THE INTERACTION OF APOE GENOTYPE BY AGE IN AMNESTIC MILD COGNITIVE IMPAIRMENT: A
VOXEL-BASED MORPHOMETRIC STUDY

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Target audience: Clinician, Clinical staff, Clinical researchers or scientist, Clinical psychologists, Psychiatrist, and Cognitive psychologist.

Purpose: The apolipoprotein E (APOE) gene has been confirmed as the major genetic risk factor for late-onset Alzheimer’s disease (AD) and the conversion of amnestic mild cognitive impairment (aMCI) to AD. The interaction of APOE polymorphism by age on brain morphology is only partly understood, particularly in aMCI patients, the assumed prestage of AD. The present study was aimed at assessing whether there is a specific interaction of APOE polymorphism by the aging process on brain morphology in the aMCI patients.

Methods: The analysis of gray matter (GM) voxel-based morphometry (VBM) by T1 magnetic resonance imaging scans were performed in 85 aMCI subjects and 135 healthy controls (HC).

Results: The aMCI patients had a lower GM volume in the left cerebellum anterior and posterior lobe, hippocampus, and parahippocampal gyrus related to HC subjects (see Fig. 1). In particular, a significant interaction of APOE genotype by age on GM volume was found in the left calcarine, the left insula and the left medial frontal gyrus in the aMCI patients. In the aMCI patients, the correlations between age and GM volumes on above brain regions confirmed the well-known negative relationship for APOE ε4 carriers and the significant positive relationship for APOE ε2 carriers (except the left insula) while no correlations were found for APOE ε3/ε3 subjects (see Fig. 2A). Moreover, the reduced GM volume in the left calcarine, left medial frontal gyrus and the left insula was closely correlated with the impairment in visuo-spatial cognition, executive function and episodic memory in APOE ε4 carriers and ε2 carriers but not ε3/ε3, respectively (see Fig. 2B).

Discussion: The results further showed that aMCI patients had the deficits of GM volume on the network of cerebellum-limbic system. Interestingly, the present results suggest an APOE-specific effect of age with GM volume on the occipito-insula-frontal neural circuit. Taken together, the results suggest that GM deficits could be accelerated by the combined effect of the aging process and the presence of the APOE ε4 allele. The APOE ε4 is thought to interact with aging-related mechanisms, leading to the deposition of amyloid-β aggregates throughout the brain and disruption of neurotransmission, thus accelerating the emergence of aMCI. Conversely, the APOE ε2 possibly reflects a protective morphometric main effect, which increases with age in aMCI patients. The ε2 isoform appears to be more able to fulfill its role in the breakdown of extracellular amyloid-β peptide in the brain. The relationship of GM alterations with neuropsychological test supported that GM atrophy was the basis of cognitive impairment in aMCI patients. In addition, understanding the underlying specific function of these regions is critical for gaining new insight into the neural circuit of the conversion of aMCI to AD.

Conclusion: These results suggest that the APOE ε4 and ε2 alleles have the opposing effects on brain morphology across the spectrum of cognitive aging. Moreover, the interaction of APOE genotype with age-related changes on brain morphology may reflect the increased vulnerability of ε4-carriers to the pathology of late-life cognitive decline and the protective effect of ε2-carriers in the aMCI patients.

Fig. 1. Results from the analysis of VBM in Statistical Parametric Maps for GM volume at a threshold of P_corrected < 0.001, extent threshold = 500 mm3. (a: the left hippocampus; b: the left parahippocampal gyrus; c: the left cerebellum anterior lobe; d: the left cerebellum posterior lobe; e: the left calcarine gyrus; f: the left insula; g: the left medial frontal gyrus.)

Fig. 2. (A): Results from the analysis of interaction for APOE by age on brain morphology in aMCI patients. (B): Behavioral significance of the disrupted brain morphology in aMCI patients. (AVMT: auditory verbal memory test; ROCFT-DR: Rey-Osterrieth complex figure test-delayed recall; TMT-B: trail-making test-B; CDT: clock drawing test.)

References