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# The analysis of BDNF gene polymorphism haplotypes and impulsivity in methamphetamine abusers

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**Abstract**

An increasing number of evidence showed that genetic factors might contribute to drug abuse vulnerability. Data from genetic scans in humans suggest that brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, may be associated with substance abuse or dependence. To test the hypothesis that the BDNF gene polymorphism is involved in methamphetamine abuse, we compared three single nucleotide polymorphisms (SNPs, rs16917204, rs16917234, and rs2030324) of the BDNF gene in 200 methamphetamine abusers and 219 healthy individuals. We also considered the association of these polymorphisms with impulsivity in methamphetamine abusers using Barratt Impulsivity Scale-11(BIS-11) Chinese version. Individual SNP analysis showed no significant differences in genotype and allele distributions between the methamphetamine abusers and controls. Haplotype analysis of rs16917204–rs16917234–rs2030324 revealed that a major C–C–T haplotype was significantly associated a lower odds of methamphetamine abuse, even after Bonferroni correction. Within the methamphetamine-abuse group, subjects carrying the T allele of rs2030324 genotype had significantly higher motor impulsivity scores of BIS compared to those with the C/C genotype. Our findings suggest that the BDNF gene polymorphism may contribute to the impulsivity in methamphetamine abusers.


## 1. Introduction

Substance abuse is a complex neuropsychiatric disorder that is characterized by repeated substance use, abstinence and relapse, and behavioral impairments. Although the mechanism of substance abuse is still unknown, twin and family studies support a common genetic liability for substance abuse [1], for example, opioid receptor gene, serotonin receptor gene, dopamine receptor gene, and catecholamine oxygen methyl transferase gene have been reported [2].

Brain-derived neurotrophic factor (BDNF) belongs to the family of neurotrophic factors; plays several important roles such as promotion of development, differentiation, and survival of neurons; and is involved in neuroadaptive changes in the dopaminergic and serotonin systems that underlie substance abuse and dependence [3]. Recent studies have demonstrated that BDNF gene might be one of the strong candidate genes to drug abuse. In the studies reporting possible association of BDNF and substance abuse, a common and functional single nucleotide polymorphism, rs6265 (Val66Met) has been discussed. Studies from Malaysia and Taiwan both found an association between Val66Met and methamphetamine dependence, but these

*Abbreviations:* BDNF, brain-derived neurotrophic factor; BIS, Barratt Impulsivity Scale; SNP, single nucleotide polymorphism; BMI, body mass index.

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results are far from consistent [4,5]. Furthermore, other BDNF SNPs, such as rs16917204, rs16917234, and rs2030324 gene polymorphisms have been studied in heroin and alcohol dependent patients [6–9]. It was reported the rs2030324 (located in the intron 3) is associated with nicotine dependence [6]. Others tried to replicate the association between the polymorphism rs16917204 and heroin dependence or alcohol dependence-related depression [7,8], and the function of the polymorphism rs16917234 (chromosomal location: 27698374, gene position: intron 8) in heroin-dependent patients [9], but the results were negative. Furthermore, studies on BDNF gene polymorphisms in methamphetamine addicts are few.

Impulsivity, as a kind of personality trait, is characterized by the propensity to act quickly and without regard for negative consequences [10]. It is a characteristic of several psychiatric disorders, such as bipolar disorder, personality disorder, and substance use disorders. Recent studies showed that impulsivity was a strong predictor in alcohol, nicotine, cocaine and methamphetamine dependence [11–13]. It may enhance the subject's vulnerability for drug addiction and relapse [10]. Compared with normal controls, methamphetamine-dependent patients showed greater impulsivity scores using the BIS-11 [14].

The relationship between BDNF gene polymorphism and impulsivity has been studied in several studies on impulsive behavior. For example, Attention Deficit Hyperactivity Disorder, a disorder characterized by higher level of hyperactivity and impulsivity, has a correlation with Val66Met [15]. Others reported the BDNF Met allele may confer a 'preferred drug-invested' phenotype in heroin-dependent patients [16]. Serotonergic and dopaminergic mechanisms were thought to play an important role in the form of impulsivity. Our previous study just revealed an association between Val66Met and attentional impulsivity in methamphetamine abusers [17]. However, other BDNF gene polymorphism has not been reported so far.

Based on the higher impulsivity observed among methamphetamine abusers, and possible relationship between BDNF and impulsivity, we hypothesize that BDNF gene polymorphisms (rs16917204, rs16917234, and rs2030324) may play a role in the impulsivity of methamphetamine-abuse patients. The purposes of this study were to determine (1) differences in genotype and allele distributions of BDNF gene polymorphism between methamphetamine abusers and healthy controls, (2) associations between BDNF gene polymorphisms distribution and impulsivity using Barratt Impulsivity Scale-11(BIS-11) Chinese version in methamphetamine abusers.

## 2. Material and methods

### 2.1. Subjects

Two hundred methamphetamine-abuse inpatients were recruited from Sanyang Detoxification Institute, which is located in Wenzhou city in the Zhejiang province, with a confirmed substance abuse diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Subjects were excluded if they had: age under 18 years; current Axis I psychiatric disorders (schizophrenia, bipolar disorder, major depressive disorder, panic disorder, social phobia, obsessive–compulsive disorder, generalized anxiety disorder, attention deficit hyperactivity disorder, etc.) or substances use other than methamphetamine; histories of other diseases. 219 healthy volunteers were selected from the physical examination center at The First Affiliated Hospital of Wenzhou Medical University. All controls had no histories of substance abuse and psychiatric illnesses. Both the patients and controls are Han Chinese.

All the subjects were willing to participate in this study, and gave informed consent for the use of their DNA samples. The study was approved by the Institutional Review Board and the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University.

### 2.2. Impulsivity

The level of impulsivity was measured using the BIS-11 [18]. The BIS-11 consists of 30 four-point Likert scale (1 = rarely/never, 2 = occasionally, 3 = often, 4 = almost always/always) self-reported items. The three basic factors of impulsivity in BIS-11 are: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness. Eleven of the 30 items are reverse-scored to avoid a response bias. We used the 26-item Chinese version of the BIS-11, instead of the original English version. Previous studies in Chinese adolescents [19] and opioid-dependent subjects in Taiwan [20] demonstrate that the Chinese version of the BIS-11 has high overall internal consistency and is applicable for Chinese people. Only 138 methamphetamine abusers finished the BIS-11 during the first week of interviewing; the other 62 patients could not persist finishing it or were not willing to join it, so we could not get these data. As the BIS was used for substance-dependent subjects, it is not appropriate for controls or healthy volunteers; we did not test the impulsivity in controls.

### 2.3. Genotyping

The three SNPs: rs16917204, rs16917234, and rs2030324 were selected according to previous studies about substance dependence [6–9]. About five milliliters of peripheral blood was collected in tubes coated with EDTA. Genomic DNA was extracted from peripheral blood mononuclear cells using DNAzol reagent according to the manufacturer's instructions (Invitrogen, Carlsbad, CA). The MassArray platform (Sequenom, San Diego, CA) was used to perform the SNP genotyping, which utilizes chip-based matrix-assisted laser desorption ionization–time-of-flight mass spectrometry technology. MassArray Assay Design 3.1 was used to design polymerase chain reaction (PCR) and iPlex extension