

## Full Length Articles

# Oxytocin receptor gene and racial ingroup bias in empathy-related brain activity



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## ABSTRACT

The human brain responds more strongly to racial ingroup than outgroup individuals' pain. This racial ingroup bias varies across individuals and has been attributed to social experiences. What remains unknown is whether the racial ingroup bias in brain activity is associated with a genetic polymorphism. We investigated genetic associations of racial ingroup bias in the brain activity to racial ingroup and outgroup faces that received painful or non-painful stimulations by scanning A/A and G/G homozygous of the oxytocin receptor gene polymorphism (OXTR rs53576) using functional MRI. We found that G/G compared to A/A individuals showed stronger activity in the anterior cingulate and supplementary motor area (ACC/SMA) in response to racial ingroup members' pain, whereas A/A relative to G/G individuals exhibited greater activity in the nucleus accumbens (NAcc) in response to racial outgroup members' pain. Moreover, the racial ingroup bias in ACC/SMA activity positively predicted participants' racial ingroup bias in implicit attitudes and NAcc activity to racial outgroup individuals' pain negatively predicted participants' motivations to reduce racial outgroup members' pain. Our results suggest that the two variants of OXTR rs53576 are associated with racial ingroup bias in brain activities that are linked to implicit attitude and altruistic motivation, respectively.

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## Introduction

Racial ingroup bias in attitude and behavior has been widely documented in humans. People exhibit greater positive attitudes and more helping behavior toward racial ingroup than outgroup individuals (Devine et al., 2002; Johnson et al., 2002; Greenwald et al., 2009; Drwecki et al., 2011). In parallel with the behavioral findings, recent neuroimaging studies of empathy for pain have revealed a racial ingroup bias in human brain activity in response to others' suffering. While functional magnetic resonance imaging (fMRI) studies have shown that viewing others in pain activates the pain-related neural network consisting of the anterior insula (AI), anterior cingulate cortex (ACC) and supplementary motor area (SMA) (Singer et al., 2004; Jackson et al., 2005; Saarela et al., 2007; Gu and Han, 2007; Han et al., 2009; Gu et al., 2010, 2012; Fan et al., 2011; Lamm et al., 2011), recent research has revealed increased ACC/SMA activity to perceived painful stimuli applied to (Xu et al., 2009; Contreras-Huerta et al., 2013) or perceived pain expression from (Sheng and Han, 2012; Sheng et al., 2013, 2014) racial ingroup compared to outgroup individuals. Racial

intergroup relationships also modulate activity in the sensorimotor cortex (Avenanti et al., 2010), dorsal medial prefrontal cortex (Mathur et al., 2010; Cheon et al., 2011), bilateral AI (Azevedo et al., 2013; Sheng et al., 2014) and temporoparietal junction (TPJ) (Cheon et al., 2011) in response to perceived pain in others.

The ingroup bias in brain activity may influence people's cooperation/altruistic behaviors as it enhances understanding and sharing of ingroup members' feelings/intentions but induces negative feelings such as envy and schadenfreude toward outgroup members (Gonzalez-Liencre et al., 2013). Most of the previous studies emphasize the role of social experiences in producing ingroup bias in cognitive/affective processes (e.g., Hewstone et al., 2002; Cheon et al., 2011; Zuo and Han, 2013). However, there may exist genetic associations of the ingroup bias in brain activity in response to others' pain given that understanding and sharing others' emotional states such as pain have deep evolutionary, biochemical, and neurological underpinnings (Decety, 2011) and such ability undergoes genetic influences that increase with age (Knafo et al., 2008).

The present study explored potential associations between a specific genetic polymorphism and racial ingroup bias in brain activity to others' suffering. We tested whether racial ingroup bias in neural responses to perceived pain in others varies across two variants of the oxytocin receptor gene (OXTR) polymorphism for several reasons. First, oxytocin as a neurotransmitter and a hormone enhances social trust/altruism

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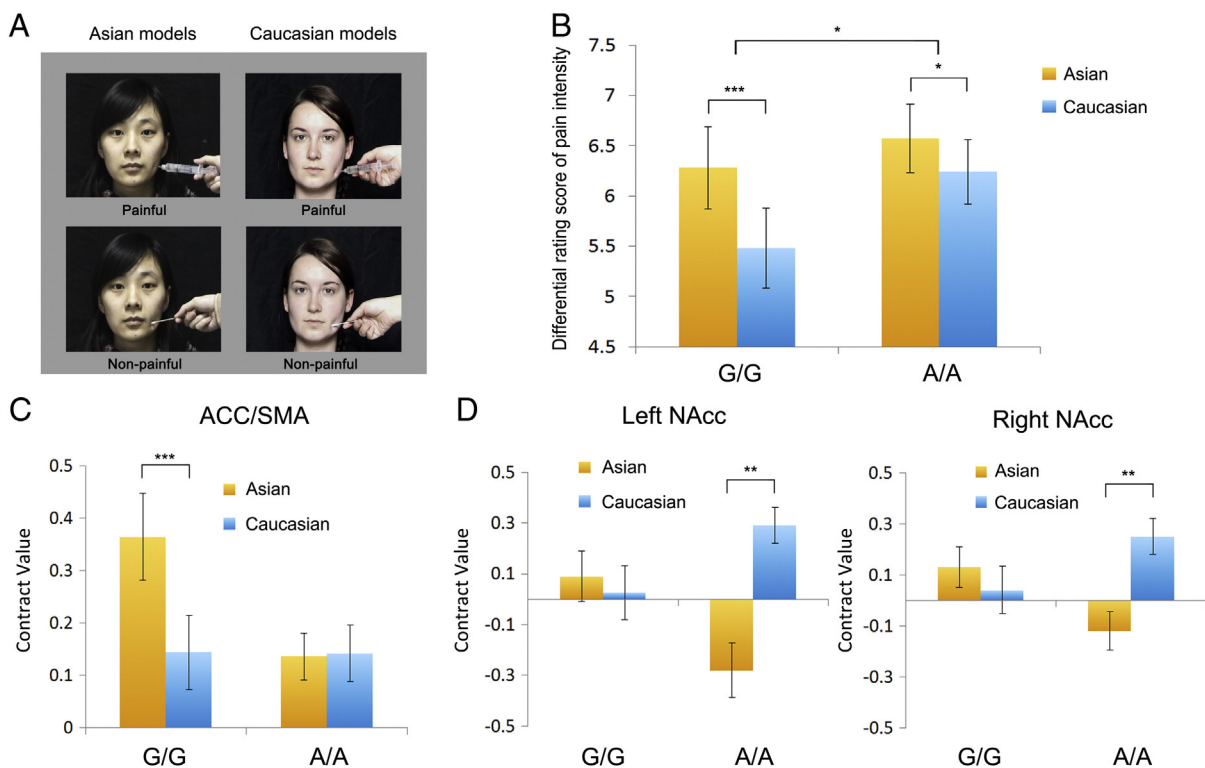
<sup>1</sup> They contributed equally to this study.

(Kosfeld et al., 2005) and emotional empathy (Hurlemann et al., 2010). Second, although the main genetic variants of OXTR consist of several single nucleotide polymorphism (SNP) (Meyer-Lindenberg et al., 2011), recent findings only suggest a strong link of a common single nucleotide polymorphism (rs53576) in the OXTR with empathy. It has been shown that carriers of the G relative to A allele of rs53576 show enhanced empathic parenting (Bakermans-Kranenburg and van IJzendoorn, 2008) and higher empathic accuracy (Rodrigues et al., 2009). Moreover, individuals homozygous for the G allele show higher trust, empathic concern, and prosocial behavior than A allele carriers (Tost et al., 2010; Kogan et al., 2011; Krueger et al., 2012; Smith et al., 2014). Third, intranasal administration of oxytocin promotes intergroup bias in behavior by motivating ingroup favoritism (De Dreu et al., 2010, 2011). Most importantly, our recent event-related brain potential research has shown that intranasal administration of oxytocin increases the racial ingroup bias in neural responses to perceived pain in others (Sheng et al., 2013). These findings suggest that the oxytocin system plays a key role in empathy and individuals who carry different variants of OXTR may vary in the racial ingroup bias in empathy for pain.

The current study tested the hypothesis that there is an association between OXTR and racial ingroup bias in brain activity in response to others' suffering. We scanned Chinese adults homozygous for the A (A/A) or G (G/G) allele of OXTR rs53576 while they viewed racial ingroup (Asian) and outgroup (Caucasian) faces that received painful or non-painful stimulations (Fig. 1A) and made judgments on whether the model was feeling pain by a button press. Individuals with A/G genotype were not included in the current neuroimaging study because questionnaire measures of sociality do not consistently categorize A/G genotype with A/A or G/G genotypes (e.g., Tost et al., 2010; Kogan et al., 2011; Smith et al., 2014). The analysis of OXTR association with racial ingroup bias in brain activity focused on two antagonistic

motivational systems that respond to perceived pain in others (Hein et al., 2010) – the ACC/SMA and nucleus accumbens (NAcc) – where oxytocin receptors are located (Skuse and Gallagher, 2009; Insel and Shapiro, 1992). The ACC/SMA activity to perceived pain is associated with self-reported empathy (Jackson et al., 2005) and shows racial ingroup bias (Xu et al., 2009; Sheng et al., 2014). The NAcc is a key node of the reward system (O'Connell and Hofmann, 2011) and its activity is associated with negative attitude (Takahashi et al., 2009) and desire for revenge (Singer et al., 2006). We examined whether G/G and A/A carriers show distinct racial ingroup bias in ACC/SMA and NAcc activity in response to others' suffering. Moreover, we assessed whether OXTR rs53576 modulates the relationship between racial ingroup bias in neural activity to perceived pain and racial ingroup bias in implicit attitudes as this relationship is enhanced by oxytocin (Sheng et al., 2013).

Finally we tested whether rs53576 modulates the relationship between neural activity to perceived pain and altruistic motivations related to racial outgroup members given that increased NAcc activity to outgroup members' suffering in a context of competition predicts a decreased tendency to help the outgroup members (Hein et al., 2010). Racial ingroup/outgroup tensions have been widely documented (e.g., Orbe and Harris, 2014). Community conflict is often generated by an influx of new racial or ethnic groups (Oliver and Wong, 2003) who are typically regarded as threats by local residents (Ross, 2000). Perceived an other-race individual who receives painful stimulation may signal potential conflict or competition between racial ingroup and outgroup individuals even when there is no direct competition between an observer and a perceived other-race individual. Given Hein et al.'s (2010) findings, we hypothesized that perceiving racial outgroup members' pain activates the NAcc and such NAcc activity, if any, may be associated with motivations to reduce racial outgroup members' pain.



**Fig. 1.** (A) Illustration of video clips showing Asian and Caucasian models receiving painful and non-painful stimuli used in our study. (B) Differential rating scores of pain intensity of painful vs. non-painful stimuli in G/G and A/A individuals. (C) Illustration of ROI analyses of ACC/SMA activity to perceived painful (vs. non-painful) stimuli applied to Asian and Caucasian models in G/G and A/A individuals. (D) Illustration of ROI analyses of NAcc activity to perceived painful (vs. non-painful) stimuli applied to Asian and Caucasian models in G/G and A/A individuals. \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.001$ .

## Materials and methods

### Participants

Sixty Chinese university students were recruited from a genotyped sample of 1532 subjects as paid volunteers for fMRI scanning. There were 30 G/G individuals and 30 A/A individuals. This sample size was determined by considering both reliable group differences in blood oxygen level dependent (BOLD) signals (Ma et al., 2014) and reliable correlation between BOLD signals and behavioral measures across individuals (Yarkoni, 2009). All participants were right handed, had normal or corrected-to-normal vision, and reported no abnormal neurological history. Gender, age, trait empathy, and ethnic identity were matched between the two genotyped groups (see Table 1 for details). Informed consent was obtained from all participants before scanning. This study was approved by a local ethics committee at the Department of Psychology, Peking University.

### Genotyping

OXTR rs53576, which is located in the third intron of OXTR, was selected for genotyping. This single nucleotide polymorphism 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- $\mu$ l system containing 2.5  $\mu$ l of TaqMan Universal PCR Master mix, 0.25  $\mu$ l of 20  $\times$  TaqMan probe and 1  $\mu$ l genomic DNA using Roche LightCycler 480 II (Roche Diagnostics, Beijing, China). Allele calling was performed using LightCycler CW 1.5 software (Roche Diagnostics). Genotype distribution of OXTR rs53576 did not deviate from Hardy–Weinberg equilibrium (688 A/A, 683 A/G, 161 G/G,  $\chi^2(2, n = 1532) = 0.20$ ,  $P = 0.66$ ).

### Stimuli and procedure

Stimuli used during fMRI scanning consisted of 48 video clips used in our previous work (Xu et al., 2009) that showed 6 Asian (3 males and 3 females) and 6 Caucasian models (3 males and 3 females). The video clips were presented through a projector onto a rear-projection screen located at the subject's head. There were 4 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 (illustrated in Fig. 1A). Each clip lasted for 3 s and subtended a visual angle of 21°  $\times$  17° (width  $\times$  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 was no time limitation for participants' behavioral responses.

There were four functional scans and each one lasted 292 s. Each scan consisted of 12 video clips of Asian models and 12 video clips of Caucasian models that were presented in a random order. Half of the video clips showed painful stimuli and half showed non-painful stimuli.

**Table 1**  
Information of the two genotype groups (mean  $\pm$  SD).

	G/G homozygote	A/A homozygote	T	p
Gender	16 male, 14 female	16 male, 14 female	–	–
Age	20.33(1.65)	20.20(1.45)	–0.33	0.74
IRI	70.73(8.93)	68.40(12.65)	–0.83	0.41
Perspective taking	18.20(4.51)	17.60(3.62)	–0.57	0.57
Empathic concern	18.60(2.94)	18.90(4.39)	0.31	0.76
Fantasy	20.33(4.40)	18.13(5.65)	–1.68	0.10
Personal distress	13.60(3.11)	13.77(4.19)	0.18	0.86
Ethnic identity	34.41(6.14)	33.30(4.33)	–0.84	0.41

IRI = Interpersonal Reactivity Index Scale.

There was a 9-s interstimulus interval between two successive video 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 performed these evaluations outside the scanner so that their empathic responses during scanning were not affected by these evaluation processes. Participants completed the Interpersonal Reactivity Index Scale (Davis, 1996), and the Multigroup Ethnic Identity Measure (Phinney, 1992) to assess their trait empathy and ethnic identity, respectively.

To assess the association between neural responses to racial ingroup/outgroup individuals' pain and altruistic motivation toward a racial ingroup/outgroup person, participants were asked, after the scanning procedure, to help with another experiment that would investigate neural correlates of physical pain. Our participants were informed that this experiment would recruit a Caucasian–Asian dyad who would receive electric shocks with the default intensity of 2.1 mA that would induce a moderate painful feeling. However, our participants were asked to modify the intensity of electric shocks between 0.8 mA that induces a sensory feeling and 3.4 mA that induces an intolerant painful feeling. In the ingroup help condition, participants were informed that another Asian subject had decided to apply 1.5-mA shocks to the Caucasian subject of the dyad and they had to decide the intensity of electric shocks that would be applied to the Asian subject of the dyad. In the outgroup help condition, participants were informed that another Caucasian subject had decided to apply 1.5-mA shocks to the Asian subject of the dyad and they had to decide the intensity of electric shocks that would be applied to the Caucasian subject of the dyad. The difference between the default intensity (2.1 mA) and the intensity of electric shocks assigned by our participants was used as an index of participants' altruistic motivation to help the racial ingroup/outgroup individuals (i.e., Altruistic motivation =  $E_{\text{default}} - E_{\text{assigned}}$ ). A smaller intensity of the assigned electric shock reflects stronger altruistic motivation.

Finally, participants were asked to complete a race version of the Implicit Association Test (IAT) (Greenwald et al., 1998). The stimuli and procedure of the IAT were identical to those in the previous studies (Avenanti et al., 2010; Sheng and Han, 2012). Participants were asked to categorize Asian faces/positive words with one key and Caucasian faces/negative words with another key in two blocks, and Asian faces/negative words with one key and Caucasian faces/positive words with another key in the other two blocks. The assignment of Asian faces with the left or right hand responses was counterbalanced across participants. Latency differences between the blocks with different response associations between faces and words reflect the relative ease of making associations between Asian and Caucasian faces and concepts of good and bad. According to the established algorithm of the latencies (Greenwald et al., 2003), a positive IAT D score indicates that, relative to Caucasian faces, Asian faces are associated with good rather than bad words while a negative IAT D score indicates a reverse association.

### fMRI imaging data acquisition

Brain images were acquired using 3.0-Tesla Siemens Trio at the Beijing MRI Center for Brain Research. BOLD gradient echo planar images were obtained using a 12-channel head coil (64  $\times$  64  $\times$  32 matrix with 3.44  $\times$  3.44  $\times$  5.0 mm spatial resolution, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, field of view = 24  $\times$  24 cm). A high-resolution T1-weighted structural image (256  $\times$  256  $\times$  144 matrix with a spatial resolution of 1  $\times$  1  $\times$  1.33 mm,

TR = 2530 ms, TE = 3.37 ms, inversion time (TI) = 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  $2 \times 2 \times 2$  mm. Functional images were smoothed using a Gaussian filter with the full-width/half-maximum parameter (FWHM) set to 8 mm. The event-related neural activity was modeled using a canonical hemodynamic response function.

We first conducted region-of-interest (ROI) analyses to assess the difference in racial ingroup bias in ACC/SMA and NAcc activity to others' pain between the two genotyped groups. Following the guideline for independent ROI analyses (Kriegeskorte et al., 2009), we defined the ROI in the ACC/SMA based on the independent fMRI study that used identical video stimuli (MNI coordinates:  $x/y/z = 4/40/38$ , Han et al., 2009). The ROIs in the NAcc were defined based on the independent fMRI study that investigated oxytocin effects on face processing (MNI coordinates:  $x/y/z = -6/5/-5$  and  $6/2/-2$ , Scheele et al., 2013). The ROIs were defined as spheres with radii of 5 mm centered at the peak voxel of activated clusters using MarsBar toolbox in SPM8. Parameter estimates of signal intensity were extracted from these ROIs and subjected to a repeated measures analysis of variance (ANOVA) with Pain (painful vs. non-painful stimuli) and Race (Asian vs. Caucasian models) as within-subjects variables and Genotype (G/G vs. A/A) as a between-subjects variable.

Original effect size (ES) and standardized ES (Cumming, 2014) were also calculated to test our hypothesis. Since we assumed a racial ingroup bias in empathy for others' suffering, the original ES of racial bias was defined as the increased contrast values of painful vs. non-painful stimuli to Asian models relative to those related to Caucasian models. The standardized ES was defined as Cohen's  $d$ :

$$d_{RBE} = (M_{Asian} - M_{Caucasian}) / S_{Caucasian}$$

where  $M_{Asian}$  was the mean of contrast values of painful vs. non-painful stimuli to Asian models,  $M_{Caucasian}$  was the mean of contrast values of painful vs. non-painful stimuli to Caucasian models, and  $S_{CA}$  was standard deviation of contrast values of painful vs. non-painful stimuli to Caucasian models (Cumming, 2014). Confidence interval (CI) reported along with the ES referred to 95% CI. Based on the hypothesis that OXTR would modulate racial ingroup bias, we also calculated its standardized ES using the formula of Cohen's  $d$ :

$$d_{OXTR} = (M_{GG} - M_{AA}) / S_{Pooled} \quad S_{Pooled} = \sqrt{\frac{df_{GG}SS_{GG} + df_{AA}SS_{AA}}{df_{GG} + df_{AA}}}$$

where  $M_{GG}$  was the mean of contrast values of racial ingroup bias in G/G group,  $M_{AA}$  was the mean of contrast values of racial ingroup bias in A/A group, and  $SS_{GG}$  was the variance of racial ingroup bias in G/G group,  $SS_{AA}$  was the variance of racial ingroup bias in A/A group.

We also conducted whole brain analyses to uncover distinct patterns of neural activity in response to racial ingroup and outgroup members' pain in the two genotype groups, respectively. 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. Random effect analyses were then conducted across all participants based on statistical parameter

maps from each individual participant to allow population inference. Significant activations were defined in the whole brain analysis using a threshold of  $p < 0.001$  (uncorrected voxel threshold) and  $p < 0.05$  FWE (corrected cluster threshold).

We further conducted hierarchical regression analyses to assess whether OXTR genotype moderates the relationship between the racial ingroup bias in ACC/SMA activity and individuals' racial ingroup bias in implicit attitudes and whether OXTR genotype moderates the relationship between NAcc activity to perceived pain in racial outgroup individuals and altruistic motivation to reduce racial outgroup individuals' pain. The racial ingroup bias in ACC/SMA activity was calculated by extracting beta values in the "Han et al. (2009) ROI". The racial ingroup bias in implicit attitude was defined by the IAT D score for each participant. The NAcc activity was calculated by extracting beta values in the "Scheele et al. (2013) ROIs". The altruistic motivation to reduce racial outgroup individuals' pain was defined as the difference between the intensity of electric shocks chosen by each participant and the default intensity (2.1 mA). The ACC/SMA (or NAcc) activity was the independent variable (IV) and individuals' racial ingroup bias in implicit attitude (or altruistic motivation) was the dependent variable (DV) during the regression analyses. The IV (racial bias in ACC/SMA activity or NAcc activity to Caucasian models) and the moderator (OXTR genotype) were normalized before the hierarchical regression analyses. The interactions between the racial ingroup bias in ACC/SMA activity (or NAcc activity to Caucasian models) and OXTR genotype were calculated by multiplying the normalized variables together (Aiken and West, 1991). The normalized racial ingroup bias in ACC/SMA activity (or NAcc activity to Caucasian models), OXTR genotype and their interactions were then sequentially entered into the hierarchical regression model. The moderator effect was indicated by a significant interaction of OXTR genotype and racial ingroup bias in ACC/SMA activity (or NAcc activity to Caucasian models) on individuals' racial ingroup bias in implicit attitude (or altruistic motivation).

## Results

### Behavioral results

During scanning both genotype groups identified painful and non-painful stimuli with high accuracy (Table S1). Rating scores of pain intensity were subjected to a repeated measures analysis of variance (ANOVA) with Pain (painful vs. non-painful stimuli) and Race (Asian vs. Caucasian models) as within-subjects variables and Genotype (G/G vs. A/A) as a between-subjects variable. Rating scores of pain intensity were higher for painful than non-painful stimuli (6.84 vs. 0.70,  $F(1,58) = 565.41$ ,  $p < 0.001$ , ES = 6.14, 95% CI: [5.88, 6.40], Cohen's  $d = 7.51$ ), but did not differ between G/G and A/A genotypes ( $F(1,58) = 1.01$ ,  $p = 0.32$ , Cohen's  $d = -0.26$ ). There was a significant interaction of Pain  $\times$  Race ( $F(1,58) = 37.49$ ,  $p < 0.001$ , ES = 0.57, 95% CI: [0.47, 0.66], Cohen's  $d = 0.28$ ), indicating different patterns of subjective feelings of Asian and Caucasian models' pain. Simple main effect analyses confirmed stronger pain intensity feelings for Asian than Caucasian models when viewing painful stimuli (7.13 vs. 6.55,  $t(59) = 6.30$ ,  $p < 0.001$ , ES = 0.58, 95% CI: [0.48, 0.67], Cohen's  $d = 0.29$ ) but not when viewing non-painful stimuli (0.71 vs. 0.70,  $t(59) = 0.15$ ,  $p = 0.88$ , ES = 0.01, 95% CI: [-0.04, 0.06], Cohen's  $d = 0.01$ ). Moreover, the racial ingroup bias in subjective feelings of pain intensity was stronger in G/G than A/A groups as revealed by a significant triple interaction of Pain  $\times$  Race  $\times$  Genotype ( $F(1,58) = 6.53$ ,  $p < 0.02$ , Cohen's  $d = 0.66$ , Fig. 1B, Table 2). ANOVAs of rating scores of self-unpleasantness showed a significant main effect of Pain ( $F(1,58) = 196.52$ ,  $p < 0.001$ , Cohen's  $d = 3.50$ ) and a significant interaction of Pain  $\times$  Race ( $F(1,58) = 20.33$ ,  $p < 0.001$ , Cohen's  $d = 0.18$ ), as viewing painful rather than non-painful stimuli applied to Asian versus Caucasian models produced stronger unpleasant feelings ( $t(59) = 5.99$  and 1.65,  $p < 0.001$  and  $p = 0.10$ ,

**Table 2**  
Subjective ratings of pain intensity and self-unpleasantness.

		G/G homozygote		A/A homozygote	
		Pain intensity	Self-unpleasantness	Pain intensity	Self-unpleasantness
Asian face	Pain	6.92 ± 0.38	5.76 ± 0.52	7.33 ± 0.35	6.59 ± 0.40
	Nopain	0.64 ± 0.17	0.73 ± 0.22	0.77 ± 0.14	1.48 ± 0.30
Caucasian face	Pain	6.14 ± 0.40	5.08 ± 0.51	6.96 ± 0.33	6.10 ± 0.40
	Nopain	0.67 ± 0.18	0.66 ± 0.17	0.73 ± 0.13	1.30 ± 0.29

Cohen's  $d = 0.23$  and  $0.09$ ). However, the racial ingroup bias in self-reported unpleasant feelings associated with painful stimuli did not differ significantly between G/G and A/A groups ( $F(1,58) = 2.05$ ,  $p = 0.16$ , Cohen's  $d = 0.37$ ). ANOVAs of rating scores related to trait empathy and ethnic identity did not differ significantly between the two genotyped groups ( $ps > 0.1$ , Table 1).

### Neuroimaging results

We first conducted ROI analyses to examine the variation of racial ingroup bias in ACC/SMA activity in response to others' suffering across the two variants of OXTR rs53576. We extracted parameter estimates of signal intensity from the ACC/SMA ROI where the activity was increased to perceived pain in others (Han et al., 2009). ANOVAs of the ACC/SMA activity confirmed increased activation to painful than non-painful stimuli ( $F(1,58) = 23.04$ ,  $p < 0.001$ ) and this activation was greater in responses to Asian than Caucasian models ( $F(1,58) = 5.11$ ,  $p < 0.03$ ). Moreover, the racial ingroup bias in ACC/SMA activity (defined by the contrast of (painful vs. non-painful)<sub>Asian models</sub> minus (painful vs. non-painful)<sub>Caucasian models</sub>) was significantly positively correlated with the racial ingroup bias in subjective ratings of pain intensity ( $r = 0.33$ ,  $p < 0.02$ , see Figure S1), confirming the association between racial ingroup bias in brain activity and racial ingroup bias in subjective feelings. Most importantly, there was a significant triple interaction of Pain × Race × Genotype ( $F(1,58) = 9.78$ ,  $p < 0.005$ ), indicating greater racial ingroup bias in ACC/SMA activity in response to others' suffering in G/G than A/A individuals. Simple main effect analyses further confirmed increased ACC/SMA activity in response to the suffering of Asian compared to Caucasian models in the G/G group ( $F(1,29) = 15.71$ ,  $p < 0.001$ ) but not in the A/A group ( $F(1,29) = 0.35$ ,  $p = 0.56$ , see Fig. 1C). The original effect size (ES) of racial bias was  $0.22$  with a 95% CI:  $[0.16, 0.28]$  and the Cohen's  $d$  was  $0.57$  in G/G group, whereas the original ES of racial bias was  $-0.04$  with  $[-0.10, 0.02]$  and the Cohen's  $d$  was  $-0.12$  in A/A group (Table 3). Relative to A/A group, G/G group showed stronger racial bias in ACC/SMA activity (Cohen's  $d = 0.81$ ).

Next we investigated whether NAcc activity showed a racial ingroup bias in response to others' suffering and whether the racial ingroup bias in NAcc activity (defined by the contrast of (painful vs. non-painful)<sub>Asian models</sub> minus (painful vs. non-painful)<sub>Caucasian models</sub>) varied across the two variants of OXTR rs53576. ANOVAs of parameter estimates of signal intensity in "Scheele et al. (2013)" NAcc ROIs showed significant triple interaction of Pain × Race × Genotype (left NAcc:  $F(1,58) = 11.29$ ,  $p = 0.001$ ; right NAcc:  $F(1,58) = 7.03$ ,  $p = 0.01$ ). Separate analyses further revealed a significant interaction of Pain × Race in

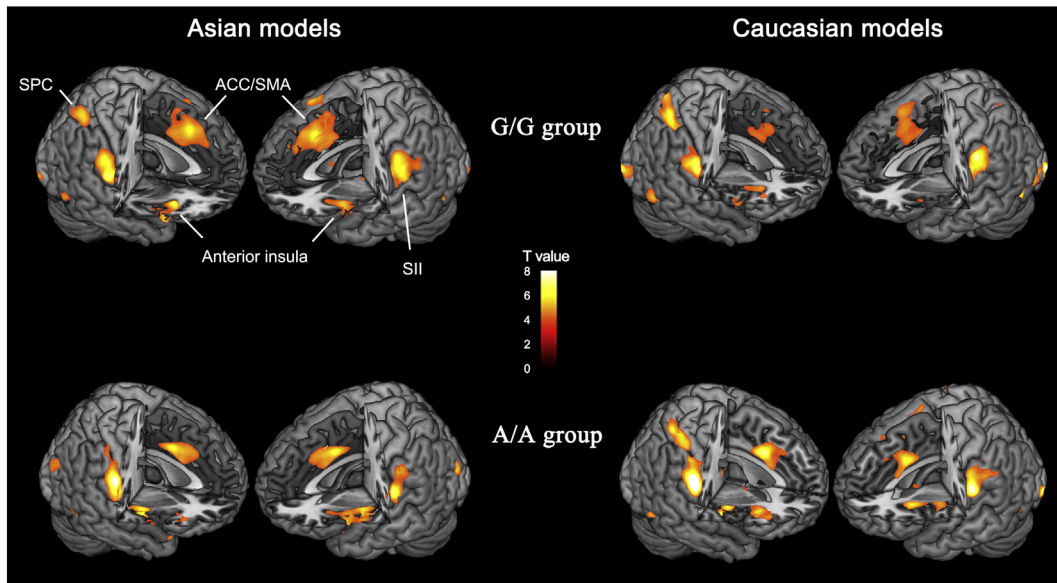
A/A individuals (left NAcc:  $F(1,29) = 14.03$ ,  $p = 0.001$ ; right NAcc:  $F(1,29) = 8.46$ ,  $p < 0.01$ ) but not in G/G individuals (left NAcc:  $F(1,29) = 0.59$ ,  $p = 0.45$ ; right NAcc:  $F(1,29) = 0.64$ ,  $p = 0.43$ , Fig. 1D), indicating that the A/A genotype showed stronger NAcc responses to painful (vs. non-painful) stimuli applied to Caucasian than Asian models whereas the G/G genotype did not show such racial ingroup bias in NAcc activity. The original effect size (ES) of racial bias was  $-0.51$  (left NAcc, 95% CI:  $[-0.65, -0.37]$ , Cohen's  $d = -0.95$ ) and  $-0.38$  (right NAcc, 95% CI:  $[-0.51, -0.25]$ , Cohen's  $d = -0.94$ ) in A/A group, whereas the original ES of racial bias was  $0.09$  (left NAcc, 95% CI:  $[-0.03, 0.20]$ , Cohen's  $d = 0.24$ ) and  $0.10$  (right NAcc, 95% CI:  $[-0.03, 0.23]$ , Cohen's  $d = 0.24$ ) in G/G group (Table 3). Relative to G/G group, A/A group showed stronger racial bias in the bilateral NAcc activity (left NAcc: Cohen's  $d = 0.87$ ; right NAcc: Cohen's  $d = 0.68$ ).

We further conducted whole-brain analyses to examine neural responses to others' suffering in the two genotype groups separately. Both groups showed significant activations in the ACC/SMA, bilateral AI, bilateral parietal operculum, second somatosensory cortex (SII), and left inferior temporal cortex in response to painful vs. non-painful stimuli applied to Asian models (Fig. 2, Table S2). The G/G group showed additional activation in the right middle frontal gyrus, right superior parietal cortex and cerebellum, whereas the A/A group showed additional activation in the bilateral middle insula and left occipital cortex to perceived pain in Asian models. Similarly, painful vs. non-painful stimuli applied to Caucasian models significantly activated the ACC/SMA, right inferior frontal cortex and bilateral parietal operculum/SII in both genotype groups. Additional activation to Caucasian models was observed in the left inferior frontal cortex, right middle frontal gyrus, right inferior temporal cortex, and left occipital cortex lobe in the G/G group but in the bilateral insula in the A/A group.

The whole-brain interaction analysis of racial ingroup bias further confirmed the distinct patterns of ACC/SMA activity to Asian and Caucasian models in the two genotype groups. The interaction analysis that compared the two contrasts ((painful–non-painful)<sub>Asian faces</sub> minus (painful–non-painful)<sub>Caucasian faces</sub>) revealed significant activations that covered the ACC/SMA and extended into the dorsal medial prefrontal cortex ( $x/y/z = 0/36/42$ ) in the G/G but not the A/A group (Fig. 3A and B). The whole-brain interaction analysis also revealed stronger activity in the left NAcc in the contrast of painful vs. non-painful stimuli ( $x/y/z = -4/12/-8$ ) when viewing Caucasian compared to Asian models in the A/A but not the G/G group (Fig. 4A and B). A whole-brain two sample interaction analysis further confirmed the distinct patterns of ACC/SMA and NAcc activity to Asian and Caucasian models' pain between the two genotype groups. The interaction analysis that

**Table 3**  
Effect sizes of racial ingroup bias in activity in different ROIs.

	ACC/SMA	L AI	R AI	L NAcc	R NAcc
G/G group					
Original ES	0.22	0.01	-0.03	0.09	0.10
95% CI	$[0.16, 0.28]$	$[-0.06, 0.08]$	$[-0.07, 0.02]$	$[-0.03, 0.20]$	$[-0.03, 0.23]$
Cohen's $d$	0.57	0.02	-0.13	0.24	0.24
A/A group					
Original ES	-0.04	0.01	-0.02	-0.51	-0.38
95% CI	$[-0.10, 0.02]$	$[-0.04, 0.06]$	$[-0.06, 0.02]$	$[-0.65, 0.37]$	$[-0.51, -0.25]$
Cohen's $d$	-0.12	0.04	-0.10	-0.95	-0.94

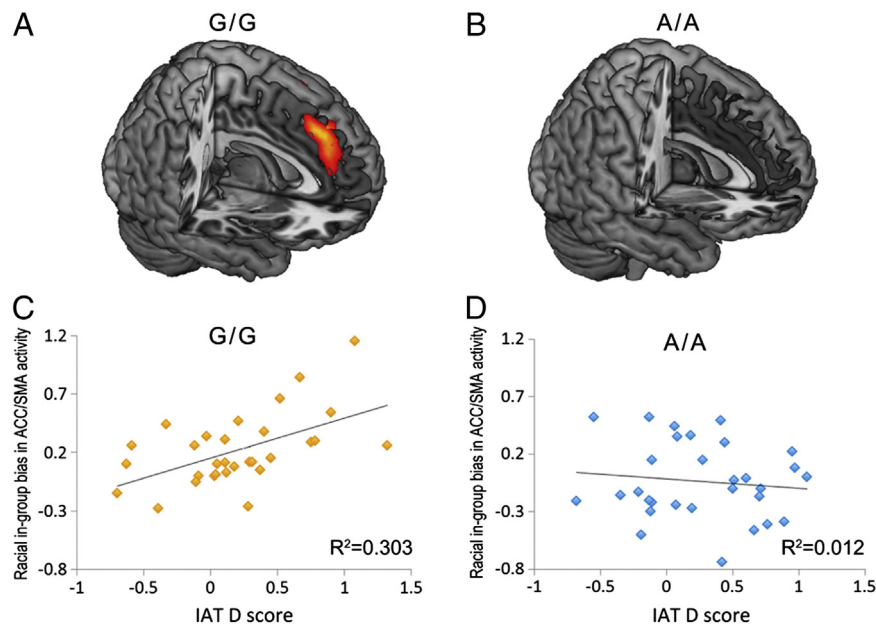


**Fig. 2.** The results of whole-brain analyses. The activations of the contrast of painful vs. non-painful stimuli applied to Asian and Caucasian models are shown separately for G/G (top panel) and A/A (bottom panel) individuals.

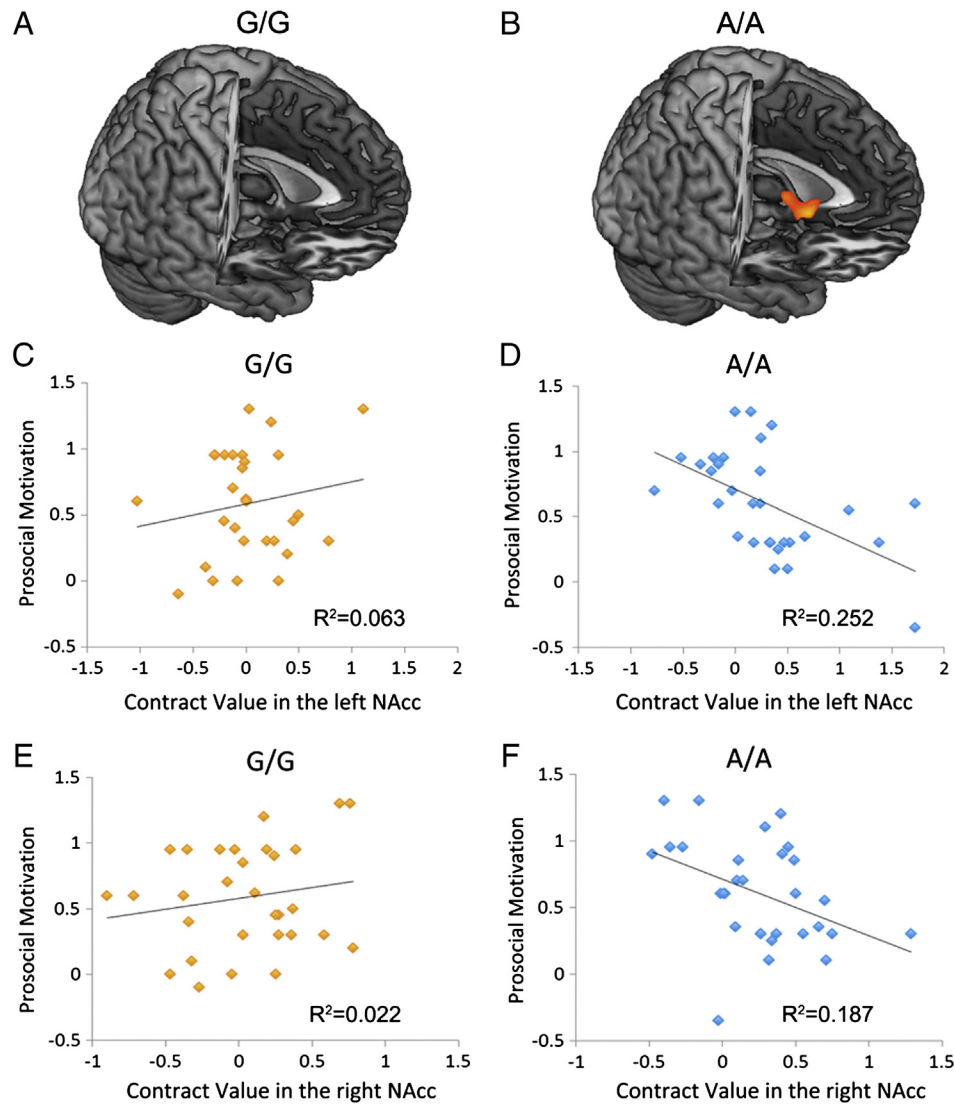
compared the two contrasts ( $(\text{painful} - \text{non-painful})_{\text{Asian models}}$  minus  $(\text{painful} - \text{non-painful})_{\text{Caucasian models}}$ ) revealed stronger activation in the ACC/SMA ( $x/y/z = 0/36/42$ ) in G/G individuals but stronger activity in the left NAcc ( $x/y/z = -4/8/-6$ ) in A/A individuals at a threshold of  $p < 0.05$  (small-volume FWE corrected).

To test whether the racial ingroup bias in ACC activity was associated with individuals' implicit attitudes toward racial ingroup/outgroup faces, we asked participants to perform a race IAT and calculated D scores as an index of the bias in implicit attitude toward Asian vs. Caucasian faces. The analysis of D scores across all participants showed that D scores were significantly larger than zero ( $0.24 \pm 0.47$ ,  $t(59) = 3.06$ ,

$p < 0.005$ ), suggesting reliable positive implicit attitudes toward Asian faces in our participants. However, the D scores did not differ significantly between the two genotype groups (G/G:  $0.21 \pm 0.48$  vs. A/A:  $0.26 \pm 0.47$ ,  $t(58) = 0.40$ ,  $p = 0.69$ ). Interestingly, the racial ingroup bias in ACC/SMA activity ( $(\text{painful} - \text{non-painful})_{\text{Asian models}}$  minus  $(\text{painful} - \text{non-painful})_{\text{Caucasian models}}$ ) was positively correlated with individuals' D scores in the G/G group ( $r = 0.55$ ,  $p < 0.005$ ) but not in the A/A group ( $r = -0.11$ ,  $p = 0.55$ , Figs. 3C and D). The distinct pattern of the coupling between the racial ingroup bias in ACC/SMA activity and that in implicit attitudes was further confirmed by hierarchical regression analyses that indicated that OXTR rs53576 significantly



**Fig. 3.** The results of whole-brain analyses. (A) and (B) Increased activations in the ACC/SMA are observed in the contrast of  $(\text{painful} - \text{non-painful})_{\text{Asian faces}}$  minus  $(\text{painful} - \text{non-painful})_{\text{Caucasian faces}}$  in G/G individuals but not in A/A individuals. The ACC/SMA activation extended into the dorsal medial prefrontal cortex. (C) and (D) The racial in-group bias in ACC/SMA activity predicted the racial IAT D scores in G/G but not A/A individuals. The ACC/SMA activation was plotted using a voxel threshold of  $p < 0.05$ .



**Fig. 4.** The results of whole-brain analyses. (A) and (B) Increased activations in the NAcc are observed in the contrast of (painful–non-painful)<sub>Asian faces</sub> minus (painful–non-painful)<sub>Caucasian faces</sub> in A/A but not G/G individuals. (C–F) The NAcc activity to racial out-group individuals' pain predicted altruistic motivation as measured by the assigned intensity of electric shocks to racial out-group members in AA but not GG individuals.

moderated the relationship between racial ingroup bias in ACC/SMA activity and racial ingroup bias in implicit attitudes (see Table S3). Similar analyses of the relationship between racial ingroup bias in NAcc activity and racial ingroup bias in implicit attitudes did not show any significant effect ( $p > 0.05$ ).

Finally, to test whether the NAcc activity was associated with individuals' altruistic motivation toward racial ingroup or outgroup individuals, we quantified the altruistic motivation as the difference between the default intensity and the intensity of electric shocks assigned by our participants to a racial ingroup or outgroup individual. The altruistic motivation across all participants was significantly stronger toward racial ingroup than outgroup individuals (Asian vs. Caucasian: 0.67 vs. 0.60,  $t(59) = 2.35$ ,  $p < 0.05$ ). However, this racial ingroup favoritism did not differ significantly between the two genotype groups ( $t(58) = 0.20$  &  $0.47$ ,  $p > 0.6$ ). We then estimated whether the NAcc activation in response to racial ingroup/outgroup individuals' pain can predict individuals' altruistic motivation toward them. Regression analyses first revealed a negative correlation between the NAcc activation and altruistic motivation toward racial outgroup members in the A/A group (left NAcc:  $r = -0.50$ ,  $p < 0.005$ , right NAcc:

$r = -0.43$ ,  $p < 0.05$ , Figs. 4C and E) but not in the G/G group (left NAcc:  $r = 0.25$ ,  $p = 0.18$ , right NAcc:  $r = 0.15$ ,  $p = 0.43$ , Figs. 4D and F). These differences were confirmed by hierarchical regression analyses that indicated that OXTR rs53576 moderated the relationship between altruistic motivation to help racial outgroup individuals and NAcc activations in response to painful stimulations applied to racial outgroup individuals (Tables S4 and S5). Similar analyses failed to find evidence for the association between the NAcc activation in response to racial ingroup individuals' pain and altruistic motivation toward them ( $p > 0.05$ ).

## Discussion

The present work investigated whether the two variants of OXTR rs53576 exhibit differential racial ingroup bias in brain activity engaged during perceiving others' suffering. Participants reported stronger feelings of pain intensity of nociceptive stimuli applied to others and of their own unpleasantness when viewing racial ingroup compared to outgroup individuals receiving painful stimulation, suggesting racial ingroup bias in subjective feelings of other's pain. In addition, we

found a more salient racial ingroup bias in self-report of others' pain intensity in G/G than A/A genotype groups, providing behavioral evidence for OXTR rs53576 association with racial ingroup bias in subjective feelings of others' pain. The previous fMRI research using the same stimuli did not report racial ingroup bias in subjective feeling possibly due to a small subject sample including both G/G and A/A individuals (Xu et al., 2009).

Similar to the previous fMRI studies (Singer et al., 2004; Jackson et al., 2005; Gu and Han, 2007; Saarela et al., 2007; Han et al., 2009; Xu et al., 2009; Corradi-Dell'Acqua et al., 2011; Sheng et al., 2014), we observed increased activity in response to perceived painful vs. non-painful stimulation in the ACC/SMA, bilateral AI, and bilateral SII, which consist of the core network engaged in both the first person pain experiences (Wager et al., 2013; Duerden and Albanese, 2013) and empathy for others' pain (Fan et al., 2011; Lamm et al., 2011). Moreover, our fMRI results provide evidence for distinct patterns of racial ingroup bias in brain activity in response to others' pain between the two genotyped groups. Specifically, G/G but not A/A individuals showed greater ACC/SMA activity to racial ingroup vs. outgroup individuals' pain, whereas the two genotype groups did not show racial ingroup bias in AI and SII activity in response to perceived pain. The ACC/SMA activity is associated with the affective motivational component of nociception (Peyron et al., 2000; Rainville, 2002) and plays a vital role in the control and execution of context-sensitive behavioral responses to pain (Perini et al., 2013). The ACC/SMA is more frequently engaged in cognitive–evaluative tasks in studies of empathy, whereas the AI is more likely to be activated in affective–perceptual forms of empathy (Fan et al., 2011). The racial ingroup bias in ACC/SMA activity may reflect distinct cognitive–evaluative processes of racial ingroup and outgroup's pain given that the racial ingroup bias in ACC/SMA activity to perceived pain can predict the racial ingroup bias in subjective evaluation of others' pain across all participants. Taken together, our findings provide the first neuroimaging evidence for a genetic association with the racial ingroup bias in ACC/SMA activity during empathy for others' suffering.

Our hierarchical regression analyses further revealed genetic moderation effects on the association between ACC/SMA activity and implicit attitude toward racial ingroup/outgroup individuals. The D scores in our race IAT uncovered a significant implicit positive attitude toward racial ingroup compared to outgroup models across all participants, consistent with the previous findings (e.g., Nosek et al., 2002; Baron and Banaji, 2006). In addition, the racial ingroup bias in D scores positively predicted the racial ingroup bias in ACC/SMA activity in G/G but not A/A individuals. The discrepant link between the racial ingroup bias in ACC/SMA activity and implicit attitude in the two genotype groups suggests that OXTR rs53576 moderates whether the racial ingroup bias in brain activity is affected by individuals' racial ingroup favoritism in implicit attitude or vice versa. It has been shown that G compared to A allele carriers of OXTR rs53576 exhibit higher dispositional empathy and social–emotional sensitivity (Rodrigues et al., 2009; Lucht et al., 2009; Tost et al., 2010; Smith et al., 2014) and that OXTR knockout mice display a variety of aberrant social and emotional behaviors (Takayanagi et al., 2005). Our results extend the previous research by showing evidence for the important role of OXTR rs53576 in moderating the relationship between implicit attitude and neural activity to the suffering of racial ingroup and outgroup individuals.

We also showed evidence for distinct associations between OXTR rs53576 and differential NAcc activity in response to racial outgroup and ingroup individuals' pain. A/A but not G/G individuals showed increased NAcc activity to racial outgroup versus ingroup individual's pain. Thus the two antagonistic motivational systems related to ingroup favoritism (i.e., the ACC and Nacc) show opposite patterns of associations with OXTR rs53576. The NAcc reward-related activity is observed both when viewing images of loved ones (Aron et al., 2005) and when witnessing disliked ones receiving painful stimulation (Singer et al., 2006), reflecting modulations of human reward activity by emotional

links between an observer and a target. The increased NAcc activity to outgroup individuals' pain (Takahashi et al., 2009), being in contrast to the increased NAcc activity linked to charitable giving (Harbaugh et al., 2007), provides a neural account of why humans may take pleasure in the outgroup members' suffering during competition (Lanzetta and Englis, 1989). Our findings further indicate that whether observing others' suffering induces increased activity in the reward system is not only affected by the intergroup relationships between an observer and a target but also modulated by one's genetic makeup (e.g., OXTR rs53576). However, it should be noted that, even though our participants intended to give stronger electric shocks to racial outgroup compared to ingroup individuals, our work lacked a direct measure of pleasure associated with electric shocks assigned to racial outgroup individuals. Thus whether the NAcc activity observed in our work reflected a pleasure of observing racial outgroup individuals' pain is still an open issue.

Similar to the association between NAcc activity to outgroup individuals' pain and the frequency of outgroup helping (Hein et al., 2010), we found a negative correlation between participants' NAcc activity and their motivations to help racial outgroup individuals. However, such an association was significantly moderated by OXTR rs53576, being significant in A/A but not G/G individuals. The NAcc is a region dense with oxytocin receptors (Insel and Shapiro, 1992) and intranasal oxytocin administration modulates reward-related NAcc activity (Strathearn et al., 2009; Scheele et al., 2013). Intranasal oxytocin administration also enhances ingroup favoritism in behavior (De Dreu et al., 2011) and neural responses to others' pain expression (Sheng et al., 2013). While these observations suggest a key role of oxytocin in shaping neural activity related to ingroup favoritism, our findings uncovered the association of OXTR rs53576 with NAcc activity that was associated with racial outgroup individuals' pain and predicted observers' altruistic motivation to reduce outgroup individuals' suffering. Thus genes may influence human altruistic behaviors by shaping their reward-related activations induced by viewing others' suffering.

Taken together, our neuroimaging results extend previous studies of racial ingroup favoritism by showing variation of racial ingroup bias in neural responses to others' suffering across the variants of a single nucleotide polymorphism. Our findings indicate that a single nucleotide polymorphism (i.e., OXTR rs53576) can modulate the racial ingroup bias in neural activities in two antagonistic motivational systems with one variant of OXTR rs53576 (i.e., G/G genotype) showing enhanced racial ingroup bias in ACC/SMA activity and another variant (i.e., A/A genotype) showing increased NAcc activity to racial outgroup individuals' pain. Moreover, the same single nucleotide polymorphism moderates the functional significance of the two antagonistic motivational systems in relation to implicit attitude and altruistic motivations, respectively. Neural responses to others' suffering are associated with complex emotions, goal-directed motivations and attitudes. Such associations in an observer reflect the interaction between his/her genetic influences on motivational systems and his/her social relationship with the target. The outcome of such interactions may finally affect an individual's decision to engage in or refrain from altruistic acts. A recent behavioral study suggests a genetic influence on racial ingroup favoritism by showing that monozygotic twins are more similar to each other than are dizygotic twins for racial ingroup favoritism (Lewis and Bates, 2010). Our findings uncovered potential underlying neural mechanisms of genetic associations with racial ingroup favoritism.

The same emotional state such as pain observed in ingroup and outgroup members may have different social meanings. Humans show ingroup bias in neural correlates of multiple cognitive/affective processes during perception of ingroup/outgroup individuals' faces, experiencing actions of ingroup/outgroup members, and understanding/sharing others' emotions (Molenberghs, 2013). Our findings raise the question of the extent to which genes are also linked to racial ingroup bias in neural activity underling other cognitive/affective



processes. Although current societies do not tolerate explicit negative emotions toward racial outgroup individuals, social distinctions based on race develop during economic or status competition between two or more social groups (Spickard, 1992) and result in racial ingroup favoritism in many societies and situations (Devine et al., 2002; Johnson et al., 2002; Greenwald et al., 2009; Drwecki et al., 2011). Ingroup favoritism may enhance collective group processes that have fostered our survival during evolution by enhancing our individual ability to adapt to group living (Caporael, 1997). The genetic effects reported here may be a part of the evolutionary heritage of neural correlates involved in multiple cognitive/affective capacities that support the development and maintenance of group membership (Brewer and Caporael, 1990).

Although our findings suggest genetic associations with racial ingroup bias in brain activity to others' suffering, recent studies indicate that such bias is not inevitable. It has been shown that enhancing a cognitive strategy that increases attention to each individual's feelings or including other-race individuals within one's own social group significantly reduces the racial ingroup bias in empathic neural responses to other's suffering (Sheng and Han, 2012). Long-term life experiences with other-race individuals also reduce the racial ingroup bias in ACC/SMA activity to others' pain (Zuo and Han, 2013). Future research should test whether compassion training that alters both neural responses to others' suffering and altruistic behavior (Weng et al., 2013; Klimecki et al., 2015) can also reduce the racial ingroup bias in empathic neural responses. Taken together, the neuroimaging findings indicate that, although the human brain may have adapted through evolution to generate differential responses to racial ingroup/outgroup members in order to adjust to both within-group altruism and intergroup conflict, the racial ingroup bias can be counteracted by cognitive strategies, life experiences, and sociocultural environments that do not tolerate explicit negative emotions toward other-race individuals.

In conclusion, while there has been increasing evidence for modulations of human brain activity by perceived racial intergroup relationships (Ito and Bartholow, 2009; Eres and Molenberghs, 2013), its genetic association has been rarely investigated. Our findings shed new light on genetic differences in empathic neural responses to others' suffering. Our results indicate that a single nucleotide polymorphism (e.g., OXTR rs53576) can interact with social relationships to shape human brain activities that respond to others' suffering and are linked to implicit attitude and altruistic motivation, respectively. A recent meta-analysis failed to find evidence for a significant association between OXTR rs53576 and human social behavior (Bakermans-Kranenburg and van IJzendoorn, 2014). Future research should reexamine the association between OXTR rs53576 and human social behavior by clarifying behaviors toward racial ingroup and outgroup individuals. Moreover, recent research has revealed that populations dominated by stronger collectivistic cultures comprise more A carriers of OXTR rs53576 (Luo and Han, 2014) and Western/East Asian cultures interact with OXTR rs53576 to shape emotion suppression (Kim et al., 2011) and emotional support seeking (Kim et al., 2010). Thus future research should investigate whether OXTR rs53576 modulates racial ingroup bias in empathic neural responses in different cultures in a similar vein. Finally, the candidate gene approach adopted in the current study did not allow us to examine the relationship between empathic neural responses and other genes. Recent research has shown evidence that other hormones such as testosterone impairs empathy in humans (e.g., Hermans et al., 2006; Van Honk et al., 2011) but tells little about the link between testosterone receptor gene and empathy. These should be investigated in future research.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2015.01.042>.

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