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Research paper

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

Jinting Liu[a,b,c,1], Pingyuan Gong[d,1], Xiaoxue Gao[c], Xiaolin Zhou[c,e,f,*]

[a] China Centre for Special Economic Zone Research, Shenzhen University, Guangdong 518060, China
[b] Research Centre for Brain Function and Psychological Science, Shenzhen University, Guangdong 518060, China
[c] Center for Brain and Cognitive Sciences and Department of Psychology, Peking University, Beijing 100871, China
[d] Key Laboratory of Resource Biology and Biotechnology in Western China (Ministry of Education), Northwest University, Shaanxi 710069, China
[e] PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China
[f] Beijing Key Laboratory of Behavior and Mental Health, Peking University, Beijing 100871, China

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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

* Correspondence author at: Department of Psychology, Peking University, Beijing 100871, China.
E-mail address: xz104@pku.edu.cn (X. Zhou).
[1] Jinting Liu and Pingyuan Gong contributed equally to this work.

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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