Neural signatures of the APOE e4 genetic predisposition to Alzheimer's Disease in healthy young adults

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Introduction
A major risk factor for Alzheimer’s Disease in older adulthood is carrying one or two copies of the Apolipoprotein E e4 allele (E4). This variant is itself a significant risk factor for age-related memory deficits independent of dementia risk in populations over 50 years of age. Paradoxically our recent work has shown that young carriers of this allele outperform their APOEe3 (E3) contemporaries on cognitive tasks requiring frontal activity (e.g. decision making, verbal fluency and prospective memory) and that in addition procholinergic nicotinic stimulation is able to selectively enhance performance in E4 subjects (Marchant et al., 2010). Possible explanations for these paradoxical findings are that the E4 polymorphism confers a disadvantage from the outset which includes a compensatory overactivation which may be responsible for the observed cognitive benefits or the E4 is associated with greater neural efficiency (and hence cognitive advantages) in youth but at the cost of neural degeneration (and cognitive disadvantages) in older adulthood. Here, using behavioural and structural indices we sought evidence for neural efficiency differences in younger E3 and E4 carriers.

Methods
Subjects:
40 volunteers age 18-28, 20 E4 and 20 E3s, matched group for IQ and episodic memory performance

Behavioural task:
Verbal fluency (FAS). "Generate in 1 minute as many words as you can beginning with the letter… F/A/S"
No repeats, proper names, numbers, prefixed or suffixed words, no variations on the same word.

Structural measures:
Voxel Based Morphometry (VBM) - estimates of white and grey matter volume
Diffusion Tensor Imaging (DTI) - measures water diffusion within axons and therefore their integrity
Quantitative Magnetization Transfer (qMT) - complimentary measure to DTI

Additional imaging measures (analysis ongoing)
FMRI during prospective memory and covert attention tasks (with placebo or nicotine (1mg) nasal spray)
Resting state (functional activation in networks where no task is given)

Blood flow – ASL (measures blood perfusion within brain tissue)

Discussion and Future Directions
The behavioural differences we anticipated between young adult E4 and E3 carriers were confirmed. E4 carriers showed a small cognitive advantage on tests of executive function and flexibility.

We have observed structural differences between E4 and E3 carriers that suggest enhanced neural integrity/efficiency in young E4 adults.

Early analyses of functional imaging data points to altered processing between the two genotypes, consistent with the E4s showing distinctive patterns of neural recruitment in response to task demands.

Analyses are underway to determine how nicotine affects performance in the cognitive tasks and influences brain activation across the two ApoE genotypes.

We are currently completing collection of the same measures in a mid-aged population.

Reference:Marchant et al., 2010, Neuropsychopharm. 35, 1090-6