Progress in Neuro-Psychopharmacology & Biological Psychiatry 56 (2015) 58–65

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

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

A. Kazantseva [a,*], D. Gaysina [b,1], Yu. Kutlumbetova [a,c,2], R. Kanzafarova [a,c], S. Malykh [d,3], M. Lobaskova [e], E. Khusnutdinova [a,b]

[a] Institute of Biochemistry and Genetics, Ufa Scientific Center, Russian Academy of Sciences, 71, Prospekt Oktyabrya, Ufa 450054, Russia
[b] Rudd Centre for Adoption Research and Practice, School of Psychology, University of Sussex, Falmer, Brighton BN1 9RH, United Kingdom
[c] Bashkir State University, 32, Zaki Validi, Ufa 450074, Russia
[d] Psychological Institute, Russian Academy of Education, 9/4, Mohovaya Street, Moscow 125009, Russia
[e] Udmurt State University, Universitetskaya St. 1Izhevsk, 426034, Russia

ARTICLE INFO

Article history:
Received 7 March 2014
Received in revised form 16 July 2014
Accepted 4 August 2014
Available online 15 August 2014

Keywords:
Effect modification
Gene–environment interaction
Neuroticism
Polymorphism
Prenatal effect
SNP

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.

* Corresponding author. Tel./fax: +7 347 2356088.
E-mail addresses: Kazantsa@mail.ru (A. Kazantseva), D.Gaysina@sussex.ac.uk (D. Gaysina), suleimanovaulia@mail.ru (Y. Kutlumbetova), malykhsb@mail.ru (S. Malykh).
[1] Tel.: +44 1273 877995.
[2] Tel.: +7 347 2 299 671.
[3] Tel./fax: +7 495 202 81 28.

http://dx.doi.org/10.1016/j.pnpbp.2014.08.001
0278-5846/

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%)

were selected using the Tagger algorithm implemented in the Haploview 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 confidence interval method of Gabriel et al. (2002), and measures of linkage disequilibrium (LD) between markers were obtained using Haploview 4.1. The extent of disequilibrium was demonstrated by the standardized D′ characteristic multiplied by 100 in the LD illustration generated in Haploview 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 r^2, 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 covariate × environment and covariate × gene interaction terms. So, our linear 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 conducted 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 performed 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
The investigated *BDNF* SNPs.

SNP	Chromosomal position, bp[a]	Location in gene	Minor allele	Genotype frequency			P_{HWE}
rs1519479	27624107	Intron (*BDNF-AS*)	C	C/C	C/T	T/T	0.913
				0.241	0.504	0.255	
rs2203877	27627486	Intron (*BDNF-AS*)	T	T/T	T/C	C/C	0.198
				0.263	0.469	0.268	
rs7124442	27633617	3′-UTR (*BDNF*) intron(*BDNF-AS*)	G	G/G	G/A	A/A	0.521
				0.097	0.451	0.452	
rs6265 (V66M)	27636492	Exon (*BDNF*) exon(*BDNF-AS*)	A	A/A	A/G	G/G	1.000
				0.021	0.248	0.731	
rs11030102	27638172	Intron (*BDNF*) intron(*BDNF-AS*)	G	G/G	G/C	C/C	0.447
				0.040	0.354	0.606	
rs10835211	27657941	Intron (*BDNF*) intron (*BDNF-AS*)	A	A/A	A/G	G/G	0.080
				0.032	0.361	0.607	
rs2030323	27685115	Intron (*BDNF*)	T	T/T	T/G	G/G	1.000
				0.035	0.303	0.662	
rs10767665	27690434	Intron (*BDNF*)	G	G/G	G/A	A/A	0.815
				0.246	0.507	0.247	
rs1491850	27706301	5′ near gene (*BDNF*)	C	C/C	C/T	T/T	0.185
				0.124	0.496	0.380	
rs985205	27715568	5′ near gene (*BDNF*)	T	T/T	T/A	A/A	0.162
				0.215	0.531	0.254	
rs7483883	27723114	5′ near gene (*BDNF*)	C	C/C	C/T	T/T	0.982
				0.105	0.436	0.459	
rs2172229	27733198	5′ near gene (*BDNF*)	G	G/G	G/A	A/A	0.723
				0.181	0.480	0.339	

[a] 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 ($P = 0.022$; $r^2 = 0.91\%$; power = 0.85) 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 ($P = 0.010$); *TTG*-haplotype (Block 2) ($P = 0.030$) and *ATA*-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 ($P = 0.003$, $P_{FDR} = 0.043$, $r^2 = 1.3\%$). The power to detect the interaction effect between sex and rs11030102 on Persistence was 0.83.

Table 2
Haplotype frequencies in the total sample, males and females.

Haplotype	Total	Males	Females
BDNF block1			
TCAGCGGAT	0.435	0.395	0.460
CTGGGAGGC	0.157	0.161	0.153
CTAACGTGC	0.132	0.135	0.131
CTGGCGGGT	0.110	0.126	0.098
CTGGGAGGT	0.030	0.043	0.022
CTAGCGTGC	0.025	0.023	0.027
TCAGCGGAC	0.024	0.026	0.023
TCAGCGGGT	0.011	0.013	0.011
BDNF block2			
TTA	0.443	0.475	0.426
ATA	0.088	0.075	0.095
ACG	0.273	0.251	0.285
ATG	0.115	0.136	0.103
ACA	0.046	0.037	0.051
TTG	0.031	0.026	0.034

BDNF block1 consists of rs1519479, rs2203877, rs7124442, rs6265 (Val66Met), rs11030102, rs10835211, 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.

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

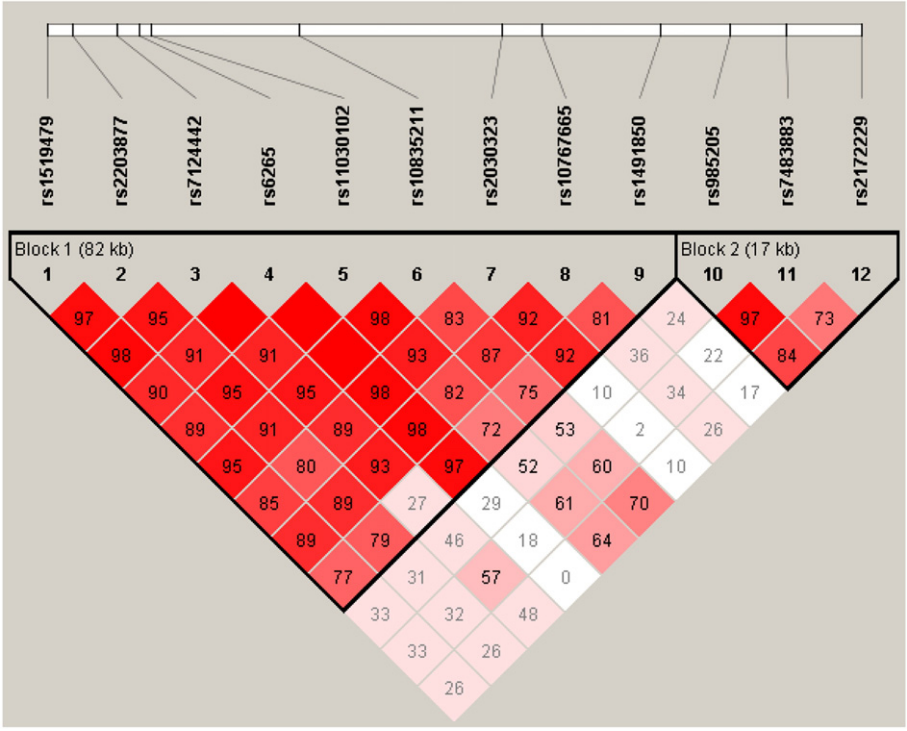

Fig. 1. Haplotype structure and D′-coefficients (multiplied by 100) in the *BDNF* gene in the total sample.

Table 3
Significant effect modifications by sex or season of birth of *BDNF* genetic associations with personality traits in the combined GxE models (according to Keller, 2014).

Personality trait	Items in linear regression model	β	*P*	r^2
Novelty Seeking	rs6265	−1.39	0.222	0.035
	SOB (spring)	−0.33	0.803	
	sex	0.93	0.302	
	rs6265*SOB	1.44	**0.037**	
	Sex*SOB	−0.96	0.129	
	Sex* rs6265	0.43	0.514	
	rs1491850	−1.53	0.140	0.037
	SOB_{ast} (summer)	1.67	0.286	
	sex	−0.25	0.803	
	rs1491850* SOB_{ast}	−1.29	0.052	
	Sex* SOB_{ast}	0.29	0.670	
	Sex* rs1491850	0.93	0.122	
Harm Avoidance	rs6265	−0.09	0.944	0.014
	SOB (spring)	2.84	0.068	
	sex	0.55	0.599	
	rs6265*SOB	−2.20	**0.006***	
	Sex*SOB	−0.18	0.808	
	Sex*rs6265	0.21	0.778	
	rs2030323	0.32	0.791	0.013
	SOB (spring)	2.27	0.141	
	sex	0.86	0.401	
	rs2030323*SOB	−1.90	**0.011***	
	Sex*SOB	−0.05	0.950	
	Sex* rs2030323	−0.06	0.935	
	rs6265	−1.20	0.366	0.019
	SOB_{ast} (autumn)	−2.59	0.150	
	sex	0.65	0.528	
	rs6265* SOB_{ast}	2.21	**0.009**	
	Sex*SOB_{ast}	−0.58	0.479	
	Sex*rs6265	0.17	0.822	
Persistence	rs11030102	0.532	0.182	0.013
	sex	0.581	0.093	
	rs11030102*sex	−0.481	**0.039***	

SOB_{ast} — season of birth according to astronomic criterion; SOB — season of birth according to traditional criterion. Significant *P*-values are in bold. Statistically significant *P*-values after FDR-correction are marked with asterisk.

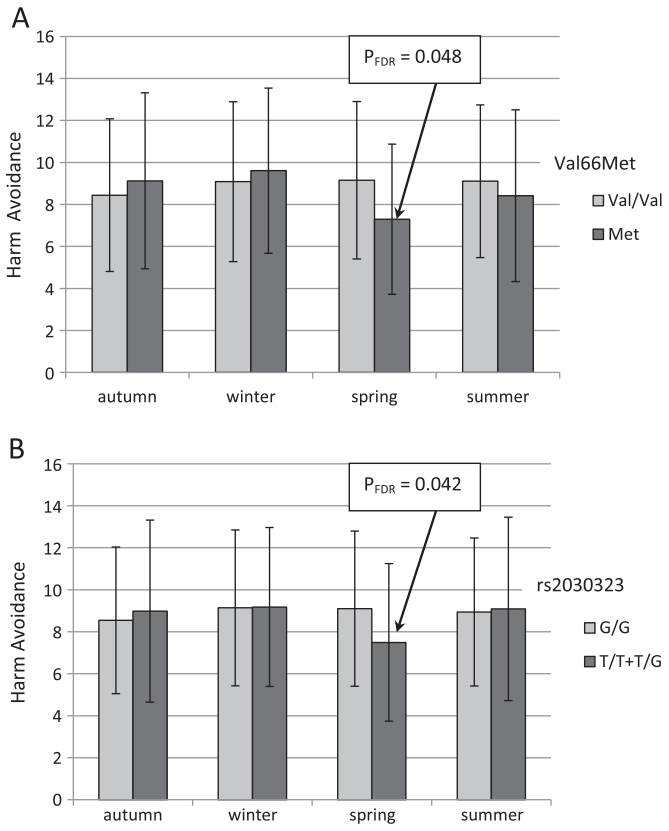

Fig. 2. Interaction effects between *BDNF* Val66Met and SOB (A), and rs2030323 and SOB (B) on Harm avoidance. Error bars stand for standard deviation.

of SOB), as well as between SOB (traditional criterion) and rs2030323 ($P = 0.011$), on Harm Avoidance (Table 3). Stratified analysis by SOB demonstrated that Val66Met Met-allele carriers born in spring had lower Harm Avoidance than Val/Val homozygotes ($P = 0.004$, $P_{FDR} = 0.048$, $r^2 = 1.4\%$; Fig. 2, A), whereas associations in other SOB groups were non-significant. Among those born in spring (but not in other seasons), rs2030323 T-allele was associated with lower Harm Avoidance ($P = 0.007$, $P_{FDR} = 0.042$, $r^2 = 1.3\%$; Fig. 2, B). The power to detect interaction effects between rs6265 and SOB, and between rs2030323 and SOB, on Harm Avoidance was 0.96 and 0.91, respectively.

4. Discussion

In the present study, we observed interaction effect between sex and *BDNF* rs11030102 on Persistence, as well as interaction effects between SOB and *BDNF* Val66Met and rs2030323 on Harm Avoidance. Our results showed that alleles associated with a decreased BDNF level (Val66Met Met-allele and linked rs2030323 T-allele) were associated with lower Harm Avoidance, but only in those born in spring.

Previous association studies of the *BDNF* gene in personality traits mainly focused on Val66Met due to its functional significance (Egan et al., 2003). Animal and human studies demonstrated that *BDNF* Met/Met-genotype (Chen et al., 2006; Montag et al., 2010) and Met-allele (Jiang et al., 2005) was associated with higher anxiety-related traits as compared with Val/Val homozygotes. However, some other studies are in agreement with the present findings showing that Met-allele is associated with lower Neuroticism (Lang et al., 2005; Sen et al., 2003) and Harm Avoidance (Ando et al., 2012).

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 et al., 2009). 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., 2012b); this might also explain why lower Harm Avoidance was associated with BDNF level in spring borns.

To our best knowledge, the present study is the first one to explore the modifying effect of SOB on genetic association of the *BDNF* gene with personality traits. Previously, interaction effects between the dopamine D4 receptor gene (*DRD4*) and SOB on personality traits (Roussos et al., 2010) and on preference for reciprocal fairness in economic game (Zhong et al., 2010) have been reported. At the same time, the influence of SOB on adult monoamine neurotransmitter turnover is well known (Chotai and Adolfsson, 2002) with a number of studies indicating the involvement of serotoninergic system genes in anxiety-related traits variation (Munafo et al., 2009). Several studies have indicated *BDNF* Val66Met × *5-HTTLPR* interaction effect on anxiety-related traits

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). Hiio 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-alelle 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 gray 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 G-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 (Grucza 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 (Simes 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.

Acknowledgments

This work was supported by the grant of Russian Foundation for Humanities (13-06-00583a).

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

Ando T, Ishikawa T, Hotta M, Naruo T, Okabe K, Nakahara T, et al. No association of brain-derived neurotrophic factor Val66Met polymorphism with anorexia nervosa in Japanese. Am J Med Genet B Neuropsychiatr Genet 2012;159B(1):48–52.
Antonsen JH, Gonda X, Dome P, Rihmer Z. Associations between season of birth and suicide: a brief review. Neuropsychopharmacol Hung 2012;14(3):177–87.
Arias B, Aguilera M, Moya J, Sáiz PA, Villa H, Ibáñez MI, et al. The role of genetic variability in the SLC6A4, BDNF and GABRA6 genes in anxiety-related traits. Acta Psychiatr Scand 2012;125(3):194–202.
Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics 2005;15(21(2)):263–5.
Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 1995;57(1):289–300.
Blegen MB, Kennedy BC, Thibert KA, Gewirtz JC, Tran PV, Georgieff MK. Multigenerational effects of fetal–neonatal iron deficiency on hippocampal BDNF signaling. Physiol Rep 2013;1(5):e00096.
Bocchio-Chiavetto L, Bagnardi V, Zanardini R, Molteni R, Nielsen MG, Placentino A, et al. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. World J Biol Psychiatry 2010;11(6):763–73.
Bouchard Jr TJ, Loehlin JC. Genes, evolution, and personality. Behav Genet 2001;31:243–73.
Brown GW, Craig TK, Harris TO, Herbert J, Hodgson K, Tansey KE, et al. Functional polymorphism in the brain-derived neurotrophic factor gene interacts with stressful life events but not childhood maltreatment in the etiology of depression. Depress Anxiety 2013. http://dx.doi.org/10.1002/da.22221. [Epub Dec 12].
Caputo V, Sinibaldi L, Fiorentino A, Parisi C, Catalanotto C, Pasini A, et al. Brain derived neurotrophic factor (BDNF) expression is regulated by microRNAs miR-26a and miR-26b allele-specific binding. PLoS One 2011;6(12):e28656.
Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, et al. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. Science 2006;314:140–3.

Chotai J, Adolfsson R. Converging evidence suggests that monoamine neurotransmitter turnover in human adults is associated with their season of birth. Eur Arch Psychiatry Clin Neurosci 2002;252(3):130–4.
Chotai J, Joukamaa M, Taanila A, Lichtermann D, Miettunen J. Novelty seeking among adult women is lower for the winter borns compared to the summer borns: replication in a large Finnish birth cohort. Compr Psychiatry 2009;50(6):562–6.
Chowanadisai W, Kelleher SL, Lönnerdal B. Maternal zinc deficiency reduces NMDA receptor expression in neonatal rat brain, which persists into early adulthood. J Neurochem 2005;94(2):510–9.
Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993;50:975–90.
Colzato LS, Van der Does AJ, Kouwenhoven C, Elzinga BM, Hommel B. BDNF val66met polymorphism is associated with higher anticipatory cortisolstress response, anxiety, and alcohol consumption in healthy adults. Psychoneuroendocrinology 2011;36(10):1562–9.
Comasco E, Sylvén SM, Papadopoulos FC, Oreland L, Sundström-Poromaa I, Skalkidou A. Postpartum depressive symptoms and the BDNF Val66Met functional polymorphism: effect of season of delivery. Arch Womens Ment Health 2011;14(6):453–63.
Comasco E, Hahn A, Ganger S, Gingnell M, Bannbers E, Oreland L, et al. Emotional fronto-cingulate cortex activation and brain derived neurotrophic factor polymorphism in premenstrual dysphoric disorder. Hum Brain Mapp 2014. http://dx.doi.org/10.1002/hbm.22486. [Feb 25., Epub ahead of print].
Cunningham WA, Zelazo PD. Attitudes and evaluations: a social cognitive neuroscience perspective. Trends Cogn Sci 2007;11(3):97–104.
De Beaumont L, Fiocco AJ, Quesnel G, Lupien S, Poirier J. Altered declarative memory in introverted middle-aged adults carrying the BDNF val66met allele. Behav Brain Res 2013;253:152–6.
de Moor MH, Costa PT, Terracciano A, Krueger RF, de Geus EJ, Toshiko T, et al. Meta-analysis of genome-wide association studies for personality. Mol Psychiatry 2012;17(3):337–49.
Dhobale M, Joshi S. Altered maternal micronutrients (folic acid, vitamin B(12)) and omega 3 fatty acids through oxidative stress may reduce neurotrophic factors in preterm pregnancy. J Matern Fetal Neonatal Med 2012;25(4):317–23.
Duclot F, Kabbaj M. Individual differences in novelty seeking predict subsequent vulnerability to social defeat through a differential epigenetic regulation of brain-derived neurotrophic factor expression. J Neurosci 2013;33(27):11048–60.
Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, et al. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 2003;112(2):257–69.
Frustaci A, Pozzi G, Gianfagna F, Manzoli L, Boccia S. Meta-analysis of the brain-derived neurotrophic factor gene (BDNF) Val66Met polymorphism in anxiety disorders and anxiety-related personality traits. Neuropsychobiology 2008;58(3–4):163–70.
Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, et al. The structure of haplotype blocks in the human genome. Science 2002;296(5576):2225–9.
Garcia D, Lundström S, Brändström S, Råstam M, Cloninger CR, Kerekes N, et al. Temperament and character in the Child and Adolescent Twin Study in Sweden (CATSS): comparison to the general population, and genetic structure analysis. PLoS One 2013;8(8):e70475.
Gauderman WJ. Sample size requirements for matched case–control studies of gene–environment interaction. Stat Med 2002;21(1):35–50.
Golimbet V, Alfimova M, Korovaitseva G, Abramova LI, Kaled VG. Emotional distress in parents of psychotic patients is modified by serotonin transporter gene (5-HTTLPR)–brain-derived neurotrophic factor gene interactions. Span J Psychol 2009;12(2):696–706.
Grucza RA, Goldberg LR. The comparative validity of 11 modern personality inventories: predictions of behavioral acts, informant reports, and clinical indicators. J Pers Assess 2007;89:167–87.
Gyekis JP, Yu W, Dong S, Wang H, Qian J, Kota P, et al. No association of genetic variants in BDNF with major depression: a meta- and gene-based analysis. Am J Med Genet B Neuropsychiatr Genet 2013;162B(1):61–70.
Hajek T, Kopecek M, Höschl C. Reduced hippocampal volumes in healthy carriers of brain-derived neurotrophic factor Val66Met polymorphism: meta-analysis. World J Biol Psychiatry 2012;13(3):178–87.
Hiio K, Merenäkk L, Nordquist N, Parik J, Oreland L, Veidebaum T, et al. Effects of serotonin transporter promoter and BDNF Val66Met genotype on personality traits in a population representative sample of adolescents. Psychiatr Genet 2011;21(5):261–4.
Hong CJ, Liou YJ, Tsai SJ. Effects of BDNF polymorphisms on brain function and behavior in health and disease. Brain Res Bull 2011;86(5–6):287–97.
Hori H, Teraishi T, Sasayama D, Matsuo J, Kawamoto Y, Kinoshita Y, et al. Relationships between season of birth, schizotypy, temperament, character and neurocognition in a non-clinical population. Psychiatry Res 2012;195(1–2):69–75.
Hosang GM, Shiles C, Tansey KE, McGuffin P, Uher R. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med 2014;12(1):7.
Itoh K, Hashimoto K, Kumakiri C, Shimizu E, Iyo M. Association between brain-derived neurotrophic factor 196G/A polymorphism and personality traits in healthy subjects. Am J Med Genet B Neuropsychiatr Genet 2004;124B(1):61–3.
Jiang X, Xu K, Hoberman J, Tian F, Marko AJ, Waheed JF, et al. BDNF variation and mood disorders: a novel functional promoter polymorphism and Val66Met are associated with anxiety but have opposing effects. Neuropsychopharmacology 2005;30:1353–61.
Kambeitz JP, Bhattacharyya S, Kambeitz-Ilankovic LM, Valli I, Collier DA, McGuire P. Effect of BDNF val(66)met polymorphism on declarative memory and its neural substrate: a meta-analysis. Neurosci Biobehav Rev 2012;36(9):2165–77.
Kazantseva AV, Gaysina DA, Faskhutdinova GG, Noskova T, Malykh SB, Khusnutdinova EK. Polymorphisms of the serotonin transporter gene (5-HTTLPR, A/G SNP in 5-HTTLPR, and STin2 VNTR) and their relation to personality traits in healthy individuals from Russia. Psychiatr Genet 2008;18(4):167–76.
Keller MC. Gene × environment interaction studies have not properly controlled for potential confounders: the problem and the (simple) solution. Biol Psychiatry 2014;75(1):18–24.
Kleim JA, Chan S, Pringle E, Schallert K, Procaccio V, Jimenez R, et al. BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. Nat Neurosci 2006;9(6):735–7.
Lang UE, Hellweg R, Gallinat J. BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits. Neuropsychopharmacology 2004;29(4):795–8.
Lang UE, Hellweg R, Kalus P, Bajbouj M, Lenzen KP, Sander T, et al. Association of a functional BDNF polymorphism and anxiety-related personality traits. Psychopharmacology (Berl) 2005;180(1):95–9.
Martínez-Ortega JM, Carretero MD, Gutiérrez-Rojas L, Díaz-Atienza F, Jurado D, Gurpegui M. Winter birth excess in schizophrenia and in non-schizophrenic psychosis: sex and birth-cohort differences. Prog Neuropsychopharmacol Biol Psychiatry 2011;35(7):1780–4.
Minelli A, Zanardini R, Bonvicini C, Sartori R, Pedrini L, Gennarelli M, et al. BDNF serum levels, but not BDNF Val66Met genotype, are correlated with personality traits in healthy subjects. Eur Arch Psychiatry Clin Neurosci 2011;261(5):323–9.
Modarresi F, Faghihi MA, Lopez-Toledano MA, Fatemi RP, Magistri M, Brothers SP, et al. Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation. Nat Biotechnol 2012;30(5):453–9.
Molendijk ML, Haffmans JP, Bus BA, Spinhoven P, Penninx BW, Prickaerts J, et al. Serum BDNF concentrations show strong seasonal variation and correlations with the amount of ambient sunlight. PLoS One 2012;7(11):e48046.
Montag C, Weber B, Fliessbach K, Elger C, Reuter M. The BDNF Val66Met polymorphism impacts parahippocampal and amygdala volume in healthy humans: incremental support for a genetic risk factor for depression. Psychol Med 2009;39(11):1831183–9.
Montag C, Basten U, Stelzel C, Fiebach CJ, Reuter M. The BDNF Val66Met polymorphism and anxiety: support for animal knock-in studies from a genetic association study in humans. Psychiatry Res 2010;179(1):86–90.
Montag C, Eichner M, Markett S, Quesada CM, Schoene-Bake JC, Melchers M, et al. An interaction of a NR3C1 polymorphism and antenatal solar activity impacts both hippocampus volume and neuroticism in adulthood. Front Hum Neurosci 2013;7:243.
Montag C. The brain derived neurotrophic factor and personality. Adv Biol 2014. http://dx.doi.org/10.1155/2014/719723. [15 pages, article ID 719723, Epub ahead of print].
Monteggia LM, Luikart B, Barrot M, Theobold D, Malkovska I, Nef S, et al. Brain-derived neurotrophic factor conditional knockouts show sex differences in depression-related behaviors. Biol Psychiatry 2007;61:187–97.
Munafo MR, Freimer NB, Ng W, Ophoff R, Veijola J, Miettunen J, et al. 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. Am J Med Genet B Neuropsychiatr Genet 2009;150B(2):271–81.
Nakazato M, Hashimoto K, Shimizu E, Kumakiri C, Koizumi H, Okamura N, et al. Decreased levels of serum brain-derived neurotrophic factor in female patients with eating disorders. Biol Psychiatry 2003;54(4):485–90.
Perroud N, Salzmann A, Prada P, Nicastro R, Hoeppli ME, Furrer S, et al. Response to psychotherapy in borderline personality disorder and methylation status of the BDNF gene. Transl Psychiatry 2013;3:e207.
Pezawas L, Verchinski BA, Mattay VS, Callicott JH, Kolachana BS, Straub RE, et al. The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology. J Neurosci 2004;24(45):10099–102.
Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–75.
Rasmusson AM, Shi L, Duman R. Downregulation of BDNF mRNA in the hippocampal dentate gyrus after re-exposure to cues previously associated with footshock. Neuropsychopharmacology 2002;27(2):133–42.
Rihmer Z, Erdos P, Ormos M, Fountoulakis KN, Vazquez G, Pompili M, et al. Association between affective temperaments and season of birth in a general student population. J Affect Disord 2011;132(1–2):64–70.
Roussos P, Giakoumaki SG, Bitsios P. Cognitive and emotional processing associated with the season of birth and dopamine D4 receptor gene. Neuropsychologia 2010;48(13):3926–33.
Sen S, Nesse RM, Stoltenberg SF, Li S, Gleiberman L, Chakravarti A, et al. A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. Neuropsychopharmacology 2003;28:397–401.
Shalev I, Lerer E, Israel S, Uzefovsky F, Gritsenko I, Mankuta D, et al. BDNF val66met polymorphism is associated with HPA axis reactivity to psychological stress characterized by genotype and sex interactions. Psychoneuroendocrinology 2009;34(3):382–8.
Shifman S, Bhomra A, Smiley S, Wray NR, James MR, Martin NG, et al. A whole genome association study of neuroticism using DNA pooling. Mol Psychiatry 2008;13(3):302–12.
Shimizu E, Hashimoto K, Okamura N, Koike K, Komatsu N, Kumakiri C, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 2003;54(1):70–5.
Shuman NK, Krug I, Maxwell M, Pinheiro AP, Brewerton T, Thornton LM, et al. Is season of birth related to disordered eating and personality in women with eating disorders? Eat Weight Disord 2010;15(3):e186–9.
Terracciano A, Sanna S, Uda M, Deiana B, Usala G, Busonero F, et al. Genome-wide association scan for five major dimensions of personality. Mol Psychiatry 2010a;15(6):647–56.
Terracciano A, Martin B, Ansari D, Tanaka T, Ferrucci L, Maudsley S, et al. Plasma BDNF concentration, Val66Met genetic variant and depression-related personality traits. Genes Brain Behav 2010b;9(5):512–8.
Terracciano A, Tanaka T, Sutin AR, Deiana B, Balaci L, Sanna S, et al. BDNF Val66Met is associated with introversion and interacts with 5-HTTLPR to influence neuroticism. Neuropsychopharmacology 2010c;35(5):1083–9.
Terracciano A, Esko T, Sutin AR, de Moor MH, Meirelles O, Zhu G, et al. Meta-analysis of genome-wide association studies identifies common variants in CTNNA2 associated with excitement-seeking. Transl Psychiatry 2011a;1:e49.

Terracciano A, Lobina M, Piras MG, Mulas A, Cannas A, Meirelles O, et al. Neuroticism, depressive symptoms, and serum BDNF. Psychosom Med 2011b;73(8):638–42.
Terracciano A, Piras MG, Lobina M, Mulas A, Meirelles O, Sutin AR, et al. Genetics of serum BDNF: meta-analysis of the Val66Met and genome-wide association study. World J Biol Psychiatry 2013;14(8):583–9.
Trajkovska V, Vinberg M, Aznar S, Knudsen GM, Kessing LV. Whole blood BDNF levels in healthy twins discordant for affective disorder: association to life events and neuroticism. J Affect Disord 2008;108(1–2):165–9.
Uher R, Huezo-Diaz P, Perroud N, Smith R, Rietschel M, Mors O, et al. Genetic predictors of response to antidepressants in the GENDEP project. Pharmacogenomics J 2009;9(4):225–33.
Yasui-Furukori N, Tsuchimine S, Kaneda A, Sugawara N, Ishioka M, Kaneko S. Association between plasma brain-derived neurotrophic factor levels and personality traits in healthy Japanese subjects. Psychiatry Res 2013;210(1):220–3.
Zhong S, Israel S, Shalev I, Xue H, Ebstein RP, Chew SH. Dopamine D4 receptor gene associated with fairness preference in ultimatum game. PLoS One 2010;5(11):e13765.