d i:10.1093/scan/nsv019 SCAN (2015) 10, 1273–1281

Int raction b tw n oxytocin r c ptor polymorphism and int rd p nd nt cultur valu s on human mpathy

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R c nt vid nc sugg sts that th association b tw n oxytocin r c ptor polymorphism (OXTR rs53576) and motion-r lat d b havioral/psychological t nd nci s diff rs b tw n individuals from East Asian and W st rn cultur s. What r mains unr solv d is which sp cific dim nsion of cultural ori ntations int racts with OXTR rs53576 to shap th s t nd nci s and wh th r such g n × cultur int ractions occurs at both b havioral and n ural l v l. This study inv stigat d wh th r and how OXTR rs53576 int racts with int rd p nd nc —a k y dim nsion of cultural ori ntations that distinguish b tw n East Asian and W st rn cultur s—to aff ct human mpathy that und rli s altruistic motivation and prosocial b havior. Exp rim nt 1 m asur d int rd p nd nc , mpathy trait and OXTR rs53576 g notyp s of 1536 Chin s participants. Hi rarchical r gr ssion analys s r v al d a strong r association b tw n int rd p nd nc and mpathy trait in G all l carri rs compar d with A/A homozygot s of OXTR rs53576. Exp rim nt 2 m asur d n ural r spons s to oth rs' suff ring by scanning A/A and G/G homozygous of OXTR rs53576 using functional magn tic r sonanc imaging. Hi rarchical r gr ssion analys s r v al d strong r associations b tw n int rd p nd nc and mpathic n ural r spons s in th insula, amygdala and sup rior t mporal gyrus in G/G compar d with A/A carri rs. Our r sults provid th first vid nc for g n × cultur int ractions on mpathy at both b havioral t nd ncy and und rlying brain activity.

K ywords: 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 *a*., 2013; Han *a*., 2013) and genetic make-up (Hariri *a*., 2006; Bigos and Weinberger, 2010; Falk *a*., 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 *a*., 2007; Sui *a*., 2009; Cheon *a*., 2011; de Greck *a*., 2012; Murata *a*., 2013; Kitayama *a*., 2014; Ma *a*., 2014a) or with different genotypes (Hariri *a*., 2002; Fang *a*., 2013; Ma *a*., 2014b; Strange *a*., 2014). For instance, de Greck *a*. (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 *a*. (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 (*s* 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 *a*., 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 *a*., 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
Advance Access publication 13 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 *a*., 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 *a*., 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 *a*., 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 *a*., 2010a).

These behavioral findings support a gene–culture interaction model that posits that genes provide a basis for the susceptibility to cultural environments (Belsky *a*., 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 *a*., 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 *a*., 2010). Oxytocin also enhanced empathic neural responses to perceived pain in others (Sheng *a*., 2013) and increased self-report empathy for others' pain (Abu-Akel *a*., 2014). Other studies demonstrate that oxytocin increases empathy-related emotion and behavior such as social trust and altruism (Kosfeld *a*., 2005) and compassion (Palgi *a*., 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 *a*., 2012), positive affect (Lucht *a*., 2009), emotional support seeking (Kim *a*., 2010a), prosocial temperament (Tost *a*., 2010) and trust behavior (Krueger *a*., 2012). In particular, the A allele carrier of OXTR rs53576 (AG/AA) exhibited lower behavioral and dispositional empathy (Rodrigues *a*., 2009) whereas the G/G allele carriers showed increased sympathetic and subjective arousal in response to the social interaction (Smith *a*., 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 *a*., 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 *a*., 2007; Wang *a*., 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 *a*., 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 *a*., 2002). Moreover, neuroimaging research found that temporary shift of interdependence *s* independence by self-construal priming modulates empathic neural responses to others' suffering (Jiang *a*., 2014; Wang *a*., 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 *a*., 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 *a*. (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 *a*. (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 *s* non-painful stimuli applied to others, similar to the previous research (Singer *a*., 2004; Jackson *a*., 2005; Gu and Han, 2007; Han *a*., 2009; Xu *a*., 2009; Luo *a*., 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

Exp rim nt 1: b havioral inv stigation

Participants

Experiment 1 recruited 1536 undergraduate and graduate Chinese students as paid volunteers (male = 826, female =

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 *a .*, 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 ×

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.

Exp rim nt 2: n uroimaging inv stigation

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 ($= 0.479$, $P < 0.01$), whereas A/A homozygotes did not ($= 0.067$, $P > 0.7$). Similarly, the interdependentmo.6 (2li)-380.397(and)-depe0ationhe typesti-dr70.29[().suber)l34pha0riers een

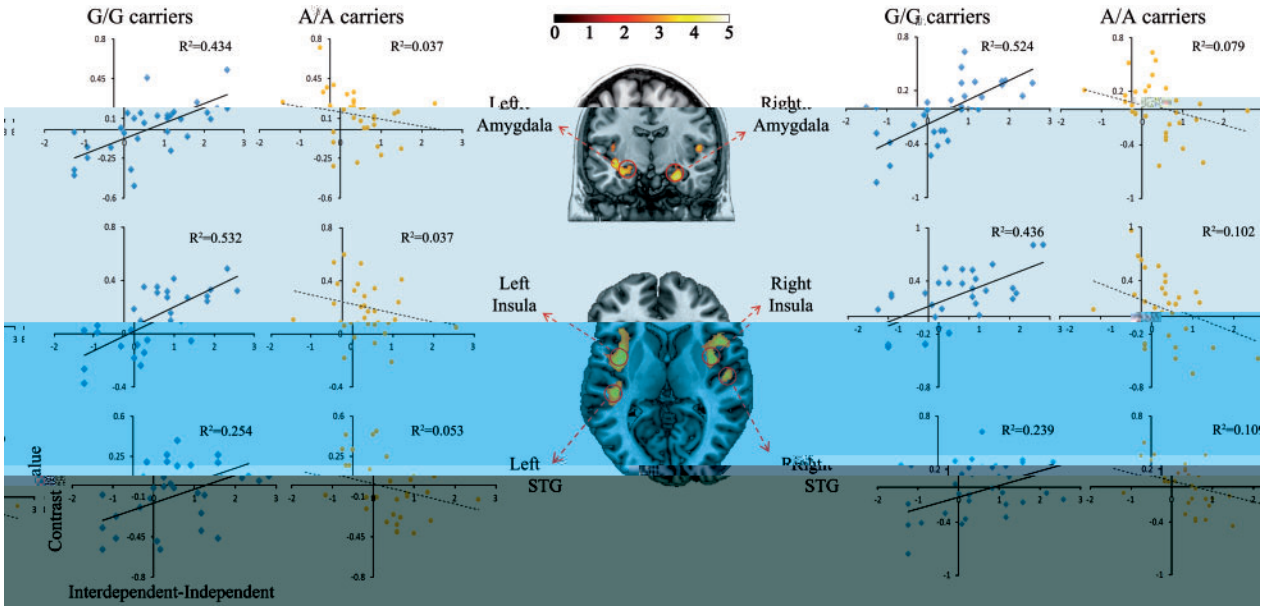

Fig. 2 Illustrations of the results in Experiment 2. Significant interactions between OXTR rs53576 and interdependence on neural response to Asian models' suffering were identified in the bilateral insula, amygdala and STG, as illustrated in the middle column. The scatter plots in the right and left 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 *s* 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 *s* Koreans (Kim *a*., 2010a,b, 2011) and American *s* Japanese (Ishii *a*., 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 *a*., 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 *a*., 2006; Ma *a*., 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 *a*., 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 *a*., 2007). The STG is also activated during perception of others who received painful stimulation and showed pain expressions (Luo *a*., 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 *a*., 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 *a*., 2014; Wang *a*., 2015). Moreover, how self-construal priming modulates empathic neural responses depends on participants' chronic cultural experiences (Jiang *a*., 2014) and perceived intergroup relationship between observers and targets (Wang *a*., 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 *a*., 2009) and empathic neural responses (Luo *a*., 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 *a*., 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 *a*., 2010a,b, 2011; Ishii *a*., 2014; Kitayama *a*., 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 *a*., 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 *a*., 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 *a*., 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 *a*., 2010a), it is possible that G/G variant of OXTR rs53576 is more sensitive to cultural values/norms

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.

REFERENCES

Abu-Akel, A., Palgi, S., Klein, E., Decety, J., Shamay-Tsoory, S. (2014). Oxytocin increases empathy to pain when adopting the other-but not the self-perspective. *Social Neuroscience*, *10*, 7–15.

Aiken, L.S., West, S.G. (1991). *Multiple Regression: Testing and Interpreting Interactions*. Thousand Oaks, CA: Sage.

Bakermans-Kranenburg, M.J., van IJzendoorn, M.H. (2008). Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Social Cognitive and Affective Neuroscience*, *3*, 128–34.

Batson, C.D. (2011). Empathy-induced altruism: friend or foe of the common good?. In: Forsyth, D.R., Hoyt, C.L., editors *For Greater Good of All: Perspectives on Individualism, Society, and Leadership*. New York: Palgrave Macmillan, pp. 29–45.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry*, *14*, 746–54.

Bigos, K.L., Weinberger, D.R. (2010). Imaging genetics-days of future past. *Neuroimage*, *53*, 804–9.

Boyd, R., Richerson, P. (1985). *Culture and Evolutionary Process*. Chicago: The University of Chicago Press.

Burkard, A.W., Knox, S. (2004). Effect of therapist color-blindness on empathy and attributions in cross-cultural counseling. *Journal of Counseling Psychology*, *51*, 387.

Burris, C.T., Rempel, J.K. (2012). The crystal globe: emotional empathy and the transformation of self. *Consciousness and Cognition*, *21*, 1526–32.

Cheon, B.K., Im, D.M., Harada, T., et al. (2011). Cultural influences on neural basis of intergroup empathy. *NeuroImage*, *57*, 642–50.

Chiao, J.Y., Blizinsky, K.D. (2010). Culture–gene coevolution of individualism–collectivism and the serotonin transporter gene. *Proceedings of the Royal Society B: Biological Sciences*, *277*, 529–37.

Chiao, J.Y., Cheon, B.K., Pornpattananangkul, N., Mrazek, A.J., Blizinsky, K.D. (2013). Cultural neuroscience: progress and promise. *Psychological Inquiry*, *24*, 1–19.

Chiao, J.Y., Harada, T., Komeda, H., et al. (2010). Dynamic cultural influences on neural representations of the self. *Journal of Cognitive Neuroscience*, *22*, 1–11.

Choi, I., Nisbett, R.E., Norenzayan, A. (1999). Causal attribution across cultures: variation and universality. *Psychological Bulletin*, *125*, 47.

Cialdini, R.B., Brown, S.L., Lewis, B.P., Luce, C., Neuberg, S.L. (1997). Reinterpreting the empathy–altruism relationship: when one into one equals oneness. *Journal of Personality and Social Psychology*, *73*, 481.

Davis, M.H. (1994). *Empathy: A Social Psychological Approach*. Boulder, CO: Westview Press.

de Greck, M., Shi, Z., Wang, G., et al. (2012). Culture modulates brain activity during empathy with anger. *NeuroImage*, *59*, 2871–82.

De Waal, F.B. (2008). Putting the altruism back into altruism: the evolution of empathy. *Annual Review of Psychology*, *59*, 279–300.

Dressler, W.W., Balieiro, M.C., Ribeiro, R.P., Santos, J.E.D. (2009). Cultural consonance, a 5HT2A receptor polymorphism, and depressive symptoms: a longitudinal study of gene × culture interaction in urban Brazil. *American Journal of Human Biology*, *21*, 91–7.

Falk, E.B., Way, B.M., Jasinska, A.J. (2012). An imaging genetics approach to understanding social influence. *Frontiers in Human Neuroscience*, *6*, 168.

Fan, Y., Duncan, N.W., de Greck, M., Northoff, G. (2011). Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. *Neuroscience & Biobehavioral Reviews*, *35*, 903–11.

Fang, Z., Zhu, S., Gillihan, S.J., Korczykowski, M., Detre, J.A., Rao, H. (2013). Serotonin transporter genotype modulates functional connectivity between amygdala and PCC/PCu during mood recovery. *Frontiers in Human Neuroscience*, *7*, 704.

Gu, X., Han, S. (2007). Attention and reality constraints on the neural processes of empathy for pain. *NeuroImage*, *36*, 256–67.

Han, S., Fan, Y., Xu, X., et al. (2009). Empathic neural responses to others' pain are modulated by emotional contexts. *Human Brain Mapping*, *30*, 3227–37.

Han, S., Northoff, G. (2008). Culture-sensitive neural substrates of human cognition: a transcultural neuroimaging approach. *Nature Reviews Neuroscience*, *9*, 646–54.

Han, S., Northoff, G., Vogeley, K., Wexler, B.E., Kitayama, S., Varnum, M.E. (2013). A cultural neuroscience approach to the biosocial nature of the human brain. *Annual Review of Psychology*, *64*, 335–59.

Kim, H.S., Sherman, D.K., Taylor, S.E., et al. (2010b). Culture, serotonin receptor polymorphism and locus of attention. *Social Cognitive and Affective Neuroscience*, *5*, 212–8.

Kitayama, S., King, A., Yoon, C., Tompson, S., Huff, S., Liberzon, I. (2014). The dopamine D4 receptor gene (DRD4) moderates cultural difference in independent versus interdependent social orientation. *Behavioral Neuroscience*, *25*, 1169–77.

Kitayama, S., Uskul, A.K. (2011). Culture, mind, and the brain: current evidence and future directions. *Annual Review of Psychology*, *62*, 419–49.

Kosfeld, M., Heinrichs, M., Zak, P.J., Fischbacher, U., Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*, 673–676.

Krueger, F., Parasuraman, R., Iyengar, V., et al. (2012). Oxytocin receptor genetic variation promotes human trust behavior. *Frontiers in Human Neuroscience*, *6*, 4.

Lamm, C., Batson, C.D., Decety, J. (2007). The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience*, *19*, 42–58.

Li, H.Z., Zhang, Z., Bhatt, G., Yum, Y.O. (2006). Rethinking culture and self-construal: China as a middle land. *The Journal of Social Psychology*, *146*, 591–610.

Liu, Y., Sheng, F., Woodcock, K.A., Han, S. (2013). Oxytocin effects on neural correlates of self-referential processing. *Biological Psychology*, *94*, 380–7.

Lucht, M.J., Barnow, S., Sonnenfeld, C., et al. (2009). Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects. *Psychoneuroendocrinology*, *33*, 860–6.

Luo, S., Han, S. (2014). The association between an oxytocin receptor gene polymorphism and cultural orientations. *Culture and Brain*, *2*, 89–107.

Luo, S., Li, B., Ma, Y., Zhang, W., Rao, Y., Han, S. (2015). Associations between an oxytocin receptor gene polymorphism and racial ingroup bias in brain activity to others' suffering. *Neuroimage*, *110*, 22–31.

Luo, S., Shi, Z., Yang, X., Wang, X., Han, S. (2014). Reminders of mortality decrease midcingulate activity in response to others' suffering. *Social Cognitive and Affective Neuroscience*, *9*, 477–86.

Ma, Y., Bang, D., Wang, C., et al. (2014a). Sociocultural patterning of neural activity during self-reflection. *Social Cognitive and Affective Neuroscience*, *9*, 73–80.

Ma, Y., Li, B., Wang, C., et al. (2014b). 5-HTTLPR polymorphism modulates neural mechanisms of negative self-reflection. *Cerebral Cortex*, *24*, 2421–9.

Ma, Y., Wang, C., Li, B., Zhang, W., Rao, Y., Han, S. (2014c). Does self-construal predict activity in the social brain network? A genetic moderation effect. *Social Cognitive and Affective Neuroscience*, *9*, 1360–7.

Markus, H.R., Kitayama, S. (1991). Culture and the self: Implications for cognition, emotion, and motivation. *Psychological Review*, *98*, 224.

Markus, H.R., Kitayama, S. (2010). Cultures and selves a cycle of mutual constitution. *Perspectives on Psychological Science*, *5*, 420–30.

Michalska, K.J., Decety, J., Liu, C., et al. (2014). Genetic imaging of the association of oxytocin receptor gene (OXTR) polymorphisms with positive maternal parenting. *Frontiers in Behavioral Neuroscience*, *8*, 21.

Murata, A., Moser, J.S., Kitayama, S. (2013). Culture shapes electrocortical responses during emotion suppression. *Social Cognitive and Affective Neuroscience*, *8*, 595–601.

Nisbett, R.E., Masuda, T. (2003). Culture and point of view. *Proceedings of National Academy of Sciences of United States of America*, *100*, 11163–70.

Palgi, S., Klein, E., Shamay-Tsoory, S.G. (2014). Intranasal administration of oxytocin increases compassion toward women. *Social Cognitive and Affective Neuroscience*, *10*, 311–7.

Pfundmair, M., Aydin, N., Frey, D., Echterhoff, G. (2014). The interplay of oxytocin and collectivistic orientation shields against negative effects of ostracism. *Journal of Experimental Social Psychology*, *55*, 246–51.

Richerson, P.J., Boyd, R., Henrich, J. (2010). Gene-culture coevolution in the age of genomics. *Proceedings of National Academy of Sciences of United States of America*, *107*(Suppl. 28985–92.

Rodrigues, S.M., Saslow, L.R., Garcia, N., John, O.P., Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proceedings of National Academy of Sciences of United States of America*, *106*, 21437–41.

Rosenberg, M. (1965). The measurement of self-esteem. *Society and Adolescent Self Image*, *297*, V307.

Sedikides, C., Skowronski, J.J. (2009). Social cognition and self-cognition: two sides of the same evolutionary coin? *European Journal of Social Psychology*, *39*, 1245–9.

Sheng, F., Liu, Y., Zhou, B., Zhou, W., Han, S. (2013). Oxytocin modulates the racial ingroup bias in neural responses to others' suffering. *Biological Psychology*, *92*, 380–6.

Singelis, T.M. (1994). The measurement of independent and interdependent self-construals. *Personality and Social Psychology Bulletin*, *20*, 580–91.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, *303*, 1157–62.

Smith, K.E., Porges, E.C., Norman, G.J., Connelly, J.J., Decety, J. (2014). Oxytocin receptor gene variation predicts empathic concern and autonomic arousal while perceiving harm to others. *Social Neuroscience*, *9*, 1–9.

Strange, B.A., Gartmann, N., Brenninkmeyer, J., et al. (2014). Dopamine receptor 4 promoter polymorphism modulates memory and neuronal responses to salience. *Neuroimage*, *84*, 922–31.

Sui, J., Liu, C.H., Han, S. (2009). Cultural difference in neural mechanisms of self-recognition. *Social Neuroscience*, *4*, 402–11.

Tost, H., Kolachana, B., Hakimi, S., et al. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proceedings of National Academy of Sciences of United States of America*, *107*, 13936–41.

Tsai, J.L. (2007). Ideal affect: cultural causes and behavioral consequences. *Perspectives on Psychological Science*, *2*, 242–59.

Walum, H., Lichtenstein, P., Neiderhiser, J.M., et al. (2012). Variation in the oxytocin receptor gene is associated with pair-bonding and social behavior. *Biological Psychiatry*, *71*, 419–26.

Wang, C., Liu, Y., Wu, B., Wu, X., Han, S. (2015). Challenge emotional prejudice by changing self-concept: priming independent self-construal reduces racial in-group bias in neural responses to other's pain. *Social Cognitive and Affective Neuroscience*, *10*, 1195–201.

Wang, G., Mao, L., Ma, Y., et al. (2012). Neural representations of close others in collectivistic brains. *Social Cognitive and Affective Neuroscience*, *7*, 222–9.

Wang, Y.W., Davidson, M.M., Yakushko, O.F., Savoy, H.B., Tan, J.A., Bleier, J.K. (2003). The scale of ethnocultural empathy: development, validation, and reliability. *Journal of Counseling Psychology*, *50*, 221.

Xu, X., Zuo, X., Wang, X., Han, S. (2009). Do you feel my pain? Racial group membership modulates empathic neural responses. *The Journal of Neuroscience*, *29*, 8525–9.

Zhu, Y., Zhang, L., Fan, J., Han, S. (2007). Neural basis of cultural influence on self-representation. *Neuroimage*, *34*, 1310–6.