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


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...
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 rs24665) 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 (Kambetz 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 (Fruscaci et al., 2008; Terracciano et al., 2010a, 2010c). Such an inconsistency 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 (Shaley 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: α = 0.76; Harm Avoidance: α = 0.81; Reward Dependence: α = 0.67; Persistence: α = 0.69; Self-directedness: φ = 0.82; Cooperation: φ = 0.76; Self-transcendence: φ = 0.84) as well as for the TCI-125 in total (φ = 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 (26.5% 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 21–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%)
were selected using the Tagger algorithm implemented in the Haploviev
4.1 (Barrett et al., 2005).

Genotyping of the 12 SNPs was performed using a PCR-RFLP method. PCR primers for each polymorphism were designed in Primer 3 (http://
bioinfo.ut.ee/primer3-0.4.0/). PCR was performed in total volume of
15 μl with 20–50 ng of genomic DNA, Taq polymerase (Silex, Russia). Subsequently, for allele detection PCR products were accomplished by
overnight incubation with 3U of corresponding restriction endonuclease
(Fermentas, Canada) according to manufactures recommendations,
resolved in 7% polyacrylamide gel (PAAG) and visualized by staining
with ethidium bromide.

2.4. Statistical analysis

Genotype and allele frequencies of the investigated SNPs, as well as
Hardy–Weinberg equilibrium, calculations were performed in a total
sample using PLINK v.1.07 (Purcell et al., 2007). Haplotype blocks
were delineated using the con
fi
dence interval method of Gabriel et al.
(2002), and measures of linkage disequilibrium (LD) between markers
were obtained using Haploviev 4.1. The extent of disequilibrium was
demonstrated by the standardized D′ characteristic multiplied by 100 in
the LD illustration generated in Haploviev v.4.1. Haplotypes with a
frequency less than 1% were excluded from the further analysis.

Since personality traits scores were distributed normally, the main
effects of the individual BDNF SNPs and haplotypes, sex and SOB, as
well as the effects of gene-by-sex and gene-by-SOB interactions on
personality traits were investigated using linear regression models in
a total sample with PLINK v.1.07. First, each of the BDNF SNPs, SOB,
and sex were entered into the model as independent variables, and
each of personality traits – as dependent variables. For the categorical
variables with the number of categories higher than two, a matrix of
dummy variables was constructed that were later used for the linear
regression analysis. Additive genetic model was used to estimate the
effect of a minor allele of each of the BDNF SNPs on personality traits.
Information on minor alleles of each BDNF SNPs is presented in Table 1.
Empirical P-value permutations were run. Effect sizes were calculated
for all statistical models. The effect sizes were reported as r2, which
describes the proportion of variance in personality traits that is accounted
for the differences in genotype or haplotype controlling for sex and
season of birth.

Second, the interaction effects of BDNF SNPs with SOB and sex were
tested in STATA v.11. According to Keller (2014), in order to control for
potential confounders in GxE analysis, along with all main effects and
gene × environment interaction effect, it is necessary to enter all covarai-
tes on environment and covariate × gene interaction terms. So, our lin-
ear regression models included the main effects of BDNF SNP, SOB, and
sex, as well as interaction terms: SNP × SOB, SNP × sex, and SOB × sex.
For the models demonstrating interaction effect of a specific SNP or
distinct haplotype modulated by SOB or sex on personality traits, we con-
trated stratification analyses to clarify the direction of effect. For the
interaction effects, those with P-value less than 0.10 were considered for
stratification analysis.

Power analysis to detect SNP associations and GxE associations with
personality traits was conducted with Quanto v.1.2.4 (Gauderman,
2002) with a type I error rate of 5%.

As multiple positive findings were expected, false discovery rate
(FDR) procedure (Simes procedure; Benjamini and Hochberg, 1995)
was carried out and P-value thresholds were calculated to quantify the
joint probability of multiple findings reflecting true associations as
opposed to false positives, taking into account all comparisons per-
formed to test our hypotheses. This procedure provides an effective
control of type I error rate in the context of multiple correlated tests
and has good agreement with the permutation test (Uher et al., 2009).
Corrected P-values (P_{FDR}) are shown for all the tests. The number of
independent tests was: 1) 12 for ANOVA (analysis of 12 SNPs); 2) 16
for haplotype analysis (analysis of 16 haplotypes); 3) 12 for GxE
analysis (analysis of 12 SNPs modified by SOB and sex). The multiple
comparison-corrected significance thresholds were then calculated as
(k × 0.05)/m, where m – the number of statistical tests, k – the order
of the tested hypothesis.

3. Results

3.1. Effects of sex and SOB on personality traits

The main effect of sex on personality traits was observed with
females scoring significantly higher on Harm Avoidance (P = 0.016),

Table 1

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chromosomal position, bp*</th>
<th>Location in gene</th>
<th>Minor allele</th>
<th>Genotype frequency</th>
<th>P_{HWE}</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1519479</td>
<td>27624107</td>
<td>Intron (BDNF-AS)</td>
<td>C</td>
<td>C/C</td>
<td>0.913</td>
</tr>
<tr>
<td>rs2203877</td>
<td>27627486</td>
<td>Intron (BDNF-AS)</td>
<td>T</td>
<td>T/T</td>
<td>0.198</td>
</tr>
<tr>
<td>rs7124442</td>
<td>27633617</td>
<td>3′-UTR (BDNF)</td>
<td>G</td>
<td>G/G</td>
<td>0.521</td>
</tr>
<tr>
<td>rs6265</td>
<td>27636492</td>
<td>Exon (BDNF)</td>
<td>A</td>
<td>A/A</td>
<td>1.000</td>
</tr>
<tr>
<td>rs11030102</td>
<td>27638172</td>
<td>Intron (BDNF)</td>
<td>G</td>
<td>G/G</td>
<td>0.447</td>
</tr>
<tr>
<td>rs10835211</td>
<td>27657941</td>
<td>Intron (BDNF)</td>
<td>A</td>
<td>A/A</td>
<td>0.080</td>
</tr>
<tr>
<td>rs2030323</td>
<td>27685115</td>
<td>Intron (BDNF)</td>
<td>T</td>
<td>T/T</td>
<td>1.000</td>
</tr>
<tr>
<td>rs10767665</td>
<td>27690434</td>
<td>Intron (BDNF)</td>
<td>G</td>
<td>G/G</td>
<td>0.815</td>
</tr>
<tr>
<td>rs1491850</td>
<td>27706301</td>
<td>5′ near gene (BDNF)</td>
<td>C</td>
<td>C/C</td>
<td>0.185</td>
</tr>
<tr>
<td>rs985205</td>
<td>27715568</td>
<td>5′ near gene (BDNF)</td>
<td>T</td>
<td>T/T</td>
<td>0.162</td>
</tr>
<tr>
<td>rs7483883</td>
<td>27723114</td>
<td>5′ near gene (BDNF)</td>
<td>C</td>
<td>C/C</td>
<td>0.982</td>
</tr>
<tr>
<td>rs21772229</td>
<td>27733198</td>
<td>5′ near gene (BDNF)</td>
<td>G</td>
<td>G/G</td>
<td>0.723</td>
</tr>
</tbody>
</table>

* According to NCBI36 genome build 36.3. P_{HWE} — P-value for Hardy–Weinberg equilibrium test. Location in both BDNF and BDNF-AS genes is shown.
Novelty Seeking ($P = 0.037$) and Reward Dependence ($P < 0.001$) as reported previously (Kazantseva et al., 2008). We also tested for the main effect of SOB on personality traits, but no significant differences in personality traits were revealed in individuals with different SOB.

### 3.2. Main effects of the BDNF gene on personality traits

The distributions of genotype frequencies for the 12 BDNF SNPs were consistent with Hardy-Weinberg equilibrium (Table 1). The analysis of pair-wise linkage disequilibrium revealed the presence of two haplotype blocks in the BDNF gene and neighboring regions spanning 82 and 17 kb ($D' > 0.73$) (Fig. 1). $D'$ coefficients, as well as haplotype structure, are shown on Fig. 1. There were nine haplotypes in block 1 and six haplotypes in block 2 with haplotype frequencies higher than 1% (Table 2).

While testing for the main effects of the BDNF SNPs on personality traits, we observed trends in carriers of rs11030102 G-allele to score lower on Persistence ($P = 0.022; r^2 = 0.91%$) and in carriers of rs1491850 C-allele to score lower on Harm Avoidance ($P = 0.021; r^2 = 0.94%$; power = 0.88); however, these associations became non-significant after FDR-correction (Table S1). Results of linear regression analysis for the associations between the BDNF SNPs and character traits are reported in Supplementary material (Table S2).

Haplotype analysis revealed a trend for associations of BDNF TCTGCG GAC-haplotype (Block 1) with higher Persistence ($P = 0.010$; $D' = 0.73$) and ATG-haplotype (Block 2) with Novelty Seeking ($P = 0.007$), which became non-significant after FDR-correction (Table S3). No statistically significant effects of BDNF SNPs or haplotypes on character traits were observed (Supplementary Tables S2 and S4).

### 3.3. Interaction effects between the BDNF gene and sex on personality traits

We tested for interaction effects of sex and the BDNF SNPs on personality traits. There was an interaction effect between sex and rs11030102 on Persistence ($P = 0.039$) (Table 3). Subsequent stratified analysis revealed that female-carriers of rs11030102 G-allele had lower Persistence as compared with C/C-genotype carriers ($P = 0.003$).

### 3.4. Interaction effects between the BDNF gene and SOB on personality traits

There were interaction effects between SOB (based on traditional criterion) and Val66Met ($P = 0.037$), as well as between SOB (based on astronomic criterion) and rs1491850 ($P = 0.052$), on Novelty Seeking (Table 3). However, when stratifying our sample according SOB, there were no effects of these SNPs on Novelty Seeking. The power to detect interaction effects between rs6265 and SOB, and between rs1491850 and SOB, on Novelty Seeking was 0.82 and 0.85, respectively.

There were interaction effects between SOB and Val66Met ($P = 0.006$ for traditional criterion of SOB, and $P = 0.009$ for astronomic criterion

---

**Table 2**

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>Total</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDNF block1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCAGCCTGAT</td>
<td>0.435</td>
<td>0.395</td>
<td>0.460</td>
</tr>
<tr>
<td>CTGGCGGGAT</td>
<td>0.157</td>
<td>0.161</td>
<td>0.153</td>
</tr>
<tr>
<td>CTAACGCTGC</td>
<td>0.132</td>
<td>0.135</td>
<td>0.131</td>
</tr>
<tr>
<td>CTACCGCGGT</td>
<td>0.110</td>
<td>0.126</td>
<td>0.098</td>
</tr>
<tr>
<td>CTGCGCGCGT</td>
<td>0.030</td>
<td>0.043</td>
<td>0.022</td>
</tr>
<tr>
<td>CTACGTGGTC</td>
<td>0.025</td>
<td>0.023</td>
<td>0.027</td>
</tr>
<tr>
<td>TCACGCGAC</td>
<td>0.024</td>
<td>0.026</td>
<td>0.023</td>
</tr>
<tr>
<td>TCAGCGGAT</td>
<td>0.011</td>
<td>0.013</td>
<td>0.011</td>
</tr>
<tr>
<td>BDNF block2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTA</td>
<td>0.443</td>
<td>0.475</td>
<td>0.426</td>
</tr>
<tr>
<td>ACA</td>
<td>0.088</td>
<td>0.075</td>
<td>0.095</td>
</tr>
<tr>
<td>ATG</td>
<td>0.273</td>
<td>0.251</td>
<td>0.285</td>
</tr>
<tr>
<td>ACA</td>
<td>0.046</td>
<td>0.037</td>
<td>0.051</td>
</tr>
<tr>
<td>TTT</td>
<td>0.031</td>
<td>0.026</td>
<td>0.034</td>
</tr>
</tbody>
</table>

$D'$ consists of rs1519479, rs2203877, rs7124442, rs6265 (Val66Met), rs11030102, rs1083521, rs2030323, rs10767665, rs1491850; block 2 — of rs985205, rs7483883, rs2172229, respectively. The most frequent haplotypes are shown in bold. Haplotypes with the frequencies less than 1% are not shown. $P_{FDR} = 0.043, r^2 = 1.3%$. The power to detect the interaction effect between sex and rs11030102 on Persistence was 0.83.

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**Fig. 1.** Haplotype structure and $D'$-coefficients (multiplied by 100) in the BDNF gene in the total sample.
Avoidance (Val66Met Met-allele and linked rs2030323 T-allele) were associated with lower Harm Avoidance, but only in those born in spring. Our results demonstrated that the association between the BDNF gene and Harm Avoidance was modified by SOB. Variations in personality traits can be influenced by prenatal differences in photoperiod, behavioral rhythms, nutrition, infections, stress and lifestyle (Chotai and Adolfsson, 2002). According to published studies, downregulation of hippocampal BDNF via epigenetic modification might be explained by neonatal iron (Blegen et al., 2013) and zinc deficiency (Chowanadisai et al., 2005), as well as by deficiency of micronutrients involved in one-carbon metabolism (folic acid, vitamin B (Chotai and Adolfsson, 2002), and docosahexaenoic acid (DHA)) (Dhobale and Joshi, 2012). For example, maternal nutrition is sufficiently enriched with micronutrients within the first pregnancy trimester (summer) of individuals born in spring, and this period is known to be important for active brain and nervous system formation, including BDNF. This could be an explanation for lower behavioral inhibition (i.e., lower Harm Avoidance) in individuals born in spring. Serum BDNF concentrations are shown to be increased in spring-summer as compared to autumn-winter (Molendijk et al., 2013), while lower BDNF level in spring borns.


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and disorders. In a Spanish sample of psychiatrically healthy individuals without familial history of mental disorder, those with BDNF Met/Met and 5-HTTLPR S/S genotypes had higher Harm Avoidance as compared with BDNF Met/Met and 5-HTTLPR L-allele carriers (Arias et al., 2012). In a Russian sample of unaffected parents of patients with major psychosis, carriers of BDNF Val/Val and 5-HTTLPR S/S genotypes scored higher on Depression and Psychasthenia scales (Golimbet et al., 2009). Hiiio et al. (2011) revealed that BDNF Met-allele carriers with 5-HTTLPR S/S-genotype scored lower on Conscientiousness. A recent study demonstrated, in agreement with our findings, the effect of BDNF Met-allele (in the presence of 5-HTTLPR S/S-genotype) on higher postnatal depression scores for those born in autumn/winter (Comasco et al., 2011). In the present study, BDNF Met-allele carriers showed lower Harm Avoidance only if they were born in spring. Another recent study revealed interaction effect of solar activity and glucocorticoid receptor gene (NR3C1 on Neuroticism (anxiety-related trait) (Montag et al., 2013). They reported that NR3C1 rs41423247 C/C-genotype carriers grown in the womb under the influence of high sun radiation (high solar activity) showed both the highest hippocampal volume in the left hemisphere and lowest Neuroticism scores.

According to published data the BDNF Met-allele was shown to be associated with grey matter deficits in hippocampus and prefrontal cortex (Pezawas et al., 2004) — brain regions associated with assigning meaning to social stimuli and stimulus evaluation (Cunningham and Zelazo, 2007). In the present study, there was a sex-specific effect of BDNF rs11030102 on Persistence — trait characterizing the maintenance of behavior despite frustration, fatigue, and intermittent reinforcement. Previously, in a large family-based cohort this SNP was associated with serum BDNF level (Terracciano et al., 2013). This SNP is located 1.6 kb apart from the functional Val66Met with C-allele being linked with Val66Met Val-allele, reported to be associated with lower Reward Dependence in females (Itoh et al., 2004). Since Persistence was the subscale of Reward Dependence (Cloninger et al., 1993), our findings of a sex-specific association of the BDNF gene with a reward-related personality trait are congruent with the study by Itoh et al. (2004).

In a sample of women with premenstrual dysphoric disorder, BDNF Met-allele was associated with lower fronto-cingulate cortex activation in the luteal phase (characterized by increased progesterone levels). It could be suggested that progesterone might modify the effect of BDNF gene on personality traits, possibly via the GABAergic system (Comasco et al., 2014).

Another gene, BDNF antisense (BDNF-AS or BDNFOS), overlaps with the BDNF gene and is transcribed in reverse orientation. Inhibition of non-coding BDNF-AS transcript upregulates BDNF mRNA by two- to sevenfold, alters chromatin marks at the BDNF locus, leads to increased protein levels and induces neuronal outgrowth and differentiation both in vitro and in vivo (Modarresi et al., 2012). Since Val66Met and rs11030102 reside in both BDNF and BDNF-AS, these SNPs may also be involved in BDNF-AS expression regulation on epigenetic level. Moreover, DNA methylation within the promoter/exon IV (Perroud et al., 2013) could be another mechanism of epigenetic regulation of BDNF gene. BDNF rs2030323 located in intron 3 (3 kb apart from exon IV) may be in linkage disequilibrium with some functional SNP in this region.

4.1. Strengths and limitations

The present study has a number of methodological strengths including homogeneity of the sample in respect to age and education. Our sample had a sufficient power (0.82 – 0.99) to detect the main effects of the investigated SNPs and the proposed GxE interaction effects under the type I error rate of 0.05. Sex as a potential confounder and/or modifier was controlled for in all the statistical models as recommended for GxE interaction studies (Keller, 2014).

However, the study has a number of limitations. First, the use of self-reports for the assessment of personality traits may result in over- or underreporting some behavior due to social desirability. To minimize these biases, in the present study, individuals were not allowed to discuss questions or answers with anyone. On the other hand, TCI self-report measures were shown to be the strong predictors of self-reported personality by both peer-report measures and ratings by non-acquainted judges (Gruca and Goldberg, 2007). Second, multiple tests have been performed in the present study that may increase the type I error. However, in order to minimize the possibility of false positive results we performed correction for multiple testing using the false discovery rate (FDR) procedure (Benjamini and Hochberg, 1995). This procedure provides an effective control of type I error rate in the context of multiple correlated tests and has good agreement with the permutation test (Uher et al., 2009). It is worth noting, that FDR-correction resulted in very few positive findings: only three interaction effects remained statistically significant. Finally, we did not use genomic control to test for genetic homogeneity of our sample; however, the risk for population stratification in our study is likely to be low since all the participants are of Caucasian origin.

5. Conclusion

The present study revealed the interaction effects between the BDNF SNPs and SOB on Harm Avoidance, and the interaction effect between the BDNF gene and sex on Persistence, in a large sample of Russian young adults. Future studies are necessary in order to replicate these findings in independent samples. Moreover, to get insight into plausible mechanisms of the interaction between the BDNF gene and SOB, samples of individuals born in different seasons with detailed information on prenatal and early postnatal influences, as well as on epigenetic markers at birth, are needed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.pnpbp.2014.08.001.

References


