Psychoneuroendocrinology 85 (2017) 165–171

Contents lists available at ScienceDirect

Psychoneuroendocrinology

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

A field study of the association between *CD38* gene and altruistic behavior: Empathic response as a mediator

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ARTICLE INFO

Keywords:
CD38
Oxytocin receptor gene (*OXTR*)
Donation
Altruism
Empathy

ABSTRACT

Inspired by the enhancement effects of oxytocin on empathic responses and altruistic behaviors, we conducted a field study with a real fundraising event and investigated to what extent oxytocin pathway genes (*CD38* and *OXTR*) modulate individual differences in charitable donation. Participants were informed that a teacher in their university was diagnosed with uremia and could not afford the cost of medication. They were given the opportunity to donate any amount of money and report their empathic responses to the misfortune of the teacher. We found a significant association between *CD38* rs3796863 and the amount of donation both before and after controlling for gender, age, subjective socioeconomic status, religious belief, and social desirability. Individuals with the genotypes (AA/AC) leading to higher oxytocin levels reported stronger empathic responses and donated more money than individuals with the CC genotype. Moreover, empathic response mediated the gene-altruism association. However, we observed no significant associations between the three polymorphisms of *OXTR* (rs53576, rs2254298, and rs1042778) and the amount of donation. This study demonstrates the importance of *CD38* as a source of individual differences in altruistic behavior and highlights the role of empathic response in bridging the link between the oxytocin pathway gene and altruism.

1. Introduction

Altruistic behavior, such as charitable donation and monetary sharing, refers to actions that are carried out voluntarily, with the primary intention of benefitting others and without the expectation of receiving rewards from external sources (Bar-Tal, 1985; Piliavin, 1990). As the purest and most selfless form of prosocial behavior, altruistic behavior offers no external reward to benefactors, although it does result in certain positive outcomes. Indeed, studies have shown that altruistic behavior promotes benefactors' happiness (Dunn et al., 2008; Kahana et al., 2013), longevity (Harris and Thoresen, 2005), and work performance (Anik et al., 2013).

It is widely acknowledged that altruistic behavior varies substantially across individuals (Israel et al., 2009; Reuter et al., 2011). Twin studies have established that a large portion of individual differences in altruistic behavior can be attributed to genetic factors, with a heritability of 31%–61% (Cesarini et al., 2009; Knafo et al., 2011; Knafo and Plomin, 2006; Rushton et al., 1986). Oxytocin, a neuropeptide hormone released in various brain regions (e.g., hippocampus, amygdala, nucleus accumbens, bed nucleus of stria terminalis, and brainstem; Meyer-Lindenberg et al., 2011) and related to parturition, lactation, maternal bonding, and affiliative behavior (Bartz et al., 2011; Feldman, 2012; Lee et al., 2009), plays an important role in human altruistic behavior (Barraza et al., 2011; Riem et al., 2013; van IJzendoorn et al., 2011). The current study aimed to investigate the contribution of oxytocin pathway genes to individual differences in charitable donation.

In the context of charitable donation, Barraza et al. (2011) found that for participants who donated to charitable organizations, those given the intranasal oxytocin treatment donated significantly more than

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http://dx.doi.org/10.1016/j.psyneuen.2017.08.010
Received 8 April 2017; Received in revised form 2 August 2017; Accepted 2 August 2017

those in the placebo treatment. Intranasal oxytocin treatment was suggested to elevate oxytocin levels in plasma and possibly oxytocin levels in cerebral spinal fluid (Striepens et al., 2013; but see Leng and Ludwig, 2016 for a debate on whether intranasal oxytocin is able to produce a significant increase in cerebral spinal fluid). Intranasal administration of oxytocin may also increase the amount of donation to a charity (van IJzendoorn et al., 2011) as well as the number of balls thrown toward a socially excluded player in the Cyberball game (Riem et al., 2013). In the context of monetary sharing, however, results concerning the effect of oxytocin administration are mixed. In the dictator game in which the receiver is forced to accept the offer from the allocator, oxytocin administration has no effect or even has a detrimental effect on altruism (Radke and de Bruijn, 2012; Zak et al., 2007). In contrast, in the ultimatum game in which the receiver can either accept or reject the offer from the allocator, oxytocin administration increases monetary sharing from the allocator (Zak et al., 2007). Zak et al. (2007) suggested that, unlike in the dictator game, in the ultimatum game, where the allocator has to forecast the receiver's negative emotions and rejection to low offers, oxytocin might stimulate perspective taking and empathy and thus motivate the allocator to increase monetary sharing.

Inspired by the enhancement effects of acute exogenous oxytocin on altruistic behaviors, a few studies have examined the role of the oxytocin receptor gene (*OXTR*) in altruism by using the dictator game and self-reported measures (including questionnaires such as the Prosocial Tendencies Measure, the Rushton Altruism Scale, and self-report charitable activities). These studies, however, produced mixed results (Apicella et al., 2010; Ci et al., 2014; Israel et al., 2009; Krueger et al., 2012; Poulin et al., 2012). Israel et al. (2009) reported that, in the dictator game, carriers of the G allele of rs1042778 (N = 192 in the first sample and 86 in the second sample) transferred more money to their recipients than TT carriers (N = 11 in the first sample and 12 in the second sample). Krueger et al. (2012) found that carriers of the A allele of rs53576 (N = 52) showed less trust behavior in a trust game than GG carriers (N = 56). Notably, the small sample size of these studies may make the findings underpowered. Indeed, in a relatively large sample of 684 Swedish participants, Apicella et al. (2010) examined the effect of 9 polymorphisms of *OXTR* (including rs53576 and rs1042778) on monetary allocation in the dictator game and the trust game and found no significant associations between any of the 9 polymorphisms and the amount of monetary transfer in either of the games. The discrepancy between studies may be partly due to the normally low level of empathic response in economic games (Apicella et al., 2010; Israel et al., 2009; Krueger et al., 2012; Leiberg et al., 2011), which could dampen the link between oxytocin and altruism (Barraza et al., 2011; Radke and de Bruijn, 2012; van IJzendoorn et al., 2011; Zak et al., 2007). The self-reported measures of altruism (Ci et al., 2014; Poulin et al., 2012) are also vulnerable to dishonest reporting, since altruism is a socially desirable trait and participants may conceal their true attitude towards the assumed events or questions. The reliance on economic games or self-reported measures could thus make the effects of oxytocin pathway genes on altruism less easy to detect.

To avoid these pitfalls, we conducted a field study with an empathy-provoking situation (i.e., a real fundraising event for a specific person) in a relatively large sample. Participants were informed that a teacher in their university was diagnosed with uremia and could not afford the cost of medication. They were given the opportunity to donate any amount of money (including no money at all) to the teacher. Given the enhancement effects of oxytocin administration on empathic responses to the misfortune of others (Abu-Akel et al., 2015; Hurlemann et al., 2010; Krueger et al., 2013) and the central role of empathic response in altruistic behavior (Batson et al., 1991, 1989, 1988), we also asked participants to report their empathic responses to the misfortune of the teacher.

Previous studies have focused mainly on the effects of polymorphisms of the oxytocin receptor gene (*OXTR*) on prosocial behaviors (Apicella et al., 2010; Ci et al., 2014; Israel et al., 2009; Kogan et al., 2011; Krueger et al., 2012; Poulin et al., 2012; Tost et al., 2010), while genes that regulate oxytocin release, such as *CD38*, have been neglected. The transmembrane glycoprotein CD38 is a key regulator of central oxytocin release and the effect of CD38 on transmitter secretion is specific to oxytocin (Jin et al., 2007). *CD38* knockout mice exhibit marked reductions of oxytocin (Jin et al., 2007; Liu et al., 2008). In humans, *CD38* gene is related to social-emotional functioning (Chong et al., 2017; McInnis et al., 2017; McQuaid et al., 2016). As such, the current study genotyped participants for the most investigated polymorphisms in both *OXTR* gene (rs53576, rs2254298, and rs1042778) and *CD38* gene (rs3796863). We selected the polymorphism rs3796863 because in the *CD38* gene, it is the most commonly studied polymorphism that its impact on oxytocin levels (Feldman et al., 2012) and social-emotional functioning (Feldman et al., 2012; McInnis et al., 2017; McQuaid et al., 2016) has been repeatedly demonstrated. Carriers of the A allele of rs2254298, the G allele of rs1042778, or the A allele of rs3796863 have higher levels of oxytocin than noncarriers (Feldman et al., 2012). Also, although the functionality of rs53576 remains unknown, some research has shown that the G allele is associated with prosocial behavior (Kogan et al., 2011; Tost et al., 2010). Although the effect of acute exogenous oxytocin may not correspond directly to the effect of endogenous oxytocin, given the effect of polymorphisms of *OXTR* and *CD38* on endogenous oxytocin levels (Feldman et al., 2012) and the effect of acute exogenous oxytocin levels on empathic responses (Abu-Akel et al., 2015; Hurlemann et al., 2010; Krueger et al., 2013) and altruistic behaviors (Barraza et al., 2011; Riem et al., 2013; van IJzendoorn et al., 2011), we nevertheless hypothesized that carriers of the alleles related to higher prosocial behaviors would experience stronger empathic responses toward the teacher in need and would donate more money to help than noncarriers.

2. Methods

2.1. Participants

Five hundred and nine unrelated Chinese Han students (74.3% female, mean age = 24.4 ± 1.4 years) from Henan University of Science and Technology voluntarily signed up for the study. They were ethnic Han Chinese without any known ancestors of other ethnic origin. Written informed consent was 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. Participants were tested in cohorts of 7–19 students. Six participants were excluded because they had attended the teacher's classes and knew him personally. Two participants were also excluded because they explicitly withdrew from the donation (see below). The last two cohorts of participants (N = 28) were excluded because they acquired the knowledge of the study from other participants prior to the test, resulting in significantly reduced donation amounts compared to other participants ($M \pm SD$, 4.15 ± 5.73 vs. 9.82 ± 11.17 *yuan*, $p < 0.001$). Note that including these participants did not change the pattern of behavioral genetic results reported for the final set of 473 participants, who did not know the teacher personally and who completed the study in a normal manner.

2.2. Procedures

Participants arrived for the study in groups of 7–19 students. They waited outside the test room in a queue. Only one participant was taken into the room at a time. After entering the room, the participant signed the consent form and received a payment of ¥ 40 (7 five-yuan notes and 5 one-yuan notes; about 6 US dollars in total) for filling in questionnaires in the subsequent tests. The participant was also informed about the situation of the sick teacher and was given an opportunity to donate any amount of money (including no money at all) to the teacher

Table 1
Primer sequences and genotype distributions of variants in the study.

Variant	PCR primers	PCR TM (°C)	Amplicon length (bp)	Restriction enzyme	Genotype frequency	Genotyping rate (%)	HWE *p*-value
CD38 rs3796863	Fwd: 5′-TTTTAGCGACGACAAG-3′ Rev: 5′-GACCCTGGATTCAACA-3′	60.5	208	BveI/BspMI	AA/AC/CC: 54/210/176	93.0	0.475
OXTR rs53576	Fwd: 5′-ATCACTGGGTCACCTCAA-3′ Rev: 5′-AACATCTGTCAGGAGCGT-3′	62.5	231	BamHI	AA/AG/GG: 201/206/47	96.0	0.587
OXTR rs2254298	Fwd: 5′-CACGGTCCCACATTTATGC-3′ Rev: 5′-CTCATCCAGTGCCCCTTTC-3′	64	236	BSeN1	AA/AG/GG: 36/243/178	96.6	< 0.001
OXTR rs1042778	Fwd: 5′-TCCCAGAATGAAGAAGTAA- 3′ Rev: 5′-GGTGATGGCGTATGTTT-3′	55.4	253	Van91I	GG/GT/TT: 403/65/5	100.0	0.202

Note: Fwd, Forward; Rev, Reverse; TM, Temperature; HWE, Hardy-Weinberg Equilibrium; for more details of genotyping, see Supplementary materials.

(see *Donation* section for details). Each donation, made by leaving the money in an envelope, was supposed to be anonymous. After the donation, the participant was taken into another room to complete a battery of questionnaires, including measures of empathic response, subjective socioeconomic status, religious belief, and social desirability (see Supplementary materials). As socioeconomic status, religious belief, and social desirability are crucial demographic and individual difference variables that affect altruistic decisions (Eisenberg et al., 2001; Saroglou et al., 2005), we included measures of these variables to examine whether the genotype effect would survive the controlling for these non-genetic factors. After completing the questionnaires, the participant was informed of the goal of the study and the deception in the donation. Permission of using each participant's data was once again obtained.

2.3. Donation

After receiving the monetary compensation for his/her participation, each participant was presented with the following fundraising details on a piece of paper:

> *Dear Students,*
>
> *Last November, a teacher in our university was diagnosed with bilateral acute renal failure. He underwent hemodialysis several times in the hospital to prevent death from kidney failure. He has no siblings and his parents are too old to provide monetary support. Thanks to his wife's contacting hospitals to search for a matched kidney donor, the teacher has recently undergone a successful kidney transplant operation in Wuhan University First Hospital. The teacher is required to take anti-rejection medication. Unfortunately, his family has used up all of their savings and now cannot afford the cost of anti-rejection medication.*
>
> *Considering the misfortune of his family, we ask for your help by ways of a financial donation. Please note:*
>
> ***The principle of anonymity**: The donation is anonymous. Please put money into the envelope provided and throw the envelope into the locked red box.*
>
> ***The principle of willingness**: You can donate any amount of money, including 0 yuan. Feel free to leave the donation by keeping the envelope for yourself. We are just offering you an opportunity to help.*

Except for anonymity, all the fundraising information was true. Colleagues of the teacher had donated a total of ¥ 23,300 to him and the event had been reported by the university newspaper. After the participant read the fundraising information, the experimenter emphasized the principles of anonymity and willingness and informed the participant that the red box was placed near the exit. In fact, there was a unique marker (e.g., 'ZLL01′) inside each envelope to allow us to identify the amount of donation for each participant. To reduce the potential effect of social desirability, nobody except the participant and the experimenter were in the room and the experimenter's back was to the red box. To control for potential influences of the experimenters, the six experimenters were trained to follow a scripted protocol to deliver identical instructions and to behave consistently towards the participants. Ultimately, we raised ¥ 5,116.30 (including contributions of the authors) and gave the money to the teacher.

2.4. Empathic responses

We assessed empathic responses with 3 items modified from Batson et al. (1987): "How strongly did you feel sympathetic towards the teacher when you heard about his misfortune?", "How strongly did you feel softhearted towards the teacher when you heard about his misfortune?", "How strongly did you feel his distress towards the heavy disease when you heard about his misfortune?" Participants were asked to report on a 7-point scale (1 = not at all, 7 = extremely). The ratings of these items were combined into an overall measure of empathic responses to the misfortune of the teacher (Cronbach's alpha = 0.72).

2.5. Genotyping

The genetic material, 3–5 hairs with hair follicle cells from each participant, was collected in a previous study unrelated to the current one (Liu et al., 2014). The participants were re-contacted for this study. We extracted genomic DNA from hair follicle cells by Chelex-100 method (de Lamballerie et al., 1994). Polymorphisms were amplified by polymerase chain reaction (PCR). The PCR reaction system contained 2.50 μl 2 × reaction MIX (Golden Easy PCR System, TIANGEN), 0.50 μl DNA Template, 1.50 μl ddH2O, 0.25 μl (25 pmol/μl) upstream primer, and 0.25 μl (25 pmol/μl) downstream primer. Details of genotyping are shown in Table 1 and Supplementary materials. Note that due to failures in genotyping, the numbers of participants retained after genotyping of *CD38* gene (rs3796863) and *OXTR* gene (rs53576, rs2254298, and rs1042778) were 440, 454, 457, and 473, respectively.

3. Results

3.1. Main effect

As the examination of the univariate distribution revealed that the amounts of donation were positively skewed (skewness = 1.788, *SE* = 0.112; Fig. S1), we log transformed the amount of donation with the formula log(amount of donation + 1) to reduce skewness (skewness = −0.056). For each polymorphism, to ensure a sufficient number of participants in each group to be analyzed, minor homozygotes and heterozygotes were collapsed into one group and compared to the major homozygotes, as done previously in the field (e.g., Feldman et al., 2012; McInnis et al., 2017). Note that when the groups were not

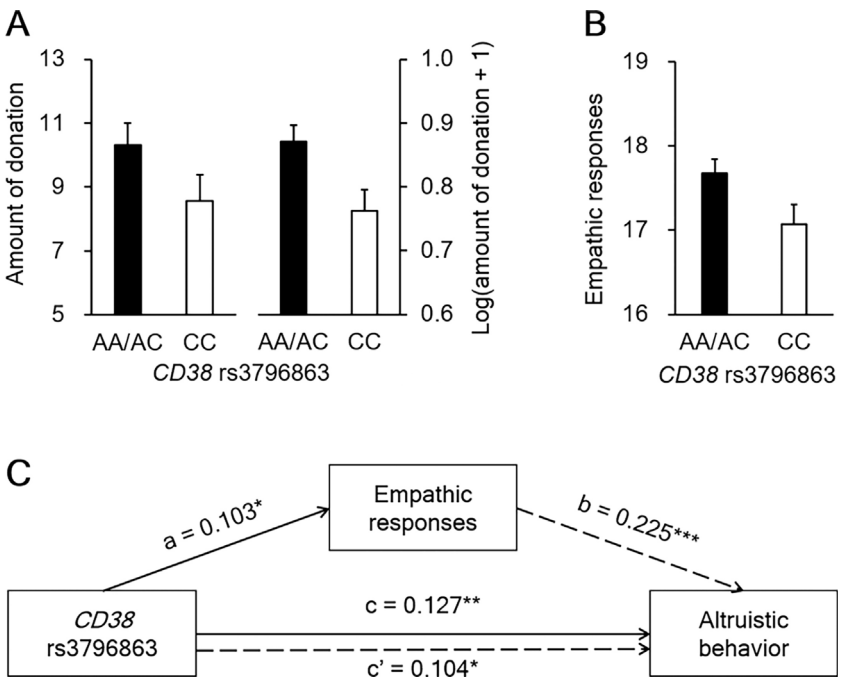

Fig. 1. *CD38* gene, empathic responses, and altruistic behavior. (A) The A allele carriers (N = 264) donated significantly more to the victim of uremia than CC carriers (N = 176). (B) The A allele carriers (N = 264) reported stronger empathic responses to the misfortune of the victim than CC carriers (N = 176). (C) Empathic responses mediated the effect of *CD38* rs3796863 polymorphism on altruistic behavior. All coefficients were derived from the following equations, $Y = cX + e_1$; $M = aX + e_2$; $Y = c'X + bM + e_3$. Y refers to the log (amount of donation + 1); X refers to the genotype of *CD38* rs3796863 (1 = AA/AC, 0 = CC); M refers to the rating of empathic response. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

collapsed (Bernhard et al., 2016; Tost et al., 2010), similar results were obtained (see Supplementary materials).

Four independent-sample *t*-tests revealed only a significant association between *CD38* rs3796863 and the amount of donation. The A allele carriers ($M \pm SD$: 0.871 ± 0.411; N = 264) donated significantly more than CC carriers (0.763 ± 0.441; N = 176), $t(438) = 2.631$, $p = 0.009$, Cohen's $d = 0.26$ (Fig. 1A). This finding survived the Bonferroni correction (Bonferroni-adjusted $p = 0.035$) for the four polymorphisms analyzed in this study. To confirm that the significant genotype effect was unlikely to arise by chance, we carried out permutation test implemented in MATLAB by shuffling the genotype across participants 20,000 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). The permutation p value confirmed that the probability of obtaining the significant genotype effect by chance was lower than 5% (permutation $p = 0.0089$). To examine whether the genotype effect continued to hold after controlling for non-genetic factors (gender, age, subjective socioeconomic status, religious belief, social desirability and the experimenter), we conducted a hierarchical regression analysis with the following procedure: Step 1, entering control variables; Step 2, entering both control variables and the polymorphism (1 = AA/AC, 0 = CC). Results again revealed a significant genotype effect on the amount of donation, $F(1, 416)_{\text{change}} = 6.781$, $p = 0.010$, $\beta = 0.121$, and $R^2_{\text{change}} = 0.015$. The permutation p value once again confirmed that the probability of obtaining the significant genotype effect after controlling for covariates by chance was lower than 5% (permutation $p = 0.0098$). Moreover, *CD38* rs3796863 did not interact with gender, subjective socioeconomic status, or the three polymorphisms of *OXTR* to affect the amount of donation, as no interactions concerning *CD38* rs3796863 were found, all $ps > 0.200$ (see Supplementary materials).

In contrast, for *OXTR* (rs53576, rs2254298, and rs1042778), independent-samples *t*-tests found no significant effects of genotypes (all $ps > 0.200$): rs53576 (AA vs. AG/GG: 0.826 ± 0.430 vs. 0.834 ± 0.434, $p = 0.831$), rs2254298 (AA/AG vs. GG: 0.843 ± 0.442 vs. 0.822 ± 0.414, $p = 0.615$), and rs1042778 (GG vs. GT/TT: 0.837 ± 0.430 vs. 0.805 ± 0.434, $p = 0.565$). For *OXTR* rs53576, to make a direct comparison between the current finding and the previous report that AA/AG carriers show less trust behavior than GG carriers (Krueger et al., 2012), we regrouped the genotypes and compared the amount of donation between AA/AG carriers (0.832 ± 0.433; N = 407) and GG carriers (0.815 ± 0.428; N = 47). No significant difference between them was found, $t(452) = 0.255$, $p = 0.799$. For *OXTR* rs1042778, to directly test the previous finding that GG/GT carriers show higher altruistic behavior than TT carriers (Israel et al., 2009), we compared the amount of donation between GG/GT carriers (0.831 ± 0.429; N = 468) and TT carriers (0.972 ± 0.624; N = 5) and found no significant difference either, $t(471) = -0.727$, $p = 0.468$. We further investigated whether the three polymorphisms of the *OXTR* gene had a combined effect on altruistic behavior. For each participant, we summed the number of alleles associated with high levels of oxytocin across the three identified polymorphisms (i.e., the G allele of rs53576, the A allele of rs2254298, and the G allele of rs1042778) to obtain a cumulative genetic score on the *OXTR* gene (Pearson et al., 2014). Linear regression analysis again failed to find a significant association between the cumulative genetic score and the amount of donation, $F(1, 438) < 1$, $p = 0.611$, $\beta = 0.024$, $R^2 = 0.001$. We also examined the three-way interaction between *OXTR* polymorphisms and again failed to find significant main effects or interactions, all $ps > 0.200$ (see Supplementary materials).

3.2. Gender effect

A 2 (*CD38* rs3796863: AA/AC vs. CC) × 2 (Gender: male vs. female) ANOVA for the amount of donation again revealed a main effect of *CD38* rs3796863, $F(1, 436) = 6.485$, $p = 0.011$, and a main effect of gender, $F(1, 436) = 5.218$, $p = 0.023$, with female participants donating significantly more money than male participants (Table S5). No interaction between the two variables were found, $F(1, 436) < 1$, $p = 0.528$.

3.3.1. Mediation analysis

For *CD38* rs3796863, independent-samples *t*-test revealed that the A allele carriers (17.7 ± 2.7) reported stronger empathic responses to the sick teacher than CC carriers (17.1 ± 3.1), $t(435) = 2.166$, $p = 0.031$, Cohen's $d = 0.21$ (Fig. 1B). The permutation p value confirmed that the probability of obtaining the significant genotype effect on empathy by chance was lower than 5% (permutation $p = 0.0325$). Individuals who reported stronger empathic responses donated more to the teacher,

$r = 0.260$, $p < 0.001$. On the basis of the causal link between empathic response and altruistic behavior shown in previous studies (Batson et al., 1991, 1989, 1988; Eisenberg and Miller, 1987) and the genotype effects on both empathic response and altruistic behavior, we conducted a mediation analysis to examine whether *CD38* rs3796863 influenced charitable donation via empathic response. We bootstrapped the mediating effect 20,000 times using the SPSS version of INDIRECT macro (http://www.afhayes.com/) developed by Preacher and Hayes (2008) and obtained the bias-corrected 95% confidence interval of the indirect effects. Results showed a significant mediating effect of empathic response on the relationship between *CD38* and the amount of donation: the mediating effect estimate = 0.0201, $SE = 0.0102$, and the 95% bias-corrected confidence interval was [0.0028, 0.0433]. As shown in Fig. 1C, the mediating effect accounted for 18.1% (1–0.104/0.127) of the effect of *CD38* gene on the amount of donation. In addition, the mediating path continues to hold after controlling for the non-genetic factors, the 95% bias-corrected confidence interval was [0.0002, 0.0306].

4. Discussion

Findings from twin studies yield heritability estimates of 31%–61% for altruistic behavior (Cesarini et al., 2009; Knafo et al., 2011; Knafo and Plomin, 2006; Rushton et al., 1986). Here we conducted a field study with a real fundraising event for a person diagnosed with uremia and identified a new polymorphism, *CD38* rs3796863, as a source of individual differences in charitable donation. Individuals with the genotype leading to a higher oxytocin levels (AA/AC) donated more money to the sick teacher than CC carriers. CD38 is a multifunctional protein, and its antigen and enzymatic roles are still being uncovered. Nevertheless, it is clear that CD38 is critical for the release of oxytocin from hypothalamic neurons (de Boer et al., 2012; Feldman et al., 2012; Jin et al., 2007). Mice with deletion of *CD38* gene exhibit marked reductions of oxytocin as well as marked defects in maternal nurturing and social behavior, and exhibit no changes in vasopressin or dopamine; the defects in behavior can be reversed by replacement of oxytocin or delivery of CD38 in the hypothalamus (Jin et al., 2007). In humans, the peripheral *CD38* gene expression is related to oxytocin levels (Kiss et al., 2011). Moreover, the A allele of *CD38* rs3796863 polymorphism is associated with high CD38 expression in lymphoblastoid cell lines (Lerer et al., 2010) and high plasma oxytocin levels (Feldman et al., 2012). Thus the allelic load for *CD38* rs3796863 is indicative of oxytocin functioning. The current findings provide support for the association between oxytocin functioning and altruism (Barraza et al., 2011; Riem et al., 2013; van IJzendoorn et al., 2011). These findings, together with previous observations (Chong et al., 2017; McInnis et al., 2017), strengthen the notion that individuals with higher levels of oxytocin are more likely to engage in prosocial behavior to seek social support (e.g., having more friends), which in turn limits the extent of negative mood outcomes (McInnis et al., 2017; McQuaid et al., 2014). Importantly, previous studies investigating the genetic basis of prosocial behavior mainly focus on the oxytocin receptor gene (Bakermans-Kranenburg and van IJzendoorn, 2014; Feldman et al., 2016). The current study went further to highlight the contribution of *CD38* gene, which regulates oxytocin release, to altruism. A testable prediction that can be naturally derived from the present study is that *CD38* could play an important role in other forms of prosocial behavior, such as trust and cooperation.

Empathy for others' misfortune is a strong predictor of the occurrence of altruistic behavior. Empathic responses motivate altruistic behaviors (Batson et al., 1991, 1989, 1988) and oxytocin administration increases empathic responses (Abu-Akel et al., 2015; Hurlemann et al., 2010; Krueger et al., 2013) and altruistic behavior (Barraza et al., 2011; Riem et al., 2013; van IJzendoorn et al., 2011). Empathic response may serve as an intermediate phenotype that links the oxytocin pathway genes and altruism. As hypothesized, we found that individuals with the genotype leading to higher oxytocin levels (AA/AC) reported stronger empathic responses to the misfortune of the teacher than CC carriers, and that the increased empathic responses motivated the A allele carriers to donate more money to the teacher. The current study is one of the first to directly test and prove the mediating role of empathic response in the link between the oxytocin functioning and altruistic behavior.

Previous studies have shown that non-genetic factors, such as socioeconomic status, religious belief, and social desirability, are crucial for decisions to offer help (Eisenberg et al., 2001; Saroglou et al., 2005). Nevertheless, our results showed that the effect of *CD38* gene on charitable donation and the mediating path from the gene via empathic response to the altruistic behavior continued to hold after controlling for these non-genetic factors. This suggests that the impact of *CD38* on empathic and altruistic tendencies cannot be simply explained away by non-genetic factors.

The finding concerning the *OXTR* gene in the current study is obviously inconsistent with certain other studies showing the links between *OXTR* gene and monetary sharing in the dictator game (Israel et al., 2009), trust behavior in the trust game (Krueger et al., 2012), and affiliative behavior in social interaction (Kogan et al., 2011). It is important to note that the latter studies used relatively small sample sizes: 23 for Kogan et al. (2011), 108 for Krueger et al. (2012), 203 for Israel et al. (2009), and 98 for the second sample of Israel et al. (2009). In a study with a relatively large sample of 684 Swedish participants, Apicella et al. (2010) failed to find significant associations between any of the 9 polymorphisms of *OXTR* (including rs53576, rs2254298, and rs1042778) and the amount of monetary transfer in either the dictator game or the trust game, a finding consistent with the current study ($N = 473$). Apicella et al. (2010) and Ebstein et al. (2012) suggested two possible reasons for the inconsistency. One is the insufficient statistical power in any given study. The other is the genetic and cultural differences between the Israeli sample (Israel et al., 2009), the Swedish sample (Apicella et al., 2010), and our Chinese sample. We suggest a third possible reason, the difference in task characteristics between the studies. A recent study revealed only a moderate correlation between the amount of monetary sharing in the dictator game and the amount of donation to the Red Cross ($r = 0.31$; Barraza et al., 2011). This may be taken as evidence for a dissociation between the two types of altruism (Leiberg et al., 2011): one more norm-based and reasoning-driven (e.g., dictator game), and one more compassion-based and emotion-provoking (e.g., charitable donation). The latter, such as donating money to support a person in need, is of high ecological validity since many of our everyday interactions are not purely rational, but involve emotions (Leiberg et al., 2011). We therefore suggest that the association between the *OXTR* gene and altruism needs further replications as well as meta-analyses.

Several limitations should be noted. First, the *CD38* rs3796863 polymorphism explains 1.5% of the overall variance in charitable donation, while the heritability of altruistic behavior was estimated at 31%–61% (Cesarini et al., 2009; Knafo et al., 2011; Knafo and Plomin, 2006; Rushton et al., 1986), suggesting that altruistic behavior is likely to be influenced by multiple genes and their interactions with environmental factors. Second, all the participants in this study were Chinese. As some studies showed that the relations between oxytocin pathway genes and social behaviors can be modulated by culture (Kim et al., 2010, 2011), future research is needed to examine the potential cultural differences in the associations between *CD38* rs3796863 polymorphism, oxytocin levels, and prosocial behaviors. Third, the current study investigated only three polymorphisms of the *OXTR* gene. Future research is needed to examine whether the uninvestigated polymorphisms with associations to other social behaviors (e.g., rs7632287, rs237887, and rs2268498) contribute to altruistic behavior and empathic responses (Feldman et al., 2016). Finally, the current study did not directly measure oxytocin levels or *CD38* gene expression.

To our knowledge, the association between the A allele of *CD38* rs3796863 polymorphism and high plasma oxytocin levels was reported only in one study in which most of the participants were parents with 4- to 6-month-old infants (Feldman et al., 2012). It remains unclear whether this association can be generalized to samples with varying characteristics. It is also unclear whether the effects of *CD38* rs3796863 on empathic responses and charitable donation is directly affected by *CD38* expression or through the effect of *CD38* on oxytocin (Chong et al., 2017; Higashida et al., 2012).

To conclude, by conducting a field study, we demonstrate the contribution of the *CD38* gene to altruistic behavior in a realistic setting and highlight the mediating role of empathic response in the gene-altruism association.

Author contributions

J. L. and P. 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., H. L., and X. Z. wrote the manuscript.

Funding

This work was supported by grants from National Natural Science Foundation of China to Xiaolin Zhou (Grant No: 31630034), to Jinting Liu (31600928, 31671158), and to Pingyuan Gong (31640037). Hong Li was supported by Shenzhen Peacock Plan (KQTD20150330161049 26).

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 Ms. Sai Li, Ms. Qiongdan Zhao, Mr. Kai Jiang, Ms. Lulu Zhang, Ms. Yunxia He, Mr. Jie Ren, and Ms. Jingjing Xing for their assistances in data collection, and Dr. Philip Blue for preparation of the manuscript.

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.2017.08.010.

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