiak et al., 2009) and the JHU labeled atlas. Voxel-based morphometric (VBM) analysis was done using the normalized and modulated tissue image. Cerebral blood flow (CBF) was quantified from pCASL using a general kinetic model (Boxton, et al, 1998) and the values in cortex (Cor), piriform cortex (Pir), hippocampus (Hip), thalamus (Tha), amygdala (Amg), cerebellum (Ceb) were compared.

Results

Brain segmentation shows hApoE4 mice have larger total brain and grey matter volume (Fig.1) but didn't change over time. VBM reveals specific enlarged regions, such as piriform cortex, thalamus, superior colliculus, and brain stem, with some of which continue to expand from 6 to 9 months (Fig.2). The CBF of the hApoE3 mice are generally higher than hApoE4 mice at the 6-months time point (Fig.3). Particularly, CBF in Hip was significantly higher in the hApoE3 (262 ± 14 ml/100g/min) compared to the hApoE4 (220 ± 20 ml/100g/min; $p < 0.05$, one-tail Student t-test) mice. But CBF variation at 9 months was larger and not significant. Nevertheless, hApoE3 mice still have significantly higher CBF in the thalamus and cerebellum at 9 months.

Discussion

This is the first study on longitudinal imaging of the influences of hApoE genes on brain structure and function. The hApoE4 mice showed lower CBF, suggesting decreased brain activity comparing to the hApoE3 mice. Larger gray matter volume was seen in hApoE4 mice, which may be due to a compensatory mechanism: having lower blood flow and brain activity, the hApoE4 mouse brain compensates by having more tissue.

Reference

Boxton, BB, Magn Reson Med (1998);40:383-96. Honea, RA, JAD (2009);18:553-64. Sawiak, SJ, Proc ISMRM (2009) p.1086.

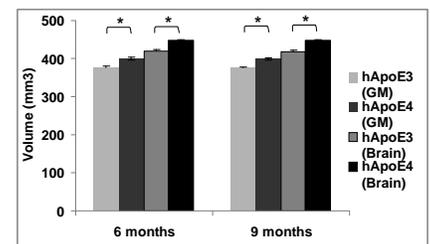


Fig. 1 Brain & gray matter (GM) volume.

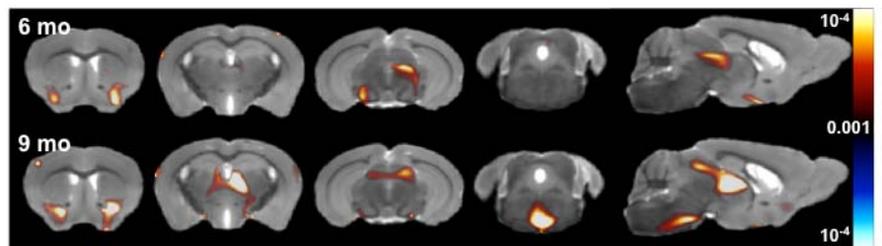


Fig.2 VBM shows increased brain tissues in hApoE4 compared to E3 ($p < 0.001$, uncorrected)

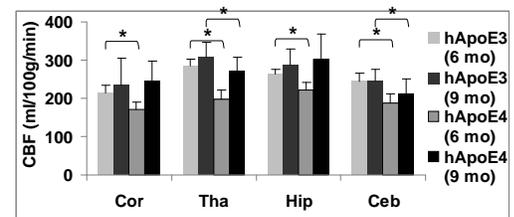


Fig.3 CBF in cortex (Cor), hippocampus (Hip), thalamus (Tha), cerebellum (Ceb).