Social Cognitive and Affective Neuroscience Advance Access published March 17, 2015

doi:10.1093/scan/nsv019 SCAN (2015) 1 of 9

Interaction between oxytocin receptor polymorphism and interdependent culture values on human empathy

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Recent evidence suggests that the association between oxytocin receptor polymorphism (OXTR rs53576) and emotion-related behavioral/psychological tendencies differs between individuals from East Asian and Western cultures. What remains unresolved is which specific dimension of cultural orientations interacts with OXTR rs53576 to shape these tendencies and whether such gene × culture interactions occurs at both behavioral and neural level. This study investigated whether and how OXTR rs53576 interacts with interdependence—a key dimension of cultural orientations that distinguish between East Asian and Western cultures—to affect human empathy that underlies altruistic motivation and prosocial behavior. Experiment 1 measured interdependence, empathy trait and OXTR rs53576 genotypes of 1536 Chinese participants. Hierarchical regression analyses revealed a stronger association between interdependence and empathy trait in G allele carriers compared with A/A homozygotes of OXTR rs53576. Experiment 2 measured neural responses to others' suffering by scanning A/A and G/G homozygous of OXTR rs53576 using functional magnetic resonance imaging. Hierarchical regression analyses revealed stronger associations between interdependence and empathic neural responses in the insula, amygdala and superior temporal gyrus in G/G compared with A/A carriers. Our results provide the first evidence for gene × culture interactions on empathy at both behavioral tendency and underlying brain activity.

Keywords: oxytocin receptor gene; empathy; culture value; fMRI

INTRODUCTION

Transcultural and genetic imaging studies have shown ample evidence that neural correlates of multiple cognitive and affective processes are shaped by both cultural experience (Han and Northoff, 2008; Kitayama and Uskul, 2011; Chiao *et al.*, 2013; Han *et al.*, 2013) and genetic make-up (Hariri *et al.*, 2006; Bigos and Weinberger, 2010; Falk *et al.*, 2012). These studies examined cultural or genetic influences on brain activity by comparing neural activity recorded from two cohorts of individuals from different cultures (Zhu *et al.*, 2007; Sui *et al.*, 2009; Cheon *et al.*, 2011; de Greck *et al.*, 2012; Murata *et al.*, 2013; Kitayama *et al.*, 2014; Ma *et al.*, 2014a) or with different genotypes (Hariri *et al.*, 2002; Fang *et al.*, 2013; Ma *et al.*, 2014b; Strange *et al.*, 2014). For instance, de Greck *et al.* (2012) found that, during empathic processing of angry, Chinese adults showed stronger hemodynamic responses in the left dorsolateral prefrontal cortex whereas Germans manifested stronger activity in the right temporoparietal junction (TPJ), right inferior and superior temporal gyrus (STG), and left middle insula. Cheon *et al.* (2011) also found that, compared with Caucasian-Americans, Koreans reported experiencing greater empathy and elicited stronger activity in the left TPJ in response to ingroup (*vs* outgroup) members' emotional pain. A recent study revealed that, in response to child stimuli during functional magnetic resonance imaging (fMRI), single nucleotide polymorphisms (SNPs) (rs53576 and rs1042778) in the oxytocin receptor gene (OXTR) were significantly associated with positive parenting and hemodynamic responses to child stimuli in the orbitofrontal cortex, anterior cingulate cortex and hippocampus (Michalska *et al.*, 2014). Although these findings suggest cultural and genetic influences on brain activity related to others' emotional states and one's own social behavior, to date, there have been relatively few empirical findings regarding the relationship between gene and culture in shaping human brain activity involved in social behavior.

Current theories that aim to explain the interplay between gene and culture at both group and individual levels predict that culture may interact with gene to shape human brain activity. The gene–culture coevolution theory postulates that culture creates novel environments under which genetic selection operates and genetic selection causes changes of the cognitive and neural architecture to facilitate transmission of those cultural values (Burkard and Knox, 2004; Richerson *et al.*, 2010). Consistent with the gene–culture coevolution theory, recent studies reported evidence for the association between collectivism cultural values and allelic frequency of two genes, i.e. the serotonin transporter functional polymorphism (5-HTTLPR) (Chiao and Blizinsky, 2010) and the OXTR rs53576 (Luo and Han, 2014). Populations dominated by stronger collectivistic values comprise more individuals carrying the short (s) allele of 5-HTTLPR and more individuals carrying the A allele of OXTR rs53576. Moreover, allele frequency and cultural values are intertwined to explain prevalence of emotional problems such that increased frequency of s allele carriers predicts decreased anxiety and mood disorder prevalence owing to increased collectivistic cultural values (Chiao and Blizinsky, 2010) and A allele frequency of OXTR rs53576 predicts major depression disorder prevalence across nations and such associated is mediated by collectivistic cultural values (Luo and Han, 2014). These findings elaborate the relationship between culture formation and genetic selection in the macroevolutionary processes and lead to the expectation of differential genetic influences across cultures on brain activities that guide human behavior. It has been suggested that cultural values may serve adaptive functions by tuning social behavior to reduce social and environmental risk factors and gene frequency plays an important role in explaining global variation in the adoption of cultural norms and comprehensive understanding of culture (Chiao and Blizinsky, 2010).

Received 21 October 2014; Revised 2 January 2015; Accepted 9 February 2015

We thank Yifan Zhang, Zhenhao Shi, Xiangyu Zuo and Xiaoyang Li for their help with recruitment of subjects. This study was supported by National Natural Science Foundation of China (Project 31470986, 31421003, 91332125 and 81161120539), National Basic Research Program of China (973 Program 2010CB833901 and 2010CB833903), Beijing Municipal Natural Science Foundation (No. Z111107067311058) and the Ministry of Education of China (Project 20130001110049).

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The gene–culture interaction model aims to explain the process in which genetic and sociocultural factors interact to shape psychological tendencies and behaviors at the individual level (Kim and Sasaki, 2014). Kim and colleagues found that, among European Americans, homozygotes of the G allele of the promoter region of the serotonin receptor gene (HTR1A) paid less attention to contextual information than homozygotes of the C allele, whereas Koreans showed a reverse pattern of the link between HTR1A and the locus of attention (Kim *et al.*, 2010b). Another study revealed that, among Japanese, short allele homozygotes (S/S) of 5-HTTLPR performed better during detection of the disappearance of facial expressions compared with the long allele carriers (S/L and L/L genotypes), whereas such a tendency was not observed in Americans (Ishii *et al.*, 2014). The gene × culture interaction was also observed on emotional processes and emotion-related behavioral tendencies. Among Americans, G/G homozygotes of OXTR rs53576 reported less suppression of emotion compared with A/A homozygotes whereas Koreans with the G/G genotype reported suppressing emotion more than those with the A/A genotype (Kim *et al.*, 2011). In a condition with great distress, Americans with either G/G or A/G genotypes sought more emotional support from others relative to those with the A/A genotype, whereas Koreans did not show such patterns of genetic differences in emotional support seeking (Kim *et al.*, 2010a).

These behavioral findings support a gene–culture interaction model that posits that genes provide a basis for the susceptibility to cultural environments (Belsky *et al.*, 2009) and influence how an individual engages in culture-specific behaviors (Kim and Sasaki, 2014). This model raises several important but unresolved questions. First, although there is evidence for distinct patterns of the association between gene and behavioral/psychological tendencies in East Asian and Western cultures, it remains unclear which specific dimension of cultural orientations interacts with genes to shape human behavior/psychological tendencies. East Asian and Western cultures are different in multiple dimensions such as attentional focus (Nisbett and Masuda, 2003), causal attribution (Choi *et al.*, 1999), self-construals (Markus and Kitayama, 1991) and affective states (Tsai, 2007). It is unclear which specific dimension of cultural orientations interacts with a genetic polymorphism to shape behavioral/psychological tendencies. Second, although the previous research suggested gene × culture interactions on behavioral/psychological tendencies, it is unknown whether such interactions occur at both behavioral and neural levels. If cultural influences on behavioral and psychological tendencies are moderated by a specific genetic polymorphism, cultural influences on the underlying neural mechanisms should also be moderated by the related gene. However, we lack neuroscience evidence for gene × culture interaction on human brain activity. Third, although the previous studies suggested gene × culture interactions on behavioral/psychological tendencies in two cultural groups, it remains unclear whether and how gene × culture interactions on behavioral/psychological tendencies and related brain activity take place across individuals from the same cultural group.

This work aimed to address these issues regarding gene × culture interaction by integrating behavioral and neuroimaging measures of empathy. Empathy is a psychological trait for understanding and sharing others' emotional states and plays a key role in altruistic motivation (Batson, 2011) and prosocial behavior (De Waal, 2008). Recent research has linked empathy to oxytocin, a neuropeptide that functions as both a hormone and a neurotransmitter produced in the hypothalamus. Behavioral measures have shown that intranasal administration of oxytocin increases emotional empathy in response to both positive and negative valence stimuli (Hurlemann *et al.*, 2010). Oxytocin also enhanced empathic neural responses to perceived pain in others (Sheng *et al.*, 2013) and increased self-report empathy for others' pain (Abu-Akel *et al.*, 2014). Other studies demonstrate that oxytocin increases empathy-related emotion and behavior such as social trust and altruism (Kosfeld *et al.*, 2005) and compassion (Palgi *et al.*, 2014). These findings suggested that the oxytocin system may be associated with empathy and raise the question of whether and how OXTR interacts with cultural orientations to shape empathy. Our study chose OXTR as a target gene because it has been associated with maternal sensitivity (Bakermans-Kranenburg and van Ijzendoorn, 2008; Walum *et al.*, 2012), positive affect (Lucht *et al.*, 2009), emotional support seeking (Kim *et al.*, 2010a), prosocial temperament (Tost *et al.*, 2010) and trust behavior (Krueger *et al.*, 2012). In particular, the A allele carrier of OXTR rs53576 (AG/AA) exhibited lower behavioral and dispositional empathy (Rodrigues *et al.*, 2009) whereas the G/G allele carriers showed increased sympathetic and subjective arousal in response to the social interaction (Smith *et al.*, 2014). Recent neuroimaging research also revealed stronger empathic neural responses to perceived pain in ingroup members in G/G compared with A/A allele carriers of OXTR rs53576 (Luo *et al.*, 2015).

We examined whether and how interdependent self-construals interact with OXTR to shape empathy because there has been ample behavioral and neuroimaging evidence for cultural differences in how people view the self in relation to others. Specifically, Western cultures encourage to view oneself as an independent and autonomous entity and emphasize one's dispositions or traits during understanding of people's behavior. In contrast, East Asian cultures underline the fundamental connections between the self and others and encourage people to organize behavior in reference to others' thoughts/feelings (Markus and Kitayama, 1991; Markus and Kitayama, 2010). The cultural difference in independent/interdependent self-construals is also supported by fMRI research that revealed overlapped neural correlates of reflection on oneself and close others in people from East Asian cultures but not in those from Western cultures (Zhu *et al.*, 2007; Wang *et al.*, 2012). In addition, during self-reflection, individuals from Western cultures showed stronger neural activity in the brain region involved in coding self-relevance (e.g. the medial prefrontal cortex, MPFC) whereas individuals from East Asian cultures exhibited greater activity in the brain region engaged in taking others' perspective (e.g. TPJ) (Ma *et al.*, 2014a). More closely related to the current research, there has been behavioral evidence for a positive correlation between interdependence self-construal and empathy trait (Joireman *et al.*, 2002). Moreover, neuroimaging research found that temporary shift of interdependence *vs* independence by self-construal priming modulates empathic neural responses to others' suffering (Jiang *et al.*, 2014; Wang *et al.*, 2015). However, although these findings suggest associations between self-construal and human empathy, it is unknown whether such associations are moderated by OXTR rs53576 that is also related to empathy.

Given that the G allele of OXTR rs53576 confers greater susceptibility to influences of cultural environment relative to the A allele (Kim *et al.*, 2010a, 2011), we hypothesized a stronger link between empathy and cultural orientations (e.g. interdependence) that arise from cultural environment in G compared with A allele carriers of OXTR rs53576. We examined whether such gene × culture interactions on empathy occur in individuals from the same culture using behavioral and neuroimaging measures of empathy. Gene × culture interactions have been observed in individuals from the same cultural group in both behavior and brain activity. Dressler *et al.* (2009) reported that, in Brazil, the effect of cultural consonance in family life on depressive symptoms was larger in the A/A variant than in the G/A or G/G variants of a serotonin receptor polymorphism (HTR2A). Ma *et al.* (2014c) found stronger associations between neural correlates of self-reflection (e.g. MPFC and TPJ activity) and interdependence

self-construal scores in the L/L than S/S homozygotes of the 5-HTTLPR among Chinese. These results illustrate an interaction between a specific genetic polymorphism and a cultural trait among individuals from the same cultural group but did not demonstrate gene × culture interactions on both behavioral/psychological tendencies and brain activity.

In this study, Experiment 1 measured self-construals using the Self-Construal Scale (Singelis, 1994) and empathy trait using the Interpersonal Reactivity Index (IRI) (Davis, 1994) from Chinese adults who were also genotyped for OXTR rs53576.[1] This allowed us to examine whether there is an association between a cultural orientation (i.e. interdependence) and an empathy trait and whether this association is moderated by OXTR rs53576. Experiment 2 further investigated whether interdependence can predict empathic neural responses to others' suffering—an objective measures of empathy—by scanning A/A and G/G homozygous of OXTR rs53576 using fMRI. Empathic neural responses to others' suffering were quantified by contrasting perceived painful *vs* non-painful stimuli applied to others, similar to the previous research (Singer *et al.*, 2004; Jackson *et al.*, 2005; Gu and Han, 2007; Han *et al.*, 2009; Xu *et al.*, 2009; Luo *et al.*, 2014). In particular, Experiment 2 assessed whether OXTR rs53576 moderates the associations between interdependence and empathic neural responses. The behavioral and neuroimaging results allow us to examine whether there are consistent gene × culture interactions on both behavioral/psychological tendencies and brain activity and provide new insight into the neural underpinnings that mediate gene × culture interactions on human empathy. Taken together, by integrating behavioral measures of a large genotyped sample and brain imaging measures of a small genotyped sample, our work developed a new cultural neuroscience approach that allows us to investigate gene × culture interactions on human social cognition. The findings have important implications for understanding how the interplay between a specific cultural orientation and genes shapes human social behavior and underlying neural mechanisms.

MATERIALS AND METHODS

Experiment 1: behavioral investigation

Participants

Experiment 1 recruited 1536 undergraduate and graduate Chinese students as paid volunteers (male = 826, female = 710; 15–33 years, mean ± s.d. = 19.41 ± 2.43; see Table S1 for additional demographic information). Four subjects were excluded from data analysis due to genotyping failure. All passed health examination when enrolled by universities. Informed consent was obtained prior to the study. All experimental procedures conformed to guidelines set by the Code of Ethics of the World Medical Association of Helsinki and were approved by a local ethics committee.

Genotyping

OXTR rs53576, which is located in the third intron of OXTR, was selected for genotyping. This SNP was genotyped by using TaqMan genotyping platform. The TaqMan probes were ordered from the Assays on Demand system of the Applied Biosystems (Applied Biosystems, Foster City, CA, USA, http://www.appliedbiosystems.com). Genotyping was performed in 5 μl system containing 2.5 μl of TaqMan Universal PCR Master mix, 0.25 μl of 20 × TaqMan probe and 1 μl genomic DNA using Roche LightCycler 480 II (Roche Diagnostics, Beijing, China). Allele calling was performed using LightCycler CW 1.5 software (Roche Diagnostics). Both genotyping call rates and concordance for duplicate samples were <0.95. The genotype distribution of rs53576 ($n = 688$ A/A, $n = 683$ A/G, $n = 161$ G/G) did not deviate from Hardy–Weinberg equilibrium ($P > 0.6$).

Measures

All participants completed the IRI (Davis, 1994) as a measure of empathy traits. The original 28-item questionnaire consisted of four 7-item subscales (Fantasy, Perspective Taking, Empathic Concern and Personal Distress), which measure separate but intercorrelated components of empathy. As the Empathic Concern and Perspective Taking subscales correspond more directly to the conceptual definition of empathy as investigated in the present article (Burkard and Knox, 2004), our study focused on IRI total score and Empathic Concern and Perspective Taking subscales, similar to the previous research (Wang *et al.*, 2003; Burkard and Knox, 2004; Jolliffe and Farrington, 2006). The alpha reliability in our sample was 0.78 for IRI total score, 0.71 for Empathic Concern subscale and 0.65 for Perspective Taking subscale. Items were presented as statements and participants rated their agreement on a 5-point Likert-type scale (1 = does not describe me well, 5 = describes me well). The Self-Construal Scale (Singelis, 1994) consists of 24 items for assessing individual differences in independent/interdependent self-construals on a 7-point Likert scale (1 = strongly disagree, 7 = strongly agree). Similar to the previous research (Chiao *et al.*, 2010; Ma *et al.*, 2014a), we calculated a measure of interdependence by subtracting the mean score of the 12 independent self-construal items from that of the 12 interdependent self-construal items.

Data analyses

Hierarchical regression analyses were conducted to examine whether OXTR genotype affected the relationship between interdependence (IV) and individuals' empathy (DV). The IV (interdependence) and the moderator (OXTR genotype) were normalized before the hierarchical regression analysis. The interactions between interdependence and OXTR genotype were calculated by multiplying the normalized variables together (Aiken and West, 1991). Normalized interdependence, OXTR genotype and their interactions were then sequentially entered into the hierarchical regression. The moderator effect was indicated by a significant interaction of interdependence and OXTR genotype on individuals' empathy traits.

Experiment 2: neuroimaging investigation

Participants

Experiment 2 recruited 30 G/G individuals and 30 A/A individuals from the sample in Experiment 1, who were available for fMRI scanning and matched in gender. This sample size was determined based on the results of our previous research that estimated the sample size for testing a reliable between-group difference in fMRI signals (Ma *et al.*, 2014a). G/A individuals were not tested in Experiment 2 because behavioral measures in Experiment 1 showed reliable differences between G/G and A/A individuals. All participants were right handed, had normal or corrected-to-normal vision, and reported no abnormal neurological history. Age, trait empathy and self-construal measures did not differ significantly between the two genotyped groups (P's > 0.1, Table S6). Informed consent was obtained from all participants before scanning.

[1] We actually tested not only rs53576. At an early stage of our research, we tested rs2254298 and rs1042778 in a sample of 700 subjects. Because the results of this sample suggested interactions of interdependence by rs53576 (but not rs2254298/rs1042778) on empathy traits, our further behavioral and neuroimaging work focused on rs53576.

Stimuli and procedure

Stimuli used during fMRI scanning consisted of 48 video clips that showed six Asian models (three males and three females) and six Caucasian models, adopted from our previous work (Xu *et al.*, 2009). Asian and Caucasian models were used in order to examine OXTR rs53576 × interdependence interaction on neural responses to racial ingroup and outgroup members. However, the whole-brain hierarchical regression analyses did not show significant OXTR rs53576 × interdependence interaction on neural responses to Caucasian faces. Thus, we only reported the results related to Asian faces in the result session. There were four video clips for each model in which he/she received painful (needle penetration) or non-painful (Q-tip touch) stimuli applied to the left or right cheeks while showing neutral expressions. Each clip lasted for 3 s and subtended a visual angle of 21° × 17° (width × height) at a viewing distance of 80 cm. After each video clip participants were asked to indicate whether or not the model was feeling pain by a button press using the right index or middle finger.

There were four functional scans and each scan consisted of 12 video clips of Asian models that were presented in a random order. Half of the video clips showed painful stimuli and half showed non-painful stimuli. There was a 9 s interstimulus interval between two successive clips during which participants fixated on a central cross. The last video clip in each scan was followed by a 12 s fixation. After scanning, participants viewed all the video clips again outside the scanner and rated the intensity of pain experienced by each model ('How painful do you think the model feels?') and their own unpleasantness associated with the stimuli ('How unpleasant do you feel when observing the video clip?', 1 = not at all painful or unpleasant, 10 = extremely painful or unpleasant). Participants also completed the IRI scale (Davis, 1994), Self-Construal Scale (Singelis, 1994), Self-Esteem (Rosenberg, 1965) and Subjective Social and Economic Status Scale (Kilpatrick and Cantril, 1960), respectively.

fMRI imaging data acquisition

Brain images were acquired using 3.0 Tesla Siemens Trio at the Beijing MRI Center for Brain Research. Blood oxygen level dependent gradient echo planar images were obtained using a 12-channel head coil [64 × 64 × 32 matrix with 3.44 × 3.44 × 5.0 mm spatial resolution, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view = 24 × 24 cm] while participants performed trait judgments. A high-resolution T1-weighted structural image (256 × 256 × 144 matrix with a spatial resolution of 1 × 1 × 1.33 mm, TR = 2530 ms, TE = 3.37 ms, inversion time = 1100 ms, flip angle = 7°) was subsequently acquired.

fMRI data analysis

The functional imaging data were analyzed by using the general linear model for event-related designs in SPM8 (the Wellcome Trust Centre for Neuroimaging, London, UK). In order to compensate for delays associated with acquisition time differences between slices during the sequential imaging, functional data were first time-corrected. Functional images were then realigned to the first scan to correct for head motion between scans. All images were then spatially normalized to the Montreal Neurological Institute (MNI) template and resampled to obtain images with a voxel size of 2 × 2 × 2 mm. Functional images were smoothed using a Gaussian filter with the full-width/half-maximum parameter set to 8 mm. The event-related neural activity was modeled using a canonical hemodynamic response function.

Fixed effect analyses were first performed to estimate effects at each voxel and to compare regionally specific effects in each individual participant using linear contrasts. To define pain specific neural activations, the contrast of painful *vs* non-painful stimuli was calculated. We then conducted a whole-brain hierarchical regression analysis to examine the interaction between OXTR rs53576 genotype and interdependence on the neural activity in response to others' suffering. We first normalized the independent variable (IV) (interdependence) and the covariate variable (genotype). Genotype group was coded as a dichotomous dummy variable in which 0 represented A/A carriers and 1 represented G/G carriers. The interactions between interdependence and genotype were calculated by multiplying the normalized variables together (Aiken and West, 1991). Normalized interdependence (IV), genotype (moderator) and their interactions were entered as regressors into the SPM multiple regression analysis along with each participant's contrast image of painful *vs* non-painful. Brain activities covaried with the interaction of genotype and interdependence indicated significant interaction of interdependence and OXTR rs53576 on the brain activities. Significant brain activations covaried with the interaction of interdependence and OXTR rs53576 were identified using a threshold of $P < 0.05$ (False discovery rate (FDR) corrected for multiple comparisons). Simple regression analyses were also conducted for each genotype group to further examine the relationship between interdependence and neural responses to other's suffering.

RESULTS

Experiment 1: behavioral investigation

Experiment 1 recruited 1536 participants (see Table S1 for related demographic information). IRI and interdependence scores were matched among the three genotype groups (Table S2). The hierarchical regression analyses first confirmed that the interaction of OXTR rs53576 genotype and interdependence reliably predicted participants' IRI score (Table S3). Separate analyses revealed significant correlations between Interdependence and IRI scores in all three genotype groups (G/G: $\beta = 0.368$, $R^2 = 0.135$, $P < 0.001$; G/A: $\beta = 0.258$, $R^2 = 0.067$, $P < 0.001$; A/A: $\beta = 0.150$, $R^2 = 0.023$, $P < 0.001$; Figure 1A). However, G allele carriers showed stronger associations between interdependence and empathy than those with A/A genotype (G/G *vs* A/A: $P < 0.01$; A/G *vs* A/A: $P < 0.05$; Fisher r-to-z transformation). The OXTR rs53576 × interdependence interaction is further illustrated in the right column of Figure 1A, which indicates that OXTR rs53576 G allele was correlated with higher IRI scores in the high (1 s.d. above the average) interdependence group but with lower IRI scores in the low (1 s.d. below the average) interdependence group.

The hierarchical regression analyses further revealed that the interaction of OXTR rs53576 genotype and interdependence reliably predicted the rating scores of perspective taking (Table S4). Separate analyses confirmed significant correlations between Interdependence scores and perspective taking scores in the three genotype groups (G/G: $\beta = 0.337$, $R^2 = 0.114$, $P < 0.001$; G/A: $\beta = 0.114$, $R^2 = 0.013$, $P < 0.01$; A/A: $\beta = 0.097$, $R^2 = 0.009$, $P < 0.05$; Figure 1B). However, but the association between interdependence and perspective taking was stronger in G/G homozygotes compared with A/A and A/G genotypes (P's < 0.01, Fisher r-to-z transformation). The OXTR rs53576 × interdependence interaction on perspective taking is further illustrated in the right column of Figure 1B, which indicates that OXTR rs53576 G allele was correlated with higher perspective taking scores in the high interdependence group but with lower perspective taking scores in the low interdependence group.

There was a significant correlation between Interdependence scores and empathic concern scores in the three genotype groups (G/G: $\beta = 0.338$, $R^2 = 0.114$, $P < 0.001$; G/A: $\beta = 0.252$, $R^2 = 0.064$, $P < 0.001$; A/A: $\beta = 0.191$, $R^2 = 0.036$, $P < 0.001$; Figure 1C), but the hierarchical regression analyses failed to show significant moderation

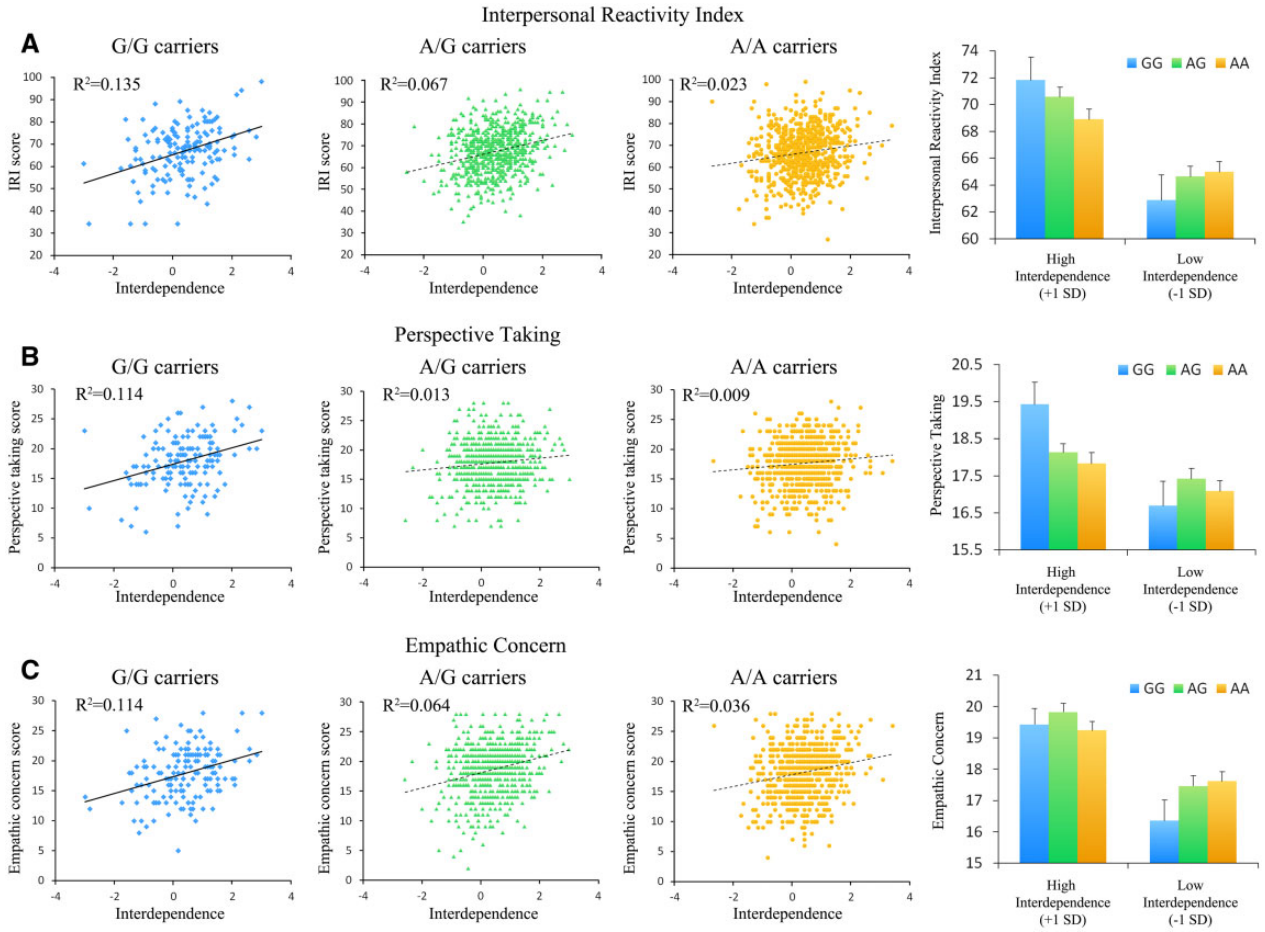

Fig. 1 Illustrations of the results in Experiment 1. **(A)** The association between IRI total score and interdependence in the variants of OXTR rs53576. **(B)** The association between the score of perspective taking subscale and interdependence in the variants of OXTR rs53576. **(C)** The association between the score of empathy concern subscale and interdependence in the variants of OXTR rs53576. The bar chart in the right column illustrates the mean scores of empathy measures in the high and low interdependence groups.

effect (Table S5). Taken together, the results of Experiment 1 indicate that there is a significant association between interdependence and the empathy trait and this association is significantly moderated by OXTR rs53576. G/G homozygotes showed stronger link between interdependence and empathy trait than A allele carriers of OXTR rs53576.

Experiment 2: neuroimaging investigation

Experiment 2 recruited 30 G/G individuals and 30 A/A individuals (Table S6) for functional brain imaging. During scanning both genotype groups identified painful and non-painful stimuli with high accuracy (>90%). Rating scores of pain intensity and self-unpleasantness obtained after scanning were higher for painful than non-painful stimuli [$F(1,58) = 580.63$ and 198.40, P's < 0.001], but did not differ between G/G and A/A groups (F's < 1, Table S7). G/G homozygotes showed significant association between the rating scores of interdependence and IRI ($r = 0.479$, $P < 0.01$), whereas A/A homozygotes did not ($r = 0.067$, $P > 0.7$). Similarly, the interdependent scores were correlated with the rating scores of perspective taking and empathic concern subscales of the IRI in G/G but not A/A individuals (perspective taking: G/G: $r = 0.676$, $P < 0.001$; A/A: $r = 0.029$, $P > 0.8$; empathic concern: G/G: $r = 0.504$, $P < 0.01$; A/A: $r = 0.196$, $P > 0.3$).

The whole-brain hierarchical regression analysis of the fMRI data first revealed significant OXTR rs53576 × interdependence interaction on empathic neural responses (in the contrast of painful *vs* non-painful stimuli applied to Asian models) in the bilateral insula, bilateral amygdala and bilateral superior temporal cortex (Table 1 and Figure 2),

Table 1 Brain activations shown in the moderation analyses of the contrast of painful *vs* non-painful in Experiment 2

			MNIcoordinates		
Brain region	Cluster size	*t*-value	*x*	*y*	*z*
Right amygdala	612	5.17	26	−12	−24
Left amygdala	2063	4.88	−24	−6	−14
Left insula		4.69	−38	−4	−6
Right insula	1201	4.81	40	12	−10
Left STG	238	3.98	−42	−28	8
Right STG	103	3.75	50	−14	6

indicating that OXTR rs53576 moderated the association between interdependence and empathic neural responses activity in these brain regions. *Post hoc* whole-brain regression analyses confirmed significant associations between interdependence and empathic neural responses in these brain regions in G/G but not A/A carriers. G/G carriers with higher interdependence showed stronger activation in the bilateral insula (left: −38/−4/−6, $r = 0.730$, $P < 0.001$; right: 40/12/−10, $r = 0.661$, $P < 0.001$), bilateral amygdala (left: −24/−6/−14, $r = 0.659$, $P < 0.001$; right: 26/−12/−24, $r = 0.724$, $P < 0.001$) and bilateral STG (left: −42/−28/8, $r = 0.504$, $P < 0.01$; right: $x/y/z = 50/-14/6$, $r = 0.490$, $P < 0.01$). No significant correlation between

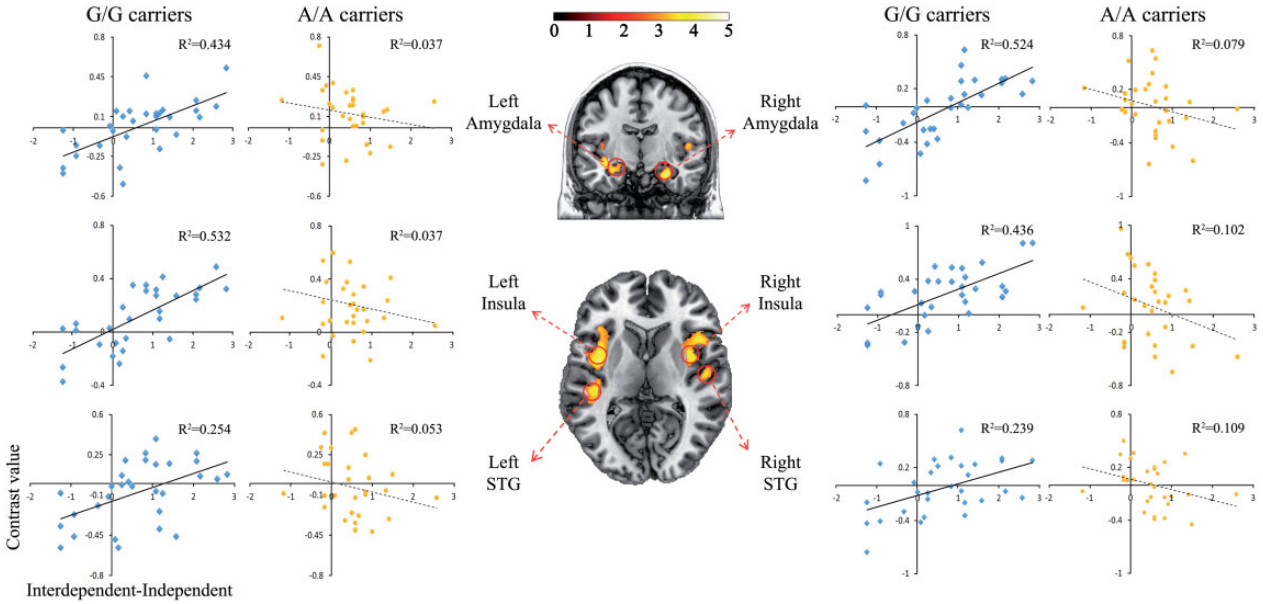

Fig. 2 Illustrations of the results in Experiment 2. Significant interactions between OXTR rs53576 and interdependence on neural response to Asian models' suffering were identified in the bilateral insula, amygdala and STG, as illustrated in the middle column. The scatter plots in the right and left columns illustrate the differential associations between interdependence and contrast value of pain *vs* non-painful stimuli in the two variants of OXTR rs53576.

interdependence and empathic neural responses was observed in A/A carriers (P's > 0.05).

To assess the functional association of the observed brain activations in G/G carriers, we conducted multiple regression analyses to inspect which subcomponents of empathy trait predict empathic neural responses in the brain regions that were modulated by the OXTR rs53576 × interdependence interaction. The contrast values of painful *vs* non-painful stimuli were extracted from the brain region shown in Table 1. The mean contrast values of the brain regions in the left and right hemisphere were then entered into the regression analyses. It was found that the empathic concern score was a significant predictor of the insular activity (empathic concern: $\beta = 0.469$, $P < 0.05$; perspective taking: $\beta = 0.185$, $P > 0.2$), whereas the perspective taking score was a significant predictor of the amygdala and STG activity (amygdala: empathic concern: $\beta = 0.154$, $P > 0.3$; perspective taking: $\beta = 0.564$, $P < 0.005$; STG: empathic concern: $\beta = -0.038$, $P > 0.8$; perspective taking: $\beta = 0.434$, $P < 0.05$).

DISCUSSION

The gene–culture interaction model that concerns the interplay between gene and culture interaction on behavioral/psychological tendencies (Kim and Sasaki, 2014) has been tested mainly by comparing genotype differences in behavioral/psychological predispositions between individuals from two cultural groups such as American *vs* Koreans (Kim *et al.*, 2010a,b, 2011) and American *vs* Japanese (Ishii *et al.*, 2014). Because multiple cognitive and affective processes are different between East Asian and Western cultures, it is essential to elucidate the specific cultural trait that plays a key role in interactions with genetic factors. This study investigated whether and how OXTR rs53576 interacts with a cultural orientation, i.e. interdependence, to shape human empathy and the underlying neural correlates. Experiment 1 showed behavioral evidence for stronger coupling between interdependence and empathy traits in G allele carriers of OXTR rs53576 compared with A/A homozygotes. Although recent research reported that the cultural difference in interdependence is more pronounced for a specific genetic polymorphisms (e.g. DRD4, Kitayama *et al.*, 2014), the interdependence measures were matched in the three variants of OXTR rs53576 in our samples. Thus, the interaction between interdependence and OXTR rs53576 observed in our study cannot be attributed to genotype differences in self-construals between G and A allele carriers. Our findings demonstrate that interdependent self-construals, that have been attested to distinguish between East Asian and Western cultures (Markus and Kitayama, 1991; Li *et al.*, 2006; Ma *et al.*, 2014a), interplay with OXTR rs53576 to shape empathy.

Consistent with the behavioral results in Experiment 1, Experiment 2 revealed reliable correlation between interdependence and neural activity in the insula, amygdala and STG in responses to perceived pain in others in G/G but not A/A homozygotes of OXTR rs53576. This provides the first neuroimaging evidence that OXTR rs53576 interacts with interdependence to modulate empathic neural responses. Together, the results of Experiments 1 and 2 demonstrate that the interaction between interdependence and OXTR rs53576 on empathy occurs in both behavioral/psychological tendency and neural correlates of empathy. Our fMRI results further suggest that the empathic neural responses in these brain regions are associated with different aspects of empathy traits because, in G/G homozygotes, individuals' ability of empathic concern predicted the insular activity and individuals' ability of perspective taking predicted the amygdala/STG activity in responses to others' suffering. These are consistent with the previous neuroimaging findings that suggest that the insula is engaged in an affective–perceptual form of empathy when participants observe others in pain and are unaware of the goal of the experiments (Fan *et al.*, 2011). The amygdala is activated by perceived pain in others when participants are required to taking others' perspective by imaging themselves to be in the same situation (Lamm *et al.*, 2007). The STG is also activated during perception of others who received painful stimulation and showed pain expressions (Luo *et al.*, 2014). Thus, similar patterns of interdependence × OXTR rs53576 interaction were observed in brain regions that mediate distinct aspects of empathy.

Social cognition consists of the processes of the self and others (Iacoboni, 2006; Sedikides and Skowronski, 2009) and the two aspects of social cognition are reciprocally interconnected. Behavioral research

has shown evidence for the link between emotional empathy and perceptions of self in relation to others (Cialdini *et al.*, 1997; Burris and Rempel, 2012), a greater sense of self-other overlap is coupled with stronger empathy concern of others. Recent neuroimaging findings further demonstrate a causal relationship between self-construal and empathy such that self-construal priming that temporarily shifted interdependence/independence resulted in modulations of empathic neural responses to others' suffering (Jiang *et al.*, 2014; Wang *et al.*, 2015). Moreover, how self-construal priming modulates empathic neural responses depends on participants' chronic cultural experiences (Jiang *et al.*, 2014) and perceived intergroup relationship between observers and targets (Wang *et al.*, 2015). The current findings broaden our understanding of the relationship between self-construal and empathy by showing that the interconnection between the two core components of social cognition, i.e. self-construal and empathy, is constrained by one's genetic makeup. Thus OXTR rs53576 not only shapes behavioral/dispositional empathy (Rodrigues *et al.*, 2009) and empathic neural responses (Luo *et al.*, 2015) but also moderates the relationship between different psychological traits (e.g. self-construal and empathy) that underlie ones' social ability.

Interestingly, the interaction between interdependence and OXTR rs53576 was evident mainly in the brain regions related to emotion (e.g. the insula, amygdala and STG). This is different from the findings of our recent work that examined the interaction between interdependence and 5-HTTLPR during a self-referential task (Ma *et al.*, 2014c). In this study, short/short (s/s) or long/long (l/l) variants of the 5-HTTLPR were scanned during reflection of personal attributes of oneself and one's mother. It was found that l/l but not s/s genotype group showed significant association between self-construals and activity in brain regions related to both cognitive and affective processes such as the MPFC, bilateral middle frontal cortex, TPJ, insula and hippocampus during reflection on mental attributes of oneself and mother. Therefore, the interaction between cultural orientations and genes may shape neural activities underlying social cognition in multiple nodes of the social brain network. However, emotional or cognitive tasks used during brain imaging may influence which brain regions are susceptible to the effects of gene × culture interplay.

The previous studies recruited two cultural groups and investigated group-level gene–culture interactions on behavioral/psychological tendencies by examining cross-group discrepancy in cultural traits between different genotypes (Kim *et al.*, 2010a,b, 2011; Ishii *et al.*, 2014; Kitayama *et al.*, 2014). This work, however, illustrated the interplay between gene and culture in individuals who were from the same cultural group but endorsed a cultural trait with different degrees. Recruiting participants from the same cultural environment who were homogenous in ethnicity, language, geometry, etc. gave prominence to individual differences in cultural orientations. Based on the results of the studies that compared two cultural groups, it has been suggested that the G allele of OXTR rs53576 confers enhanced sensitivity to cultural norms compared with A/A homozygotes and this has been used to explain why individuals carrying these differential susceptibility genes may sometimes show different and even opposite behaviors in different cultures (Kim *et al.*, 2010a, 2011; Kim and Sasaki, 2014). Our results are consistent with this proposition by showing variations of empathy tendency between individuals with high and low interdependence and a stronger link between empathy and interdependence in G/G relative to A/A carriers. Moreover, the greater susceptibility to cultural norms in G/G carriers existed in both empathy-related behavioral/psychological tendency and brain activity and these in turn may give rise to more culturally normative behavior.

How do we understand gene–culture interaction on the human brain from the perspective of gene–culture coevolution (Boyd and Richerson, 1985; Richerson *et al.*, 2010)? Two recent studies have revealed that populations dominated by stronger collectivistic values comprise less individuals carrying the long allele of 5-HTTLPR and less individual carrying the G allele of OXTR rs53576 (Chiao and Blizinsky, 2010; Luo and Han, 2014). Interestingly, both our previous (Ma *et al.*, 2014c) and current work found that it is the minority in Chinese population in terms of allele frequency (i.e. the long allele of 5-HTTLPR and the G allele of OXTR rs53576) whose brain activity is more strongly coupled with a cultural trait (i.e. interdependence) compared with the majority of the population. One possible account is that, in order to survive and increase in numbers, the minority in a population has to be more sensitive to dominant cultural values and norms than the majority in the same population and thus showed stronger associations between brain activity and cultural traits (e.g. interdependence). Alternatively, given that the finding that G/G carriers of OXTR rs53576 displayed more emotional support seeking in North America where G/G allele carriers constitute the majority of the population (Kim *et al.*, 2010a), it is possible that G/G variant of OXTR rs53576 is more sensitive to cultural values/norms independently of its frequency in a population. These, however, must be tested in future research.

There has been increasing evidence for gene × culture interaction on behavioral tendency. Besides that G and A variants of OXTR rs53576 exhibited distinct or event opposite patterns of emotion regulation and emotional support seeking in Americans and Koreans (Kim *et al.*, 2010a, 2011), a recent work also revealed that cultural differences in an independent social orientation between people born and raised in the USA and East Asia are greater for carriers of specific alleles within a dopamine receptor gene (i.e. DRD4; Kitayama *et al.*, 2014). However, the mechanisms of culture × brain interaction that mediate the effect of gene × culture interaction on behavioral tendency remain poorly understood (Hyde *et al.*, 2015). By comparing genetic differences in behavioral tendency across two cultural groups, researchers cannot clarify how the observed gene × culture interaction on behavioral tendency is mediated by a cultural variation of the underlying neural mechanisms. In addition, this approach is confronted with potential differences in other genes or differences in diet and geographic location between two cultural groups that are investigated. Thus, it is essential to clarify which specific cultural orientations interact with brain activity involved in a particular task by controlling the potential confounds. The approach developed in our study, i.e. to examine gene × culture interaction on both behavioral tendency and brain activity related to the same social behavior in individuals from the same culture, has important implication for further research of the core issue of cultural neuroscience.

What are the implications of our findings for understanding the effect of oxytocin on human brain activity and behavior? Given that intranasal administration of oxytocin affects brain activity by combining with oxytocin receptors in the brain, our findings of interdependence × OXTR interaction on empathy suggest that intranasal administration of oxytocin may also interact with individuals' cultural orientations to modulate brain activity or behavior. Although there has been no research to examine the effect of oxytocin × cultural-orientation interaction on empathy, recent research indeed suggested an oxytocin × interdependence interaction on brain activity and behavior. Liu *et al.* (2013) found that oxytocin *vs* placebo treatment reduced the neural activity association with self-reflection on personality traits and this oxytocin effect was positively correlated with a measure of interdependence of self-construals (Liu *et al.*, 2013). Pfundmair *et al.* (2014) also reported that intranasal administration of oxytocin attenuated negative affect in responses to ostracism and the

oxytocin effect was more salient in individuals with collectivistic (*vs* individualistic) orientations. Future research should seek additional evidence for the constraints of cultural orientations on oxytocin effects on human behavior and related social/affective processes.

Finally, most of the previous cultural neuroscience studies focused on cultural effects or gene × culture interaction on brain activity. There has been little research on the contribution of brain–gene relations to our understanding of culture. Our findings suggest that our genetic background may restrain whether and how brain activity underlying cognitive/affective processing is associated with our cultural orientations. Both the previous (Ma *et al.*, 2014c) and current studies found evidence that one variant of a gene showed stronger association between brain activity and a cultural orientation compared with another variant of the same gene. Future research should clarify whether these findings reflect that brain activity in one compared with another variant of a gene is more sensitive to cultural environments. To investigate this issue may open an avenue to the understanding of biological influences or constraints on cultural effects on human brain activity and behavior.

In conclusion, our behavioral and neuroimaging findings cast new light on gene–culture interaction on human empathy by showing evidence that OXTR rs53576 moderated the relationship between a cultural trait (i.e. interdependence) and empathy tendencies/empathic neural responses. This is the first evidence for the interaction between an SNP (e.g. OXTR rs53576) and a specific dimension of cultural orientations. Our results unveil similar patterns of gene–culture interaction on behavioral/psychological tendencies and related brain activity, which may together determine how gene interacts with culture to guide empathy-related behavior (e.g. altruism). Our findings indicate that genotype alone cannot well predict individuals' behavioral or neural indices of empathy and it is the gene × culture interaction that well predicts human ability of empathy. Future research should further clarify whether the patterns of gene–culture interaction reported in our work may provide a biological basis of the assumption that genetic polymorphism influences the probability that a particular cultural trait will be adopted by people in a specific cultural environment.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

CONFLICT OF INTEREST

None declared.

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