Journal of Affective Disorders 214 (2017) 115–121

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

The association between well-being and the *COMT* gene: Dispositional gratitude and forgiveness as mediators

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ARTICLE INFO

Keywords:
COMT
Well-being
Depression
Gratitude
Forgiveness

ABSTRACT

Backround: Previous studies have demonstrated the contributions of genetic variants and positive psychological traits (e.g. gratitude and forgiveness) to well-being. However, little is known about how genes interact with positive traits to affect well-being.
Methods: To investigate to what extent the *COMT* Val158Met polymorphism modulates well-being and to what extent dispositional gratitude and forgiveness mediate the individual differences in well-being, 445 participants were recruited and required to complete a battery of questionnaires.
Results: We found that individuals with a smaller number of the Met alleles reported greater well-being, less depressive symptoms, and greater tendencies for gratitude and forgiveness. Moreover, dispositional gratitude and forgiveness mediated the genotype effects on well-being and depressive symptoms. These results remained significant after controlling for non-genetic factors (socioeconomic status, religious beliefs, romantic relationship status, parenting style).
Limitation: The sample size limits the generalizability of results.
Conclusion: This study demonstrates the contribution of the *COMT* Val158Met polymorphism to individual differences in well-being and suggests a potential psychobiological pathway from dopaminergic and noradrenergic systems to happiness.

1. Introduction

Well-being (also termed "happiness") refers to the positive cognitive and affective evaluations of the evaluator's life (Diener et al., 1999) as well as the evaluator's experience of self-realization and good social relationships (Ryan and Deci, 2001). Well-being is beneficial to multiple life domains including physical and mental health and work performance (Lyubomirsky et al., 2005). The pursuit of well-being is one of the unalienable rights of human beings, as stated in the Declaration of Independence of the United States. However, the Declaration of Independence only guarantees the right to pursue well-being, not well-being per se.

The experience of well-being is strikingly variable between individuals. Twin studies have established that a large portion of individual differences in well-being can be attributed to genetic factors, with heritability estimates of 38–54% (Lykken and Tellegen, 1996; Røysamb et al., 2002; Stubbe et al., 2005). Genetic studies also showed the involvement of serotoninergic genes in well-being (Chen et al., 2013; De Neve, 2011). Moreover, a recent large-scale genome-wide association study identified a set of genetic variants associated with well-being and depressive symptoms (Okbay et al., 2016). However, the existing evidence is insufficient for us to understand the psychobiological basis of well-being. The purpose of the current study is to investigate to what extent a particular polymorphism on the catechol-O-methyltransferase (*COMT*) gene would modulate well-being and to what extent individual differences in well-being are mediated by personality traits such as dispositional gratitude and forgiveness.

The *COMT* gene is located on chromosome 22q11 (Grossman et al., 1992). It encodes COMT protein, one of the major enzymes to degrade catecholamines such as dopamine and norepinephrine. Within the

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http://dx.doi.org/10.1016/j.jad.2017.03.005
Received 9 September 2016; Received in revised form 16 January 2017; Accepted 5 March 2017
Available online 07 March 2017
0165-0327/

gene, a transition of guanine (G) to adenine (A) at codon 158, namely *COMT* Val158Met (rs4680), leads to a mutation of valine (Val) to methionine (Met). The Val/Val genotype is associated with about a 40% increased enzyme activity in the brain compared to the Met/Met genotype (Chen et al., 2004; Lachman et al., 1996).

Previous studies have demonstrated the role of the *COMT* Val158Met in response to positive and negative emotional stimuli (Bouhuys et al., 1999; Cohn et al., 2009), a fundamental process involved in well-being (Diener et al., 2009a, 1999; Gross and John, 2003). A handful of studies reported that the Met allele was associated with increased sensitivity to pleasant stimuli (Wichers et al., 2008) and decreased sensitivity to unpleasant stimuli (Amstadter et al., 2012). Other studies, however, did not find a link between the *COMT* gene and the experience of positive affects (Bakker et al., 2014; Desmeules et al., 2012; Wacker et al., 2012) or anticipation of positive affects (Katz et al., 2015). Indeed, more studies showed an opposite pattern with increased negativity bias in affective processing for the Met allele (Gao et al., 2016; Kia-Keating et al., 2007; Ohara et al., 1998; Smolka et al., 2005; Williams et al., 2010). For example, clinical research demonstrated that the susceptibilities to depression and suicidal behavior were increased in the Met allele carriers (Kia-Keating et al., 2007; Ohara et al., 1998); neuroimaging studies also showed that the Met allele was associated with increased neural responses to negative emotional stimuli (Smolka et al., 2005) and decreased neural responses to positive facial expressions (Williams et al., 2010).

As far as we know, there is no study directly investigating the effect of the *COMT* Val158Met polymorphism on well-being, which is related to, but much more complex than, say, affective processing. Moreover, although a few previous studies demonstrated the involvement of serotoninergic genes in well-being (Chen et al., 2013; De Neve, 2011), these studies asked participants to evaluate their satisfaction with lives in no more than 4 items and, more seriously, did not reveal what factors might mediate the association between gene and well-being. Psychological studies have found that well-being can be mostly accounted for by positive personality traits, particularly dispositional gratitude and forgiveness (Bono et al., 2008; Emmons and McCullough, 2003). Dispositional gratitude predicts subjective well-being ratings (Wood et al., 2008a) and gratitude training promotes well-being (Emmons and McCullough, 2003). Similarly, increases in forgiveness predict increases in well-being (Bono et al., 2008) and forgiveness intervention improves well-being (Zhang et al., 2014). Taking into account the causal links of gratitude and forgiveness to well-being (Bono et al., 2008; Emmons and McCullough, 2003; Wood et al., 2008a; Zhang et al., 2014) and the general knowledge that genetic factors affect behavioral phenotypes through psychological traits (Davis and Loxton, 2013; Saphire-Bernstein et al., 2011), we hypothesized that *COMT* Val158Met may affect well-being through dispositional gratitude and forgiveness.

2. Experimental procedures

2.1. Participants

Four hundred and forty-five unrelated Chinese Han students (75% female, mean age =24.3 ± 1.5 years) were recruited from Henan University of Science and Technology, China. Written informed consents were obtained from each participant. This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Department of Psychology, Peking University.

2.2. Measures

As well-being is a complex construct, current research on well-being takes two different approaches: the subjective/hedonic approach, which defines well-being in terms of cognitive and affective evaluations of the evaluators' lives (Diener et al., 1999); the psychological/eudaimonic approach, which defines well-being in terms of self-realization and good social relationships (Ryan and Deci, 2001). In this study, we combined the two approaches by using three instruments to measure cognitive, affective, and psychological aspects of well-being. Satisfaction With Life Scale (SWLS; Diener et al., 1985; Wang et al., 2008) was used to assess *cognitive well-being*. SWLS is a 5-item scale that measures to what extent the respondents are satisfied with their lives in general. Participants rated on a 7-point Likert scale (1= strongly disagree, 7= strongly agree) their agreement with each statement (e.g. "In most ways my life is close to my ideal"). Scale of Positive and Negative Experience (SPANE; Diener et al., 2009b) was applied to measure *affective well-being*. SPANE is a 12-item scale with 6 items measuring positive feelings (e.g. "Joyful") and 6 items measuring negative feelings (e.g. "Sad"). Participants rated on a 5-point Likert scale (1= very rarely or never, 5= very often or always) how often they experienced the feeling during the past four weeks. The total score on negative items was subtracted from the total score on the positive items to derive an overall score, i.e., affect balance. Flourishing Scale (FS; Diener et al., 2009b) was used to assess *psychological well-being*. FS is an 8-item scale that evaluates positive relationships and meaningfulness of life. Participants selected on a 7-point Likert scale (1= strongly disagree, 7= strongly agree) to indicate their agreements with each statement (e.g. "I lead a purposeful and meaningful life"). The scores on the three scales were standardized and then averaged to obtain a single aggregate index of well-being, with higher scores indicating greater well-being.

We also used Zung Self-rating Depression Scale (SDS; Wang et al., 1999; Zung, 1965) to measure *depressive symptoms*. SDS is a 20-item scale quantifying the affective, psychological, and somatic symptoms associated with depression. Participants rated on a 4-point Likert scale (1= a little of time, 4= most of time) to indicate how often they experienced the described symptom (e.g. "I feel down-hearted and blue") during the past week.

Gratitude, Resentment and Appreciation Test (GRAT; Gan, 2009; Watkins et al., 2003) was used to assess *dispositional gratitude*. GRAT is a 44-item questionnaire measuring the extent to which the respondent would not feel deprived in life (the Sense of Abundance subscale), would appreciate the contribution of others to his/her well-being (the Appreciation for Others subscale), and would appreciate the simple things that are readily available to most people (the Simple Appreciation subscale). Participants rated on a 5-point Likert scale (1= strongly disagree, 5= strongly agree) to indicate their agreements with each item (e.g. "I'm really thankful for friends and family").

Heartland Forgiveness Scale (HFS; Thompson et al., 2005; Zhang, 2009) was employed to assess *dispositional forgiveness*. HFS is an 18-item scale assessing how forgiving the respondent tends to be of oneself (the Forgiveness of Self subscale), other people (the Forgiveness of Others subscale), and negative situations that are beyond anyone's control (the Forgiveness of Situations subscale). Participants rated on a 7-point Likert scale (1= almost /always false of me, 7= almost/always true of me) to indicate how often they typically respond to the type of negative situation described (e.g. "With time I am understanding of others for the mistakes they have made").

For each participant, the mean scores on measures of depression, gratitude, and forgiveness were calculated. All the questionnaires described above are widely used and have good psychometric properties, with internal consistency estimates ranging from .76 to .91 in this study (Table 1).

2.3. Genotyping

Genomic DNA was extracted from hair follicle cells by using Chelex-100 method. *COMT* Val158Met was amplified by polymerase chain reaction (PCR). The upstream primer, 5′-CCAGCGGATGGTGGATTTCGCACGC-3′ and the downstream primer, 5′-TGGGGGGGTCTTTCCTCAGCC-3′, were recruited. The AC in the

Table 1
Descriptive statistics and correlations for measures of well-being, depression, gratitude, and forgiveness.

Scale	No. of items	α	Range	Mean	SD	Correlations					
						1	2	3	4	5	6
1. Satisfaction With Life Scale	5	.84	1.0–6.8	3.41	1.18						
2. Scale of Positive and Negative Experience	12	.86	-2.3–3.7	1.38	1.00	.39					
3. Flourishing Scale	8	.82	2.6–7.0	5.32	.77	.47	.55				
4. Well-being index	25	.90	-2.9–2.2	.00	.80	.77	.80	.84			
5. Zung Self-rating Depression Scale	20	.79	1.0–3.1	1.68	.30	−.15	−.32	−.33	−.33		
6. Gratitude, Resentment and Appreciate Test	44	.91	2.7–4.9	3.86	.37	.37	.47	.64	.62	−.31	
7. Heartland Forgiveness Scale	18	.76	3.2–6.3	4.71	.55	.22	.41	.47	.46	−.24	.47

Note. Well-being index was derived from a mean of standardized scores on three scales: The Satisfaction with Life Scale, the Scale of Positive and Negative Experience, and the Flourishing Scale. All the correlations were significant at the $p < .01$ level (two-tailed).

upstream primer was site-directed mutagenesis for introducing a restriction site of *Mlu*I. The PCR reaction system contained 2.50 μL 2× reaction MIX (Golden Easy PCR System, TIANGEN), .50 μL DNA Template, 2.50 μL ddH2O, .25 μL (25 pmol) upstream primer, and .25 μL (25 pmol) downstream primer. A product of 206 bp was amplified with an initial 4 min denaturation at 94 ℃, followed by 30 cycles of 94 ℃ for 30 s, 63.5 ℃ for 30 s, 72 ℃ for 30 s, and a final extension at 72 ℃ for 3 min. The PCR product was incubated with *Mlu*I (FERMENTAS, MBI) at 37 ℃ overnight. According to the protocols provided, the 5.0 μL incubation system contained 1.5 μL PCR products, 4.0 U MluI (10U/μL), .4 μL R buffer, and 3.1 μL ddH2O. The digested mixture was analyzed using 8% polyacrylamide gel electrophoresis in 200 V for 1.5 h, which was followed by silver staining. Finally, the genotypes were scanned by using the Bio-imaging System. The distribution of genotypes (Met/Met =29 (10 males), Val/Met =147 (32 males), Val/Val =269 (68 males)) showed no deviation from the Hardy-Weinberg Equilibrium (χ^2 =2.078, p =.149).

2.4. Statistical analysis

PASW statistics 18 (formerly SPSS Statistics; http://www.spss.com.hk/statistics/) was used to analyze data. First, to calculate correlations between measures of well-being, depression, gratitude, and forgiveness, we used Pearson's correlation test. Second, to test the effects of the *COMT* Val158Met polymorphism on well-being, depression, gratitude, and forgiveness, we conducted 4 separate univariate linear regression analyses with the genotypes (0= Met/Met, 1 = Val/Met, 2 = Val/Val) as a single predictor. Third, to confirm that the significant genotype effects observed in this study were unlikely to arise by chance, we carried out permutation tests implemented in MATLAB for each outcome variable by shuffling the genotype across participants 10,000 times. This procedure was to estimate the regression coefficient in each shuffled sample and the probability of the estimated regression coefficients being greater than the observed regression coefficient (i.e., permutation p). Fourth, to test for the mediating roles of dispositional gratitude and forgiveness in the associations between the *COMT* Val158Met polymorphism and well-being and depressive symptoms, we bootstrapped 20,000 times the indirect effects of the polymorphism on well-being and depressive symptoms through dispositional gratitude and forgiveness, using the SPSS version of INDIRECT macro (http://www.afhayes.com/; Preacher and Hayes, 2008) and obtained the bias-corrected 95% confidence intervals of the indirect effects. The indirect effects were considered statistically significant at $p < .05$ when the 95% confidence intervals did not include zero. Finally, to examine whether the genotype effects survived even when the potential contributions of non-genetic factors were partialled out, we used hierarchical regression analysis (see *Supplementary Materials*).

3. Results

Descriptive statistics and correlations for measures of well-being, depression, gratitude, and forgiveness are presented in Table 1. As reported previously (Bono et al., 2008; Reed and Enright, 2006; Wood et al., 2008a; Wood et al., 2008b), both dispositional gratitude and forgiveness correlated positively with well-being and negatively with depressive symptoms (Table 1).

3.1. Regression Analyses

COMT Val158Met polymorphism significantly predicted individuals' *well-being* (β=.111, t=2.353, p=.019, R^2 =.012), *depression* (β=−.102, t=−2.161, p=.031, R^2 =.010), *gratitude* (β=.116, t=2.468, p=.014, R^2 =.014), and *forgiveness* (β=.106, t=2.243, p=.025, R^2 =.011). Individuals with a smaller number of the Met alleles, which is associated with higher activity of COMT, reported greater well-being, less depressive symptoms, and greater tendencies in gratitude and forgiveness (Fig. 1). The permutation p values confirmed that the probability of obtaining the significant genotype effects by chance was lower than .05 (permutation *ps* for well-being, depression, gratitude, and forgiveness were .020, .034, .015, and .027, respectively).

Considering the gender differences in well-being, depression, gratitude, and forgiveness (Hyde et al., 2008; Pinquart and Sörensen, 2001), for the four outcome variables, we conducted 2 (gender: male vs. female) ×3 (genotype: Met/Met vs. Val/Met vs. Val/Val) ANOVAs for different scales and found no significant interactions between gender and genotype, all *ps* > .345, suggesting that the genotype effects were similar across genders.

3.2. Mediation Analyses

As longitudinal and interventional studies have demonstrated the causal links of gratitude and forgiveness to well-being and depressive symptoms (Bono et al., 2008; Emmons and McCullough, 2003; Reed and Enright, 2006; Seligman et al., 2005; Zhang et al., 2014), we conducted mediation analyses to examine whether the effects of the *COMT* Val158Met on well-being and depressive symptoms were mediated by dispositional gratitude and forgiveness. Given that gratitude and forgiveness were both assumed to account for the effect of the *COMT* gene on well-being and that gratitude scores correlated with forgiveness scores in the sample (r =.47), we used a multiple mediation model suggested by Preacher and Hayes (2008). Results showed significant mediating effects of gratitude and forgiveness on the relationship between *COMT* and well-being: For gratitude, the mediating effect estimate =.0595, *SE* =.0260, and the 95% bias corrected confidence interval was [.0119, .1138]; for forgiveness, the mediating effect estimate =.0227, *SE* =.0119, and the 95% bias corrected confidence interval was [.0028, .0505]. As shown in Fig. 2A, the total mediating effects accounted for 74% (1-.029/.111) of the effect of the *COMT* gene on well-being.

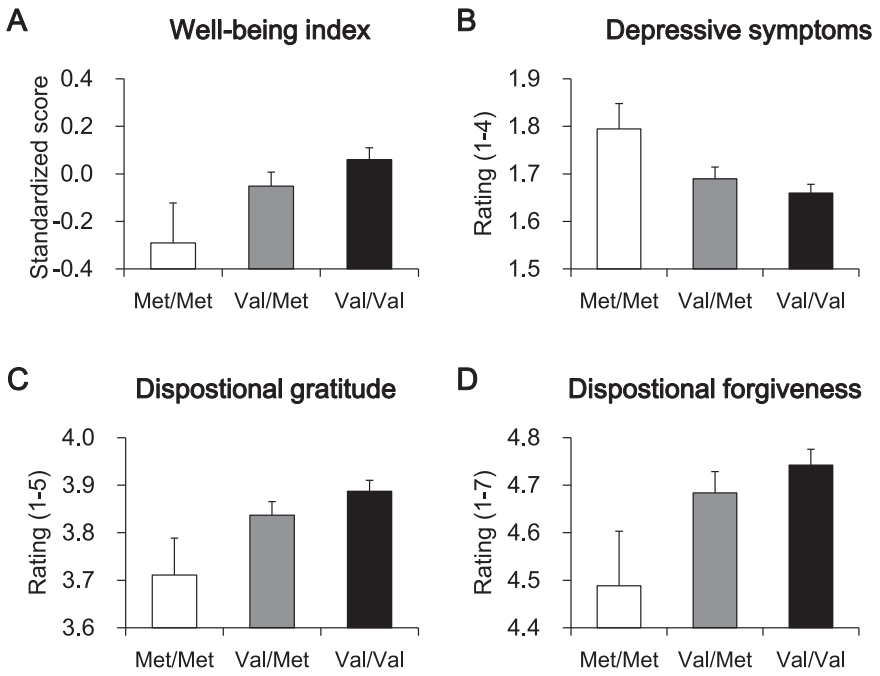

Fig. 1. Effects of the *COMT* Val158Met polymorphism on well-being, depressive symptoms, dispositional gratitude, and dispositional forgiveness. (**A**) Individuals with a smaller number of the Met alleles, which is associated with higher activity of COMT, scored higher in the well-being index. Well-being index was derived from a mean of standardized scores from three scales designed to assess cognitive, affective, and psychological aspects of well-being. (**B**) Individuals with a smaller number of the Met alleles reported less depressive symptoms, as measured by the Zung Self-rating Depression Scale. (**C**) Individuals with a smaller number of the Met alleles displayed a greater tendency in gratitude, as measured by the Gratitude, Resentment and Appreciation Test. (**D**) Individuals with a smaller number of the Met alleles demonstrated greater tendency in forgiveness, as measured by the Heartland Forgiveness Scale. Error bars represent the standard error of the mean (see also Table S5 in the *Supplementary Materials*).

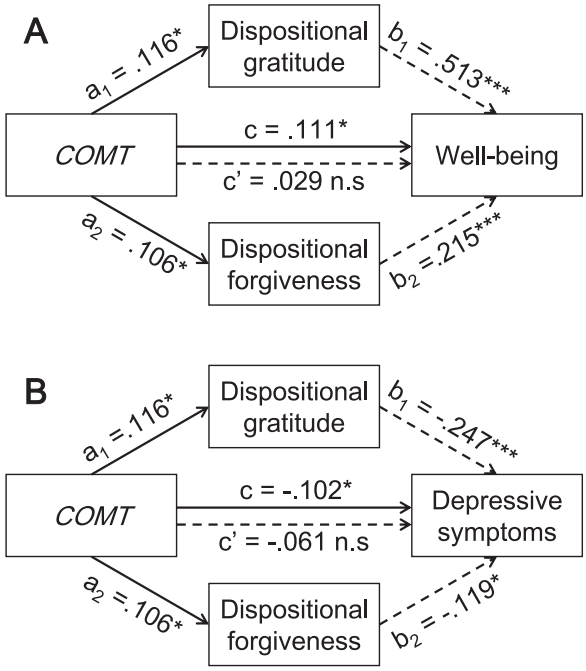

Fig. 2. Both Dispositional gratitude and forgiveness mediated the effects of the *COMT* Val158Met polymorphism on well-being (**A**) and depressive symptoms (**B**). All coefficients were derived from the following equations, $Y = cX + e_1$; $M1 = a_1X + e_2$; $M2 = a_2X + e_3$; $Y = c'X + b_1M_1 + b_2M_2 + e_4$. *Y* refers to the ratings of well-being or depressive symptoms; *X* refers to the genotype of the *COMT* Val158Met polymorphism (0= Met/Met, 1= Val/Met, 2= Val/Val); M_1 refers to the ratings of dispositional gratitude; M_2 refers to the ratings of dispositional forgiveness. n.s, $p \geq .10$; †, $.05 \leq p < .10$; *, $p < .05$; **, $p < .01$; ***, $p < .001$.

The same statistical procedure was applied to scores on depressive symptoms. Results from bootstrapping revealed significant mediating effects of gratitude and forgiveness on depression: For gratitude, the mediating effect estimate = −.0290, *SE* = .0144, and the 95% bias corrected confidence interval was [−.0634, −.0056]; for forgiveness, the mediating effect estimate = −.0126, *SE* = .0081, and the 95% bias corrected confidence interval was [−.0345, −.0012]. As shown in Fig. 2B, the total mediating effects accounted for 40% (1-.061/.102) of the effect of the *COMT* gene on depressive symptoms.

Note that the mediated paths from the gene through gratitude and forgiveness to well-being and depressive symptoms remained significant when gratitude and forgiveness scores were separately entered into the single-mediator mediation models (see Table S4, Fig. S2).

3.3. Controlling for non-genetic factors

To make sure that the effects of genotype on dispositional gratitude and forgiveness and the total/mediating effects of genotype on well-being and depressive symptoms survived even when potential contributions of non-genetic factors were controlled, we collected data concerning parents' levels of education, parents' occupation, household income, average monthly expenditure, religious beliefs, romantic relationship status, and perceived mother's and father's parenting style, and entered them as control variables into regression models (see *Supplementary Materials*). Compared with the model which included only the control variables, the model which used both the genotype and the control variables as predictors was more effective in predicting well-being, $F(1, 412)_{\text{change}} = 5.188$, $p = .023$, depressive symptoms, $F(1, 412)_{\text{change}} = 3.931$, $p = .048$, dispositional gratitude, $F(1, 412)_{\text{change}} = 7.272$, $p = .007$, and dispositional forgiveness, $F(1, 412)_{\text{change}} = 6.814$, $p = .009$. Furthermore, dispositional gratitude and forgiveness both continued to significantly mediate the genotype effects on well-being, with the 95% bias corrected confidence intervals being [.0191, .1292] and [.0080, .0684], respectively, and on depressive symptoms, with the 95% bias corrected confidence intervals being [−.5953, −.0652] and [−.3204, −.0056], respectively.

4. Discussion

Our study demonstrated that the increased number of the Met alleles was associated with increased depressive symptoms and decreased well-being. These findings, together with previous studies showing the increased negativity bias of the Met alleles in affective processing (Gao et al., 2016; Kia-Keating et al., 2007; Ohara et al., 1998; Smolka et al., 2005; Williams et al., 2010), highlight the involvement of the *COMT* gene in the susceptibility to depression. Our findings suggest a shared genetic basis of depressive symptoms and well-being, which is consistent with the high genetic overlap between depressive symptoms and well-being (Okbay et al., 2016). Moreover, the current findings went further by demonstrating the role of the *COMT* gene in well-being, a complex positive experience. Although previous research has shown the involvement of serotoninergic genes in well-being (Chen et al., 2013; De Neve, 2011), an important advance made by this study is that we identified *COMT* Val158Met, a common functional polymorphism that has no direct link to the serotoninergic system, as an additional genetic contributor to well-being. Indeed, the *COMT* gene encodes COMT enzyme that degrades catecholamines such as dopamine and norepinephrine, while previous studies have already demonstrated the importance of dopamine and norepinephrine functions in well-being (Nutt et al., 2007; Rutledge et al., 2015) and depression (Arango et al., 1993; Cohn et al., 1970). Thus, our results provide new genetic evidence indicating the fundamental roles of catecholamines (dopamine and norepinephrine) in human well-being.

The associations between genetic factors and socio-emotional functioning are complex and almost certainly not direct. They are mediated through a variety of developmental processes including individual differences in personality traits (Davis and Loxton, 2013; Saphire-Bernstein et al., 2011). For the *COMT* gene, the genotype effects on personality traits may be more prominent than its influence on socio-emotional functioning (Calati et al., 2011); thus personality traits may serve as intermediate phenotypes that bridge the gap between the *COMT* gene and socio-emotional functioning. As demonstrated in the current study, the effects of the *COMT* gene on well-being and depression are substantially mediated by dispositional gratitude and forgiveness, two positive personality traits that serve as keys to pursuing well-being and combating depression (Bono et al., 2008; Reed and Enright, 2006; Wood et al., 2008a; Wood et al., 2008b).

In recent years, positive psychology has paid extensive attention to the measurement, application, and improvement of the 24 positive personality traits that contribute to human well-being (Park et al., 2004; Peterson et al., 2005; Peterson and Seligman, 2004; Seligman et al., 2005). They found that individuals vary considerably in positive personality traits (Peterson et al., 2005) and that a large portion of well-being could be accounted for by the 24 positive personality traits (Park et al., 2004). However, little attention has been paid to the genetic basis underlying the heterogeneity of positive personality traits as well as the potential mediating roles of these traits in the impacts of genetic and environmental factors on well-being and depression. The current findings suggest that a large portion of genetic contributions to well-being shown in the twin studies (Lykken and Tellegen, 1996; Røysamb et al., 2002; Stubbe et al., 2005) results from the effects of the genes on positive personality traits.

One might wonder how the gene polymorphism affects positive personality traits. Given the increased negativity bias in the Met allele carriers (Gao et al., 2016; Kia-Keating et al., 2007; Ohara et al., 1998; Smolka et al., 2005; Williams et al., 2010) and the detrimental effects of the negativity bias on the development of positive personality traits (Hanson, 2013), our findings suggest that the *COMT* Met allele predisposes individuals to be hyposensitive to positive life events but hypersensitive to negative life events. These individuals may gradually form, over the developmental course of life, a habit of neglecting the positive aspects of life events and complaining about misfortunes, resulting in decreased positive personality traits, such as gratitude and forgiveness. As for how gratitude and forgiveness promote well-being, Bono and McCullough have given extensive review on the issue (Bono and McCullough, 2006).

Previous studies have shown that non-genetic factors, such as socioeconomic status, religious beliefs, relationship status, and parenting environment, are crucial for the cognitive, affective, and psychological aspects of well-being (Dush, 2005; Ellison, 1991; Huppert et al., 2010; Pinquart and Sörensen, 2000). Nevertheless, our results showed that the effect of the *COMT* gene on well-being and the mediated paths from the gene through gratitude and forgiveness to well-being continued to hold after controlling for these environmental factors. This finding suggests that *COMT* may play an important role in fostering positive experiences and attitudes toward life independently of environmental contributions.

Several limitations of this study should be noted. First, like all candidate gene association studies (Ebstein et al., 2012), the sample size of this study was relatively small, particularly for the male group. As women in general report lower well-being than men (Pinquart and Sörensen, 2001), we examined whether the observed genotype effects depended on gender but found a non-significant gene×gender interaction. However, because of the relatively small sample size for the male group, this study could be underpowered to detect a small interaction effect in the two-way between-subjects ANOVA. As such, further studies with larger samples are needed to investigate the potential gene×gender interaction. Second, *COMT* Val158Met polymorphism accounted for 1.2% variance of well-being while the heritability of well-being was estimated at 38–54% (Lykken and Tellegen, 1996; Røysamb et al., 2002; Stubbe et al., 2005), suggesting that well-being are likely to be influenced by multiple polymorphisms (Okbay et al., 2016). It would be important for future studies to consider simultaneously a variety of genetic factors underlying individual differences in well-being. Finally, all the participants in the current study were Chinese. Therefore, our findings should be interpreted with caution in generalizing to other populations. As some studies have showed that the associations between genes and positive personality traits can be modulated by culture (Kim et al., 2011; Kitayama et al., 2014), it would be interesting to investigate the potential cultural differences in the relationship between *COMT* polymorphisms and well-being.

To conclude, our findings demonstrate the contribution of the *COMT* gene to well-being, dispositional gratitude, and dispositional forgiveness, highlight the importance of gratitude and forgiveness in the relationship between the gene and well-being, and suggest a psychobiological pathway for well-being and depression.

Author Contributions

J. L., P. G., and X. G. designed the experiment and analyzed the data, under the supervision of X. Z.. J. L. and P. G. performed the experiment. J. L., P. G., and X. Z. wrote the manuscript.

Funding

This study was supported by grants from National Basic Research Program of China (973 Program: 2015CB856400) and National Natural Science Foundation of China (31630034) to Xiaolin Zhou, Natural Science Foundation of China (31640037) to Pingyuan Gong, and National Natural Science Foundation of China (31600928) and China Postdoctoral Science Foundation (2015M582399) to Jinting Liu.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

Acknowledgments

We thank Mr. She Li, Mr. Peizhe Zhang, Miss Yunxia He and Miss Lin Lei for their assistances in data collection, and Mr. Philip Blue for preparation of the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jad.2017.03.005.

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