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KIBRA gene variants are associated with synchronization within the default-mode and executive control networks

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ABSTRACT

Genetic variation at the KIBRA rs17070145 polymorphism has been linked to episodic memory, executive function, and Alzheimer's disease (AD), which are related to the structural and functional integrity of the default-mode network (DMN) and executive control network (ECN). We hypothesize that the KIBRA polymorphism could modulate the structure and function of the DMN and ECN in healthy young subjects, which might underlie the association between this gene and cognitive function. To test our hypothesis, we analyzed the resting-state synchronization in the DMN and ECN in 288 young, healthy Chinese Han subjects. We found that carriers of the KIBRA C-allele demonstrated an increased synchronization in the posterior cingulate cortex (PCC) and medial prefrontal cortex (MPFC) of the DMN and in the right anterior insula, bilateral caudate nuclei, and bilateral dorsal anterior cingulate cortices (dACC) of the ECN compared to individuals with a TT genotype. Moreover, KIBRA C-allele carriers also showed a smaller gray matter volume (GMV) in the MPFC and bilateral dACCs than TT individuals. In contrast, there were no significant genotype differences in the synchronization of either the visual network or the sensorimotor network. These findings suggest that the polymorphism in the KIBRA gene affects GMV and the function of the DMN and ECN. This increased synchronization is likely a reflection of compensation for the regional gray matter deficits in these networks in young healthy subjects. The association between KIBRA polymorphisms and the DMN and ECN should be further explored in a healthy older population and in patients with AD.

Introduction

The neural mechanisms underlying the association between the polymorphism in the KIBRA gene and cognitive function remain largely undefined. A common rs17070145 polymorphism in the KIBRA gene has been associated with episodic memory (Almeida et al., 2008; Bates et al., 2009; Kauppi et al., 2011; Papassotiropoulos et al., 2006; Preuschhof et al., 2010; Schaper et al., 2008; Vassos et al., 2010; Yasuda et al., 2010) and executive function (Wersching et al., 2011; Zhang et al., 2009a) in healthy subjects and has also been linked to the risk for late-onset Alzheimer's disease (AD) (Beecham et al., 2009; Burgess et al., 2011; Corneveaux et al., 2010; Rodriguez-Rodriguez et al., 2009). Only three studies have investigated the neural mechanisms of the polymorphism in the KIBRA gene and two of these studies focused on hippocampal activation (Kauppi et al., 2011; Papassotiropoulos et al., 2006). The present study aimed to test the hypothesis that the polymorphism in the KIBRA gene specifically affects cognitive-related functional networks.

The association between the polymorphism in the KIBRA gene and episodic memory has been extensively investigated (Table S1). Most of these studies showed a beneficial effect of the T-allele on episodic memory (Almeida et al., 2008; Bates et al., 2009; Kauppi et al., 2011; Papassotiropoulos et al., 2006; Preuschhof et al., 2010; Schaper et al., 2008; Vassos et al., 2010; Yasuda et al., 2010), although non-significant (Bates et al., 2009; Burgess et al., 2011; Jacobsen et al., 2009; Need et al., 2008; Wersching et al., 2011) and deleterious effects (Nacmias et al., 2008; Wagner et al., 2012) have also been demonstrated. As for executive functions (Table S2), a non-significant association has commonly been reported (Nacmias et al., 2008; Papassotiropoulos et al., 2006; Preuschhof et al., 2010; Schaper et al., 2008; Wagner et al., 2012; Zhang et al., 2009a); however, two studies found a significant association (Wersching et al., 2011; Zhang et al., 2009a). The KIBRA C-allele homozygote is frequently associated with an increased risk for AD (Burgess et al., 2011; Corneveaux et al., 2010), although negative (Hayashi et al.,

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2010) and contradictory findings (Rodriguez-Rodriguez et al., 2009) have also been reported (Table S3).

The effects of the polymorphism in the KIBRA gene on brain functions have been investigated in three functional neuroimaging studies. Two functional MRI studies focused on the activation of the hippocampus during memory retrieval in healthy individuals and reported increased activation in young CC carriers (Papassotiropoulos et al., 2006) or in old T-allele carriers (Kauppi et al., 2011). A positron emission tomography (PET) study revealed lower resting-state glucose metabolism in KIBRA T-allele non-carriers relative to carriers in the posterior cingulate cortex and precuneus (PCC/Pcu) (Corneveaux et al., 2010).

It is generally accepted that a specific cognitive function is controlled by a distributed neuronal network rather than a brain region. For example, episodic memory is associated with the default-mode network (DMN) (Daselaar et al., 2004; Greicius et al., 2004; Otten and Rugg, 2001; Wagner et al., 2005; Wheeler and Buckner, 2003), whereas executive function is controlled by the executive control network (ECN) (Beckmann et al., 2005; Fox et al., 2006; Greicius et al., 2003; Roosendaal et al., 2010; Seeley et al., 2007).

The DMN is mainly composed of the PCC/Pcu, the medial prefrontal and anterior cingulate cortices (MPFC/ACC), and the bilateral inferior parietal cortices (IPC) (Buckner et al., 2008; Fox et al., 2005; Greicius et al., 2004; Raichle et al., 2001). This network is deactivated during cognitively demanding tasks and shows increased activity during resting-state and self-referential tasks (Buckner et al., 2008; Schacter et al., 2007; Spreng et al., 2009; Svoboda et al., 2006). In patients with AD, both the structural and functional deficits have been frequently reported in areas within the DMN (Greicius et al., 2004; Sorg et al., 2007; Wang et al., 2007; Zhang et al., 2009b). Even in cognitively normal participants, the ε4 allele of apolipoprotein E (APOE4), the major genetic susceptibility factor for late-onset AD, has a substantial influence on the functional characteristics of the DMN (Filippini et al., 2009). If the KIBRA polymorphism is associated with episodic memory and AD, we hypothesize that this gene may also affect the structure and function of the DMN, even in healthy young subjects. Indeed, two pieces of evidence have suggested that the functional characteristics of the DMN are affected by the polymorphism in the KIBRA gene. One study of healthy young subjects reported that CC-carriers showed increased activation in the MPFC during an associative episodic memory task compared with T-allele (TT + CT) carriers (Papassotiropoulos et al., 2006). In cognitively normal, late-middle-aged individuals, KIBRA CC-carriers exhibited lower glucose metabolism in the PCC/Pcu, compared to T-allele carriers (Corneveaux et al., 2010). However, it remains unclear how the polymorphism of the KIBRA gene modulates the resting-state synchronization of the DMN and how the structural and functional characteristics of the DMN affect each other. Moreover, the effect of the polymorphism of the KIBRA gene on the ECN has never been investigated.

Here, we used a multimodal neuroimaging approach to investigate the structural and functional characteristics of the DMN and ECN in 121 KIBRA C-allele carriers and 167 KIBRA TT-individuals, with ages ranging from 20 to 33 years old. Our first aim was to test the differences in synchronization within the DMN and ECN between the two genotype groups using resting-state functional MRI. Then, we further investigated whether the gray matter volumes (GMV) of the DMN and ECN regions with significant differences in synchronization differed between the two genotype groups.

Materials and methods

Subjects

A total of 288 healthy, young, right-handed subjects (mean age: 22.7 ± 2.5 years; 133 males) were selected from 323 subjects who participated in this study after giving written informed consent, in accordance with the local Medical Research Ethics Committee of Tianjin Medical University. Thirty-five subjects were excluded from further analysis due to a lack of genetic data or excessive head movement during the fMRI examinations. Careful screening was performed to ensure that all participants were free of any lifetime history of psychiatric or neurological illness, psychiatric treatment, or drug or alcohol abuse, and MR contraindications. To avoid population stratification artifacts, only Chinese Han subjects were included. Memory function was assessed by the Chinese Revised Wechsler Memory Scale (WMS-RC) (Gong, 1989) and executive function was assessed by the Wisconsin Card Sorting Test (WCST) (Heaton, 1999). In addition, 9 subjects were excluded from the analysis of the WMS-RC and one was excluded from the analysis of the WCST due to the lack of behavioral data.

Genotyping

We extracted genomic DNA from 3000 μL of whole blood using the EZgeneTM Blood gDNA Miniprep Kit (Biomiga Inc., San Diego, CA, USA). Then, we genotyped the KIBRA rs17070145 in each subject using the PCR and ligation detection reaction (LDR) method (Thomas et al., 2004; Yi et al., 2009) with technical support from the Shanghai Biowing Applied Biotechnology Company.

The PCR primer sequences were as follows: forward: 5′ CACTG GGGACCCACATTTAC 3′, reverse 5′ CACAATGAACAAGGCTGTGG 3′. PCR was carried out in 20 μL volume containing 1 μL genomic DNA, 0.4 μL primer mixture, 2 μL dNTPs, 0.6 μL Mg^{2+}, 2 μL buffer, 4 μL Q-Solution, and 0.3 μL Taq DNA polymerase. The amplification protocol consisted of an initial denaturation and enzyme activation phase at 95 °C for 15 min followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 59 °C for 1 min and 30 s, extension at 72 °C for 1 min, and then a final extension at 72 °C for 7 min. PCR products were verified in 3% agarose gels that had been stained with ethidium bromide to regulate the amount of DNA added to the LDR.

Three probes were designed for the LDR reactions, including one common probe (rs17070145_modify: P-AGGTCCAGGATCAAGGAGCA GCTGGTTTTTTTTTTTTTTT-FAM) and two discriminating probes for the two alleles (rs17070145_C: TTTTTTTTTTTTTTTTAAAAGGAAAGC TCAGGAACAGTTG; rs17070145_T: TTTTTTTTTTTTTTTTTTAAAAGGAA AGCTCAGGAACAGTTA). These reactions were carried out in a 10 μL mixture containing 1 μL buffer, 1 μL probe mix, 0.05 μL Taq DNA ligase, 1 μL PCR product, and 6.95 μL deionized water. The reaction program consisted of an initial heating at 95 °C for 2 min followed by 35 cycles of 30 s at 94 °C and 2 min at 50 °C. Reactions were stopped by chilling the tubes in an ethanol–dry ice bath and adding 0.5 mL of 0.5 mM EDTA. Aliquots of 1 μL of the reaction products were mixed with 1 μL of loading buffer (83% formamide, 8.3 mM EDTA and 0.17% blue dextran) and 1 μL ABI GS-500 Rox-Fluorescent molecular weight marker, denatured at 95 °C for 2 min, and chilled rapidly on ice prior to being loaded on an 5 M urea–5% polyacrylamide gel and electrophoresed on an ABI 3100 DNA sequencer at 3000 V. Finally fluorescent ligation products were analyzed and quantified using the ABI GeneMapper software.

Image acquisition

MR images were acquired using a Signa HDx 3.0 Tesla MR scanner (General Electric, Milwaukee, WI, USA). Tight but comfortable foam padding was used to minimize head movement, and earplugs were used to reduce scanner noise. Resting-state fMRI data were obtained using Gradient-Echo Single-Shot Echo-Planar Imaging sequence (GRE-SS-EPI) with the following imaging parameters: repetition time (TR)/echo time (TE) = 2000/30 ms; field of view (FOV) = 240 mm × 240 mm; matrix = 64 × 64; flip angle (FA) = 90°; slice thickness = 4 mm; no gap; 40 transversal slices; and 180 volumes. During the fMRI scans, all subjects were instructed to keep their eyes closed, to stay as still as possible, to think of nothing in particular, and to not fall asleep. Sagittal 3D T1-weighted images were