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Effect of Val66Met polymorphism in *BDNF* on attentional bias in an extroverted Chinese Han population

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Studies have indicated that a functional polymorphism (Val66Met) in a brain-derived neurotrophic factor (*BDNF*) gene can influences human cognitive functions and mood disorders. In this study, we examined associations of *BDNF* Val66Met with attentional bias and personality in an unaffected population. The results showed that *BDNF* Val66Met was significantly associated with attentional disengagement for positive cueing words in extraverts. Moreover, there was a positive correlation between the dosages of Met allele and attentional disengagement, however, we did not observe any significant influences of *BDNF* Val66Met on personality traits. These preliminary results indicate that the individual differences in attentional bias for positive words are partially underpinned by *BDNF*.

Key words: brain-derived neurotrophic factor, functional polymorphism, attentional bias, personality trait

INTRODUCTION

Attentional bias is a tendency for individuals to exhibit higher sensitivity and selective attention to particular stimuli or relevant information (Keogh et al. 2001, Hunt et al. 2006, 2007). This tendency is essential to human survival and social interactions in various environments (Hunt et al. 2007) because the relevant information was processed earlier or given priority (Wieser et al. 2011). Studies have indicated this bias is linked to many mental processes and behaviors, such as enhancement in visual search, working memory maintenance, perceptual processing of distractors, even human mating efforts (Rinck et al. 2003, Sreenivasan and Iha 2007, Conway et al. 2008). In the past few years, individual differences in attentional bias, especially for negative emotional stimuli, have received increased interest due to their possible roles in disorders or affective states (Spector et al. 2003, Ellenbogen and Schwartzman 2009).

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A wealth of evidence has demonstrated that attentional bias is influenced by personality dimensions and mood states (Asmundson et al. 2005, Helzer et al. 2009, Perlman et al. 2009, Becker and Leinenger 2011, Nakagawa and Sukigara 2012). The trait-congruency hypothesis claims that personality traits are linked to processing of trait-congruent information (Rusting 1998, 1999). Personality traits, such as extroversion and neuroticism, affect attentional bias for both positive and negative stimuli. Extroverts often show manifest attentional bias for positive stimuli, while neurotics often display obvious emotional bias for negative stimuli (Rusting 1998, Canli et al. 2001). Furthermore, it has been well established that anxious individuals preferentially attend to threatening stimuli and interpret emotional ambiguity in a threatening way (Brosan et al. 2011), while patients with depression demonstrate obvious attentional bias for negative stimuli (Spector et al. 2003, Le et al. 2009, De Raedt and Koster 2010).

Plenty of evidence has suggested that *BDNF* is a candidate gene underlying attentional bias. This gene is located on the chromosome 11p14.1 (Hanson et al. 1992), and encodes a small dimeric protein which plays critical roles in synaptic plasticity by regulating syn-

apse numbers and by controlling activity-dependent axon arbor growth (Hwang et al. 2006). This protein is also a key regulator of the survival and differentiation of cholinergic, dopaminergic and 5-hydroxytryptaminergic neurons (Zhou et al. 1996). Val66Met (rs6265) is a common non-synonymous single nucleotide polymorphism (SNP) in *BDNF*. This SNP can affect the intracellular trafficking and activity-dependent secretion (Miyajima et al. 2008) by exchanging an amino acid from valine (Val) for methionine (Met) at the codon 66 in BDNF. Several studies have indicated that *BDNF* Val66Met contributes to individual variability in the functional responses of the prefrontal cortex to working memory, and the amygdala to emotional faces (Cerasa et al. 2010, Lau et al. 2010). However, so far, no studies have directly tested the association of *BDNF* Val66Met with attentional bias.

In recent years, a number of studies have been performed to investigate the association of *BDNF* with personality traits. Those results were, however, usually inconsistent with one another. A meta-analysis has indicated that non-Met individuals achieve significantly lower neuroticism scores in some anxiety-related personality populations (Frustaci et al. 2008). On the contrary, some other studies have found that Val66Met polymorphism was associated with extraversion, but not with neuroticism. Moreover, there is indicated that BDNF levels in serum, but not the *BDNF* Val66Met genotype, were correlated with avoidance in healthy subjects (Minelli et al. 2011). In general, these discrepancies might derive from sample-related differences.

Most of the previous studies on attentional bias have been conducted in populations with anxiety or depression. In those studies, psychological traits and mood states were often not considered. Furthermore, the relationship between genes and attentional bias for emotional words has been rarely studied.

The purpose of this paper was to investigate the associations of *BDNF* with attentional bias and personality in a healthy Chinese population.

METHODS

Participants

Eight hundred and twenty right-handed participants, from age 20 to 22, were recruited from the Henan University of Science and Technology according to their roll numbers. These participants were unrelated Chinese Han individuals. All the potential subjects underwent mental health examinations by using the Self-Rating Depression Scale (SDS), Self-Rating Anxiety Scale (SAS) and loneliness scale (University of California at Los Angeles). Over 160 participants with depression, anxiety or loneliness were excluded from this study. To thoroughly exclude individuals with mood disorders, the 660 selected subjects were further examined in respect of their mental health with the Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI) and State-Trait Loneliness Scales (STLS). After those examinations, 56 subjects with mental problems were further ruled out from this study. Finally, 594 unrelated Chinese Han volunteers (452 females and 142 males), with about 13 years of formal education, were officially recruited. Their ethnicity was investigated by asking the subjects and their parents. These subjects were in good physical health, without alcohol dependence, drug abuse or other dependence. Hair follicle cells were collected after informed consent was obtained. The study followed the Helsinki declaration, revised by the World Medical Association in 2000.

Personality trait assessment

The personality traits of the subjects were assessed by using the Chinese version of the Eysenck Personality Questionnaire (EPQ-RSC) (Gong 1986). This questionnaire was composed of 88 items which were categorized into three independent biologically-based dimensions.

Attentional biases assessment

Materials

One hundred and eighty words, including 60 nouns, 60 verbs and 60 adjectives, were selected from the Chinese Affective Words System (CAWS) (Wang et al. 2008). The affective words system was prepared and assessed by the State Key Laboratory of Cognitive Neuroscience and Learning, BNU. The valence, arousal and dominance were assessed on a 9-point rating scale. According to the valence (mean ± SD), these words were separated into positive, neutral and negative groups (positive 7.368 ± 0.165, neutral 4.852 ± 0.300, negative 2.596 ± 0.267). Each group consisted of 60 words including 20 nouns, 20 verbs and 20 adjectives. The three groups of emotional

Table I

The participant characteristics (mean ± SD) of the genotype groups

Genotype	Met/Met (*n*=138)	Val/Met (*n*=287)	Val/Val (*n*=134)	*P*
Gender: female *n* (%)	110 (25.64%)	211 (49.18%)	108 (25.17%)	0.628
Age (years)	22.040 ± 1.316	21.974 ± 1.226	21.942 ± 1.344	0.824
DEPRESSION				
SDS	33.379 ± 5.369	33.086 ± 5.671	33.917 ± 6.519	0.400
BDI	4.0146 ± 3.234	3.920 ± 3.766	4.481 ± 3.704	0.332
ANXIETY				
SAS	28.060 ± 6.020	29.030 ± 6.143	28.832 ± 5.970	0.313
STAI-state	35.634 ± 6.711	35.807 ± 8.166	35.943 ± 7.174	0.948
STAI-trait	37.000 ± 6.759	37.368 ± 8.240	37.778 ± 7.397	0.721
LONELINESS				
UCLA	38.664 ± 7.764	38.944 ± 8.478	40.130 ± 8.719	0.317
STLS-state	26.217 ± 6.210	26.057 ± 7.013	25.542 ± 6.334	0.699
STLS-trait	26.450 ± 5.403	26.316 ± 6.708	26.458 ± 7.019	0.972
PERSONALITY TRAITS				
Extraversion/Introversion	11.949 ± 4.507	12.094 ± 4.372	11.128 ± 4.269	0.082
Neuroticism/Stability	9.362 ± 4.836	9.424 ± 5.566	9.687 ± 5.132	0.895

words were matched for frequency (positive 30.866 ± 24.107, neutral 26.517 ± 24.918, negative 27.550 ± 13.923) and stroke (positive 18.100 ± 4.884, neutral 17.167 ± 3.547, negative 18.683 ± 5.177). In the study, the words were presented in white lettering on a black background in 48-point Times New Roman font.

Design and procedure

A spatial cueing task was performed to assess attentional bias (Cisler et al. 2009, Cisler and Koster 2010). In the task, the participants focused on a fixation point located between two rectangles. The cue was then presented, and a target followed in one of the two rectangles. The subjects were required to press a key to discriminate where the target had appeared. In the trails, the cue was valid when the cue and the target were located in the same rectangle; otherwise, the cue was invalid. The valid cues drew the attention to the targets, while the invalid cues directed the attention away. In this task, attentional bias was indicated by faster responses on valid cued trials relative to invalid cued trials, as stimulus-onset asymptotic is an asynchrony less than 250 ms, or indicated by slower responses on validly-cued trials relative to invalid trials, as stimulus-onset asymptotic is an asynchrony exceeding 250 ms (Gibson and Amelio 2000, Chao 2010). The attentional bias was deconstructed into three components, including cue validity, engagement and disengagement, by using the spatial cueing task. Generally, cue validity expressed an attention-orienting bias and was calculated by subtracting the reaction times (RTs) of invalid cues from the RTs of valid cues (Jongen and Smulders 2007, Le et al. 2009), while the engagement expressed sustained bias and was calculated by subtracting the RTs of neutral valid cues from negative valid cues (Amado et al. 2009, Le et al. 2009, Demeter et al. 2011, Fisher et al. 2012). Furthermore, disengagement denoted a shifting bias and was calculated by the subtraction of RTs of negative invalid cues from neu-

Table II

The effects of *BDNF* Val66Met on attentional bias in extraverts

Attentional biases	Met/Met (93)	Val/Met (210)	Val/Val (90)	F (2, 393)	P	η^2 (%)
CUE VALIDITIES						
Positive words	−7.803 ± 20.089	−5.725 ± 20.463	−0.120 ± 15.804	3.991	0.019	2.00
Neutral words	26.385 ± 38.556	22.931 ± 41.213	35.333 ± 40.613	2.963	0.053	1.50
Negative words	25.694 ± 39.411	16.193 ± 43.322	23.250 ± 43.035	1.985	0.139	1.00
ENGAGEMENTS						
Negative words	−8.494 ± 20.876	−12.752 ± 19.654	−12.203 ± 18.552	1.594	0.204	0.80
Positive words	−10.108 ± 17.658	−7.008 ± 18.987	−10.659 ± 15.898	1.709	0.182	0.90
DISENGAGEMENTS						
Negative words	7.803 ± 20.089	5.725 ± 20.463	0.120 ± 15.804	3.991	0.019	2.00
Positive words	3.764 ± 18.996	2.029 ± 17.521	−4.843 ± 19.203	6.024	0.003	3.00

tral invalid cues (Mogg et al. 2008, Le et al. 2009, Ellenbogen et al. 2012, Ishizaki et al. 2012).

In this study, the spatial cueing task comprised 180 randomly presented trails. In each trail, participants viewed a fixation point which was presented for 300 ms, then one cueing word appeared in one of the two rectangles for 500 ms, and a horizontal arrow (target stimulus) was presented immediately in the right or left rectangle after the cue word disappeared. The subjects were asked to press a key indicating the rectangle in which the arrow was located. When an arrow appeared in the right rectangle, the participants were instructed to press the "Alt" key, otherwise they pressed the "Ctrl" key. The horizontal arrow would disappear in 2 000 ms even if the subject did not make a response. The cue words and arrows were presented in cycles. Among the 180 trails, half of the cues and targets were located in the right rectangles, and half in the left rectangles. To promote the attractiveness of words, we added three detective trails to the procedure. During the detective test, a cueing word was displayed for 500 ms in one of the rectangles. Then, a red fixation cross was immediately presented in the central portion of the black background after the cueing word disappeared. Once the subjects saw the red fixation cross, they had to report the cueing word displayed just before the red fixation cross. We explained the details of the detective trail in the instructions. The subjects were excluded if they made two mistakes in the detective trails.

The testing program was compiled by DMDX display software. This software (version number: 3.2.6.4) was set up on a computer with video card at 640×480 with 8 bits per pixel. In the study, 594 unrelated Chinese Han volunteers underwent the attentional bias assessment.

Genotyping

Genomic DNA was extracted from hair follicle cells by the Chelex-100 method. The Val66Met polymorphism in *BDNF* was amplified by a polymerase chain reaction (PCR). The upstream primer, 5'-GCAAACATCCGAGGACAA-3' and the downstream primer, 5'-TACTGAGCATCACCCTGG-3' were recruited. A 223 bp product was amplified with an initial 5 min denaturation at 95°C, followed by 35 cycles at 95°C for 30 s, 60°C for 30 s, 72°C for 30 s, and a final extension period at 72°C for 10 min. Genotyping was performed by the single strand conformation polymorphism (SSCP) method. After genotyping, six randomly-selected samples were sequenced to determine the alleles of the genotyping results.

Statistical Analysis

Microsoft Visual FoxPro 6.0 software was used for preparing preliminary data. A Hardy-Weinberg equi-

Table III

The effects of *BDNF* Val66Met on attentional bias in introverts

Attentional biases	Met/Met (42)	Val/Met (78)	Val/Val (44)	F (2, 161)	P	η^2 (%)
CUE VALIDITIES						
Positive words	−4.283 ± 21.345	−5.737 ± 22.733	−6.557 ± 20.380	0.121	0.886	0.10
Neutral words	30.550 ± 33.8220	24.234 ± 37.439	24.822 ± 40.464	0.420	0.658	0.50
Negative words	20.694 ± 34.379	17.492 ± 43.403	20.044 ± 46.759	0.097	0.908	0.10
ENGAGEMENTS						
Negative words	−14.139 ± 17.369	−12.479 ± 18.751	−11.335 ± 18.959	0.251	0.779	0.30
Positive words	−10.905 ± 22.526	−7.411 ± 15.774	−3.974 ± 20.123	1.449	0.238	1.80
DISENGAGEMENTS						
Negative words	4.283 ± 21.345	5.737 ± 22.733	6.557 ± 20.380	0.121	0.886	0.10

librium test was carried out with FINETI (Sasieni 1997). The effects of genotypes on attentional bias were confirmed in a one-way analysis of variances (ANOVAs). All descriptive statistics were displayed as mean (M) and standard deviation (SD). The analysis of variance was performed by using SPSS 15.0 software for Windows (SPSS, Chicago). Correction for multiple testing was conducted by the Benjamin-Hochberg FDR-controlling method (Keselman et al. 2002). Furthermore, statistical power analysis was performed with the G*Power program (Faul et al. 2007).

RESULTS

Genotype analysis

Genotyping for Val66Met in *BDNF* was carried out for 594 unrelated participants. Five hundred and seventy nine subjects were genotyped successfully, and there were 139 subjects with Met/Met, 288 subjects with Met/Val and 152 subjects with Val/Val. Genotype frequencies of the polymorphism showed no deviation from the Hardy–Weinberg equilibrium ($\chi 2$=0.013, P=0.910).

Data screening

The analysis of the original data was based on the RTs of correct responses in the spatial cueing task. Fifteen subjects, whose error responses were above 10%, were excluded from further participation in the study. Thirty participants were selected randomly from the 579 participants to establish the standards of data analysis. The mean and standard deviation (SD) (439.568 ± 108.365) of RTs were computed for the 30 subjects after we had ruled out outlying values from the original data. Finally, we excluded the extreme RTs, defined as those with RTs above 3 SD (439.568 + 325.096) or below 200 ms, from the original data for all the subjects. The average RTs were calculated for each participant after ruling out the erroneous data.

Participant characteristics

Table I displays the mean and SD of the participant characteristics for each genotype group. We did not find significant differences in gender, depression, anxiety and loneliness among the three genotype groups. Furthermore, there were also no differences in the levels of extraversion/introversion (P=0.082), neuroticism/stability (P=0.895) or psychotics/socialization (P=0.556) among the genotype groups.

Spatial cueing tasks

In this study, we analyzed the effects of Val66Met in *BDNF* on cue validities, engagements and disengagements in extraverts (scores above 9) and introverts (scores below 9) because there was a marginal significant difference in the influence of the polymorphism

between extraverts and introverts. The results indicated that there were significant differences in the effects of Val66Met on the cue validities of positive words (P=0.019), along with disengagements of negative (P=0.019) and positive words (P=0.003) in the extraverted group. We found there were no significant associations of Val66Met with cue validities, engagements and disengagements in the introverts (P>0.05). We performed effect sizes assessments for Val66Met on the cue validities of positive words and the disengagements of negative and positive words in the extraversion group. The effect sizes indicated that the variant could explain 2.00%, 2.00% and 3.00% variances in the cue validities of positive words and disengagements of negative and positive words, respectively. The effects of the polymorphism on attentional bias in extraverts and introverts are displayed in Table II and Table III.

Since 14 comparisons were conducted during analysis of the associations of Val66Met with attentional bias, a multi-test correction of 0.05/14=0.004 was made. After correcting for multi-test, the significant association of Val66Met with disengagement of positive words was still observed in the extraverts. There was a positive correlation between the dosage of the Met allele and the disengagement (r=0.158, P=0.002). Furthermore, we conducted an analysis of the interaction between Val66Met and extraversion/introversion on disengagement for positive words. The result showed that there was no a significant interaction between the genetic variant and personality trait on disengagement (P=0.207).

When the tested variation displayed a small to medium genetic effect (an effect size index below 0.25), the sample size demonstrated greater than 95% strength in detecting the significant associations (P<0.05).

DISCUSSION

In this study, we investigated the influences of Val66Met on attentional bias and personality in an unaffected population. We found that there was a significant association of *BDNF* with disengagement for positive words in the extraversion group. However, we did not detect observable influences of *BDNF* on personality traits.

We did not detect significant associations of Val66Met with personality traits measured by using the EPQ-RSC. There was, however, a marginal significant association of Val66Met with extraversion, and the Met carriers exhibited more instances of extraversion and fewer instances of neuroticism. The discrepancy between our study and the previous results (Frustaci et al. 2008, Terracciano et al. 2010) might derive from methodological and sample-related differences. Furthermore, the smaller sample size of the introverts in this study was a limitation in looking for a genetic effect.

In this study, we found that the functional genetic variant was related to disengagement of positive emotional cues, and that there was a positive correlation between the Met allele and disengagement. These findings indicated that subjects with the Met allele had great difficulty in turning attention away when viewing positive cueing words. Therefore, the difficulty in disengagement would cause individuals with Met allele to devote more attention resources to positive stimuli. In most cases, this psychological mechanism could keep these individuals with the Met allele in a positive emotional state. This result further indicated that the Met allele plays a protective role in certain neurological conditions for its roles in disengagement for positive stimuli (Lang et al. 2005, Neves-Pereira et al. 2005, Kremeyer et al. 2006, Ribeiro et al. 2007).

Shifting was an important ability involved in attention. This cognitive ability is related to working memory and executive function (Toplak et al. 2010). Many studies have indicated that the Met allele can impair working memory and decrease brain activation in cognitive control tasks (Gong et al. 2009, Li et al. 2010, Wang et al. 2012). In these cognitive tasks, participants were often affected by the emotional properties of the stimuli. The individuals with the Met allele showed a sustained processing during disengagement, which could impair working memory due to its detrimental effects on the capacity for shifting. Taken together, those results imply that the Met allele of *BDNF* has opposite effects on cognitions and on neurological conditions.

In the study, we only observed that Val66Met affected disengagement in the extraverts. The sample size of extroverts had sufficient strength to reveal the influence of Val66Met on attentional bias, while the smaller sample size of introverts limited investigation of the effects of Val66Met on attentional bias. Thus, further work is needed to test these findings.

CONCLUSION

A healthy Chinese Han sample was collected to investigate the influences of *BDNF* on attentional bias and personality. We observed that *BDNF* Val66Met was significantly associated with disengagement in extraverts. However, there were no significant associations of the genetic variant with personality. These results might shed light on individual differences in attentional bias and the partial underpinning of *BDNF*.

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