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Promoter haplotypes of interleukin-10 gene linked to cortex plasticity in subjects with risk of Alzheimer's disease

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ABSTRACT

The Alzheimer's disease (AD) aetiologic event is associated with brain inflammatory processes. In this study, we consider a haplotype of the IL-10 gene promoter region, − 1082A/ − 819 T/ − 592A (*ATA haplotype*), which is an additive and independent genetic risk factor for AD. Episodic memory change is the most striking cognitive alteration in AD. It remains unclear whether episodic memory networks can be affected by the *ATA haplotype* variant in amnestic mild cognitive impairment (aMCI), and if so, how this occurs. Thirty-nine aMCI patients and 30 healthy controls underwent resting-state functional magnetic resonance imaging. An imaging genetics approach was then utilized to investigate disease-related differences in episodic memory networks between the groups based on *ATA haplotype*-by-aMCI interactions. Gene-brain-behaviour relationships were then further examined. This study found that the *ATA haplotype* risk variant was associated with abnormal functional communications in the hippocampus-frontoparietal cortices, especially in the left hippocampal network. Moreover, these *ATA haplotype* carriers showed a distinct phase of hyperactivity in normal aging, with rapid declines of brain function in aMCI subjects when compared to non-*ATA haplotype* carriers. These findings added to the accumulating evidence that promoter haplotypes of IL-10 may be important modulators of the development of aMCI.

1. Introduction

Alzheimer's disease (AD) is characterized by progressive synapse and neuronal loss, formation of extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) (Mawuenyega et al., 2010). Amnestic mild cognitive impairment (aMCI) is an intermediate state between normal cognitive aging and dementia, which is markedly more frequent than the expected 1–2% annual incidence of AD (Petersen et al., 2009). Intense focus has been directed towards studying the genetic causes of these neuropathologic features. Knowledge of the implicated pathways could potentially lead to the development of novel treatments for the AD spectrum (Giri et al., 2016).

The brain inflammatory processes coordinated by the cerebral innate immune system are accepted as an AD aetiologic event (Wyss-Coray and Mucke, 2002). Pro-inflammatory and anti-inflammatory cytokines both play a crucial role in Aβ plaques in the brains of patients suffering from AD (Guillot-Sestier et al., 2015a). Mounting evidence has supported the notion that interleukin 1 (IL-1) is the most important pro-inflammatory cytokine contributing to an increased incidence of AD and that weak expression of anti-inflammatory cytokines (i.e., IL-10 genes) are likely to cause patients to be more prone to AD (McGeer and McGeer, 1998; Lio et al., 2003). AD animal model research has further revealed that reactive glia-neighbouring Aβ plaques are associated with elevated IL-10 signaling (Apelt and Schliebs, 2001). IL-10 is polymorphic, and its expression is correlated to allelic variants of single nucleotide polymorphisms (SNPs) in the promoter region (− 1082G/A, − 819C/T, − 592C/A). Polymorphisms in the promoter region of IL-10 have been linked to increased risk of AD (Vural et al., 2009; Guillot-Sestier et al., 2015b; Mun et al., 2016). In particular, − 1082A/ − 819 T/ − 592A mutations (*ATA haplotype*) are associated with low production of IL-10, which is considered to be an additive and independent genetic risk factor for AD (Lio et al., 2003).

Episodic memory change is the most striking cognitive alteration in AD (Tromp et al., 2015), and it provides a highly reliable and sensitive index for Aβ-related cognitive decline (Lim et al., 2015). Interestingly, previous observations suggested a possible link between elevated inflammatory molecules and memory dysfunction (Barrientos et al., 2002; Hein et al., 2007). Although how elevated inflammatory processes impair memory is largely unknown, a potential mechanism has been suggested by the fact that pharmacological elevation of prostaglandin levels (a class of lipid mediators which can have inflammatory actions) is sufficient to impair hippocampal-dependent

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memory processes (Hein and O'Banion, 2009). On a macro level, memory processes are subserved by a set of distributed neural networks. Functional magnetic resonance imaging (fMRI) has the potential to detect subtle functional abnormalities in these brain networks, which support complex episodic memory processes that become progressively impaired over the course of AD progression (Sperling et al., 2010). Recent studies have suggested that episodic memory networks demonstrate markedly abnormal responses during memory tasks (Golby et al., 2005; Hämäläinen et al., 2007) and during the resting state (Liu et al., 2015; Cai et al., 2017) in clinical AD patients as well as in subjects at risk for AD (e.g., aMCI patients). Intriguingly, early manifestations of episodic memory dysfunction in prodromal phases of AD may include paradoxical evidence of increased neural activity along with loss of function (Sperling et al., 2010). Increasing attention is being paid to MRI detection of structural brain changes associated with inflammation biomarkers, measured in cognitively challenged older adults and individuals with AD (Frodl and Amico, 2014). In the aging brain, a combination of chemokine cytokines (IL-1β, sIL-4R, IL-6, IL-8, IL-10, IL-12, TNF-α) may contribute to inflammatory processes associated with cortical atrophy (Baune et al., 2009). Homozygotes for the IL-1β-511T allele and carriers of the C-reactive protein-286T allele, which are associated with increased inflammatory responses, had larger white matter hyperintensities (Raz et al., 2012). Moreover, the combination of serum markers for inflammation (such as plasma cytokines and chemokines) and MRI automated imaging analysis have provided an improvement in prediction of conversion from MCI to AD (AUC 0.78) (Furney et al., 2011). However, it remains unclear whether and how the integrity of the hippocampal memory system is affected by inflammatory factors in aMCI subjects.

Thus, the development of AD is associated with an inflammatory genotype, and the genetic control resulting in low anti-inflammation factors might play a harmful role in AD development. In this study, we have evaluated the role of the *ATA haplotype* of the IL-10 promoter, which involves three SNPs at − 1082 (rs1800896), − 819 (rs1800871) and − 592 (rs1800872), on episodic memory function in aMCI subjects and controls. We hypothesized that this *ATA haplotype* variant may be associated with more severe functional abnormalities in episodic memory networks in aMCI.

2. Materials and methods

2.1. Subjects

The present study recruited 39 aMCI subjects and 30 healthy controls. The Research Ethics Committee of the Affiliated Zhong-Da Hospital of Southeast University approved the experimental protocols, and informed consent was obtained from all subjects. aMCI diagnoses were made following the recommendations of Petersen et al. (1999) and others (Winblad et al., 2004), including (i) subjective memory impairment corroborated by subject and an informant; (ii) objective memory performances documented by an Auditory Verbal Learning Test (AVLT)-delayed recall score less than or equal to 1.5 SD of age- and education-adjusted norms (cut-off of ≤ 4 correct responses on 12 items for ≥ 8 years of education); (iii) Mini mental state exam (MMSE) score of 24 or higher; (iv) Clinical dementia rating (CDR) of 0.5; (v) no or minimal impairment in activities of daily living; (vi) absence of dementia, or not sufficient to meet the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's Criteria. In addition, controls were required to have a CDR of 0, an MMSE score ≥ 26, and an AVLT-delayed recall score > 4 for those with 8 or more years of education. Participants (aMCI and controls) were excluded from the study if they had a history of known stroke, alcoholism, head injury, Parkinson's disease, epilepsy, major depression or other neurological or psychiatric illness, major medical illness, severe visual or hearing loss. These subjects were recruited through normal community health screening and newspaper advertisement and had no medication history of intelligence-modulating drugs.

2.2. Neuropsychological evaluation

Cognitive functioning was evaluated using MMSE, and the degree of dementia was determined using CDR. In addition, a neuropsychological battery that consisted of AVLT-delayed recall, Rey-Osterrieth complex figure test-delayed recall, digit span test, symbol digit modalities test, trail-making test-A and B, and clock-drawing test was used to evaluate the function of episodic memory, attention, psychomotor speed, executive function and visuospatial skills respectively.

2.3. Typing of IL-10 haplotypes

DNA samples were obtained from 69 subjects (39 aMCI subjects and 30 healthy controls). For IL-10 gene analysis, three different bi-allelic polymorphisms at − 1082 (G → A), − 819 (C → T) and − 592 (C → A) nucleotides were processed and analysed by MassARRAY TYPER 4.0 software (Sequenom). The *ATA haplotype* (− 1082A/− 819 T/− 592A) was previously described (Lio et al., 2003; Scassellati et al., 2004). Hardy-Weinberg equilibrium was checked with the χ^2-test. The allele frequencies for − 1082 (rs1800896), − 819 (rs1800871) and − 592 (rs1800872) in the participant cohort did not deviate from the Hardy–Weinberg equilibrium. Subjects were genotyped for IL-10 (aMCI: without *ATA haplotype* = 18, with *ATA haplotype* = 21; controls: without *ATA haplotype* = 18, with *ATA haplotype* = 12).

2.4. Magnetic resonance imaging procedures

The subjects were scanned using a General Electric 1.5 Tesla scanner (General Electric Medical Systems, USA) with a homogeneous birdcage head coil. Subjects lay supine with the head snugly fixed by a belt and foam pads to minimize head motion. To rule out major white matter changes, cerebral infarction or other lesions, conventional axial Fast Relaxation Fast Spin Echo sequence T2 weighted anatomic MR images were obtained with the following parameters: repetition time (TR) = 3500 ms; echo time (TE) = 103 ms; flip angle (FA) = 90°; acquisition matrix = 320 × 192; field-of-view (FOV) = 240 mm × 240 mm; thickness = 6.0 mm; gap = 0 mm; number of excitations (NEX) = 2.0. High-resolution T1-weighted axial images covering the whole brain were acquired using a 3D spoiled gradient echo sequence using the following parameters: TR = 9.9 ms; TE = 2.1 ms; FA = 15°; acquisition matrix = 256 × 192; FOV = 240 mm × 240 mm; thickness = 2.0 mm; gap = 0 mm. The functional scans (T2* weighted images) involved the acquisition of 30 contiguous axial slices using a GRE-EPI pulse sequence with the following parameters: TR = 3000 ms; TE = 40 ms; FA = 90°; acquisition matrix = 64 × 64; FOV = 240 × 240 mm; thickness = 4.0 mm; gap = 0 mm and 3.75 × 3.75 mm^2 in-plane resolution parallel to the anterior commissure–posterior commissure line. This acquisition sequence generated 142 volumes in 7 min and 6 s. All subjects kept their eyes closed during scanning. T2-weighted structural MRI images were reviewed for the presence of major white matter changes, cerebral infarction or other lesions by an experienced neuroradiologist.

2.5. Data preprocessing

Data analyses of groups were conducted with SPM5 (http://www.fil.ion.ucl.ac.uk/spm). The first eight volumes of the scanning session were discarded to allow for T1 equilibration effects. The remaining images were corrected for timing differences and motion effects. Participants with head motion of > 3 mm maximum displacement along any axis, or 3° of any type of angular motion were excluded. The resulting images were spatially normalized into the SPM5 Montreal Neurological Institute echo-planar imaging template using default settings and resampling to 3 × 3 × 3 mm^3 voxels. The normalized images