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Brain derived neurotrophic factor gene (*BDNF*) and personality traits: The modifying effect of season of birth and sex

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ABSTRACT

Personality traits are complex phenotypes influenced by interactions of multiple genetic variants of small effect and environmental factors. It has been suggested that the brain derived neurotrophic factor gene (*BDNF*) is involved in personality traits. Season of birth (SOB) has also been shown to affect personality traits due to its influences on brain development during prenatal and early postnatal periods. The present study aimed to investigate the effects of *BDNF* on personality traits; and the modifying effects of SOB and sex on associations between *BDNF* and personality traits. A sample of 1018 young adults (68% women; age range 17–25 years) of Caucasian origin from the Russian Federation was assessed on personality traits (Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence, Self-directedness, Cooperativeness, Self-transcendence) with the Temperament and Character Inventory-125 (TCI-125). Associations between personality traits and 12 *BDNF* SNPs were tested using linear regression models. The present study demonstrated the effect of rs11030102 on Persistence in females only ($P_{FDR} = 0.043$; $r^2 = 1.3\%$). There were significant interaction effects between Val66Met (rs6265) and SOB ($P_{FDR} = 0.048$, $r^2 = 1.4\%$), and between rs2030323 and SOB ($P_{FDR} = 0.042$, $r^2 = 1.3\%$), on Harm Avoidance. Our findings provide evidence for the modifying effect of SOB on the association between *BDNF* and Harm Avoidance, and for the modifying effect of sex on the association between *BDNF* and Persistence.

1. Introduction

Personality traits are predictors of important life outcomes including well-being, academic achievement, health risk behaviors, and longevity; they are also considered as endophenotypes for major psychiatric disorders (De Beaumont et al., 2013; Duclot and Kabbaj, 2013; Terracciano et al., 2010a).

Personality traits are complex phenotypes affected by interactions of multiple genes of small effect with environmental factors. The estimated heritability of personality traits variability is 30–40% (Bouchard and Loehlin, 2001; Garcia et al., 2013). However, candidate gene studies, as well as genome-wide association studies (GWAS), often failed to confirm initial findings of specific genetic risk factors for personality traits (de Moor et al., 2012; Shifman et al., 2008; Terracciano et al., 2010a, 2011a). Difficulties in identifying specific genetic risk factors are likely to be related to influences of sex, age, ethnicity, as well as of various environmental factors that can modify the effects of genes. To date, the role of candidate gene approach focusing on genetic factors with known functional role in manifestation of personality traits in the context of gene–environment interactions remains significant.

Brain derived neurotrophic factor gene (*BDNF*) is one of the strong candidate genes for personality traits (Montag, 2014). BDNF is involved in the growth and maintenance of several neuronal systems, serves as a neurotransmitter modulator, and participates in use-dependent plasticity mechanisms, such as learning and memory (Nakazato et al., 2003; Rasmusson et al., 2002). Therefore, it has been suggested that BDNF can play an important role in anxiety-related personality traits and disorders. In humans, decreased serum BDNF levels were associated with depression (Bocchio-Chiavetto et al., 2010; Trajkovska et al., 2008), high Neuroticism (Lang et al., 2004; Terracciano et al., 2011b) and

Abbreviations: BDNF, Brain derived neurotrophic factor; SOB, Season of birth; GWAS, Genome-wide association study; SNP, Single nucleotide polymorphism; UTR, Untranslated region; ANOVA, One-way analysis of variance; GxE, Gene–environment interaction; FDR, False discovery rate; PCR, Polymerase chain reaction; HA, Harm Avoidance; NS, Novelty Seeking; RD, Reward Dependence; PS, Persistence; SD, Self-directedness; ST, Self-transcendence; TCI, Temperament and Character Inventory.

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Harm Avoidance (Minelli et al., 2011), while increased BDNF concentrations have been reported after treatment with antidepressants (Shimizu et al., 2003). On the contrary, lower plasma BDNF levels were observed in men who scored lower on depression and vulnerability to stress, higher on Conscientiousness and Extraversion (Terracciano et al., 2010b), and lower on Harm Avoidance (Yasui-Furukori et al., 2013).

Human molecular genetic studies of the *BDNF* gene can provide further evidence for the role of this protein in personality traits. Human *BDNF* gene (11p13) consists of eleven exons and tissue- and brain-region specific nine functional promoters. The replacement of Val-allele by Met-allele in *BDNF* gene (Val66Met, or rs6265) disrupts cellular processing, trafficking, and activity-dependent secretion of BDNF (Hong et al., 2011). The *BDNF* Met-allele has been associated with gray matter volume deficits especially in the hippocampus, prefrontal cortex (Hajek et al., 2012; Pezawas et al., 2004), and in the right amygdala (Montag et al., 2009). Moreover, Met-allele has been associated with reduced hippocampal activation (Kambeitz et al., 2012), deficient intracellular transport of BDNF to dendrites and reduced magnitude of long term potentiation (Kleim et al., 2006).

Animal studies demonstrated that Met/Met mice showed increased anxiety-related behaviors in stressful conditions (Chen et al., 2006). In humans, a number of studies have reported association between Met-allele and depression that was modified by the presence of stressful life events (Brown et al., 2013; Hosang et al., 2014), or enhanced reactions to external stressful stimuli (Colzato et al., 2011). However, a recent meta-analysis failed to support association between Val66Met and depression (Gyekis et al., 2013). One possible explanation for this inconsistency is that *BDNF* gene might be involved in variation of anxiety-related traits rather than in depression itself. As it has been demonstrated, *BDNF* Met-allele carriers have higher Harm avoidance (Jiang et al., 2005; Montag et al., 2010), Reward Dependence and Extraversion (Itoh et al., 2004) as compared with Val/Val homozygotes. However, associations between Met-allele and lower Harm Avoidance (Ando et al., 2012) and Neuroticism (Sen et al., 2003) have also been reported. A recent GWAS of personality traits has confirmed an association of Met-allele and lower Extraversion, however, together with the meta-analyses has provided no evidence for the effect of Val66Met on anxiety-related traits (Frustaci et al., 2008; Terracciano et al., 2010a, 2010c). Such an inconsistence across the studies could be explained by epistatic effect between *BDNF Val66Met* and other polymorphisms, for example *5-HTTLPR* (linked polymorphic region in serotonin transporter gene) as demonstrated by Terracciano et al. (2010c). This study showed that *5-HTTLPR L/L* homozygotes scored lower on Neuroticism in the presence of *BDNF Val*-allele, but scored higher on Neuroticism in the presence of *BDNF Met*-allele (Terracciano et al., 2010c).

The majority of previous studies of the *BDNF* gene in personality traits have focused on the role of a single *BDNF* polymorphism — Val66Met. However, other genetic variants could be involved in regulation of the *BDNF* gene expression. It has been reported that *BDNF* expression is regulated by a group of miRNAs and that common genetic variants (i.e., rs11030100 and rs11030099 in 3′-UTR) influence miRNA targeting and participate in expression modulation (Caputo et al., 2011). A number of other *BDNF* SNPs, such as rs11030102, rs11030107, rs10835211, have also been shown to be associated with serum BDNF level (Terracciano et al., 2013).

A sex-specific effect of the *BDNF* gene on cortisol level has been reported (Shalev et al., 2009). Moreover, animal studies demonstrated that female *BDNF* conditional knockouts displayed an increase in depression-like behaviors, while male knockouts reported normal depression-related behaviors (Monteggia et al., 2007).

Environmental factors may also modify the effect of the *BDNF* gene on personality traits. Season of birth (SOB) can influence anxiety-related personality traits and psychiatric disorders (Antonsen et al., 2012; Chotai et al., 2009). For example, the effect of SOB was demonstrated on Novelty Seeking (Chotai et al., 2009), hyperthymic personality (characterized with high Novelty Seeking and low Harm Avoidance), and depressive temperament (Rihmer et al., 2011). The findings suggest that people born in spring/summer are more likely to have lower anxiety-related traits (i.e., Harm Avoidance) and higher approach-related traits (i.e., Novelty Seeking) than those born in winter.

The present study aims to explore whether the *BDNF* gene is involved in anxiety-related traits, (i.e., Harm avoidance). In addition, the study aims to investigate whether Val66Met and other *BDNF* SNPs are associated with Novelty Seeking that is correlated with Extraversion. Moreover, since both sex and SOB can affect personality traits (Chotai et al., 2009), the present study aims to test whether associations between the *BDNF* gene and personality traits are modified by sex and SOB.

2. Materials and methods

2.1. Sample

In total, 1018 young adults (68% women; mean age ± SD: 19.81 ± 2.65 years, age range: 17–25 years), enrolled at the Universities in the Russian Federation. Socio-demographic data including sex, ethnicity, and date of birth were obtained from all the participants. All participants were of Caucasian origin: Russians (N = 409), Tatars (N = 290), Bashkirs (N = 130) and Udmurts (N = 189). Exclusion criteria were self-reported individual and/or family (of a first and/or second degree relative) history of any psychiatric disorders. The study was approved by the Biological Ethics Committee of Institute of Biochemistry and Genetics (Ufa, Russia), and written informed consent was obtained from all the participants after the procedure had been explained to them. All the participants were informed about the voluntary and confidential nature of their participation.

2.2. Measures

2.2.1. Personality traits

Personality traits were assessed using the Russian version of the Temperament and Character Inventory (TCI-125). The TCI-125 evaluates four temperament traits: Novelty Seeking, Harm Avoidance, Reward Dependence, Persistence, and three character traits: Self-directedness, Cooperation and Self-transcendence (Cloninger et al., 1993). Cronbach's alpha reliability, which measures internal consistency of test items, was high for all seven personality scales (Novelty Seeking: $\alpha = 0.76$; Harm Avoidance: $\alpha = 0.81$; Reward Dependence: $\alpha = 0.67$; Persistence: $\alpha = 0.69$; Self-directedness: $\alpha = 0.82$; Cooperation: $\alpha = 0.76$; Self-transcendence: $\alpha = 0.84$) as well as for the TCI-125 in total ($\alpha = 0.87$).

2.2.2. Season of birth (SOB)

Since all the participants were born in the northern hemisphere, SOB was classified according to traditional Russian definition of the four seasons: March, April and May represented spring (26.9% of all the participants); June, July and August represented summer (24.0%); September, October and November represented autumn (24.2%); and December, January and February represented winter (24.9%). We also used astronomical criterion of SOB taking in account the equinoxes (i.e., March 22–June 21 represented spring; June 22–September 21 — summer; September 22–December 21 — autumn; December 22–March 21 — winter). These two definitions of the four seasons were used since some of the previous studies of the effects of SOB on personality traits have used the traditional criterion (Hori et al., 2012; Martínez-Ortega et al., 2011), while others used the astronomical criterion (Hori et al., 2012; Rihmer et al., 2011; Shuman et al., 2010).

2.3. SNP selection and genotyping

Genomic DNA was isolated from the whole blood using a standard phenol–chlorophorm technique. In total, 12 *BDNF* SNPs (MAF > 10%)