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Association between the common functional *FKBP5* variant (rs1360780) and brain structure in a non-clinical population

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ABSTRACT

FK506 binding protein 5 (FKBP5) is induced by stress and regulates glucocorticoid receptor sensitivity. The T allele of the single nucleotide polymorphism (SNP) *FKBP5* rs1360780 (C/T) is associated with an increased risk of post-traumatic stress disorder (PTSD) and reduced hippocampal volume in traumatized or depressed subjects. To examine whether this SNP affects brain structures that regulate stress response, we obtained magnetic resonance imaging data of the brain in 162 healthy subjects using a 1.5 T system. Gray matter volumes and diffusion tensor imaging data were compared between individuals with and without the T allele, using optimized voxel-based morphometry. We found that the dorsal anterior cingulate cortex (dACC) volume was smaller in T carriers than in non-T carriers ($P < 0.001$). T carriers also showed significantly higher mean diffusivity values in the dACC and posterior cingulate cortex (PCC) compared with non-T carriers ($P < 0.001$). Our results suggest that carrying the T allele of *FKBP5* rs1360780 is associated with smaller gray matter volumes in the dACC and altered white matter integrity in the dACC and PCC in the non-clinical population, which might constitute the structural basis of stress-related psychiatric disorders including PTSD.

1. Introduction

Accumulating evidence suggests that FK506 binding protein 5 (FKBP5) plays a key role in the stress response and the development of stress-related psychiatric diseases such as post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). FKBP5 is a glucocorticoid receptor (GR)-regulating molecule, a co-chaperone of heat shock protein 90, and binds to GRs in the cytosol, decreasing GR ligand affinity and nuclear translocation (Binder, 2009). To our knowledge, rs1360780 is the only common single nucleotide polymorphism (SNP) that has been demonstrated to have effects on *FKBP5* function. This SNP is associated with FKBP5 protein expression levels in lymphocytes; that is, the minor T allele is associated with higher FKBP5 induction by cortisol compared with the C allele (Binder et al., 2004). The sequence containing the T allele of rs1360780 forms a putative TATA box and exhibits stronger binding to the TATA box binding protein when compared with the C allele. This single base substitution enhances *FKBP5* mRNA transcription by altering chromatin interaction between the *FKBP5* transcription start site and long-range enhancer (Klengel et al., 2013).

FKBP5 rs1360780 is associated with peri-traumatic dissociation, a well-established risk factor for the development of PTSD, and the T allele has been identified as a risk allele (Koenen et al., 2005). This SNP significantly interacts with the severity of child abuse to predict the level of PTSD symptoms in adults (Binder et al., 2008). Exposure to early trauma significantly increases the risk of PTSD in T carriers, but not in non-T carriers (Klengel et al., 2013). The interaction between childhood trauma and rs1360780 influences suicidal behavior (Roy et al., 2010), and in adults exposed to childhood physical abuse, homozygotes for the T allele show more severe depressive symptoms than C allele homozygotes or heterozygotes (Appel et al., 2011). In T allele homozygotes, trauma exposure during childhood and adolescence is a risk factor for developing subsequent depression (Zimmermann et al., 2011). In patients with MDD, the T allele is more frequent among those with

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a comorbidity of anxiety disorders than those without (Minelli et al., 2013). In a non-clinical population, enhanced-suppressors in HPA reactivity were significantly more common in T carriers than in non-T carriers (Fujii et al., 2014). In a non-clinical aged (>50 years) population, we also found a lower cortisol response to the dexamethasone/corticotropin-releasing hormone (DEX/CRH) test in T carriers compared with non-T carriers (Fujii et al., 2014). These results could represent an endophenotype for PTSD (Fujii et al., 2014). In general, patients with PTSD tend to show hypocortisolism in the hypothalamic-pituitary-adrenal (HPA) axis (Grossman et al., 2003; Yehuda, 2001).

Accumulating evidence from magnetic resonance imaging (MRI) studies suggests that *FKBP5* rs136780 contributes to abnormalities in the function or volume of specific brain regions (Fani et al., 2013a, 2013b; Pagliaccio et al., 2014; Zobel et al., 2010). In a sample of 110 German Caucasian patients with recurrent unipolar depression, non-T carriers showed a smaller mean volume of the right hippocampus than T carriers (Zobel et al., 2010). In a sample of 36 traumatized African-American women, global and local shape analysis revealed morphological differences in the hippocampus between T carriers and non-T carriers (Fani et al., 2013a). The T allele was also associated with decrements in the microarchitecture of the left posterior cingulum with diffusion tensor imaging (DTI) in a further larger sample of 82 traumatized African-American women (Fani et al., 2013b). In 120 children with depression (58 females; 57.5% European-American, 30.0% African-American, and 12.5% of other/mixed race), the T allele was suggested to be one of the risk factors for amygdala and hippocampal volume reductions (Pagliaccio et al., 2014). However, there has not been a similar study in a non-clinical population or in Asian subjects. It is important to examine non-clinical subjects to see whether brain differences observed between genotypes are the result of an endophenotype causing a vulnerability to psychiatric disorders, or an effect of such disorders. In a non-clinical population, one can investigate the association of rs1360780 without any confounding effects of medication. It is also important to determine whether *FKBP5* rs1360780 is associated with brain structures regardless of ethnic differences (i.e., different genetic backgrounds).

The aim of the present study was to examine the possible association between *FKBP5* rs1360780 and brain morphological differences in a Japanese non-clinical population. We hypothesized that individuals carrying the risk allele (T) would show structural brain differences (i.e., endophenotype) seen in stress-related psychiatric disorders such as PTSD. Given the abovementioned evidence, we expected T carriers to show smaller gray matter volumes of the hippocampus/amygdala and decrements in the microarchitecture of the posterior cingulum than non-T carriers. In view of PTSD vulnerability, we predicted that the T carriers would have smaller gray matter volumes in the anterior cingulate cortex, ventromedial prefrontal cortex, left temporal pole/middle temporal gyrus, or left hippocampus, consistently identified as brain regions of gray matter reduction in PTSD patients compared with individuals exposed to trauma without PTSD in a recent quantitative whole-brain meta-analysis (Kuhn and Gallinat, 2013).

2. Methods

2.1. Subjects

Non-clinical volunteers were recruited from the community through local magazine advertisements and an announcement on our website. Subjects were 162 Japanese volunteers who had no current or past history of psychiatric disorders. Among them, only 52 subjects overlapped in the present MRI study and the previous DEX/CRH test study groups (Fujii et al., 2014). All subjects were biologically unrelated. All participants were screened using the Japanese version of the Mini International Neuropsychiatric Interview (M.I.N.I.) (Otsubo et al., 2005; Sheehan et al., 1998) and unstructured interviews by a research psychiatrist. Individuals who had a prior medical history of central nervous system disease, substance abuse/dependence, severe head injury, dementia, or intellectual disability were not enrolled in the study. Mean age, years in education, and gender distribution of the subjects are shown in Table 1. The study protocol was approved by the ethics committee at the National Center of Neurology and Psychiatry, Japan. After providing a description of the study, written informed consent was obtained from every subject.

2.2. Genotyping

Venous blood was drawn from subjects and genomic DNA was extracted from whole blood according to standard procedures (Fujii et al., 2011). The SNP, rs1360780, was genotyped using the TaqMan 5′ exonuclease allelic discrimination assay (Applied Biosystems, Foster City, CA; assay ID C___8852038_10). PCR thermal cycling conditions were as follows: one cycle at 95 °C for 10 min followed by 50 cycles at 92 °C for 15 s and 60 °C for 1 min. The genotyping protocol was performed according to our previous studies (Fujii et al., 2012). Genotype data were assessed blind to case–control status. Deviation of genotype distributions from the Hardy–Weinberg equilibrium (HWE) was assessed with the χ^2 test for goodness of fit.

2.3. MRI data acquisition

MRI was performed using a Magnetom Symphony 1.5 T system (Siemens, Erlangen, Germany). For the morphometric study, high spatial resolution, three-dimensional (3D) T1-weighted brain images were obtained by scanning in the sagittal plane (echo time [TE]/repetition time [TR], 2.64/1580 ms; flip angle, 15°; effective slice thickness, 1.23 mm; slab thickness, 177 mm; matrix, 208 × 256; field of view [FOV], 256 × 315 mm^2; acquisition, 1), generating 144 contiguous slices through the head. The MRI protocols were performed according to our previous studies (Ota et al., 2011, 2013b).

DTI was performed in the axial plane (TE/TR, 106/11 200 ms; FOV, 240 × 240 mm^2; matrix, 96 × 96; acquisitions, 2; slice thickness, 2.5 mm with no interslice gap), generating 75 continuous transverse slices. Diffusion was measured along 12

Table 1
Age, education years, and gender distribution of subjects for MRI.

	Total $n = 162$	Genotype groups		Statistics	P
		CC ($n = 94$)	CT/TT ($n = 68$)		
Mean age, years (SD)	47.3 (15.9)	47.3 (14.9)	47.4 (17.2)	$t(160) = -0.028$	0.98[a]
Mean education years (SD)	14.51 (2.57)	14.38 (2.35)	14.69 (2.85)	$t(160) = -0.77$	0.45[a]
Gender, female, n (%)	117 (72.2)	73 (77.7)	44 (64.7)	$\chi^2(1) = 3.30$	0.069

MRI = magnetic resonance imaging.
[a] determined using an independent samples t-test.