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Research paper

Interaction between job stress and the *BDNF* Val66Met polymorphism affects depressive symptoms in Chinese healthcare workers

Shu-Chang He[a,*], Shuang Wu[a], Chao Wang[a], Xiang-Dong Du[b], Guangzhong Yin[b], Qiufang Jia[b], Yingyang Zhang[b], Li Wang[c], Jair C. Soares[d], Xiang Yang Zhang[c,d,**]

[a] School of Psychological and Cognitive Sciences and Beijing Key Laboratory of Behavior and Mental Health, Peking University, 5 Yiheyuan Road, Haidian district, Beijing100871 China

[b] Suzhou Psychiatric Hospital, The Affiliated Guangji Hospital of Soochow University, Jiangsu, China

[c] Institute of Psychology, Chinese Academy of Sciences, Beijing, China

[d] Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, 1941 East Road, Houston, TX 77054, USA

A B S T R A C T

Background: Chronic exposure to job-related stress can lead to depression and *BDNF* polymorphism may play an important role in this process. The role of the stress × *BDNF* Val66Met interaction in depression has been studied widely using childhood stress, but few studies have utilized chronic stress in adulthood as a moderator. This study was to examine the chronic stress × *BDNF* Val66Met interaction in job-related depression in the healthcare workers in a Chinese Han population, which has not been reported yet.

Methods: Using a cross-sectional design, 243 doctors and nurses were recruited from a general hospital in Beijing, and were assessed for depression with Self-rating Depression Scale (SDS), and the stress using the House and Rizzo's Work Stress Scale. The *BDNF* Val66Met polymorphism was genotyped.

Results: There was a significant positive association between job stress and depressive scores ($p < 0.001$). No significant main effect of the *BDNF* Val66Met genotype on depressive symptoms was observed ($p > 0.05$). A statistically significant interaction between *BDNF* Val66Met and job stress on depressive symptoms was found ($p < 0.05$); individuals with Val/Val genotype showed a higher SDS score than Met allele carriers only in the low-stress group, without significant differences in SDS score between the *BDNF* Val66Met subgroups in medium- or high-stress group.

Limitations: Limitations include cross-sectional study design, the small sample size only in healthcare workers and only one polymorphism in *BDNF* gene was analyzed.

Conclusions: Our results suggest a close relationship between job-related stress and depression, and the interaction of the *BDNF* Val66Met polymorphism and chronic stress in adulthood may impact the depressive symptoms.

1. Introduction

Job stress is usually defined as an adverse relationship of person and work environment in which work tasks exceed an individual's knowledge, skills, or ability, inhibiting one's behavior to cope and triggering a lot of psychological and physical issues (Lazarus and Folkman, 1984). Due to the nature of their jobs, the individuals working in healthcare professions are exposed to chronically high levels of stress, making them particularly susceptible to job stress-related mental health problems (McVicar, 2003; Chou et al., 2014). Many studies have shown that the long-term stressful work conditions lead to depressive symptoms (Ahola and Hakanen, 2007). Moreover, the researchers have used stress paradigms as the model of depression for a long time (Willner, 1997). Depression is a common mental disorder among healthcare workers with complex origins that is linked with considerable morbidity and mortality (Kiecolt-Glaser and Glaser, 2002; Cheung and Yip 2015; Wurm et al., 2016). For example, a study of 3474 nurses showed that 38% of nurses had depressive symptoms, and they reported tension in nurse–patient relationships and work load as the main reasons for those symptoms (Gong et al., 2014). A series of consequences may be caused by depression, including sleep problems, physical illness, and even impaired cognitive performance (Asarnow et al., 2013;

* Corresponding author.

** Corresponding author at: Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, 1941 East Road, Houston, TX 77054, USA

E-mail addresses: shuchangh@pku.edu.cn (S.-C. He), xiang.y.zhang@uth.tmc.edu (X.Y. Zhang).

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Clarke et al., 2009; Rock et al., 2014). Further, depression not only endangers the health and well-being of occupational staff themselves, but also is associated with lower job performance and work productivity (Lerner and Henke, 2008). The projection for depression has become the second most common cause of disability by 2020 (Moussavi et al., 2007). Therefore, it is necessary to understand the relevant risk factors and susceptibility of depression.

Although many risk factors for depression have been identified, the underlying mechanisms for depression are still unknown. Both environmental factors, such as stressful life events (SLEs), and genetic predisposition play an important role in the etiology of depression (Levinson, 2006), highlighting the importance of gene–environment interactions. Brain derived neurotrophic factor (BDNF), an important member of the neurotrophin family, is a protein with a broad range of activities in the central nervous system, such as the regulation of synaptic function, synaptic plasticity and the promotion of neuronal survival (Hyman et al., 1991;Kowianski et al., 2017), suggesting its implication for synaptogenesis and neurogenesis, especially for hippocampal neurogenesis (Kowianski et al., 2017). Many studies have shown that BDNF plays a central role in the neuropathology of depression by modulating the neuroplastic response (Brunoni et al., 2008; Jiang et al., 2013). The neurotrophin hypothesis of depression, one of leading hypotheses to explain the etiology and clinical course of this disorder, proposes that depression results from stress-induced reduction of BDNF expression levels while increases in BDNF levels could cause an antidepressant effect (Martinowich et al., 2007; Molendijk et al., 2014). Decreased brain levels of BDNF could contribute to cell loss and neuronal atrophy in the hippocampus and prefrontal cortex in depressed subjects (Duman and Monteggia, 2006). A meta-analyses study found reduced serum BDNF levels in major depression patients, indicating peripheral BDNF alteration in depression (Bocchio-Chiavetto et al., 2010).

The *BDNF* Val66Met polymorphism (rs6265) leads to an amino acid substitution from valine to methionine at codon 66 that alters intracellular trafficking and secretion of BDNF (Egan et al., 2003). Many studies have examined the association of this functional *BDNF* val66met polymorphism with depression, with mixed results. Some studies reported positive association (Ribeiro et al., 2007; Taylor et al., 2007; Licinio et al., 2009; Verhagen et al., 2010; Czira et al., 2012), but others did not (Gratacos et al., 2008; Surtees et al., 2007; Chen et al., 2008). However, some studies did not find a significant association of *BDNF* Val66Met with depressive symptom (Brown et al., 2014). These contradictory associations between both alleles and increased depressive levels suggest that the environmental factors may regulate the impact of val66met on BDNF expression and thus the association of *BDNF* genotype with depression or depressive symptoms (Jiang et al., 2013).

Increasing evidence shows that chronic stress may moderate the association between *BDNF* Val66Met and depressive symptoms, since this polymorphism has been found to be involved in stress-sensitivity, depressive states and the development of brain structures related to emotional processing and depression, like the hippocampus and amygdala (Joffe et al., 2009; van Wingen et al., 2010). Some studies reported that the influence of early life stress on depression is moderated by *BDNF* Val66Met, which may be related to stress-mediated damage to hippocampus and amygdala (Gatt et al., 2009, 2010). Interestingly, they also found that the combination of *BDNF* Met carriers and exposure to early life stress predicted reduced gray matter in hippocampus and poorer working memory (Gatt et al., 2009, 2010). Moreover, a previous study reported that childhood sexual abuse had a greater impact on depressive symptoms in Met carriers of *BDNF* gene than in Val/Val group in young adults (Aguilera et al., 2009). These results suggest that effects of early life stress on stress are more prominent in *BDNF* Met carriers (Jiang et al., 2013).

However, the effects of childhood stress on adult depressive symptoms may be different from the effects of chronic stress in adulthood. A recent systematic meta-analysis found that the Met allele of *BDNF* Val66Met could moderate the influence of life stress (childhood adversity and recent stressful events) on depression, and the effect of stressful life events was stronger than childhood adversity (Hosang et al., 2014). Up to date, however, the interaction between *BDNF* Val66Met and chronic stress in adulthood has received much less attention. Only one study evaluated the impact of the interaction of *BDNF* Val66Met and chronic stress caused by caregiving for a spouse or relative diagnosed with dementia and chronic burden from self-reported health problems, job, finance and relationship problems in adulthood on depressive symptoms (Jiang et al., 2013), showing that the main effect of this genotype on depressive symptoms was non-significant, but the *BDNF* Val66Met genotype by adulthood chronic stress interaction was significant. Moreover, the impact of chronic stress in adulthood on depressive symptoms was significantly larger in Val/Val genotype individuals than Met carriers (Jiang et al., 2013).

In view of the close relationship between depression and job stress, and the important role of *BDNF* Val66Met in the risk of developing depression, especially the gene × stress interactions (G × E) on depression, it would be of interest to examine the interaction of *BDNF* Val66Met and job stress in adulthood depression, which, to our best knowledge, has not been reported in a Chinese Han sample. We hypothesized that the impact of the interaction of *BDNF*Val66Met and chronic job stress on depressive symptoms may be significant, and the effects of job stress on depression may be greater in *BDNF* Met carriers.

2. Materials and methods

2.1. Participants

Using a cross-sectional design, 243 healthy Han Chinese doctors and nurses (97 men and 146 women) were recruited from a general hospital in Beijing from June 2015 to May 2016. They were between 18 and 62 years old (average: 31.8 ± 9.2 years) from 20 clinical departments of the hospital. General and socio-demographic information of participants was collected in face-to-face interviews. A clinical interview was used to exclude potential subjects with Axis I disorders on DSM-IV by a research psychiatrist, who ruled out any psychiatric disorders in their lifetime or at present, including a variety of anxiety disorders, major depressive disorder, bipolar disorder, schizophrenia, attention deficit/hyperactivity disorder, drug abuse/addiction and any other psychiatric illnesses. In addition, a complete medical history, physical examination, and laboratory tests were obtained from all subjects. All participants were in good physical health without any physical diseases, and no one was taking medications and abusing drugs.

The protocol and explanatory documents of this study was approved by the Institutional Review Board (IRB) of Peking University. After a full description of our study was provided, all the participants understood the aim of the study and completed a written informed consent.

2.2. Clinical measures

Participants completed a self-report inventory for job stress using the Chinese version of the House and Rizzo's Work Stress Scale (House and Rizzo, 1972). It contains 11 items, each of which consists of a 6-point rating scale (1 = completely disagree to 6 = completely agree). The total score ranges from 11 to 66 points and a higher score indicates the greater stress individuals experience in their jobs. In the current study, the internal consistency coefficient was 0.89.

The level of depression was measured using the Chinese version of Zung's Self-rating Depression Scale, which was recommended as one of scales for the psychopharmacology research by the U.S. Department of Health, Education and Welfare (Zung, 1965). This is a self-report questionnaire with 20 items, rating on a scale of 1–4. The total score ranges from 20 to 80. A higher score indicates higher levels of depression. Many previous studies have shown that this scale has good reliability and validity (Lin et al., 2016).

Generally, these stress and depression testing were performed in the morning from 9 a.m. to 11 a.m. and on the same day as the blood samples were taken.

2.3. Blood sampling and serum BDNF measurements

Serum samples were collected between 7 and 9 a.m. following an overnight fast. Serum BDNF levels were measured by sandwich enzyme linked immunosorbent assay using a commercially available kit. This assay was fully described in our previous report (Zhang et al., 2012). All blood samples were assayed by a research assistant blind to the clinical situation. Inter- and intra-assay variation coefficients were 8% and 5%, respectively.

2.4. Genotyping

All participants gave a 3-ml fasting venous blood sample at 8 a.m. for *BDNF* genotyping. Genomic DNA was extracted from lymphocytes using a genomic DNA purification kit (Beijing Thinkout Sci-Tech Co., Ltd.). DNA fragments of *BDNF* Val66Met were amplified by the polymerase chain reaction. We designed the primers using primer premier 6.0 software, with 2nd-PCRP: ACGTTGGATGCGAACTTTCTGGTCCTC ATC, and 1st-PCRP: ACGTTGGATG GGTTCAAGAGGCTTGACATC; UEP_SEQ: CATCCAACAGCTCTTCTATCA. The *BDNF* Val66Met was genotyped using the high-throughput genotyping platform, performed by Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS) in the Mass ARRAY System (Sequenom Inc., San Diego, CA, USA). Genotyping was repeated in 5% of samples for verification and quality control. Quality control testing revealed that genotype data had an error rate of $<0.1\%$.

2.5. Statistical analysis

Statistical analysis was carried out using the SPSS ver. 21.0. The Hardy–Weinberg equilibrium for genotype distribution was tested using the χ^2 test for goodness of fit. The power of the sample was calculated using Quanto Software (Gauderman, 2002), with known risk allele frequencies (0.477 in the present study) and a depression population prevalence of 2.68%. We examined recessive and dominant models.

All demographic and clinical variables, job stress and depression scores were normally distributed in the participants (Kolmogorov–Smirnov one sample test; all $p > 0.05$). Thus, these parameters among different groups were compared using analysis of variance (ANOVA) for continuous variables and chi-squared for categorical variables. Pearson correlation analysis was used to assess the correlations between variables including job stress and depression. Bonferroni corrections were applied to each test to adjust for multiple testing. Further, we used the average of job stress as cut off to divide into three subgroups: low, medium and or high-stress subgroups. One-way ANOVA was then used to examine demographic characteristics in different job stress subgroups and differences in stress/depression levels between *BDNF* Val66Met genotypes. In addition, based on the recommendation made by Uher et al., (2011), we used generalized linear models controlling for covariate to test the *BDNF* Val66Met genotype and job stress interaction in depression. We used $p < 0.05$ as the significance level for all tests. Data are presented as mean ± SD.

3. Results

The participants ($n = 243$) were from 20 departments and 67% of them had a junior college or university degree. The mean depression scores of the participants were 33.8 ± 8.0. Table 1 shows a significant difference in educational level ($p = 0.011$; Bonferroni corrected $p < 0.05$) between the different depression groups, with higher depression in advanced degree subgroup. Also, Table 1 shows significant differences in job stress score between the age groups, or between the education groups (both $p < 0.001$; Bonferroni correctred $p < 0.01$), with higher job stress in young subgroup or in advanced degree subgroup.

Table 1
Analysis of job stress and depression score according to demographic data ($n = 243$).

Characteristic	Number (Percentage)	Job stress	Depressive symptoms
Gender			
Male	97(39.9%)	29.94 ± 12.067	32.87 ± 6.986
Female	146(62.4%)	31.14 ± 10.317	34.48 ± 8.538
p value		$p = 0.408$	$p = 0.123$
Age in years			
<30	119(49.0%)	31.66 ± 10.696	34.27 ± 8.152
30–39	78(32.1%)	32.55 ± 11.091	34.29 ± 8.086
40–49	28(11.5%)	26.50 ± 10.373	30.96 ± 5.412
≥50	18(7.4%)	22.33 ± 9.375	33.44 ± 9.294
p value		$p < 0.001$	$p = 0.234$
Education			
High school below	32(14.0%)	22.19 ± 9.992	30.13 ± 6.862
Junior college	72(31.4%)	30.18 ± 10.020	34.08 ± 7.832
Bachelor above	125(54.6%)	33.26 ± 10.831	34.82 ± 8.020
p value		$p < 0.001$	$p = 0.011$

Note: One-way ANOVA was used to examine differences of job stress and depression among different gender, age and education groups.

There was a significant positive correlation between job stress and depression ($r = 0.554$, df = 243, $p < 0.001$), suggesting a close relationship between job stress and depression.

Table 2 shows the demographic characteristics and BDNF serum levels in different job stress groups. Job stress was divided into three subgroups according to mean ± SD of the House and Rizzo's Work Stress Scale score: high stress group, at least 1 SD above the mean score (>43.49); low stress group, at least 1 SD below the mean score (<21.07); and middle stress group, score between high and low group (21.07–43.49). Thus, 37 (15.2%), 166 (68.3%) and 40 (16.5%) participants were in the low, middle and high work stress groups, respectively. Serum BDNF levels were available from 19 subjects in low-stress, 166 in middle-stress and 40 in high-stress groups. There was a significant difference in BDNF levels among three different job stress groups ($F = 5.025$, df = 2, 124, $p = 0.008$; Bonferroni corrected $p = 0.024$), with lower BDNF levels in high-stress group. In addition, a significant difference in age was also found in different job stress group, with younger subjects having higher job stress.

Genotyping was available for all 243 subjects, showing 57 (23.46%) with Met/Met, 118 (48.56%) with Val/Met and 68 (27.98%) with Val/Val. The $\chi 2$ goodness-of-fit test showed that the genotypic distributions of the *BDNF* Val66Met were consistent with Hardy–Weinberg equilibrium ($\chi 2 = 1.14$, $p = 0.286$).

As shown in Table 3, no significant differences in job stress were found between the Val66Met genotypes (all $p > 0.05$). In addition, one-way ANOVA revealed no significant main effect of Val66Met on depression ($p > 0.05$), suggesting that *BDNF* Val66Met genotype might not directly influence depression. Further, one-way ANOVA revealed no significant main effect of Val66Met on BDNF levels ($p > 0.05$).

We further compared the depression score of the three genotype groups in the low-stress group, middle-stress group and the high-stress group, respectively. Fig. 1 showed a statistically significant interaction between *BDNF* Val66Met and job stress in depressive symptoms ($F = 4.057$, df = 2, 234, $p = 0.019$; Bonferroni corrected $p > 0.05$) (Fig.1). After adjusting for covariants including educational level, age and gender, this significance remained ($F = 2.54$, df = 5, 234, $p = 0.041$; Table 4). In the low-stress group, the Met allele carriers had significantly lower depressive score than Val homozygote (28.00 ± 6.20 *vs.* 34.83 ± 9.95; $F = 4.98$, df = 1,35, $p = 0.032$),

Table 2
Demographic characteristics in different job stress groups.

Characteristics	Low-stress group (n = 37)	Middle-stress group (n = 166)	High-stress group (n = 40)	F/x^2	df	p
Gender (F/M)	16/21	104/62	26/14	5.234	2	0.073
Age (years)	37.89 ± 12.267 (n = 19)	31.21 ± 8.831 (n = 82)	29.80 ± 5.459 (n = 26)	9.768	2240	< 0.001
BDNF(ng/ml)	13.71 ± 4.626	11.73 ± 4.617	9.59 ± 3.134	5.025	2124	0.008

Notes: Demographic, BDNF serum levels of the different job stress groups were compared using one-way ANOVA for continuous variables, and chi-squared for categorical variables.

Table 3
The job stress and depression grouped by *BDNF* genes.

		Job stress	Depression
Val66Met	Val/Val	32.49 ± 10.520	33.84 ± 7.309
	Val/Met	32.45 ± 11.353	33.77 ± 7.807
	Met/Met	30.21 ± 11.668	33.96 ± 9.157
	F	1.390	0.011
	P	0.250	0.989
	95%CI	(29.26,32.05)	(32.07,35.61)

Note: One-way ANOVA was used to detect differences of level of stress/ depression between different genotypes of *BDNF* Val66Met (Val/Val; Val/Met; Met/Met). No significant difference was found.

while in the high-stress group, the Met allele carriers had non-significantly higher depressive score in comparison to Val homozygote (43.93 ± 7.44 *vs* 40.15 ± 6.479; $F = 2.441$, df = 1,38, $p = 0.12$), although without significant difference probably due to limited sample size. In the medium-stress group, there was no significant difference in depressive score between Met allele carriers and Val homozygote (33.05 ± 6.79 *vs* 32.04 ± 6.29; $F = 0.797$, df = 1,164, $p = 0.37$).

4. Discussion

In this study, we had the following major findings. (1) Exposure to job stress was associated with depression in healthcare workers. (2)

Table 4
The interaction between job stress and *BDNF* Val66Met on depression adjusted for covariates.

	Sum of squares	df	Mean square	*F*	Sig.
Gender	22.766	1	22.766	0.494	0.483
Age	0.006	1	0.006	0.000	0.991
Education	5.650	1	5.650	0.123	0.726
Stress	3294.275	2	1647.137	35.762	0.000***
Val66Met	28.781	2	14.391	0.312	0.732
Stress × Val66Met	486.465	4	117.116	2.543	0.041*

Note: Gender, age, and education as covariates.
* $p < 0.05$.
*** $p < 0.001$.

There was no significant association between *BDNF* Val66Met polymorphism and depressive symptoms. (3) We found a significant association between serum BDNF and job stress, showing lower BDNF levels in high-stress group. (4) The *BDNF* Val66Met and job stress interacted to influence depression, showing higher depression level in the *BDNF* Val homozygote compared to Met allele carrier only in the low-stress group. To the best of our knowledge, this is the first study to investigate the gene and stress interaction in job-related depression in a Chinese Han population.

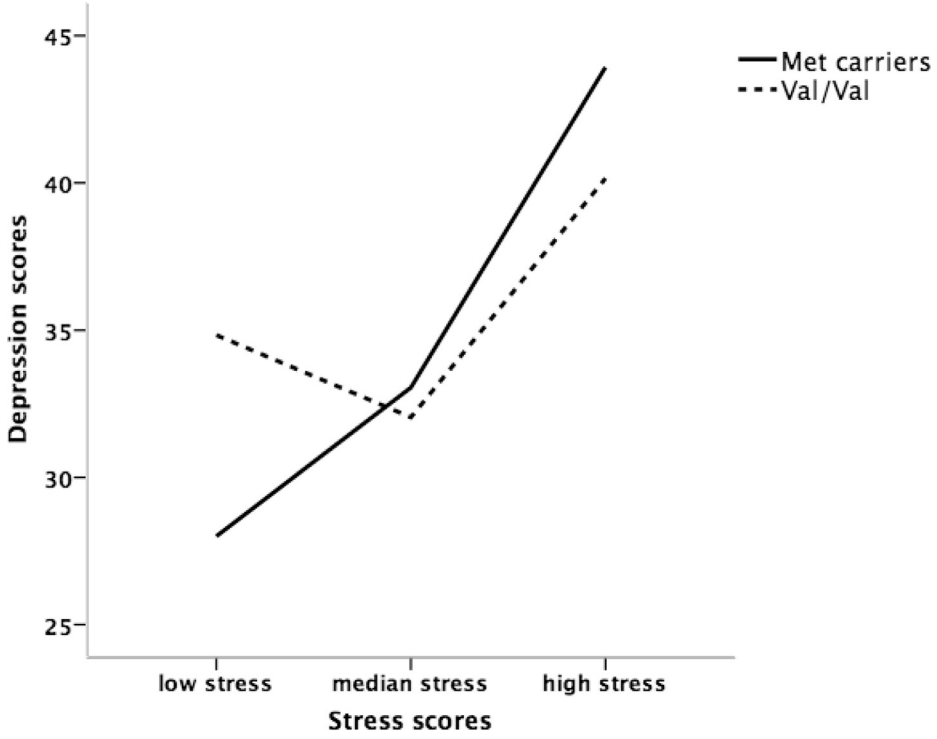

Fig. 1. Interaction between *BDNF* Val66Met genotypes and job stress groups in depression was significant ($F = 4.057$, df = 2, 234, $p = 0.019$).

4.1. The relationship between job stress and depression

We found significant positive correlation between job stress and depression, which passed the Bonferroni correction, suggesting a close relationship between job stress and depression. Also, the finding implys that those individuals under higher job stress may have more depressive symptoms, which are in line with most of previous studies (Iacovides et al., 2003; Clays et al., 2007; Chou et al., 2014). The medical practice is highly stressful especially in a large general hospital in Beijing, since the healthcare workers including the doctors and nurses have to see a lot of patients daily, with excessive and often overtime workload and job demands. Also, they have to face death and suffering of patients, uncertainly of a treatment given to patients, poor outcome, conflict with patients and peers, and lack of social support, which are really big challenges in their work (Chayu and Kreitler 2011; Garrosa et al., 2011). Moreover, the healthcare workers have to take night work, shift work and long work hours very frequently (Chou et al., 2014), which are also very stressful for them. It is well documented that long-term exposure to stressful working environments may lead to depression (Ahola and Hakanen, 2007). Our finding in this study supports this point. Therefore, it is imperative to develop strategies for reducing or managing stressors in hospitals and thus preventing the development of depression among medical personnel.

4.2. The relationship between BDNF Val66Met and depression

We did not find a significant association between *BDNF* Val66Met polymorphism and depression, suggesting that the *BDNF* Val66Met polymorphism appears not to be involved in the development of job-related depression in the Chinese Han population. However, several previous studies reported that the *BDNF* Val66Met was associated with depression or depressive symptoms (Ribeiro et al., 2007; Taylor et al., 2007; Licinio et al., 2009; Verhagen et al., 2010; Czira et al., 2012), but others did not find their association (Gratacos et al., 2008; Surtees et al., 2007; Chen et al., 2008). Interestingly, among those studies reporting positive association, some showed an association between Met/Met and more severe depressive symptoms (Taylor et al., 2007; Verhagen et al., 2010; Czira et al., 2012), whereas others reported such an association between Val/Val and increased depressive trait (Licinio et al., 2009; Ribeiro et al., 2007; Chen et al., 2012). One important reason for this discrepancy is related to the difference in genetic background, since the genotype distribution of the *BDNF* Val66Met polymorphism shows marked difference among different ethnic population. For example, we found that the Met allele frequency was about 40% in this study, which is similar to other reports in Chinese and Korean population (Kim et al., 2007; Yi et al., 2011), but significantly higher than around 20% in Caucasian populations (Pae et al., 2011; Perea et al., 2012; Van et al., 2012). Thus, genetic background differences in the allele frequency distribution of the *BDNF* Val66Met polymorphism may be related to these divergent results in the relationship between the *BDNF* Val66Met polymorphism and depression across the different populations. Other factors may also play a role in accounting for the disagreement of the results, such as clinical diagnosis, small gene effects, population stratification, heterogeneous subjects studied or genotyping errors. In addition, as predicated, we did not find a significant association between serum BDNF levels and Val66Met polymorphism, suggesting that the peripheral BDNF biological functions are not related to Val66Met genotype. It would be interesting to examine the relationship between BDNF serum levels and other polymorphisms.

Interestingly, we found a significantly negative association between serum BDNF and job stress, showing lower BDNF levels in high-stress group. Numerous studies have shown that stress and stress hormones, glucocorticoids (GCs), produce widespread actions in central nervous system, and prolonged exposure to stress and elevated GC levels may result in neuro- and psychopathology (Vyas et al., 2016). Many studies showed a negative influence of systemic administration of GCs on BDNF mRNA expression in hippocampal and cortical regions (Numakawa et al., 2017). Importantly, animal models of depression caused by chronic stress have demonstrated that reduced levels in both BDNF expression and hippocampal neurogenesis occur along with depressive behaviors (Numakawa et al., 2017). Thus, our result of negative association of decreased serum BDNF and high job stress is consistent with these previous studies indicating that low serum BDNF levels were association with stress as well as depression induced by stress.

4.3. The interaction between job stress and BDNF Val66Met in depression

The most important finding in this study was that the participants with *BDNF* Val homozygote had significantly higher depression level in comparison to Met allele carriers only in the low-stress group, suggesting that the *BDNF* Val66Met and job stress interacted to influence depressive symptoms. The interaction between the *BDNF* Val66Met polymorphism and job stress could be explained by two possible theory architectures: the diathesis-stress model and the differential-susceptibility hypothesis (Belsky et al., 2009; Chen et al., 2012). The former proposes that the subjects with 'vulnerability genes' are more susceptible to psychopathology when they have stressful or adverse environmental factors. The latter proposes that the subjects with 'plasticity genes' are more prone to both negative and positive environmental factors, while those with less susceptible gene are not or less influenced by the environmental factors (Belsky et al., 2009; Belsky and Pluess, 2009). In our present study, the participants with *BDNF* Met allele carriers had significantly lower depressive symptoms than Val homozygote in the low-stress group; however, Met allele carriers had comparatively high depressive symptoms in comparison to Val homozygote in the high-stress group although without significant difference probably due to limited sample size. Thus, the interaction of *BDNF* Val66Met with job-related stress on depressive symptoms appears to conform to the 'differential-susceptibility' hypothesis, whereby the Met allele confers higher sensitivity to changes in environmental stress (both increased and reduced stress), suggesting that Met allele renders individuals more sensitive to the stress environment (Fig. 1). Interestingly, a previous study investigated whether *BDNF* Val66Met modulated the influence of stressful life events on adolescent depressive symptoms in Chinese (Chen et al., 2012). They found that individuals with Val alleles showed a greater susceptibility to both the detrimental effects of higher stress and the beneficial effects of lower stress compared to the Met/Met genotype, suggesting the 'differential-susceptibility' hypothesis (Chen et al., 2012). Although both studies support the differential-susceptibility model, this previous study demonstrated Val alleles as 'plasticity allele' (Chen et al., 2012), which is in contrast to our result. A recent study reported that the *BDNF* Val66Met genotype by adulthood chronic stress interaction was significant on depressive symptoms, showing that the subjects with the Val/Val genotype had higher depressive symptoms than those carrying the Met allele, which is inconsistent with our finding (Jiang et al., 2013). However, some other studies reported that the adults with the *BDNF* 66Met allele had higher possibility to develop depression or higher depressive symptoms with early adverse exposure (Aguilera et al., 2009; Gatt et al., 2009; Carver et al., 2011; Perea et al., 2012; Van et al., 2012), which are in agreement with our current result. We could not provide a reasonable explanation for this discrepancy, maybe due to age (adolescent vs. adult), study design, different stress and rating scale for depression. It is worthy of mentioning that the majority of previous studies investigated the long-term effects of severe early adversity including abuse, neglect or parental loss on adult depression (Aguilera et al., 2009; Gatt et al., 2009; Van et al., 2012), and a few studies investigated the short-term or chronic influences of recent mild or moderate stressful life events on adolescent (Chen et al., 2012) or adult depression (Jiang et al., 2013), whereas we examined the chronic effects of job-related stress on depressive symptoms in this current study. Previous studies have reported

significant difference in the effects of chronic stress between childhood and adulthood on depression (Jiang et al., 2013). For example, a previous study reported differential influences of severe child adversity on juvenile vs. adult onset depression (Jaffee et al., 2002). Another study reported that most subjects suffering from adult depression did not experience child depression (Klein et al., 1999). Moreover, childhood and adolescent depression responded differently to antidepressant drugs, suggesting that they may have different pathological mechanisms, which may lead to differential responses to chronic stress (Bylund and Reed, 2007). A recent study showed that the *BDNF* Val66Met polymorphism moderated the effect of stress differentially during childhood and college years (Perea et al., 2012). Moreover, the peripheral BDNF levels are lower in childhood and higher in early adulthood, producing varying functions during development, which may be associated with different behavioral outcomes (Perea et al., 2012).

Taken together, different BDNF-related neurobiological mechanisms may exist in childhood and adulthood, which may be partially responsible for the inconsistent results regarding the *BDNF* Val66Met by adulthood chronic stress interaction in depression or depressive symptoms.

This study still has some limitations. First, all the participants were physicians or nurses, who had experienced more severe job stress and selection bias could not be fully excluded. Thus, our findings in this study could not be generalized to other subjects. Second, although BDNF serum level is a potential biomarker for depression, we did not test the association of serum BDNF levels with depression since only several subjects had both serum BDNF level and depression rating due to limited sample size. Third, we only analyzed one polymorphism in *BDNF* gene in this study and no haplotype analysis was performed, which can include more information and more stable findings. Thus, further researches including genome-wide association study and haplotype analysis will be needed in the future. Fourth, the sample size was small, which may result in false positive or negative results due to the lack of statistical power and selection of samples. Thus, our current results should be considered preliminary, as further validation in larger sample in different ethnic population is necessary to draw any firm conclusion. If the sample is over 360 subjects at dominant models and over 390 subjects at recessive models, that would help to reach a power of 0.80, with the relative risk of two for the Val66Met polymorphism in the present study, which could help to clarify a possible association of the *BDNF* polymorphisms and job-related depression. Fifth, a cross-sectional study design was used, which cannot show direct causality of the stress × *BDNF* Val66Met gene in the development of depressive symptoms. Sixth, some factors related to work stress, such as duration of work and work type may produce effects on the interaction of *BDNF* Val66Met and work stress on depression. Meanwhile, we did not measure exercise level, smoking and alcohol etc. that may influence the BDNF serum levels. Unfortunately, we did not collect these data, which should be further explored in the future studies.

In summary, our results show that long-term exposure to job stress may lead to depression in medical workers. In our present study, we did not find the association of *BDNF* Val66Met polymorphism with job-related depression. However, interestingly, this polymorphism and job stress interacted to impact job-related depression, showing that the individuals with *BDNF* Val homozygote had higher depression level compared to Met allele carriers only in low-stress group. These findings suggest that the influence of job-related stress on depression was adjusted by genotype. Moreover, the Met allele carriers displayed significantly lower depressive symptoms than Val homozygote in the low-stress group. On the contrary, Met allele carriers had non-significantly high depressive symptoms than Val homozygote in the high-stress group. Thus, our results support the differential-susceptibility hypothesis, suggesting that Met allele renders individuals more sensitive to the stress environment. However, due to the cross-sectional study design and the *BDNF* Val66Met genotyping results available from limited sample, we cannot attribute causality to associations between job-related stress, the *BDNF* Val66Met genotypes and depression. Further studies in larger sample size from other populations and ethnic groups would help clarify the role of the *BDNF* Val66Met genotypes in regulation of association between job-related stress and depression.

Contributors

Shu-Chang He and Xiang Yang Zhang were responsible for study design, statistical analysis, and manuscript preparation. Shu-Chang He, Shuang Wu, and Chao Wang were responsible for recruiting the subjects, performing the clinical rating and collecting the samples. Xiang-Dong Du, Guangzhong Yin, Qiuwang Jia, Yingyang Zhang, Li Wang and Jair C. Soares were involved in evolving the ideas and editing the manuscript. Shu-Chang He and Xiang Yang Zhang were involved in writing the protocol, wrote the paper and were responsible for providing the funding for the study. All authors have contributed to and have approved the final manuscript.

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Conflict of interest

No conflict of interest was disclosed for each author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2018.04.089.

References

Aguilera, M., Arias, B., Wichers, M., Barrantes-Vidal, N., Moya, J., Villa, H., van Os, J., Ibáñez, M.I., Ruipérez, M.A., Ortet, G., Fañanás, L, 2009. Early adversity and 5-HTT/BDNF genes: new evidence of gene-environment interactions on depressive symptoms in a general population. Psychol. Med. 39 (9), 1425–1432.

Ahola, K., Hakanen, J, 2007. Job strain, burnout, and depressive symptoms: a prospective study among dentists. J. Affect. Disord. 104 (1), 103–110.

Asarnow, L.D., Soehner, A.M., Harvey, A.G, 2013. Circadian rhythms and psychiatric illness. Curr. Opin. Psychiatry 26, 566–571.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R, 2009. Vulnerability genes or plasticity genesquest. Mol. Psychiatry 14, 746–754.

Belsky, J., Pluess, M, 2009. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol. Bull. 135, 885–908.

Bocchio-Chiavetto, L, Bagnardi, V, Zanardini, R, Molteni, R, Nielsen, MG, Placentino, A, Giovannini, C, Rillosi, L, Ventriglia, M, Riva, MA, Gennarelli, M, 2010. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. World J. Biol. Psychiatry 11 (6), 763–773.

Brown, G.W., Craig, T.K.J., Harris, T.O., Herbert, J., Hodgson, K., Tansey, K.E., Uher, R., 2014. Functional polymorphism in the brain-derived neurotrophic factor gene interacts with stressful life events but not childhood maltreatment in the etiology of depression. Depression and Anxiety 31 (4), 326–334.

Brunoni, A.R., Lopes, M., Fregni, F., 2008. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. Int. J. Neuropsychopharmacol. 11 (8), 1169–1180.

Bylund, D.B., Reed, A.L., 2007. Childhood and adolescent depression: why do children and adults respond differently to antidepressant drugs? Neurochem. Int. 51 (5), 246–253.

Carver, C.S., Johnson, S.L., Joormann, J., Lemoult, J., Cuccaro, M.L., 2011. Childhood adversity interacts separately with 5-HTTLPR and BDNF to predict lifetime depression diagnosis. J. Affect. Disord. 132 (1-2), 89–93.

Chayu, T., Kreitler, S., 2011. Burnout in nephrology nurses in Israel. Nephrol. Nurs. J. 38 (1), 65–77.
Chen, J., Li, X., McGue, M., 2012. Interacting effect of BDNF Val66Met polymorphism and stressful life events on adolescent depression. Genes. Brain Behav. 11 (8), 958–965.
Chen, L., Lawlor, D.A., Lewis, S.J., Yuan, W., Abdollahi, M.R., Timpson, N.J., Day, I.N., Ebrahim, S., Smith, G.D., Shugart, Y.Y., 2008. Genetic association study of BDNF in depression: finding from two cohort studies and a meta-analysis. Am. J. Med. Genet. B 147B (6), 814–821.
Cheung, T., Yip, P.S., 2015. Depression, anxiety and symptoms of stress among Hong Kong nurses: a cross-sectional study. Int. J. Environ. Res. Public Health 12 (9), 11072–11100.
Chou, L.P., Li, C.Y., Hu, S.C., 2014. Job stress and burnout in hospital employees: comparisons of different medical professions in a regional hospital in Taiwan. BMJ Open 4, 1–7.
Clarke, D.M., 2009. Depression and physical illness: more complex than simple comorbidity. Med. J. Aust. 190 (7 Suppl), S52–S53.
Clays, E., Leynen, F., Kornitzer, M., Kittle, F., Backer, G.D., 2007. Job stress and depression symptoms in middle-aged workers-prospective results from the Belstress study. Scand. J. Work Environ. Health 33, 252–259.
Czira, M.E., Wersching, H., Baune, B.T., Berger, K., 2012. Brain-derived neurotrophic factor gene polymorphisms, neurotransmitter levels, and depressivesymptoms in an elderly population. Age 34 (6), 1529–1541.
Duman, R.S., Monteggia, L.M., 2006. A neurotrophic model for stress-related mood disorders. Biol. Psychiatry 59 (12), 1116–1127.
Egan, M.F., Kojima, M., Callicott, J.H., Goldberg, T.E., Kolachana, B.S., Bertolino, A., Zaitsev, E., Gold, B., Goldman, D., Dean, M., Lu, B., Weinberger, D.R., 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112 (2), 257–269.
Garrosa, E., Moreno-Jiménez, B., Rodríguez-Muñoz, A., Rodríguez-Carvajal, R., 2011. Role stress and personal resources in nursing: a cross-sectional study of burnout and engagement. Int. J. Nurs. Stud. 48 (4), 479–489.
Gatt, J.M., Nemeroff, C.B., Dobson-Stone, C., Paul, R.H., Bryant, R.A., Schofield, P.R., Gordon, E., Kemp, A.H., Williams, L.M., 2009. Interactions between BDNF Val66Met polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. Mol. Psychiatry 14 (7), 681–695.
Gatt, J.M., Nemeroff, C.B., Schofield, P.R., Paul, R.H., Clark, C.R., Gordon, E., Williams, L.M., 2010. Early life stress combined with serotonin 3A receptor and brain-derived neurotrophic factor valine 66 to methionine genotypes impacts emotional brain and arousal correlates of risk for depression. Biol. Psychiatry 68 (9), 818–824.
Gauderman, W.J., 2002. Sample size requirements for matched case-control studies of gene-environment interaction. Stat. Med. 21 (1), 35–50.
Gong, Y., Han, T., Yin, X., Yang, G., Zhuang, R., Chen, Y., Lu, Z., 2014. Prevalence of depressive symptoms and work-related risk factors among nurses in public hospitals in southern China: a cross-sectional study. Sci. Rep. 4, 7109.
Gratacòs, M., Soria, V., Urretavizcaya, M., González, J.R., Crespo, J.M., Bayés, M., de Cid, R., Menchón, J.M., Vallejo, J., Estivill, X., 2008. A brain-derived neurotrophic factor (BDNF) haplotype is associated with antidepressant treatment outcome in mood disorders. Pharmacogenomics J. 8 (2), 101–112.
Hosang, G.M., Shiles, C., Tansey, K.E., Peter, M.G., Rudolf, U., 2014. Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis. BMC Med. 12 (1), 7.
House, R.J., Rizzo, J.R., 1972. Role conflict and ambiguity as critical variables in a model of organizational behavior. Organ. Behav. Hum. Perform. 7 (3), 467–505.
Hyman, C., Hofer, M., Barde, Y.A., Juhasz, M., Yancopoulos, G.D., Squinto, S.P., Lindsay, R.M., 1991. BDNF is a neurotrophic factor for dopaminergic neurons of the substantianigra. Nature 350 (6315), 230–232.
Iacovides, A., Fountoulakis, K.N., Kaprinis, S., Kaprinis, G., 2003. The relationship between job stress, burnout and clinical depression. J. Affect. Disord. 75 (3), 209–221.
Jaffee, S.R., Moffitt, T.E., Caspi, A., Fombonne, E., Poulton, R., Martin, J., 2002. Differences in early childhood risk factors for juvenile-onset and adult-onset depression. Arch. Gen. Psychiatry 59 (3), 215–222.
Jiang, R., Brummett, B.H., Babyak, M.A., Siegler, I.C., Williams, R.B., 2013. Brain- derived neurotrophic factor (BDNF) Val66Met and adulthood chronic stress interact to affect depressive symptoms. J. Psychiatr. Res. 47 (2), 233–239.
Joffe, R.T., Gatt, J.M., Kemp, A.H., Grieve, S., Dobson-Stone, C., Kuan, S.A., Schofield, P.R., Gordon, E., Williams, L.M., 2009. Brain derived neurotrophic factor Val66Met polymorphism, the five factor model of personality and hippocampal volume: implications for depressive illness. Hum. Brain Mapp. 30 (4), 1246–1256.
Kiecolt-Glaser, J.K., Glaser, R., 2002. Depression and immune function: central pathways to morbidity and mortality. J. Psychosom. Res. 53 (4), 873–876.
Kim, J.M., Stewart, R., Kim, S.W., Yang, S.J., Shin, I.S., Kim, Y.H., Yoon, J.S., 2007. Interactions between life stressors and susceptibility genes (5-HTTLPR and BDNF) on depression in Korean elders. Biol. Psychiatry 62 (5), 423–428.
Klein, D.N., Schatzberg, A.F., McCullough, J.P., Dowling, F., Goodman, D., Howland, R.H., Markowitz, J.C., Smith, C., Thase, M.E., Rush, A.J., LaVange, L., Harrison, W.M., Keller, M.B., 1999. Age of onset in chronic major depression: relation to demographic and clinical variables, family history, and treatment response. J. Affect. Disord. 55 (2-3), 149–157.
Kowiański, P., Lietzau, G., Czuba, E., Waśkow, M., Steliga, A., Moryś, J., 2017. BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity. Cell. Mol. Neuroiol. 1–15.
Lazarus, R.S., Folkman, S., 1984. Stress. Appraisal, and Coping. Springer Publishing Company.
Lerner, D., Henke, R.M., 2008. What does research tell us about depression, job performance, and work productivity? J. Occup. Environ. Med. 50 (4), 401–410.
Levinson, DF., 2006. The genetics of depression: a review. Biol. Psychiatry 60 (2), 84–92.
Licinio, J., Dong, C., Wong, M.L., 2009. Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. Arch. Gen. Psychiatry 66 (5), 488–497.
Lin, X., Lin, J., Liu, H., Teng, S., Zhang, W., 2016. Depressive symptoms and associated factors among renal-transplant recipients in China. Int. J. Nurs. Sci. 3 (4), 347–353.
Martinowich, K., Manji, H., Lu, B., 2007. New insights into BDNF function in depression and anxiety. Nat. Neurosci. 10 (9), 1089–1093.
McVicar, A., 2003. Workplace stress in nursing: a literature review. J. Adv. Nurs. 44 (6), 633–642.
Molendijk, M.L., Spinhoven, P., Polak, M., Bus, B.A., Penninx, B.W., Elzinga, B.M., 2014. Serum BDNF concentrations as peripheral manifestations of depression: evidence from asystematic review and meta-analyses on 179 associations (n = 9484). Mol. Psychiatry 19 (7), 791–800.
Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., Ustun, B., 2007. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet 370 (9590), 851–858.
Numakawa, T., Odaka, H., Adachi, N., 2017. Actions of brain-derived neurotrophic factor and glucocorticoid stress in neurogenesis. Int. J. Mol. Sci. 18 (11), pii E2312. http://dx.doi.org/10.3390/ijms18112312.
Pae, C.U., Chiesa, A., Porcelli, S., Han, C., Patkar, A.A., Lee, S.J., Park, M.H., Serretti, A., De Ronchi, D., 2011. Influence of BDNF variants on diagnosis and response to treatment in patients with major depression, bipolar disorder and schizophrenia. Neuropsychobiology 65 (1), 1–11.
Perea, C.S., Paternina, A.C., Gomez, Y., Lattig, M.C., 2012. Negative affectivity moderated by BDNF and stress response. J. Affect. Disord. 136 (3), 767–774.
Ribeiro, L., Busnello, J.V., Cantor, R.M., Whelan, F., Whittaker, P., Deloukas, P., Wong, M., Licinio, J., 2007. The brain-derived neurotrophic factor rs6265 (Val66Met) polymorphism and depression in Mexican-Americans. Neuroreport 18 (12), 1291.
Rock, P.L., Roiser, J.P., Riedel, W.J., Blackwell, A.D., 2014. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol. Med. 44 (10), 2029.
Surtees, P.G., Wainwright, N.W., Willis-Owen, S.A., Sandhu, M.S., Luben, R., Day, N.E., Flint, J., 2007. No association between the BDNF Val66Met polymorphism and mood status in a non-clinical community sample of 7389 older adults. J. Psychiatr. Res. 41 (5), 404–409.
Taylor, W.D., Züchner, S., McQuoid, D.R., Steffens, D.C., Speer, M.C., Krishnan, K.R., 2007. Allelic differences in the brain-derived neurotrophic factor Val66Met polymorphism in late-life depression. Am. J. Geriatr. Psychiatry 15 (10), 850–857.
Uher, R., Caspi, A., Houts, R., Sugden, K., Williams, B., Poulton, R., Moffitt, T.E., 2011. Serotonin transporter gene moderates childhood maltreatment's effects on persistent but not single-episode depression: replications and implications for resolving inconsistent results. J. Affect. Disord 35 (1-3), 56–65.
Van, O.I., Franke, B., Rijpkema, M., Gerritsen, L., Arias-Vásquez, A., Fernández, G., Tendolkar, I., 2012. Interaction between BDNF Val66Met and childhood stressful life events is associated to affective memory bias in men but not women. Biol. Psychol. 89 (1), 214–219.
van Wingen, G., Rijpkema, M., Franke, B., van Eijndhoven, P., Tendolkar, I., Verkes, R.J., Buitelaar, J., Fernández, G., 2010. The brain-derived neurotrophic factor Val66Met polymorphism affects memory formation and retrieval of biologically salient stimuli. Neuroimage 50 (3), 1212–1218.
Vyas, S., Rodrigues, A.J., Silva, J.M., Tronche, F., Almeida, O.F., Sousa, N., Sotiropoulos, I., 2016. Chronic stress and glucocorticoids: from neuronal plasticity to neurodegeneration. Neural Plast., 6391686 2016.
Verhagen, M., van der Meij, A., van Deurzen, P.A.M., Janzing, J.G.E., Arias-Vásquez, A., Buitelaar, J.K., Franke, B., 2010. Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. Mol. Psychiatry 15 (3), 260–271.
Willner, P., 1997. Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology 134 (4), 319–329.
Wurm, W., Vogel, K., Holl, A., Ebner, C., Bayer, D., Mörkl, S., Szilagyi, I.S., Hotter, E., Kapfhammer, H.P., Hofmann, P., 2016. Depression-burnout overlap in physicians. PLoS One 11 (3), e0149913.
Yi, Z., Zhang, C., Wu, Z., Hong, W., Li, Z., Fang, Y., Yu, S., 2011. Lack of effect of brain derived neurotrophic factor (BDNF) Val66Met polymorphism on early onset schizophrenia in Chinese Han population. Brain Res. 27 (12), 146–150.
Zhang, X.Y, Liang, J., Chen, D.C., Xiu, M.H., Yang, F.D., Kosten, T.A., Kosten, T.R., 2012. Low BDNF is associated with cognitive impairment in chronic patients with schizophrenia. Psychopharmacology 222, 277–284.
Zung, W.W.K., 1965. A self-rating depression scale. Arch. Gen. Psychiatry 12 (1), 63–70.