Psychoneuroendocrinology 80 (2017) 131–136

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

Revisiting the impact of *OXTR* rs53576 on empathy: A population-based study and a meta-analysis

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ARTICLE INFO

Article history:
Received 21 October 2016
Received in revised form 2 March 2017
Accepted 2 March 2017

Keywords:
Empathy
Oxytocin
Polymorphism
Association analysis
Meta-analysis

ABSTRACT

Oxytocin in the brain is related to empathy, which refers to the ability to understand and share others' internal states or responses. Previous studies have investigated the impact of *OXTR* rs53576, the most intensively examined polymorphism in the oxytocin receptor (*OXTR*) gene, on individual differences in empathy. However, these studies produced inconsistent results. In the current study, we reexamined the association of *OXTR* rs53576 with empathy in a relatively large population (N = 1830) and also evaluated the association by a comprehensive meta-analysis (N = 6631, 13 independent samples). The replication study indicated that *OXTR* rs53576 was indeed associated with individual differences in empathy. Individuals with a greater number of G alleles showed better empathic ability, particularly in fantasizing other's feelings and actions. The meta-analysis not only confirmed this association, but also indicated that the impact of this polymorphism was significant in both Europeans and Asians. These findings provide convincing evidence for the impact of *OXTR* rs53576 on empathy, highlighting the importance of *OXTR* gene in individuals' social cognition.

1. Introduction

Empathy refers to an individual's ability to understand and share others' internal states or responses (Davis, 1983). This ability is a core cognitive-emotional component of human social behaviors. For instance, empathy is associated with the understanding of others' intentions and thoughts, which could act to promote individuals' altruistic behaviors and foster positive relationships (Paleari et al., 2005; Pavey et al., 2012; Stocks et al., 2009). Previous studies have indicated that individual differences in empathy are related to the availability of neuromodulators in the brain such as oxytocin (e.g., Radke and de Bruijn, 2015; Rodrigues et al., 2009) and dopamine (Gong et al., 2014; Uzefovsky et al., 2014), among which oxytocin draws the largest share of interest from the scientific community.

The availability of oxytocin in the brain is regulated by the oxytocin receptor (*OXTR*) gene (Feldman et al., 2012; Feng et al., 2015). This gene is a potential genetic factor contributing to individual differences in empathy. Indeed, previous studies have investigated the association of empathy with single nucleotide polymorphisms (SNPs) in *OXTR*, among which *OXTR* rs53576 is the most intensively examined genetic polymorphism (Huetter et al., 2016; Lucht et al., 2013; Rodrigues et al., 2009; Smith et al., 2014; Uzefovsky et al., 2015; Weisman et al., 2015). This polymorphism has also been shown to influence a variety of human behaviors, including sociality and parenting behaviors (Klahr et al., 2015; Li et al., 2015). In this study, we focused on the impact of *OXTR* rs53576 on empathy.

Twelve studies with 13 independent samples have investigated the association of *OXTR* rs53576 with the individual differences in empathy. However, inconsistent findings were reported by these studies. Six studies demonstrated that this polymorphism could

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http://dx.doi.org/10.1016/j.psyneuen.2017.03.005
0306-4530/

significantly predict individual differences in empathy: five studies showed that individuals with the GG genotype had higher levels of empathy than those with the A allele (Huetter et al., 2016; Lucht et al., 2013; Rodrigues et al., 2009; Smith et al., 2014; Uzefovsky et al., 2015; Weisman et al., 2015), while one study showed the opposite pattern, as individuals with AA genotype evidenced higher empathic accuracy (Laursen et al., 2014). The other seven studies, however, failed to find an association between this polymorphism and empathy at all (Buffone and Poulin, 2014; Christ et al., 2016; Luo et al., 2015a; McDonald et al., 2016; Montag et al., 2012; Taschereau-Dumouchel et al., 2016; Wu et al., 2012). The discrepancy between studies may partly due to the relatively small sample of participants in individual studies and the cultural influences on the polymorphism's effect (see the next paragraph). To truly understand the impact of *OXTR* rs53576 on empathy, this study reexamined the association between the polymorphism and empathy in a relatively large population and conducted a meta-analysis of the previous studies.

Studies have shown that the genotype proportion of *OXTR* rs53576 significantly varies across different races (Bakermans-Kranenburg and van Ijzendoorn, 2014; Butovskaya et al., 2016), such that there is a lower proportion of the G allele of the polymorphism in Eastern nations (e.g., Japan, China, and Korea), while there is a higher proportion in Western nations (e.g., USA, UK, Australia, Canada, Netherlands, Italy, Sweden, Germany, and Finland; Butovskaya et al., 2016). Moreover, *OXTR* rs53576 also interacts with culture on individuals' psychological manifestations (Kim et al., 2011; Sasaki et al., 2011). For instance, Koreans with the GG genotype showed greater psychological well-being if they were more religious, while European Americans with the GG genotype had lower psychological well-being if they were more religious (Sasaki et al., 2011). Therefore, given the racial differences in the genotype proportion and the interaction of *OXTR* rs53576 with culture, it is important to investigate the potential racial differences in the impact of the polymorphism on empathy. To this end, the current study also conducted meta-analyses to compare the impacts of *OXTR* rs53576 on empathy between Europeans and Asians.

2. Methods

2.1. Participants

We recruited 1830 unselected college students (68.68% female, mean age = 20.41 ± 1.28 years) from Henan University of Science and Technology, China. These participants were ethnic Chinese Han, without any known ancestors of other ethnic origin. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Life Science College, Northwest University, China.

2.2. Interpersonal Reactivity Index (IRI) assessment

Empathy was measured with the Chinese version (Rong et al., 2010) of the 28-item Interpersonal Reactivity Index (IRI; Davis, 1983). This scale consists of four subscales: Perspective Taking, Fantasy, Empathic Concern, and Personal Distress. Perspective Taking evaluates cognitive propensity to spontaneously adopt the viewpoint of others (e.g., '*Before criticizing somebody, I try to imagine how I would feel if I were in their place*'); Fantasy assesses the extent to which people immerse themselves in fictitious characters' feelings and actions (e.g., '*When I am reading an interesting story or novel, I can imagine how I would feel if the events in the story were happening to me*'); Empathic Concern measures other-oriented feelings of sympathy and concern for unfortunate others (e.g., '*I often have tender, concerned feelings for people less fortunate than me*'); Personal Distress taps self-oriented feelings of personal anxiety and unease in tense interpersonal settings (e.g., '*I go to pieces when I see someone who badly needs help in an emergency*'). For each item, the respondent scores on a 5-point Likert scale, with 0 indicating 'does not describe me well' and 4 indicating 'describes me very well'. The total score of IRI provides a comprehensive index of individuals' empathic ability. The score procedure in the current study followed Davis' suggestion. The internal consistency of this scale, as measured with Cronbach's α, was 0.718 in the current sample. Note that, while the Perspective Taking and Fantasy subscales measure mostly cognitive empathy (i.e. theory of mind), the Empathic Concern and Personal Distress subscales measure mostly affective empathy (Davis, 1983).

2.3. Genotyping

We extracted genomic DNA from hair follicle cells with the Chelex-100 method. The *OXTR* rs53576 polymorphism was amplified by polymerase chain reaction (PCR) with upstream primer, 5′- ATCACTGGGTCACTCAA-3′ and the downstream primer 5′-AACATCTGTCAGGAGGT-3′. The PCR was conducted in a 5 μl system which contained 2.50 μl reaction MIX (Golden Easy PCR System, TIANGEN), 0.50 μl DNA template, 1.50 μl ddH_2O, 0.25 μl (25 pmol/μl) upstream primer, and 0.25 μl (25 pmol/μl) downstream primer. A 231 bp PCR product was amplified with an initial 3 min denaturation at 94 °C, followed by 35 cycles of 94 °C for 30 s, 62.5 °C for 35 s, 72 °C for 45 s, and a final extension at 72 °C for 8 min. The PCR fragment was incubated overnight with BamHI (FERMENTAS, MBI) at 37 °C. The 5.0 μl incubation system contained 1.0 μl PCR products, 4.0 U BamHI (10U/μl), 0.4 μl Tango buffer, and 3.2 μl ddH_2O. The digested fragments were identified by using 8% polyacrylamide gel electrophoresis with 200 voltages for 1.5 h, followed by silver staining. Finally, the genotypes were scanned with the Multi-Spectral imaging System. In the sample, the distribution of genotypes (AA = 848, AG = 815, GG = 167) showed no deviation from Hardy-Weinberg equilibrium, $\chi^2 = 2.10$, $p = 0.147$.

2.4. Statistical analysis

Data were analyzed with SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). The Hardy-Weinberg equilibrium test was assessed with the FINETTI software (Sasieni, 1997). When evaluating the impact of *OXTR* rs53576 on empathy, gender was treated as a control variable in hierarchical regression equations: Step 1, entering gender; Step 2, entering both the gender variable and the genotypes (0 = AA, 1 = AG, 2 = GG). Bonferroni corrections were carried out for multi-tests. The meta-analysis (Supplementary online materials) was performed with Comprehensive Meta-Analysis 2.0 software (Biostat, Inc.). In this study, the statistical significance was considered at two-tailed $p < 0.05$.

3. Results

3.1. The replication study

As previously reported, we found that the subscale scores and total score of the females were higher than those of the males (female vs. male: 2.62 ± 0.02 vs. 2.53 ± 0.03 for Perspective Taking, 2.43 ± 0.02 vs. 2.25 ± 0.03 for Fantasy, 3.04 ± 0.02 vs. 2.86 ± 0.03 for Empathic Concern, 2.53 ± 0.02 vs. 1.72 ± 0.03 for Personal Distress, and 2.54 ± 0.01 vs. 2.34 ± 0.02 for the total score), $t\ (1828) > 5.42$, $ps < 0.001$.

The hierarchical regression analysis indicated that the *OXTR* rs53576 polymorphism could predict individual differences in the total score of IRI, $\beta = 0.058$, $R^2 = 0.058$, $t = 2.566$, uncorrected $p = 0.010$, Bonferroni-adjusted $p = 0.050$. One-way ANOVA also

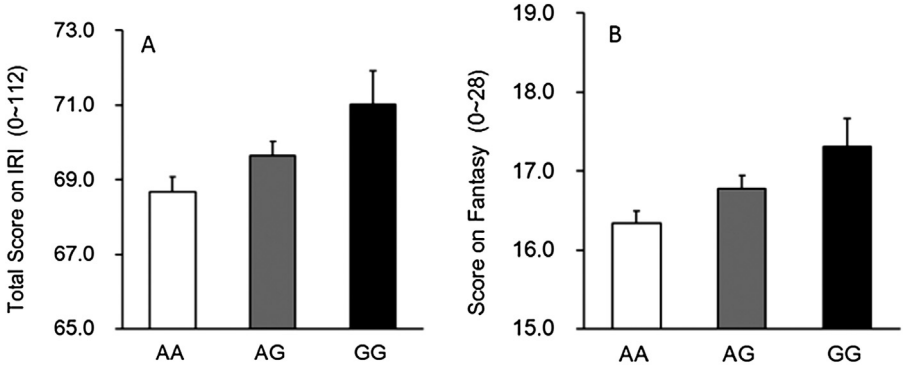

Fig. 1. IRI scores and *OXTR* rs53576 genotype groups. Fig. 1A shows the total score on IRI for *OXTR* rs53576 genotype groups. Individuals with the GG genotype ($N = 167$, $M \pm SE = 71.011 \pm 0.903$) showed a higher mean score than those with the AG ($N = 815$, $M \pm SE = 69.653 \pm 0.360$) and AA genotypes ($N = 848$, $M \pm SE = 68.686 \pm 0.381$), $F(2, 1829) = 3.879$, $p = 0.021$, $\eta^2 = 0.004$. Fig. 1B displays individual differences in the Fantasy subscale for *OXTR* rs53576 genotype groups. Individuals with the GG genotype ($N = 167$, $M \pm SE = 17.304 \pm 0.363$) showed a higher mean empathic fantasy score than those with the AG ($N = 815$, $M \pm SE = 16.777 \pm 0.165$) and AA genotypes ($N = 848$, $M \pm SE = 16.335 \pm 0.157$), $F(2, 1829) = 3.886$, $p = 0.021$, $\eta^2 = 0.004$.

Table 1
Regression analysis of *OXTR* rs53576 on the subscales of IRI.

	β	*Adjusted* R^2	*t*	*p*
OXTR rs53576				
Fantasy	0.062	0.019	2.659	0.008
Empathic Concern	0.026	0.022	1.117	0.264
Perspective Taking	0.004	0.003	0.165	0.869
Personal Distress	0.044	0.046	1.948	0.052
Total scale	0.058	0.058	2.566	0.010
OXTR rs53576 Gender*				
Fantasy	0.020	0.040	1.730	0.084
Empathic Concern	−0.006	0.002	−0.252	0.801
Perspective Taking	−0.023	0.003	−1.003	0.316
Personal Distress	−0.026	0.046	−1.121	0.263
Total scale	0.057	−0.006	−0.283	0.777

showed a significant linear trend in the total score, with the score increasing as a function of the number of G alleles, $F(1, 1829) = 6.431$, $p = 0.011$ (Fig. 1A). As for the four subscales, this polymorphism significantly predicted the individual differences in the Fantasy subscale, $\beta = 0.062$, $R^2 = 0.019$, $t = 2.659$, uncorrected $p = 0.008$, Bonferroni-adjusted $p = 0.040$. The linear trend was also significant, $F(1, 1829) = 6.11$, $p = 0.014$ (Fig. 1B). Of note, this polymorphism was not associated with the individual differences in the scores on Empathic Concern, Perspective Taking, or Personal Distress (Table 1). Additionally, given the significant influence of gender on empathy, we also examined the interaction between *OXTR* rs53576 and gender but observed no significant interactions (Table 1).

3.2. Meta-analysis

We conduct a meta-analysis to confirm the findings of our association study, with a measure of effect size as Cohen's $d = (\text{Mean}_{\text{GG genotype}} - \text{Mean}_{\text{A allele carriers}})/\text{pooled SD}$ (Supplementary online materials) by pooling 12 primary studies (13 independent samples and total 6631 participants, see in Table S1). In the meta-analysis, both the asymmetry of funnel plot and Duval and Tweedie's trim and fill method (Duval and Tweedie, 2000) indicated that our selection of publications had no obvious bias (Supplementary online materials). Moreover, the homogeneity test indicated that Eta square of these studies was homogeneous, $Q(8) = 3.488$, $p > 0.05$. As shown in Table S1 of the Supplementary online materials, two of the studies used the Reading Mind in the Eyes Test (RMET) to measure (cognitive) empathy, ten of the studies used IRI to measure both cognitive and affective empathy.

As a whole, the meta-analysis revealed that *OXTR* rs53576 was significantly associated with individual differences in empathy, with Cohen's $d = 0.148$, 95% CI = 0.082 – 0.213, $Z = 4.429$, $p < 0.01$ for the Fixed model, and Cohen's $d = 0.152$, 95% CI = 0.056–0.248, $Z = 3.094$, $p = 0.002$ for the Random model (Fig. 2). Moreover, given the racial differences in empathy between Europeans and Asians and the different proportions of G allele between races (Butovskaya et al., 2016), we conducted two meta-analyses separately to examine the impacts of this polymorphism on empathy in Europeans and Asians, with Cohen's $d = (\text{Mean}_{\text{GG}} - \text{Mean}_{\text{A allele carriers}})/\text{pooled SD}$ for Europeans and Cohen's $d = (\text{Mean}_{\text{AA genotype}} - \text{Mean}_{\text{G allele carriers}})/\text{pooled SD}$ for Asians. Results indicated that this polymorphism could predict individual differences in empathy in both Asians and Europeans, with the Fixed model: Cohen's $d = 0.140$, 95% CI = 0.055–0.225, $Z = 3.242$, $p = 0.001$ for Asians, Cohen's $d = 0.165$, 95% CI = 0.060–0.270, $Z = 3.085$, $p = 0.002$ for Europeans; and with Random model: Cohen's $d = 0.143$, 95% CI = 0.029–0.257, $Z = 2.460$, $p = 0.014$ for Asians, Cohen's $d = 0.168$, 95% CI = −0.001–0.338, $Z = 1.953$, $p = 0.051$ for Europeans (Fig. 3). A comparison of effect sizes between Asians and Europeans indicated that the impact of *OXTR* rs53576 on empathy had essentially the same strength for Europeans and Asians (Europeans vs. Asians: Cohen's $d = 0.140$–0.143 vs. Cohen's $d = 0.165$–0.168).

4. Discussion

In this study, we replicated the association of *OXTR* rs53576 with empathy in a relatively large population and further evaluated this association with a meta-analysis. Results indicated that *OXTR* rs53576 is associated with individual differences in empathy, with individuals with GG genotype having better empathetic abilities. Our findings provide robust evidence for the role of *OXTR* rs53576 in the neurobiological architecture of empathy.

Previous findings concerning the association between *OXTR* rs53576 and empathy were inconsistent. In the current study, we demonstrated the link between *OXTR* rs53576 and empathy by both an association study and a meta-analysis. Based on the overall effect size from the meta-analysis ($d = 0.15$), a total of over 700 participants is needed in order to achieve 95% power (Faul et al., 2009) when observing the effect of rs53576 genotype on empathy. This goes a long way in explaining why results from previous studies were so inconsistent. Given our larger sample size and the advantages of meta-analysis in increasing statistical power (Abreu et al., 2005; Stanley et al., 2008), the current study provides robust evidence that *OXTR* rs53576 indeed contributes to the individual

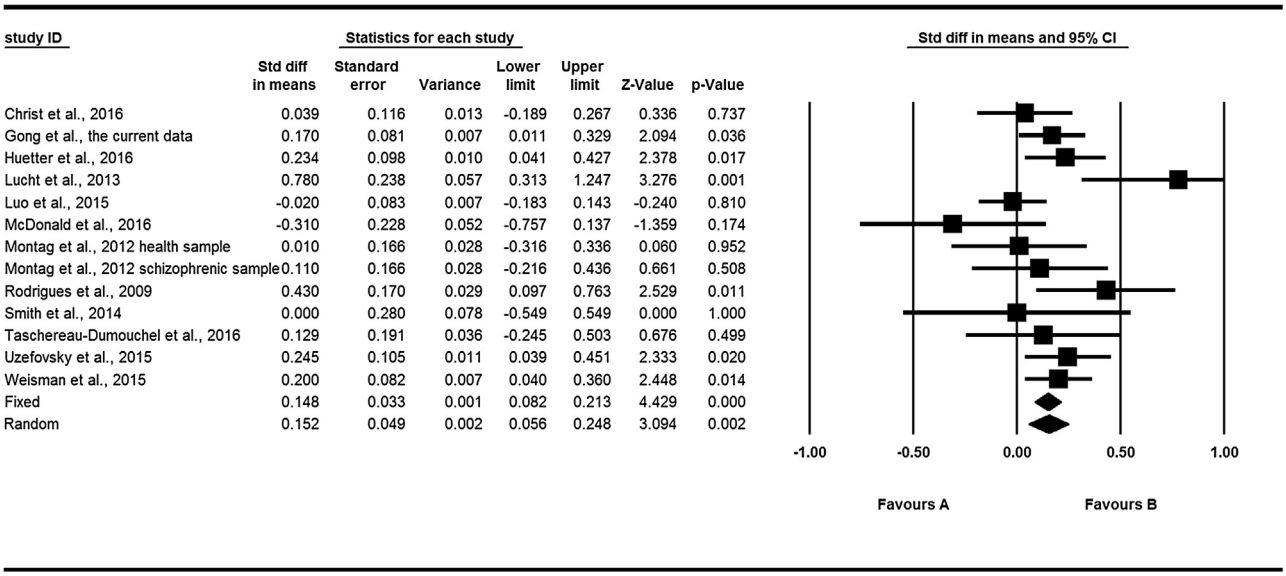

Fig. 2. The assocation between *OXTR* rs53576 and empathy. Fixed model: Cohen's $d = 0.148$, 95% CI = 0.082–0.213, $Z = 4.429$, $p < 0.01$; for Random model: Cohen's $d = 0.152$, 95% CI = 0.056–0.248, $Z = 3.094$, $p = 0.002$. In this analysis, 12 primary studies with 13 independent samples ($N = 6631$) were included.

differences in empathy. Moreover, consistent with previous studies showing that the G allele of *OXTR* rs53576 is associated with higher oxytocin sensitivity (Chen et al., 2015; Feng et al., 2015; Marsh et al., 2012) and more efficient brain functions, such as greater activation in empathic-related brain areas (e.g., the insula, anterior cingulate, and superior temporal gyrus) (Luo et al., 2015a,b) and stronger connectivity between amygdala and hypothalamus (Tost et al., 2010), the current study demonstrated that the GG genotype of this polymorphism is related to higher levels of empathy, particularly in the extent to which people fantasize other's feelings and actions.

In this study, we found that the impact of *OXTR* rs53576 on empathy showed similar strength for Europeans and Asians. In line with previous studies indicating that there is a lower proportion of the G allele of this polymorphism in Asians (Sasaki et al., 2011), we also observed a lower proportion of the G allele as compared with the A allele in our sample. Although the proportions of the G allele are inverse in Europeans and Asians, this allele is nevertheless related to the higher level of empathy in both ethnic groups. Therefore, combined with the evidence that the G allele of *OXTR* rs53576 is associated with higher oxytocin sensitivity (Chen et al., 2015; Feng et al., 2015; Marsh et al., 2012) and more efficient brain functions, we may conclude that the impact of *OXTR* rs53576 on empathy is independent of the frequency distribution of the G allele in populations.

Cross-cultural psychological studies showed that empathy is greatly varied between races. For example, Europeans display stronger empathic responses to strangers of out-groups than Asians (Atkins et al., 2016; Cassels et al., 2010; Ma-Kellams and Blascovich, 2012). There are two potential explanations for these racial differences. One might argue that the racial difference in empathy are largely modulated by cultural adaptation (Boyd and Richerson, 2009; Chiao, 2011). Asians do not rely on empathy as much as

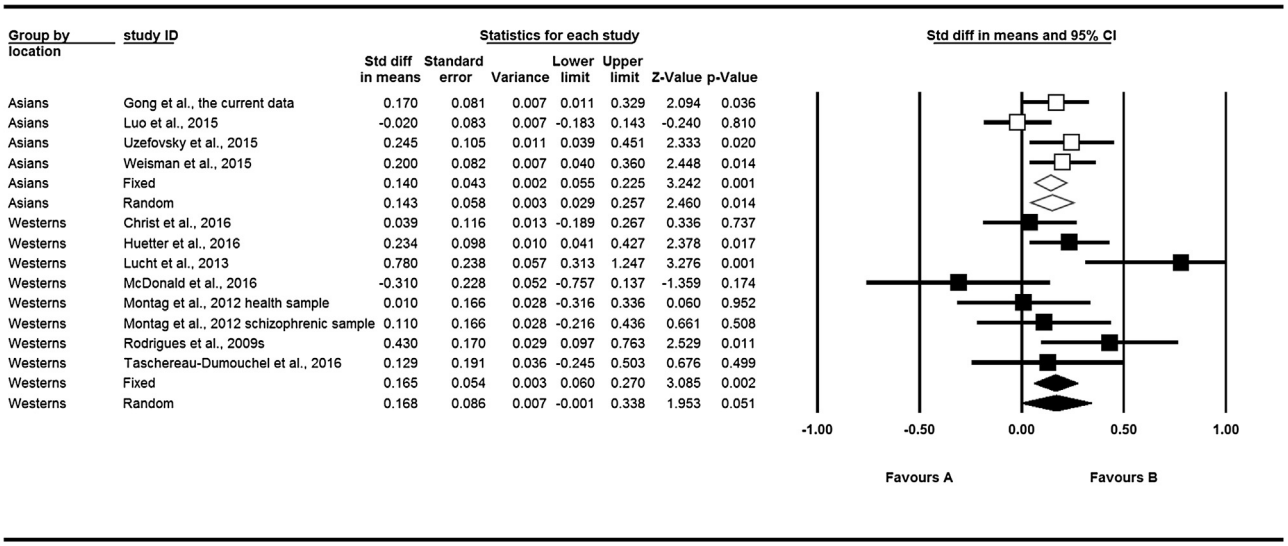

Fig. 3. The comparison between Asians and Europeans. The impacts of *OXTR* rs53576 on empathy were similar across cultures. Fixed model: Cohen's $d = 0.140$, 95% CI = 0.055–0.225, $Z = 3.242$, $p = 0.001$ for Asians, and Cohen's $d = 0.165$, 95% CI = 0.060–0.270, $Z = 3.085$, $p = 0.002$ for Europeans; Random model: Cohen's $d = 0.143$, 95% CI = 0.029–0.257, $Z = 2.460$, $p = 0.014$ for Asians, and Cohen's $d = 0.168$, 95% CI = −0.001–0.338, $Z = 1.953$, $p = 0.051$ for Europeans. Given that the sample in Smith et al. (2014) was race mixed, this sample was excluded in this analysis. Note: Euro denotes the ethnicities from Europe and America.

Europeans to understand strangers' behavior in social interactions (Prevost et al., 2014), despite the fact that empathic responses in interactions are encouraged in all races. However, one might also argue that the differences in empathic skills between Europeans and Asians are in part modulated by genetic factors, despite the fact that the lower empathic responses in social interactions are compensated by collectivism in Asians (Duan et al., 2008; Heinke and Louis, 2009). Assuming that genetic selection can refine the cognitive and neural architectures that are responsible for the storage and transmission of cultural influences (Boyd and Richerson, 2009; Chiao, 2011), we believe that the differences in the proportions of the G allele and in empathic responses between Europeans and Asians are results of culture-gene co-evolution. In many occasions this co-evolution may overshadow the subtle differences in the simple association between genetic polymorphism and behavior between races. The current study hence extends our understanding of the racial differences of empathy and other empathic-related social behaviors.

Limitations of the current study need to be mentioned. Of note, the available data for our arguments are relatively insufficient, particularly for separately analyzing Europeans and Eastern Asians. Further meta-analysis is needed once more individual studies are reported. Moreover, two different measures of empathy (IRI and RMET) were included in our meta-analysis. The IRI is a multifactor survey while the Reading the Mind in the Eyes (RMET) is a behavioral measure focusing on cognitive empathy. Thus our meta-analysis to some extent neglected the difference between the two measures when pooling the samples together. Although the two measures both showed significant impacts of *OXTR* rs53576 on empathy (Fig. S3), it remains unclear whether these findings could be extrapolated given the smaller number of independent samples assessed by RMET. Additionally, while *OXTR* rs53576 and gender showed no significant interaction with empathy in the current study, this issue needs to be further addressed when sufficient data on different sexes are available. Nevertheless, our association study and the current meta-analysis are sufficient to conclude that the G allele of *OXTR* rs53576 increases individuals' empathy, a core component of social cognition.

Author contributions

Performed the experiments: Pingyuan Gong, Jinting Liu, Xing Yang, Kejin Zhang; Analyzed the data: Pingyuan Gong, Huiyong Fan; Wrote the paper: Pingyuan Gong, Xiaolin Zhou; Designed the study: Pingyuan Gong, Xiaolin Zhou; Provided overall guidance during the whole process: Pingyuan Gong, Xiaolin Zhou.

Funding

This study was supported by the Natural Science Foundation of China (31640037), Opening Foundation of Shaanxi Key Laboratory for Animal Conservation (Northwest University), and Science Research Foundation of Northwest University (338050067) to Pingyuan Gong.

Acknowledgments

We thank Mr. Guomin Shen, Haijun Han, Kunpeng Du, She Li, and Miss Tan Zhao for their assistance in data collection and two anonymous reviewers for their constructive suggestions.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.psyneuen.2017.03.005.

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