Gender-specific Associations of the Brain-derived Neurotrophic Factor Val66Met Polymorphism with Neurocognitive and Clinical Features in Schizophrenia

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Objective: To explore associations of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism with cognitive functioning and psychopathology in patients with schizophrenia.

Methods: We included 133 subjects meeting the DSM-IV criteria for schizophrenia who were in the post-acute stage of the disease. BDNF Val66Met genotypes were identified via polymerase chain reaction. The computerized neurocognitive function battery, Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Social and Occupational Functioning Scale (SOFAS), and the Subjective Well-being under Neuroleptic Treatment (SWN-K) were administered. Gender-stratified sub-analysis was also conducted to identify gender-specific patterns in the findings.

Results: In male patients, no significant difference in any measure by BDNF genotype was evident. In female patients, scores on the CDSS and total PANSS and all subscales were significantly higher in valine (Val) carriers. In addition, scores on the SOFAS and SWN-K were significantly lower in Val carriers. In terms of neurocognitive measures, female patients with the Val allele had significantly poorer reaction times and fewer correct responses on the Continuous Performance Test (CPT) and the Trail Making Test (Parts A and B). After adjustment of PANSS total scores and log-transformed CDSS scores, CPT outcomes were significantly poorer in female patients with than in those without the Val allele.

Conclusion: Gender-specific associations of the Val allele with poor neurocognitive function and more severe psychopathology were evident. Further studies are required to explore the mechanisms of these differences and the potential utility of the BDNF genotype as a predictor of outcome in patients with schizophrenia.

KEY WORDS: Brain-derived neurotrophic factor; Cognition; Gender; Genetic polymorphism; Schizophrenia; Val66Met.

INTRODUCTION

Neurocognitive impairment is a core feature of schizophrenia. Cognition is one of key domains of psychopathology that require dimensional assessment in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Brain-derived neurotrophic factor (BDNF) has been widely investigated in the context of the neurodevelopmental hypothesis of schizophrenia, given the role played by the factor in development and maintenance of the central nervous system. BDNF is a peptide involved in neuronal development, differentiation, and plasticity. In addition, BDNF modulates the expression levels of dopamine D3 receptors and is involved in the maturation and plasticity of the mesolimbic dopaminergic system. A functional single-nucleotide polymorphism that creates a valine (Val)-to-methionine (Met) substitution at BDNF codon 66 (Val66Met) triggers aberrant sorting and release of mature BDNF via the activity-dependent secretion pathway. The Met variant of the Val66Met polymorphism is related to impaired BDNF release. The effects of the BDNF Val66Met polymorphism on cognition have been extensively documented in healthy carriers. The Met allele has been reported to negatively affect hippocampal volume and to alter neurocognitive functioning in healthy subjects. Although the Val66Met polymorphism per se may not be associated with a major risk of schizophrenia development, increasing evidence indicates that the polymorphism modulates several clinical features of the illness, as well as neurocognitive functioning. Many previous studies have shown that the 66Met allele is asso-
associated with impairments in episodic memory, executive function, attentional processing, visuospatial ability, and cognitive flexibility in patients with schizophrenia. However, one earlier work found that the Val allele was associated with reduced memory function in patients with psychosis, but not in a healthy population.9) A recent meta-analysis found that patients with schizophrenia differing in BDNF genotype did not exhibit significant between-genotype differences in most neurocognitive domains. In addition, any correlations between peripheral BDNF levels and neurocognitive phenotypes were minimal.10)

Such inconsistent results require further evaluation. One possible explanation is that some effects of the BDNF polymorphism are gender specific; a few prior studies found that BDNF levels differed by gender.11,12) In addition, a few recent studies have identified between-gender differences in associations of BDNF levels and the Val66Met polymorphism with cognitive impairment in patients with schizophrenia.13,14) The sex hormones are well known to influence BDNF levels.15) Therefore, in the present study, we explored the association between the BDNF Val66Met polymorphism and cognitive function in patients with schizophrenia, paying particular attention to possible between-gender differences, which were explored via gender-stratified analysis.

**METHODS**

**Subjects**

Subjects meeting the criteria of the fourth edition of DSM (DSM-IV)16) for schizophrenia were enrolled. All patients were required to be symptomatically stable, as judged by their treating psychiatrists, to allow evaluation of neurocognitive functioning, and to have experienced no change in medication for a minimum of 2 weeks prior to enrollment. The key exclusion criteria were acute psychotic symptoms including severe behavioral disturbance, severe and unstable physical illnesses, and a diagnosis of mental retardation. The studies were carried out according to the latest version of the Declaration of Helsinki and were approved by the Chonnam National University Hospital Institutional Review Board. All patients gave written informed consent before participating in the study.

**Psychiatric Measures**

The sociodemographic and clinical characteristics recorded included age, gender, duration of illness, type of antipsychotic (risperidone or other) prescribed, and risperidone-equivalent dosages, which was calculated from daily defined dose.17) Psychiatric measures included the Positive and Negative Syndrome Scale (PANSS)18,19) to assess psychotic symptoms and other psychopathologies; the Social and Occupational Functioning Scale (SOFAS).20) to evaluate general functioning; the Calgary Depression Scale for Schizophrenia (CDSS)21,22) to measure depressive symptoms in patients with schizophrenia;23) and the Subjective Well-Being under Neuroleptic Treatment-short form (SWN-K)24,25) to assess quality of life in patients with schizophrenia. Higher scores of the PANSS and the CDSS represents more severe psychopathology, whereas higher scores of the SOFAS and the SWN-K represents better social functioning and quality of life, respectively.

**Neurocognitive Assessment**

A computerized battery of neurocognitive tests, standardized for the Korean population,25) was administered to all participants. The neurocognitive tests used in the study were as follows: Attention span, vigilance, and working memory were measured by forward and backward Digit Span Test. Verbal memory was assessed by the modified Rey Auditory Verbal Learning Test.26,27) Long-term delayed recall memory after 20 minutes was used as an outcome measure of verbal learning test. Executive function and cognitive flexibility were measured by numbers of categories completed on the Wisconsin Card Sorting Test.28) Sustained attention was assessed by the number of correct responses and reaction time on the Continuous Performance Test (CPT). Finally, the Trail Making Test (TMT)29) was performed; Part A of the test measures visuomotor speed and attention and Part B measures executive function and visuospatial working memory.

**Genotype**

Venous blood samples were obtained from all participants, and DNA was extracted using standard procedures. Polymerase chain reaction (PCR) and PCR-based restriction fragment length polymorphism assays were performed. Hydrolysis by the restriction enzyme BbrPI identified PCR products characteristic of the 66Val (490- and 208-bp fragments) and the 66Met (a 698-bp fragment) alleles; the genotypes were categorized as Val/Val, Val/Met, or Met/Met.

**Statistical Analysis**

Deviation from Hardy-Weinberg equilibrium was assessed using the chi-squared test. Subjects were divided into two groups by Val allele status: Val/Val and Val/Met.
vs. Met/Met. Sociodemographic and clinical variables and neurocognitive outcome measures were compared according to Val allele status and gender, respectively using the chi-squared test, the independent \( t \)-test, and the Mann-Whitney \( U \)-test, as appropriate. Variables and outcome measures were compared by Val allele status by gender using same analyses. The effects of genotype on outcome measures and their interactions with gender were assessed using general linear models. Same exploratory analysis on neurocognitive function was conducted in subjects who received risperidone monotherapy to control confounding effects of antipsychotic medication on neurocognitive function. Finally, we conducted an analysis of covariance (ANCOVA) to compare the effects of the Val allele on cognitive functioning after adjustment for variables that significantly differed by BDNF genotype. Neurocognitive function measures that were statistically significant in unadjusted analysis were used as dependent variables, with Val allele carrier as the categorical independent variable in ANCOVA. Values that were not normally distributed were entered as covariates after log transformation. All statistical tests were two tailed, and the significance level was set at \( p < 0.05 \). All analyses were performed with IBM SPSS Statistics software version 21.0 (IBM Co., Armonk, NY, USA).

**RESULTS**

**Subjects**

A total of 133 subjects, 71 females (53.4%) and 62 males (46.6%), participated in the study. The mean participant age was 33.6 years (standard deviation [SD], 8.7 years), and the median number of years of education was 14 (interquartile range [IQR], 12-16 years). The median duration of illness was 5.6 years (IQR, 2.6-10.2 years), and about 75% of all participants received risperidone monotherapy.

**Sociodemographic and Clinical Characteristics and Neurocognitive Functioning by BDNF Polymorphism**

Of all patients, 23.3% were homozygous for the Met allele, consistent with the existence of Hardy-Weinberg equilibrium \( (p > 0.05) \). No significant difference in sociodemographic characteristics by Val allele status was evident (Table 1). In terms of psychiatric measures, the total PANSS and negative symptom subscale scores were significantly higher in patients with Val allele than in those with the Met/Met genotype. The CDSS, SOFAS and SWN scores did not significantly differ by Val allele.

Performances on the TMT Part B and correct response of the CPT were significantly poorer in patients with Val allele than in those without Val allele. No sociodemographic or clinical characteristic, and no measure of neurocognitive functioning, differed by gender.

**Sociodemographic and Clinical Characteristics and Neurocognitive Functioning by Val Allele Status in Each Gender**

Table 2 compares sociodemographic and clinical characteristics and neurocognitive measures by Val allele status by gender. In males, no significant difference was observed based on Val allele status. However, in females, the CDSS and total PANSS and all subscale scores, were significantly higher in Val carriers, and the SOFAS and SWN scores significantly lower. In terms of neurocognitive measures, females with the Val allele had significantly longer response times on the CPT, TMT-Part A, and TMT-Part B and significantly fewer correct responses on the CPT compared with those without the Val allele. Significant gender×gene interactions were evident for all psychiatric scales and the two CPT outcomes (reaction time and correct response). Exploratory analysis in risperidone monotherapy group showed almost same results; females with the Val allele had longer response times on the CPT, TMT-Part A, and TMT-Part B \( (p=0.046, 0.055, \) and \( 0.026, \) respectively) and significantly fewer correct responses on the CPT \( (p=0.028) \) compared with those without the Val allele (data not shown).

Table 3 shows the results of multivariate analysis of neurocognitive measures according to Val allele status in female patients. After adjustment for the PANSS total score and the log-transformed CDSS score as covariates, the reaction time was significantly longer, and correct responses significantly fewer in females with than in those without a Val allele.

**DISCUSSION**

The principal findings of the present study were that female Val allele carriers with schizophrenia exhibited significantly more severe psychotic and depressive symptoms, poorer social functioning, and a lower quality of life than did homozygous Met/Met patients. In addition, Val allele carriers scored lower on tests of neurocognitive functioning than did others. After adjustment for psychotic and depressive symptoms, significant between-group differences remained in terms of sustained attention and measures of psychomotor speed. We observed sig-
Table 1. Sociodemographic and clinical characteristics and neurocognitive measures by BDNF genotypes

|                         | Total sample (n=133) | BDNF polymorphism | p value | Gender | p value |
|-------------------------|----------------------|-------------------|---------|--------|---------|
|                         |                      | Val carrier n=102 (76.7) | Met/Met n=31 (23.3) |       | Male n=62 (46.6) | Female n=71 (53.4) |
| **Sociodemographic and clinical characteristics** | | | | | | |
| Gender, male            | 62 (46.6)            | 45 (44.1)          | 17 (54.8) | 0.295 | NA |
| Age (yr)                | 33.6±8.7             | 33.8±8.5           | 32.7±8.5 | 0.541 | 32.9±7.9 | 34.1±9.3 | 0.419 |
| Duration of illness (yr)| 5.6 (2.6-10.2)       | 5.4 (2.5-10.8)     | 6.8 (3.0-10) | 0.888 | 5.0 (2.1-10.0) | 6.2 (3.3-12.1) | 0.080 |
| Education (yr)          | 14 (12-16)           | 14 (12-16)         | 13 (12-16) | 0.861 | 13 (12-16) | 14 (12-16) | 0.790 |
| Antipsychotics; risperidone (n) | 104 (78.2)       | 80 (78.4)          | 24 (77.4) | 0.905 | 51 (82.3) | 53 (74.6) | 0.289 |
| Dose of antipsychotics (mg/d)* | 4 (3-5)             | 4 (3-6)            | 4 (2-5) | 0.278 | 4 (3-6) | 4 (2-5) | 0.102 |
| Positive and Negative Syndrome Scale, Positive | 18.0±6.2 | 18.4±6.4 | 16.5±5.4 | 0.123 | 17.7±5.4 | 18.1±6.9 | 0.800 |
| Negative                | 20.0±6.2             | 20.6±6.2           | 18.0±5.7 | **0.045** | 20.6±6.2 | 19.4±6.2 | 0.257 |
| General                 | 39.2±10.9            | 40.2±11.5          | 35.8±7.7 | 0.052 | 39.1±9.4 | 39.2±12.1 | 0.946 |
| Total                   | 77.0±21.0            | 79.1±22.0          | 70.3±15.9 | **0.041** | 77.4±18.2 | 76.7±23.2 | 0.858 |
| Calgary Depression Scale for Schizophrenia | 4 (2-9) | 4 (2-10) | 4 (0-7) | 0.316 | 4 (1-8) | 5 (2-10) | 0.278 |
| Social and Occupational Functioning Assessment Scale | 47.5±11.1 | 46.6±11.2 | 50.4±10.2 | 0.091 | 48.4±9.7 | 46.7±12.1 | 0.364 |
| Subjective Well-being under Neuroleptics-short form | 75.1±17.8 | 74.8±16.5 | 76.4±22.2 | 0.677 | 75.8±18.6 | 74.5±17.2 | 0.671 |
| **Neurocognitive function** | | | | | | |
| Digit span test, Forward (n) | 5.3±2.2 | 6.2±1.2 | 5.9±1.4 | 0.298 | 6.2±1.4 | 6.1±1.1 | 0.477 |
| Backward (n)            | 4.8±1.4             | 4.7±1.4           | 4.8±1.6 | 0.882 | 4.9±1.4 | 4.6±1.4 | 0.208 |
| Verbal Learning Test, Delayed recall (n) | 8.4±3.8 | 8.3±3.6 | 8.7±4.6 | 0.641 | 7.8±4.0 | 8.3±3.6 | 0.113 |
| Wisconsin Card Sorting Test, Category completed (n) | 3.5±2.1 | 3.4±2.1 | 3.6±2.4 | 0.608 | 3.4±2.2 | 3.5±2.0 | 0.732 |
| Continuous Performance Test, Reaction time (msec) | 637.4±59.1 | 642.2±56.8 | 621.2±46.7 | 0.088 | 631.6±54.7 | 642.6±62.7 | 0.287 |
| Correct response (n)    | 114.4±20.0          | 112.4±20.2        | 121.1±17.9 | **0.036** | 118.0±17.1 | 111.2±21.9 | 0.050 |
| Trail Making Test, Part A (sec) | 34.1±19.4 | 35.4±20.1 | 29.9±16.3 | 0.171 | 33.5±20.2 | 34.7±18.8 | 0.720 |
| Part B (sec)            | 67.6±43.8           | 71.6±46.9         | 54.2±27.5 | **0.013** | 68.5±46.2 | 66.9±41.9 | 0.837 |

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
*Risperidone equivalent dosage which was calculated from daily defined dose.
Values in bold show statistical significance (p<0.05).
Table 2. Sociodemographic and clinical characteristics and neurocognitive measures by Val allele status by gender

|                          | Male                      | Female                    | p-value | Gender interaction | p-value |
|--------------------------|---------------------------|---------------------------|---------|--------------------|---------|
| Val carrier              | Met/Met                   |                           |         |                    |         |
| Age (yr)                 | 32.8 ± 7.2                | 33.2 ± 9.6                | 0.831   | 34.6 ± 9.7         | 32.1 ± 7.1 | 0.363 | 0.401 |
| Duration of illness (yr) | 5.0 (1.8-10.0)            | 3.3 (1.5-9.4)             | 0.832   | 6.0 (3.0-11.9)     | 7.0 (5.5-13.3) | 0.428 | 0.736 |
| Education (yr)           | 14 (12-16)                | 12 (12-16)                | 0.423   | 14 (12-16)         | 14 (12-16) | 0.465 | 0.359 |
| Antipsychotics, risperidone (n) | 36 (80.0) | 15 (88.2)                | 0.712   | 44 (77.2)          | 9 (64.3) | 0.324 | 0.219 |
| Dosage of antipsychotics (mg/d)* | 4 (3-5.3)  | 3 (1-5.4)                | 0.087   | 3 (2-4)            | 3 (2-4) | 0.436 | 0.571 |
| Positive and Negative Syndrome Scale, Positive |                       |                           |         |                    |         |
| General                  | 38.7 ± 10.6               | 40.2 ± 5.8                | 0.460   | 41.4 ± 12.2        | 30.5 ±6.3 | <0.001 | 0.005 |
| Total                    | 76.6 ± 20.3               | 79.6 ±11.3                | 0.461   | 81.1 ± 23.2        | 59.1 ±13.4 | <0.001 | 0.003 |
| Calgary Depression Scale for Schizophrenia | 3 (1-8)  | 6 (2-8)                  | 0.414   | 6 (3-10.5)         | 2.5 (0-7) | 0.045 | 0.018 |
| Social and Occupational Functioning Assessment Scale | 48.9 ±10.4 | 47.2 ± 7.9              | 0.554   | 44.8 ± 11.6        | 54.3 ±11.6 | 0.008 | 0.014 |
| Subjective Wellbeing under Neuroleptics-short form | 77.8 ±14.9 | 70.1 ±26.5             | 0.166   | 72.0 ±17.4         | 84.3 ±12.2 | 0.025 | 0.010 |
| Neurocognitive function  |                          |                           |         |                    |         |
| Digit span test, Forward (n) | 6.4 ± 1.4  | 5.7 ±1.6                | 0.118   | 6.1 ± 1.1          | 6.1 ±1.2 | 0.794 | 0.158 |
| Backward (n)             | 5.1 ± 1.1                | 4.5 ± 1.5                | 0.220   | 4.5 ± 1.4          | 5.1 ±1.7 | 0.179 | 0.069 |
| Verbal Learning Test, Delayed recall (n) | 7.8 ±3.8  | 7.7 ±4.8                | 0.920   | 8.6 ± 3.4          | 9.9 ±4.3 | 0.242 | 0.383 |
| Wisconsin Card Sorting Test, Categories completed (n) | 3.5 ±2.2  | 3.1 ± 2.4               | 0.582   | 3.3 ± 1.9          | 4.3 ±2.2 | 0.122 | 0.142 |
| Continuous Performance Test, Reaction time (msec) | 629.0±52.0 | 638.4±63.0           | 0.550   | 652.8±58.8         | 598.8±62.6 | 0.004 | 0.009 |
| Correct response (n)     | 118.2±16.2               | 117.5±19.8               | 0.886   | 107.8±22.0         | 125.9±14.3 | 0.001 | 0.021 |
| Trail Making Test, Part A (sec) | 33.6±21.1  | 33.2±17.9               | 0.953   | 36.8±19.3          | 25.5±13.2 | 0.048 | 0.176 |
| Part B (sec)             | 73.0±50.4                | 56.6±30.6                | 0.215   | 70.5±44.5          | 51.0±23.6 | 0.033 | 0.864 |

Values are presented as number (%), mean ± standard deviation, or median (interquartile range).
*Risperidone equivalent dosage which was calculated from daily defined dose.
Values in bold show statistical significance (p<0.05).
significant gender interactions when the effects of the BDNF polymorphism on neurocognitive functioning and psychopathology were explored in patients with schizophrenia.

Our present findings are not compatible with the notion that BDNF is involved in neurogenesis and neuroprotection; the Val allele is known to increase secretion of BDNF. Most studies on healthy populations have found that the BDNF Met allele was associated with poor neurocognitive functioning; many studies with schizophrenia patients have yielded similar results. However, a recent meta-analysis found no evidence that the BDNF Val66Met polymorphism was associated with neurocognitive functioning in patients with schizophrenia. The gender-specific influence of the BDNF Val66Met polymorphism may be explained by the fact that BDNF and sexual hormones interact significantly. Animal studies suggest that estrogen increases BDNF levels. Thus, female patients with schizophrenia may express more BDNF than males do, and this may be further exacerbated in patients with higher BDNF secretion rates (Val carriers). BDNF controls the development of dopamine D3 receptors and maintenance of receptor expression. Activation of these receptors inhibited working memory ability in animal experiments using D3 receptor agonists and antagonists. Therefore, relatively elevated secretion of BDNF (in Val carriers) may negatively impact neurocognitive functioning by increasing D3 receptor expression. Indeed, a study on patients with Parkinson’s disease, in whom the dopaminergic system is compromised, showed that those with the Met allele performed significantly better on working memory tasks and delayed recall tests. We also speculate that sex hormones such as estrogen may play roles in the sexually dimorphic effects of BDNF genotypes.

In the present study, the Val allele was significantly associated with more severe psychotic and depressive symptoms. This seems to contradict previous findings showing negative relationships between BDNF levels and the severity of depression in populations with depressive disorder. Moreover, the Met allele was associated with a higher depression score in patients with schizophrenia. However, a positive correlation between BDNF level and the severity of depression has been reported in females, but not males. In addition, the Val allele was associated with an elevated cortisol response to stress and increased anxiety and neurotisism. Further study is warranted to investigate the roles played by BDNF polymorphisms and BDNF levels in depressed patients with schizophrenia.

Associations between the Val66Met polymorphism and the severity of psychotic symptoms in patients with schizophrenia have been inconsistent. In one study on Chinese
inpatients, the Val allele was associated with lower PANSS scores, particularly on the negative and depression panels.\(^{43}\) In addition, in a study using CAITIE data, the Met allele was associated with treatment resistance.\(^{49}\)

By contrast, a study on Polish patients with paranoid schizophrenia found that the Val/Val genotype was associated with more severe symptoms in males but not in females.\(^{50}\) In a previous study on Chinese patients with schizophrenia, the Val allele tended to be associated with higher subscores on negative symptoms of the PANSS, but no gender-stratified sub-analysis was performed.\(^{51}\)

The BDNF Met allele was found to be associated with poor BDNF secretion, reduced expression of dopamine D3 receptor, and less severe psychotic symptoms.\(^{52}\) In addition, as previously suggested, it may be the case that the Val genotype is associated with treatment-resistant symptoms, resulting in reports of more severe symptoms.\(^{53}\) This would explain why the Val allele was associated with more severe psychotic or more treatment-resistant symptoms both in earlier studies and in the present work.

A few limitations of our work should be borne in mind. First, BDNF genotypes are trait dependent, whereas assessments of cognitive functioning and the intensity of illness using the PANSS are state dependent. We believe that the post-acute status of our present patients and their relatively low PANSS scores reduce the confounding problem. However, relationships between clinical symptoms and genotypes warrant further investigation in first-episode drug-naive patients.\(^{51}\) Second, gene×gene and gene×environment interactions, as well as epigenetic modification, may influence the role played by the BDNF Val66Met polymorphism in patients with schizophrenia. Third, it remains possible that the effects of the Val66Met polymorphism on the cognition and psychopathology of females with schizophrenia may be attributable to linkage disequilibrium between this polymorphism and a functional polymorphism lying in or near the BDNF gene.\(^{54}\)

Fourth, all of our patients were Korean. Indeed, there is some evidence that Val66Met genotype frequencies may vary by ethnicity, with the Met allele being more prevalent in Asians than in other ethnic groups.\(^{55}\) Finally, sample size was relatively small to have enough statistical power, particularly for interaction effects of gender.

In conclusion, the present study found out that gender-specific associations of the Val allele with poor neurocognitive function and more severe psychopathology. Furthermore, the significance of the association between the Val allele and poor neurocognitive functioning was maintained after adjustment for severity of psychopathology in female patients with schizophrenia. These results suggest that BDNF action may vary by gender in patients with schizophrenia, explaining the conflicting results of earlier genetic studies. Further studies are required to explore the mechanisms of these differences and the potential utility of the BDNF genotype as a predictor of outcome in patients with schizophrenia. Large samples of subjects varying in ethnicity should be studied longitudinally.

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