Divergent episodic memory networks among APOE alleles in cognitively normal elderly

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Target audience Researchers studied on translational medicine in neuroimaging and neurodegenerative disease.

Purpose The apoliprotein E (APOE) ε4 allele is a confirmed risk factor and the ε2 allele is a protective factor for Alzheimer's disease (AD) [1-2]. Episodic memory (EM) deficit is the foremost AD symptom at predementia stage [3]. It is demonstrated that the APOE ε4 allele accelerates EM decline but the ε2 allele delays the EM loss in cognitively normal elderly cohort [4-5]. This study aimed to identify the neural basis of APOE polymorphism modulation on the EM function in cognitively normal elderly subjects, which may provide insight into the AD insidious pathogenesis at neural system level.

Methods We assessed 129 cognitively normal elderly subjects' (36 ε2 carriers, 44 ε3 homozygotes, and 49 ε4 carriers) EM function and performed resting-state functional MRI scans (Simens Verio 3.0T scanner). Seed-based approach was employed to establish the hippocampal functional connectivity (HFC) network bilaterally. Three voxelwise multivariate linear regression analyses were employed to investigate the hippocampal-related EM network characteristics across APOE allele groups. First, a within-group regression analysis between the HFC strength and the EM score investigated the EM network pattern for each APOE allele group (equation 1). Then, an across-group regression analysis examined how the EM network changed as a function of APOE allele (equation 2). In addition, another within-group regression analysis including the term of EM score and age interaction detected the aging influence on the EM network for each group (equation 3).

$$m_i = \beta_0 + \beta_1 EM + \beta_2 age + \beta_3 edu + \beta_4 gender + \beta_5 FH + \varepsilon \quad (1)$$

$$m_i = \beta_0 + \beta_1 APOE2 + \beta_2 APOE4 + \beta_3 EM + \beta_4 (APOE2 \times EM) + \beta_5 (APOE4 \times EM) + \beta_6 age + \beta_7 edu + \beta_8 gender + \beta_9 FH + \varepsilon \quad (2)$$

$$m_i = \beta_0 + \beta_1 EM + \beta_2 age + \beta_3 (age \times EM) + \beta_4 edu + \beta_5 gender + \beta_6 FH + \varepsilon \quad (3)$$

Where m_i is the HFC strength of the *i*th voxel; EM indicates the episodic memory score; $APOE2$ and $APOE4$ are the indicator variables of the APOE allele group; FH denotes the family history.

Results Each APOE allele group's bilateral hippocampal-related EM networks were identified (**Fig.1**). The discrepancy of the EM network among groups was further detected (**Figs. 2**, **3** and **4**). Specifically, for the ε3 homozygote group, its EM network was characterized in the bilateral thalamus and medial temporal lobe regions (**Figs.1 and 2**); for the ε4 carrier group, its EM network was mainly in the bilateral sensorimotor and temporoparietal regions (**Figs.1 and 3**); oppositely, the ε2 carrier group showed negative EM network (**Figs.1 and 4**). Furthermore, aging increased the regression coefficient between right HFC strength and EM score in the bilateral inferior parietal lobe, right lateral temporal lobe and left lateral prefrontal cortex, and decreased the regression coefficient in the middle cingulate cortex, for the ε4 carriers (**Fig.5**).

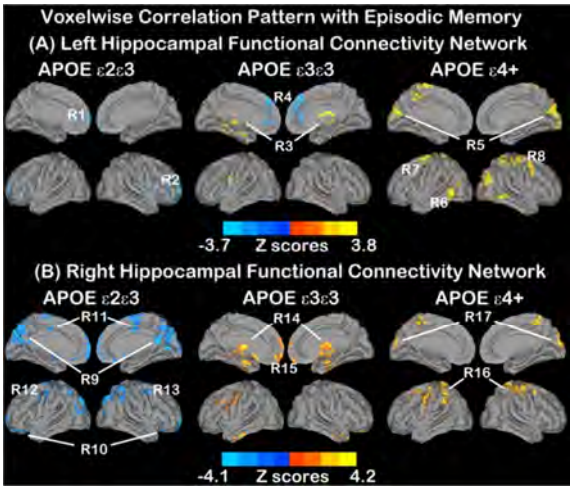

Fig 1 Voxelwise correlation pattern with EM function for left (A) and right (B) HFC networks in each APOE allele group.

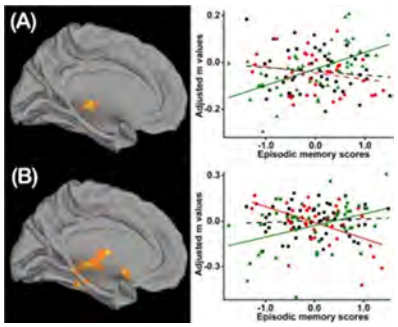

Fig 2 Discrepant left (A) and right (B) EM networks among the three APOE allele groups. For ε3 homozygotes, their bilateral HFC strengths were positively correlated with EM function in the bilateral thalamus.

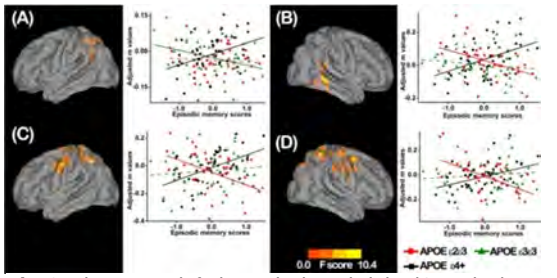

Fig 3 Discrepant left (A and B) and right (C and D) EM networks among the three APOE allele groups. For ε4 carriers, their HFC strengths in the temporoparietal and sensorimotor regions were positively correlated with EM function.

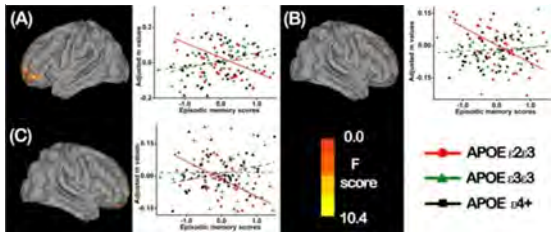

Fig 4 Discrepant left (A and B) and right (C) EM networks among the three APOE allele groups. For ε2 carriers, their bilateral HFC strengths were negatively correlated with EM function in the bilateral frontopolar cortex.

Discussion and Conclusion This study demonstrates the divergence of hippocampal-related EM networks among the three APOE alleles in cognitively normal elderly cohort. Deviating from the ε3 homozygotes' EM network as the established brain EM system, ε4 carriers' EM network was distributed in neocortices extraneous to EM function typically, while ε2 carriers exhibited a negative EM network oppositely. These findings reveal the neural degeneracy for EM function over APOE alleles, which may contribute to the APOE polymorphism effects on brain activation and associated with their different AD risks. Additionally, it indicates that analysis combining intrinsic HFC network and EM performance may provide a potential tool in uncovering the APOE imaging endophenotype.

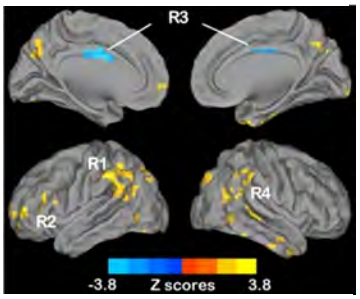

Fig 5 Aging effects on the right EM network in APOE ε4 carriers.

Reference 1. Corder EH et al. Science 1993, 261:921-3. 2. Corder EH et al. Nat Genet 1994, 7:180-4. 3. Dubois B et al. Lancet Neurol 2010, 9:1118-27. 4. Caselli RJ et al. N Engl J Med 2009, 361:255-63. 5. Wilson R et al. J Neurol Neurosurg Psychiatry 2002, 73:672-7.