



The effects of 5-HTTLPR and BDNF Val66Met polymorphisms on neurostructural changes in major depressive disorder

Kyu-Man Han^a, Sunyoung Choi^b, Aram Kim^c, June Kang^c, Eunsoo Won^d, Woo-Suk Tae^e, Yong-Ku Kim^a, Min-Soo Lee^d, Byung-Joo Ham^{d,e,*}

^a Department of Psychiatry, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea

^b Department of Brain and Cognitive Engineering, Korea University, Seoul, Republic of Korea

^c Department of Biomedical Sciences, Korea University College of Medicine, Seoul, Republic of Korea

^d Department of Psychiatry, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Republic of Korea

^e Brain Convergence Research Center, Korea University Anam Hospital, Seoul, Republic of Korea

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ABSTRACT

The serotonin-transporter-linked polymorphic region (5-HTTLPR) and brain-derived neurotrophic factor (BDNF) Val66Met polymorphism have been implicated in the pathophysiology of major depressive disorder (MDD). We aimed to investigate the effects of genetic variants of the 5-HTTLPR and BDNF Val66Met polymorphisms and their interactions with MDD on cortical volume and white matter integrity. Ninety-five patients with MDD and 65 healthy participants aged 20–65 years were recruited. The subjects were genotyped for the 5-HTTLPR and BDNF Val66Met polymorphisms and scanned with T1-weighted and diffusion tensor imaging. The gray matter volumes of 24 gyri in the prefrontal and anterior cingulate cortices and the fractional anisotropy values of nine white matter tracts in both hemispheres were determined. In the pooled sample of subjects from both groups, 5-HTTLPR L-allele carriers had significantly decreased cortical volume in the right anterior midcingulate gyrus compared to S-allele homozygotes. A significant effect of the interaction of the BDNF Val66Met polymorphism and MDD on the fractional anisotropy values of the right uncinate fasciculus was observed. Our results suggested that these genetic polymorphisms play important roles in the neurostructural changes of emotion-processing regions in subjects with MDD.

1. Introduction

Major depressive disorder (MDD), which is one of the most common mental disorders, affects over 120 million people worldwide (Kessler et al., 2003; Lepine and Briley, 2011). Findings of dysfunctional synaptic monoamines, neuronal plasticity, hypothalamic-pituitary-adrenal axis, and immune systems in patients with MDD have suggested a biological etiology of MDD (aan het Rot et al., 2009; Kupfer et al., 2012). The etiology of MDD is greatly influenced by genetic predisposition (Lohoff, 2010). In particular, serotonergic neurotransmission and brain-derived neurotrophic factor (BDNF) genes are strongly associated with MDD (aan het Rot et al., 2009; Kupfer et al., 2012).

The serotonin-transporter-linked polymorphic region (5-HTTLPR), which is located in the promoter region of the serotonin transporter gene (SLC6A4), affects serotonergic neurotransmission (Kenna et al., 2012; Lesch et al., 1996). The insertion of 44 base pairs in the 5'-flanking region of the SLC6A4 gene creates a long (L) allele, while the absence of this tandem repeat results in a short (S) allele (Won and

Ham, 2016). The S allele of this single nucleotide polymorphism (SNP) is associated with decreased serotonin transporter (5-HTT) expression and serotonin reuptake and the development of MDD during stressful life events (Kenna et al., 2012). BDNF, which is a neurotrophic factor that modulates neuronal survival, growth, and differentiation, affects neuronal plasticity and long-term synaptic connectivity (Alexopoulos et al., 2010). The neurotrophic hypothesis of MDD postulates that BDNF has a critical role in the pathophysiology of MDD (Lisiecka et al., 2015). The BDNF gene, which is located on 11p13, encodes the precursor BDNF peptide, and the Val66Met polymorphism, which involves the substitution of methionine (Met) for valine (Val) in the 66th codon in the prodomain BDNF region, is associated with impaired intracellular BDNF trafficking and reduced activity-dependent BDNF cellular secretion (Carballedo et al., 2012). The Met allele of this SNP is associated with increased vulnerability to MDD during stress (Kim et al., 2007; Verhagen et al., 2010).

Multiple lines of evidence suggest that the 5-HTTLPR and BDNF Val66Met polymorphisms affect the neurostructure of emotion-

* Correspondence to: Department of Psychiatry, Korea University Anam Hospital, 73, Incheon-ro, Seongbuk-gu, Seoul 02841, Republic of Korea.
E-mail address: hambj@korea.ac.kr (B.-J. Ham).

processing networks, which might serve as intermediaries between these SNPs and MDD predisposition (Carballedo et al., 2013; Frodl et al., 2004; Won and Ham, 2016). The risk alleles of these polymorphisms are associated with decreased anterior cingulate cortex (ACC), orbitofrontal, and hippocampal volume (Carballedo et al., 2013; Frodl et al., 2007; Gerritsen et al., 2012; Ide et al., 2015; Won and Ham, 2016). The *5-HTTLPR* and *BDNF Val66Met* SNPs affect the microstructure of white matter pathways, including the uncinate fasciculus, cingulum, corpus callosum, corona radiata, and inferior longitudinal fasciculus (Alexopoulos et al., 2010; Carballedo et al., 2012; Klucken et al., 2015; Pacheco et al., 2009; Tatham et al., 2016a; Tost et al., 2013). Although these findings suggest pivotal roles of these SNPs in MDD-related neuromorphologic changes, few studies have simultaneously investigated the effects of both SNPs. A recent study found that the *5-HTTLPR* moderately affected pallidum volume in a pooled sample of patients with MDD and controls (Jaworska et al., 2016). A diffusion tensor imaging (DTI) study found associations between the *5-HTTLPR* and internal capsule integrity and between *BDNF Val66Met* and uncinate fasciculus integrity in individuals with severe depression (Tatham et al., 2016b). However, these two SNPs were not associated with neurostructural alterations in other emotion-regulation circuits, such as the ACC, prefrontal cortex (PFC), cingulum, and corpus callosum (Keedwell et al., 2012; Liao et al., 2013; Phillips et al., 2015). The lack of findings in those studies might have been due to their relatively small sample sizes (Jaworska et al., 2016; Tatham et al., 2016b). Therefore, comprehensive studies of the associations of these SNPs with neurostructure and white matter in a larger sample of patients with MDD are needed.

Thus, the aim of this study was to investigate the effects of *5-HTTLPR* and *BDNF Val66Met* SNPs and their interactions with MDD on cortical volume and white matter tract integrity in patients with MDD and healthy controls. Based on the corticolimbic circuit model of depression (Phillips et al., 2015, 2008), the regions of interest (ROIs) in this study were the ACC, PFC, corpus callosum, cingulum, uncinate fasciculus, and fornix. The white matter tract ROIs were the fiber bundles connecting the PFC with limbic regions including the hippocampus and amygdala (Carballedo et al., 2012). Our a priori hypotheses were as follows. 1) The risk allele(s) of *5-HTTLPR* and/or *BDNF Val66Met* and/or their interactions with MDD are associated with ACC and/or PFC volume reduction. 2) The risk allele(s) of *5-HTTLPR* and/or *BDNF Val66Met* and/or their interactions with MDD are associated with decreased integrity in the corpus callosum, cingulum, uncinate fasciculus, and/or fornix.

2. Methods

2.1. Participants

We recruited 95 patients with MDD from the outpatient psychiatric clinic of Korea University Anam Hospital (Seoul, Republic of Korea). Our inclusion criteria for the MDD group were adults aged 20–65 who met the criteria for MDD in the Diagnostic and Statistical Manual of Mental Disorder (DSM)-IV-TR. A board-certified psychiatrist diagnosed the patients with MDD according to the DSM-IV-TR criteria with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-1), and another psychiatrist confirmed the diagnoses. The concordance rate between the two psychiatrists for the diagnosis of MDD was greater than 95%. The durations of the MDD episode(s) in the patients were assessed by two psychiatrists with life-chart methodology. The following exclusion criteria were applied to the MDD group: (1) any other major psychiatric illnesses including substance use disorders and personality disorders within the previous six months; (2) MDD with psychotic features; (3) acute suicidal or homicidal thoughts requiring inpatient treatment; (4) history of serious or unstable medical illnesses; (5) abnormal physical examination or routine laboratory test findings; (6) primary neurological illnesses; or (7) any contraindications for

Table 1

Demographic and clinical characteristics of major depressive disorder patients and healthy controls.

	MDD (n = 95)	HC (n = 65)	p value (t or χ^2)
Age	43.14 ± 11.89	40.20 ± 13.55	0.160 (t = 1.415)
Sex (female)	76	45	0.136 (χ^2 = 2.428)
HDRS-17 score	15.00 ± 7.91	2.12 ± 2.14	< 0.001 (t = 15.076)
First episode/Recurrent	20/75		
Duration of illness (months)	45.61 ± 47.51		
<i>5-HTTLPR</i>			
SS	54	34	0.833 (χ^2 = 0.366)
LS	35	27	
LL	6	4	
HWE	0.918	0.654	
SS	54	34	0.629 (χ^2 = 0.321)
LL + LS	41	31	
<i>BDNF</i> gene Val66Met (rs6265)			
Val/Val	20	19	0.453 (χ^2 = 1.584)
Val/Met	51	33	
Met/Met	24	13	
HWE	0.461	0.846	
Val/Val	20	19	0.264 (χ^2 = 1.400)
Val/Met + Met/Met	75	46	
Drug-naïve / Antidepressant	44 / 51		
SS	23 / 31		0.416 (χ^2 = 0.698)
LL + LS	21 / 20		
Val/Val	8 / 12		0.617 (χ^2 = 0.406)
Val/Met + Met/Met	36 / 39		
Antidepressant type			
SSRI	24		
SNRI	9		
NDRI	5		
NaSSA	4		
Combination	9		

Data are mean ± standard deviation in age, HDRS-17 scores, and duration of illness.

The P values for distribution of sex, genotype of the *BDNF* Val66Met and *5-HTTLPR*, and medication difference according to the genotype were obtained by chi-square test.

The P values for comparison in age and HDRS-17 scores were obtained by independent *t*-test.

Allele frequencies (S/L): MDD patients 0.75/0.25, HC subjects 0.73/0.27.

Allele frequencies (Val/Met): MDD patients 0.48/0.52, HC subjects 0.55/0.45.

MDD, major depressive disorder; HC, healthy controls; HDRS-17, the 17-item Hamilton Depression Rating Scale; HWE, Hardy-Weinberg equilibrium; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; Combination, combinations of two or more types of antidepressants.

magnetic resonance imaging (MRI). For the control group, we recruited 65 healthy participants aged 20–65 from the community via advertisements. Two board-certified psychiatrists performed full psychiatric assessments with the SCID-1 on the healthy participants and confirmed that they had no current or previous psychiatric disorders. The same exclusion criteria for the MDD group were applied for the control group. We investigated the ethnic origins of all participants and confirmed that they were all self-identified Koreans. The severity of the depressive symptoms of the subjects in both groups were evaluated on the day of the MRI scans with the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). The details of the antidepressant treatments of the patients are listed in Table 1. The data for 88 patients and 62 healthy controls and for 78 patients and 55 healthy controls have been reported in previous genetic imaging studies on cortical volume (Han et al., 2017) and fractional anisotropy (FA) (Choi et al., 2016), respectively. The present study examined the effects of the genotype(s) and/or genotype-by-diagnosis interactions on neurostructural measurements. The previous studies investigated different genetic variants (Han et al., 2017: *FKBP5* rs1360780; Choi et al., 2016: *SLC6A15* rs1545843). The protocol of this study was approved by the Institutional Review Board of Korea University Anam Hospital. Per the

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