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Does self-construal predict activity in the social brain network? A genetic moderation effect

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Neural activity in the social brain network varies across individuals with different cultural traits and different genetic polymorphisms. It remains unknown whether a specific genetic polymorphism may influence the association between cultural traits and neural activity in the social brain network. We tested whether the serotonin transporter promoter polymorphism (5-HTTLPR) affects the association between self-construals and neural activity involved in reflection of personal attributes of oneself and a significant other (i.e., mother). Using functional MRI, we scanned Chinese adults with short/short (s/s) or long/long (l/l) variants of the 5-HTTLPR during reflection of personal attributes of oneself and one's mother. We found that, while s/s and l/l genotype groups did not differ significantly in self-construals measured by the Self-Construal Scale, the relationship between self-construal scores and neural responses to reflection of oneself and mother was significantly different between the two genotype groups. Specifically, l/l but not s/s genotype group showed significant association between self-construal scores and activity in the medial prefrontal cortex, bilateral middle frontal cortex, temporoparietal junction, insula and hippocampus during reflection on mental attributes of oneself and mother. Our findings suggest that a specific genetic polymorphism may interact with a cultural trait to shape the neural substrates underlying social cognition.

Keywords: 5-HTTLPR; fMRI; social brain network; self-construal; culture

INTRODUCTION

Social cognition consists of processing information about oneself and others (Iacoboni, 2006; Sedikides and Skowronski, 2009) and plays a key role in appropriate social communication and behavior. Neuroimaging evidence indicates that social cognition is mediated by a distributed neural network in the human brain (referred as the social brain network, Brothers, 1990; Lieberman, 2007). For example, self-processes, such as reflection of one's own personality traits and social roles, engage the ventral medial prefrontal cortex (vmPFC), precuneus/posterior cingulate and temporoparietal junction (TPJ) (Kelley *et al.*, 2002; Zhu *et al.*, 2007; Heatherton *et al.*, 2006; Han *et al.*, 2008, 2010; Ma and Han, 2011, Jenkins and Mitchell, 2011; Sul *et al.*, 2012; Ma, Bang *et al.*, 2014). Attributing mental states such as desires and beliefs to others engages the dorsal medial prefrontal cortex (dmPFC), TPJ and precuneus (Gallagher *et al.*, 2000; Saxe and Kanwisher, 2003; Lieberman, 2007). The activity in the social brain network can predict both performance in laboratories (e.g. Ma and Han, 2011) and behaviors in daily life (e.g. Ma *et al.*, 2011; Falk *et al.*, 2010).

Interestingly, recent cultural neuroscience studies indicate that activity in the social brain network is contextually dependent and is affected by sociocultural experiences (Han and Northoff, 2008, 2009; Kitayama and Park, 2010; Chiao *et al.*, 2013; Han *et al.*, 2013). Early studies showed evidence for cultural group differences in brain activity underlying social cognition. For example, mental state judgements on another individual produce stronger bilateral TPJ and right dmPFC activity in Americans than in Japanese (Kobayashi *et al.*, 2006). Trait judgments of a close other (e.g. mother) *vs* a celebrity activate the mPFC to a greater degree in Chinese than in English-speaking Westerners (Zhu *et al.*, 2007). Reflection on one's own attributes induces stronger mPFC activity in Danes but greater TPJ activity in Chinese (Ma, Bang *et al.*, 2014). Later studies found evidence for associations between a cultural trait and brain activity involved in social cognition. For instance, the mPFC and TPJ activity underlying self-reflection is associated with individual differences in a specific cultural trait (i.e. interdependence of self-construals, Chiao *et al.*, 2009; Sul *et al.*, 2012; Ma, Bang *et al.*, 2014). Recent research further showed evidence that cultural group differences in the neural activity underlying social cognition (e.g. TPJ activity involved in self-reflection of social roles) may be mediated by a cultural trait (e.g. interdependence of self-construal, Ma, Bang *et al.*, 2014). Taken together, these findings suggest that cultural experiences may strongly affect the neural activity underpinning social cognition and these effects may be mediated by a specific cultural trait.

However, cultural experiences are not the only force to shape the neural basis of social cognition. Our recent research has shown evidence that a specific genetic polymorphism affects the neural activity in the social brain network (Ma, Li, *et al.*, 2014). We tested a candidate a genetic polymorphism, i.e. the serotonin transporter promoter polymorphism (5-HTTLPR), which interacts with one's life experiences to influence human traits and behaviors so that depression symptoms (Caspi *et al.*, 2003; Taylor *et al.*, 2006) and neuroticism (Pluess *et al.*, 2010) were more closely associated with stressful life events in short (s) allele carriers than in homozygous long allele (l/l) carriers of 5-HTTLPR. We found that the 5-HTTLPR modulates the neural activity involved in self-reflection of personality traits. Specifically, relative to l/l carriers, s/s carriers showed stronger distressed feelings and greater activity in the dorsal anterior cingulate (dACC)/dmPFC and the right anterior insula (AI) during reflection of one's own unfavorable personality traits. Moreover, we found that the 5-HTTLPR effect on the distressed feelings was mediated by the AI/inferior frontal activity during negative self-reflection. These findings reveal that a specific genetic polymorphism also shapes the neural activity associated with social cognition.

Gene–culture coevolution theory suggests that culture and gene are both inheritable and influence each other during evolution (Boyd and Richerson, 1985; Richerson *et al.*, 2010; Chiao *et al.*, 2013). Behavioral studies have shown that genes interact with culture to affect social

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cognition and behaviors such as emotional support seeking (Kim *et al.*, 2010, 2011) and willingness to volunteer for prosocial causes (Sasaki *et al.*, 2013). However, to date, little is known about whether and how genes interact with cultural traits to shape the brain activity underlying social cognition. The current study investigated this by examining whether a specific genetic polymorphism influences the association between a cultural trait and activity in the social brain network. Given that the 5-HTTLPR modulates the neural activity associated with social cognition (Ma, Li, *et al.*, 2014) and the frequency of 5-HTTLPR variants is associated with the cultural trait of self-construal across nations (Chiao and Blizinsky, 2010), we tested the hypothesis that a candidate genetic polymorphism, i.e. the 5-HTTLPR, may interact with the self-construal to shape activity in the social brain network during reflection of oneself and a significant other.

Specifically, we assessed whether 5-HTTLPR polymorphism modulated the association between interdependence of self-construals and neural activity during the processing of personal attributes of oneself and one's mother using functional magnetic resonance imaging (fMRI). We scanned s/s and l/l genotype groups during judgments on personal attributes of oneself, one's mother and a celebrity. We first conducted whole-brain simple regression analyses to identify brain regions in which activations related to reflection of oneself (defined in the contrast of self- *vs* celebrity-judgments) or of one's mother (defined in the contrast of mother- *vs* celebrity-judgments) were associated with interdependence of self-construals measured using the Self-Construal Scale (SCS, Singelis, 1994). These brain regions were then used as masks in further hierarchical regression analyses to estimate whether the 5-HTTLPR moderates the association between the activities in these brain regions and the self-construal scores. Recent studies have shown that self-reflection on different dimensions of personal attributes is associated with both common and distinct brain regions. The mPFC is commonly activated during self-reflection on personality traits, physical attributes and social roles (Jenkins and Mitchell, 2011; Sul *et al.*, 2012; Ma, Bang, *et al.*, 2014). The TPJ is engaged during self-reflection on social roles (Sul *et al.*, 2012; Ma, Bang, *et al.*, 2014) and the precuneus, superior temporal sulcus and cerebellum are involved in self-reflection on physical attributes (Jenkins and Mitchell, 2011; Ma, Bang *et al.*, 2014). These findings raise the question whether 5-HTTLPR moderates the association between interdependence and brain activity during personal attributes judgment on different dimensions in a similar vein. To test this, we asked participants to make judgments on three dimensions of personal attributes (i.e. personality traits, social roles and physical features) during fMRI scanning, similar to our previous study (Ma, Bang *et al.*, 2014). We would expect a genetic effect on the association between the cultural trait and the neural substrates underlying self-reflection on mental attributes because the neural activity underlying self-reflection on mental attributes is sensitive to both cultural (Ma, Bang *et al.*, 2014) and genetic (Ma, Li *et al.*, 2014) influences. Similar analyses of the 5-HTTLPR moderation effect were applied to the neural activity underlying self-reflection on different dimensions of personal attributes.

METHOD

Genotyping

We used PCR method (Ota *et al.*, 2007) to determine the genotypes of 5-HTTLPR. In a total volume of 50 µl, ~25 ng of genomic DNA were amplified in the presence of 1× TransStart FastPfu DNA Polymerase (TransGen Biotech) reaction system and oligonucleotide primers (forward 5′-GCATCCCCCATTATCCCCCCCT-3′ and reverse 5′-AGGCTTGGAGGCCGGGATGC-3′) at final concentration of 200 nM. Thermal cycling consisted of 15 min of initial denaturation at 95°C followed by 35 cycles of 95°C (20 s), 69°C (20 s) and 72°C (15 s) each with a final extension step of 10 min at 72°C. Subsequently, PCR product was loaded onto a 3% agarose gel (BioWest G-10), to perform electrophoresis to distinguish genotypes of s/s, s/l and l/l. All genotyping was performed in duplicate.

Participants

Twenty-two Chinese college students homozygous for the s allele and 18 Chinese college students homozygous for the l allele were recruited in the fMRI experiment as paid volunteers. All participants were right-handed, reported no history of neurological or psychiatric diagnoses, and had normal or corrected-to-normal vision. Six participants were excluded from data analysis due to excessive head movement during scanning. Thus 17 s/s and 17 l/l genotype individuals were included in behavioral and fMRI data analysis. The two genotype groups were matched in gender, and did not differ significantly in age, self-construal, self-esteem and anxiety trait (see Table 1 for the mean of each measurement and independent-sample *t*-test results). Informed consents approved by a local ethics committee were provided prior to the study.

Stimuli and procedure

Stimuli and procedure during scanning were the same as those used in Ma, Bang *et al.* (2014). There were three categories of words or phrases describing the mental (i.e. personality traits), physical (i.e. the physical appearance) and social (i.e. social roles) attributes. The mental category consisted of 80 trait adjectives (40 positive and 40 negative, e.g. smart, greedy). The physical category consisted of 80 items describing one's physical features (e.g. long arm, curly hair). The social category consisted of 80 items describing one's social roles/identities (e.g. student, tourist, see the complete list in the original paper). The trait adjectives presented to each participant consisted of half positive and half negative attributes.

In separate blocks of trials, each participant was asked to judge whether a given word/phrase described the self (self-judgment), one's mother (mother-judgment) or a well-known gender-matched athlete (celebrity-judgment) by pressing one of the two buttons using the index or middle finger. Participants also judged whether a word/phrase was bold-faced or light-faced (font-judgment) to control low-level sensory/perceptual processing and motor responses. Each type of judgments was presented once in a single block using a block design. Each participant finished five functional scans. There were 10 blocks in each scan (i.e. judgments of mental/physical/social attributes of the self/mother/celebrity and a font-judgment, see Supplementary Figure S1). Eight items were presented in each block. Each item was presented for 2 s followed by a 1-s central fixation. Two successive blocks were intervened by a 10-s rest block during which participants viewed a white fixation on a black screen. Different blocks in each scan were presented in a random order. Of the 80 items of each category for each participant, 40 items were randomly chosen.

Table 1 Participant information by 5-HTTLPR Genotype

Variables	s/s carriers	l/l carriers	Independent *t*-test	
	Mean (SD)	Mean (SD)	T-value	*p*
Gender	13 males	14 males	–	–
Age (years)	19.6 (0.7)	19.5 (0.8)	0.684	0.499
Self-esteem	29.0 (2.6)	28.9 (4.3)	0.049	0.962
Anxiety	14.9 (6.9)	15.6 (6.2)	−0.288	0.775
Interdependence	2.1 (10.3)	7.2 (9.5)	−1.487	0.147

After the fMRI scanning, participants were asked to complete Self-esteem Scale (Rosenberg, 1965), SCS (Singelis, 1994) and the harm avoidance subscale from the Tridimensional Personality Questionnaire (Cloninger *et al.*, 1993). The SCS scale consists of 24 items for assessing individual differences in independent/interdependent self-construals on a 7-point Likert scale (1 = strongly disagree, 7 = strongly agree). Interdependence was defined by the difference between the sum score of the12 interdependent self-construal items and the sum score of the 12 independent self-construal items. Higher scores indicate greater levels of interdependent self-construals.

Imaging parameters

Functional brain images were acquired using a 3.0-Tesla Siemens Trio scanner at the Beijing MRI Center for Brain Research. Blood oxygen level-dependent (BOLD) gradient echo planar images (EPIs) 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 (FOV) = 24×24 cm] while participants were performing the judgment tasks. 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.

Imaging analysis

SPM2 (the Wellcome Trust Centre for Neuroimaging, London, UK) was used for data analysis. The functional images were realigned to the first scan to correct for head motion. Six movement parameters (translation: *x*, *y*, *z*; rotation: pitch, roll, yaw) were included in the statistical model. The anatomical image was coregistered with the mean functional image produced during the process of realignment. The anatomical images and functional images were normalized to the standard T1 and EPI Montreal Neurological Institute (MNI) templates, respectively. Functional images were then spatially smoothed using an isotropic Gaussian kernel of 8 mm full-width half-maximum.

The onsets and durations of each block were modeled using a General Linear Model (GLM) according to stimulus conditions for each participant. A box-car function was used to model the response to each condition. The box-car function was convolved with the canonical hemodynamic response. The design matrix also included the realignment parameters to account for any residual movement-related effect. Contrasts of self- (or mother-) *vs* celebrity-judgments in mental, physical and social blocks separately defined neural activities related to the processing of mental, physical and social aspects of the self (or mother).

We first conducted whole-brain simple regression analyses to identify brain regions in which activations related to self- (or mother-) *vs* celebrity-judgments were significantly correlated with interdependence of self-construals. Rating scores of interdependence were entered as a regressor into the SPM simple regression analysis along with each participant's contrast image of self- (or mother-) *vs* celebrity-judgments in the mental, social and physical blocks, respectively. As genetic differences were not taken into account during the simple regression analysis, fMRI data from both l/l and s/s carriers were included in this analysis. Because the brain regions identified in this regression analysis were used as masks for the next step analysis, we used a lenient threshold of $P < 0.005$ (uncorrected, $k > 50$) to identify brain regions that covaried with rating scores of interdependence.

Next we conducted whole-brain hierarchical regression analysis to examine whether 5-HTTLPR genotype affected the relationship between interdependence and the neural activity underlying personal judgments on the self and one's mother. We first normalized the independent variable (IV) (the measure of interdependence) and the covariate variable (genotype). Genotype group was coded as a dichotomous dummy variable in which 0 represented s/s carriers and 1 represented l/l carriers. The interactions between interdependence and genotype were calculated by multiplying the normalized variables together (Aiken and West, 1991). Normalized genotype (the moderator), interdependence (IV) and their interactions were entered as regressors into the SPM multiple regression analysis along with each participant's contrast image of self- or mother-judgment *vs* celebrity-judgment. Brain activities covaried with the interaction of genotype and interdependence indicated significant interaction of interdependence and 5-HTTLPR on the brain activities. Brain regions that covaried with interdependence in the simple regression analysis were used as masks for multiple correction using the WFU PickAtlas (Maldjian *et al.*, 2003). Because these brain regions were defined based on the data from all the participants, using these brain regions in the multiple regression analysis does not bias any within-group variables in this study. Significant brain activations covaried with gene × culture interaction were identified using a threshold of $P < 0.05$ (FDR corrected for multiple comparisons in masked areas). Simple regression analyses were also conducted for each genotype group to further reveal patterns of the relationship between interdependence and neural responses underlying self-/mother-judgments.

RESULTS

Behavioral performance

s/s and l/l carriers did not differ significantly in age and subjective ratings on the Self-Construal Scale, Anxiety scale and Self-Esteem Scale ($Ps > 0.05$, Table 1). The two genotype groups did not differ in reaction times (RTs) {874 *vs* 917 ms, [F (1, 32) = 1.020, $P = 0.320$, $\eta_p^2 = 0.031$]} and response accuracy {89% *vs* 89%, [F (1, 32) = 0.072, $P = 0.790$, $\eta_p^2 = 0.002$]} during font-judgments (Supplementary Table S1). RTs to trait judgments were subjected to ANOVAs with Judgment (self-judgment *vs* celebrity-judgment or mother-judgment *vs* celebrity-judgment) and Dimension (mental, physical or social) as independent within-subjects variables and Genotype (s/s *vs* l/l genotype) as a between-subjects variable. As ANOVAs of RTs revealed a significant three-way interaction [self *vs* celebrity: F (2, 64) = 3.456, $P = 0.038$, $\eta_p^2 = 0.097$; mother *vs* celebrity: F (2, 64) = 4.134, $P = 0.020$, $\eta_p^2 = 0.114$], 2 (Judgment) × 2 (Group) ANOVAs were then conducted on RTs in the social, mental and physical blocks, respectively. Significant Judgment × Group interactions were found only during judgments of social roles [self *vs* celebrity: F (1, 32) = 11.938, $P = 0.002$, $\eta_p^2 = 0.272$; mother *vs* celebrity: F (1, 32) = 7.331, $P = 0.011$, $\eta_p^2 = 0.186$], suggesting that l/l carriers responded slightly slower to judgments of the celebrity's social roles compared with s/s carriers [F (1, 32) = 5.449, $P = 0.026$, $\eta_p^2 = 0.146$] whereas RTs to self- and mother-judgments did not differ between the two genotype groups ($Fs < 1$). The Judgment × Group interactions during judgments of physical and mental attributes did not reach significance ($Ps > 0.26$), suggesting that l/l and s/s carriers showed similar patterns of responses during reflection of physical and mental attributes.

Brain imaging results

Association between interdependence and brain activity during self-reflection

The whole-brain simple regression analysis of the brain activity related to self-reflection on mental attributes across all participants revealed significant positive correlation between the measure of interdependence and activations shown in the contrast of self- *vs* celebrity-judgments in the bilateral insula, right middle temporal cortex, left hippocampus, left superior frontal cortex, mPFC and right middle

Table 2 Brain activations in simple regression and moderation analyses of the contrast of self- *vs* celebrity-judgments

Dimension region	*x*, *y*, *z*	T-value	cluster size
Simple regression analysis			
Mental attributes			
Positive correlation			
Insula (R)	48, 14, −6	4.78	611
Middle temporal (R)	58, −12, −10	4.36	167
Insula (L)	−50, 18, −6	4.07	83
Hippocampus (L)	−16, −52, 2	4.06	205
Superior Frontal (L)	−32, 48, 16	3.41	152
mPFC	2, 50, 16	3.31	75
Middle Frontal (R)	38, 30, 30	3.44	317
negative correlation			
Superior Parietal and TPJ (R)	30, −62, 58	4.71	1182
	54, −52, 36	4.56	
Middle Frontal (L)	−54, 12, 40	4.67	68
Cerebellum (L)	−16, −68, −20	4.62	355
Cerebellum (R)	24, −68, −26	4.63	266
Superior Parietal (L)	−38, −60, 58	4.47	396
Middle Frontal (R)	38, 30, 30	3.44	317
Social attributes			
positive correlation			
Inferior Parietal (L)	−46, −34, 58	3.52	185
negative correlation			
Superior Frontal (L)	−6, 24, 40	4.15	324
Middle and Superior Frontal (L)	−22, 16, 68	3.87	150
Physical attributes			
positive correlation			
Superior Parietal(L)	−6, −56, 64	5.35	1166
Middle Frontal (R)	32, 42, 28	4.43	223
Inferior Parietal (L)	−64, −26, 26	4.35	284
Inferior Parietal (R)	58, −34, 44	4.42	299
Middle temporal (R)	52, −66, 10	4.33	299
Moderation analysis			
Mental attributes			
Cerebellum (R)	18, −42, −42	4.78	51
mPFC	4, 48, 14	3.96	75
Middle Frontal (L)	−30, 50, 34	3.71	133
Middle Frontal (R)	24, 56, 24	2.96	131
Hippocampus (L)	−20, −36, 0	3.91	121
TPJ (R)	56, −54, 36	4.27	726
Superior Parietal (R)	14, −80, 40	4.12	134
Middle Frontal (R)	50, 26, 28	3.32	239
TPJ (L)	−64, −38, 20	6.17	119

frontal cortex (Table 2). The brain activity related to self-reflection on mental attributes was negatively correlated with the measure of interdependence in the bilateral superior parietal cortex, right TPJ, left middle frontal cortex, right middle frontal cortex and cerebellum.

Interestingly, the hierarchical regression analysis showed significant gene × interdependence interaction on the activity in the mPFC, bilateral middle frontal cortex, bilateral TPJ, superior parietal cortex, left hippocampus, cerebellum (Table 2 and Figure 1), suggesting different associations between the interdependence and brain activity in these regions related to self-reflection on mental attributes in l/l and s/s carriers. *Post hoc* regression analyses confirmed that the relationship between interdependence and neural activity in these brain regions related to self-reflection on mental attributes was significant for l/l but not for s/s carriers. l/l carriers with higher interdependence showed stronger activation in the mPFC (2, 52, 16), left frontal cortex (−32, 48, 16), left hippocampus (−16, −42, 2), and cerebellum (20, −42, −44), but weaker activation in the bilateral TPJ (left: −64, −40, 40; right: 58, −52, 38).

Similar simple regression analyses of the fMRI data during self reflection of social roles showed that the measurement of interdependence was positively correlated with the left inferior parietal activity but was negatively correlated with the left middle and superior frontal activity and the medial superior frontal activity (Table 2). The measure of interdependence was positively correlated with the activity in the superior parietal cortex, right middle frontal cortex and bilateral inferior parietal cortex during self-reflection of physical attributes (Table 2). However, further hierarchical regression analyses did not reveal significant gene × interdependence interactions in any brain region during reflection of social roles and physical attributes.

Association between interdependence and brain activity during reflection on mother

The whole-brain simple regression analysis of fMRI data during reflection of mother's mental attributes showed that the interdependence positively correlated with activations in the contrast of mother- *vs* celebrity-judgments in the bilateral insula, mPFC, and bilateral middle/superior frontal cortex (Table 3). The measure of interdependence was negatively correlated with activations in the right precentral cortex, right superior temporal cortex and left superior parietal cortex during reflection of mother's mental attributes. The hierarchical regression analysis showed significant gene × interdependence interactions in the mPFC, bilateral middle frontal cortex, right insula, and the superior parietal cortex (Table 3, Figure 2), suggesting different associations between the measure of interdependence and brain activity in these regions during reflection on mother's mental attributes in l/l and s/s carriers. Post-hoc regression analyses confirmed that the association between interdependence and neural responses in these brain regions was significant for l/l but not for s/s carriers. During reflection on mother's mental attributes, l/l carriers with higher interdependence showed stronger activation in the mPFC (2, 54, 20), bilateral middle frontal cortex (left: −26, 44, 6; right: 26, 48, 12), bilateral insula (left: −50, 20, −4; right: 40, 16, −14), but weaker activation in the superior parietal cortex (12, −54, 54, −10, −42, 54), inferior frontal cortex (48, 6, 8), inferior parietal cortex (left: −58, −40, 18; right: 62, −40, 28).

Similar simple regression analyses of the fMRI data during reflection of mother's social attributes showed that the measure of interdependence was positively correlated with activities in the bilateral superior parietal cortex, right precuneus, right fusiform, right inferior parietal cortex, right insula and right inferior frontal cortex, but was negatively correlated with the left frontal activity (Table 3). The measure of interdependence was positively correlated with the activations in the contrast of mother- *vs* celebrity-judgments on physical attributes in the left precentral cortex but negatively correlated with the activity in the PCC, bilateral middle occipital cortex and left lingual gyrus (Table 3). However, the hierarchical regression analyses did not show significant gene × interdependence interactions in brain activities related to judgments on mother's social and physical attributes.

DISCUSSION

Human behavior manifests both environmental and genetic variations during evolution and has been shaped by the interaction between gene and culture (Boyd and Richerson, 1985; Kendler and Prescott, 2006; Richerson *et al.*, 2010; Laland *et al.*, 2010). However, the effect of gene × culture interactions on human brain activity related to social behaviors is poorly understood. Here we reported neuroimaging evidence that a specific genetic polymorphism (i.e. 5-HTTLPR) may interact with a specific cultural trait (i.e. interdependence of self-construals) to shape the activity in the social brain network.

Unlike the previous transcultural imaging studies that compared two cultural groups (e.g. Zhu *et al.*, 2007; Chiao *et al.*, 2009; Ma, Band, *et al.*, 2014), the current study recruited participants from the

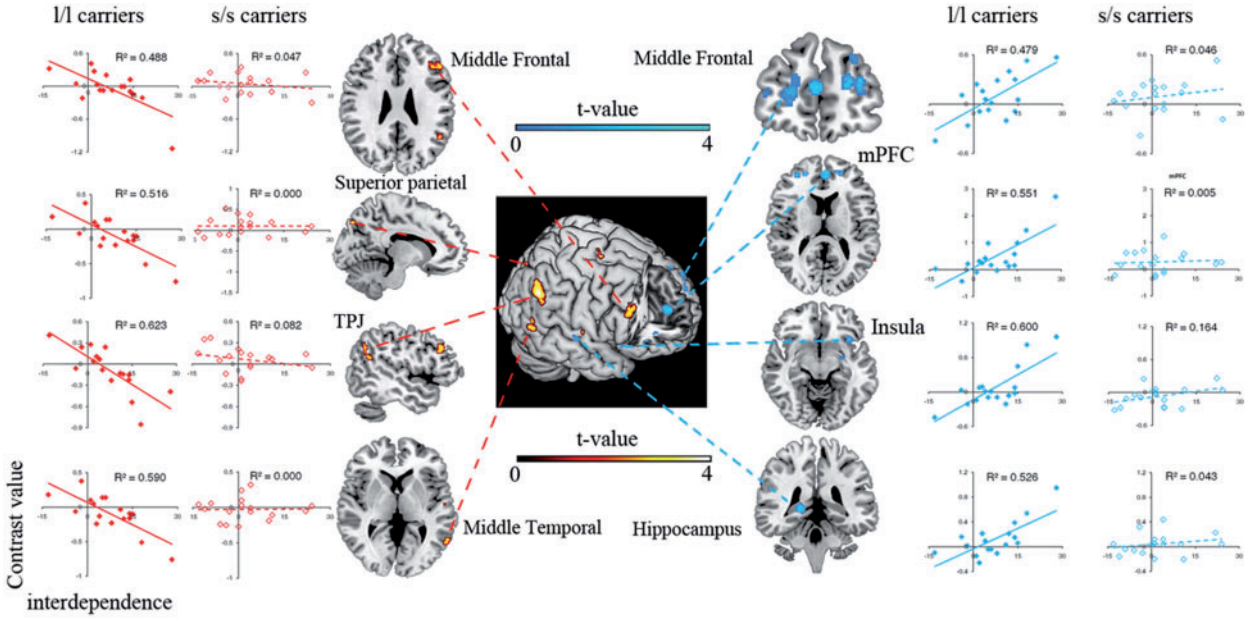

Fig. 1 Genotype differences in the association between the measure of interdependence and neural activity related to judgments of mental attributes of the self. The middle panel shows the brain regions in which the association between interdependence of self-construals and brain activity related to self- *vs* celebrity-judgments were significantly different between the two genotype groups, as identified in the hierarchical regression analysis. The *x*- and *y*-axes of each scatterplot index the interdependence scores and the contrast values of self- *vs* celebrity-judgments, respectively. Blue and red scatterplots illustrate the brain regions in which interdependence scores were respectively positively and negatively correlated with brain activities involved in self- *vs* celebrity-judgments in the l/l genotype group.

Table 3 Brain activations in simple regression and moderation analyses of the contrast of mother- *vs* celebrity-judgments

Dimension Region	x, y, z	T-value	cluster size
Simple regression analysis			
Mental attributes			
Positive correlation			
Insula (L)	−50, 20, −2	5.08	345
Middle Frontal (L) and mPFC	−20, 56, 30	4.72	555
	−6, 48, 38	3.39	
Insula (R)	46, 16, −4	4.13	280
Middle Frontal (R)	20, 54, 18	3.92	502
Negative correlation			
Precentral (R)	22, −28, 78	4.04	246
Superior Parietal (L)	−22, −62, 62	3.81	210
Superior Temporal (R)	56, −42, 14	3.90	150
Social attributes			
Positive correlation			
Superior Parietal (R)	12, −60, 68	4.56	416
Precuneus (R)	18, −66, 22	3.97	260
Fusiform (R)	32, −50, −18	3.96	114
Inferior Parietal (R)	48, −44, 28	3.92	282
Insular (R)	46, −16, 4	3.81	90
Inferior Frontal (R)	40, 36, 16	3.71	173
Superior Parietal (L)	−30, −40, 70	3.38	224
Negative correlation			
Frontal (L)	−32, 44, 18	4.26	247
Physical attributes			
Positive correlation			
Precentral (L)	−18, −12, 74	4.21	168
Negative correlation			
Middle Occipital (L)	−44, −70, −10	4.32	324
Lingual gyrus (L)	−4, −76, −12	4.13	262
Middle Occipital (R)	24, −92, −12	3.83	124
PCC	2, −54, 20	3.83	54
Moderation analysis			
Mental attributes			
Middle Frontal (L) and mPFC	−16, 52, 18	4.34	423
	−8, 54, 20	4.25	
Middle Frontal (R)	26, 44, 10	3.65	397
Insula (R)	38, 18, −12	3.39	50
Superior Parietal (R)	16, −78, 42	4.12	42

same cultural context to exclude effects such as language and environmental differences. Cultural influences were scrutinized by examining variations of neural activity as a function of interdependence of self-construals across individuals. We assessed whether 5-HTTLPR modulates the association between cultural orientation in interdependent self-construals and brain activity underlying judgments on personal attributes of the self and mother. We first demonstrated that, across all participants, the measure of interdependence was correlated with the activity during the processing of the self and mother in the social brain network including the mPFC, TPJ, superior parietal cortex, insula, hippocampus, etc. Thus the brain activity involved in social cognition varies across individuals with different levels of interdependence.

More importantly, we found that the association between interdependence and the social brain network activity was moderated by 5-HTTLPR polymorphism. The neural activity underlying self-reflection on personality traits was significantly associated with the measure of interdependence in l/l carriers but not in s/s carriers. This effect was evident in multiple brain regions and was true regardless of patterns (i.e. positive or negative) of correlation results. The moderator effects were not self-specific because similar effects were also observed with the association between self-reported interdependence and the neural activity related to reflection on mother's personality traits. These moderator effects were observed in two genotype groups who were comparable in gender, age, and education. Subjective evaluations of self-construals, anxiety traits, and self-esteem did not differ between the two genotype groups. Thus the differential association between interdependence and brain activity reflects essentially the influences of genetic variation rather than the effects of personal experiences or traits.

Our findings have several implications for understanding the effect of gene × culture interaction on human brain activity. First, previous cultural neuroscience studies have shown that activity in a specific brain region (e.g. mPFC in Chiao *et al.*, 2009; TPJ in Ma, Bang *et al.*, 2014) can be associated with a cultural trait (e.g. interdependence). The results of our simple regression analyses suggest that the

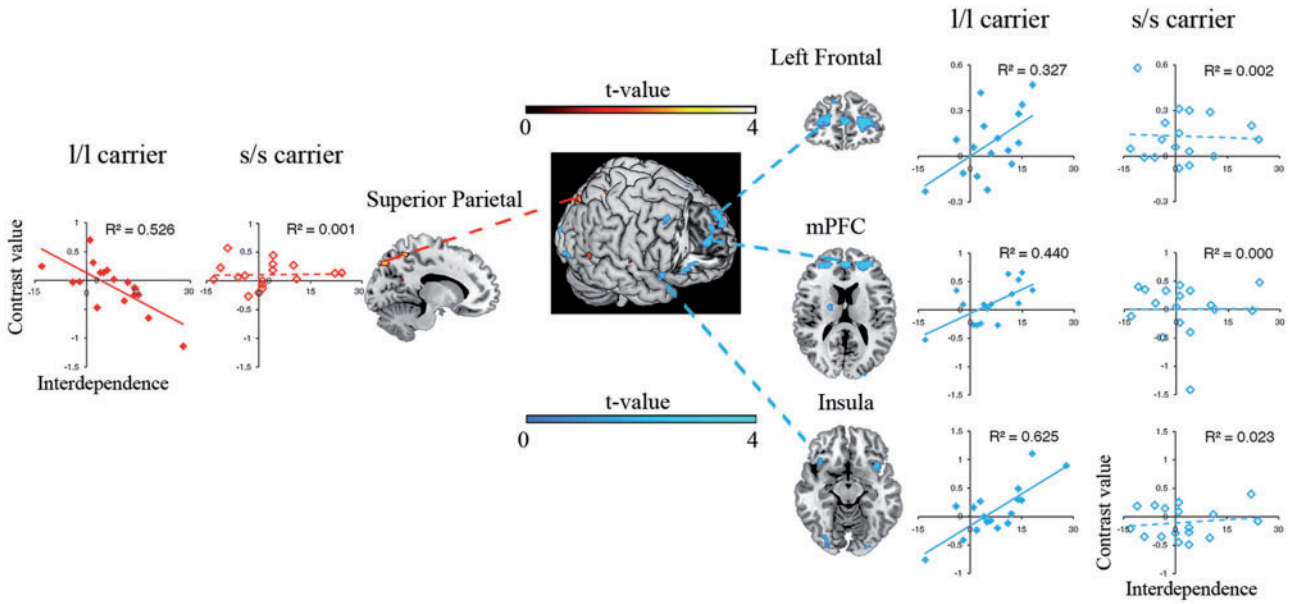

Fig. 2 Genotype differences in the association between the measure of interdependence and neural activity related to judgments of mental attributes of mother. The middle panel shows the brain regions in which the association between interdependence of self-construals and brain activity related to mother- *vs* celebrity-judgments were significantly different between the two genotype groups, as identified in the hierarchical regression analysis. The *x*- and *y*-axes of each scatterplot index the interdependence scores and the contrast values of mother- *vs* celebrity-judgments, respectively. Blue and red scatterplots illustrate the brain regions in which interdependence scores were, respectively, positively and negatively correlated with brain activities involved in mother- *vs* celebrity-judgments in the l/l genotype group.

activity in multiple brain regions in the social brain network during reflection on oneself and mother can vary significantly across individuals in the same cultural group with different levels of a cultural trait. Our results are consistent with the previous findings that two cultural groups showed distinct activities in multiple brain regions involved in varieties of social cognitive tasks (Han and Northoff, 2008; Han *et al.*, 2013) and suggest that human cultural experiences may shape multiple brain regions underlying social cognitive processing.

Second, our findings suggest that the association between a cultural trait and brain activity involved in social cognition may differ even within a cultural population. The association between a cultural trait and neural activity in the social brain network may be constrained by a specific genetic polymorphism. Moreover, the moderator effects of 5-HTTLPR were evident in the brain areas that constitute the social brain network rather than limited to a specific brain region. This network has been shown to be involved in self-reflection (e.g. mPFC and left frontal cortex, Kelley *et al.*, 2002; Zhu *et al.*, 2007; Han *et al.*, 2008; 2010; Wang *et al.*, 2012), episodic memory (e.g. hippocampus, Tulving and Markowitsch, 1998; Cavanna and Trimble, 2006), mental attribution of others (e.g. mPFC and TPJ, Gallagher *et al.*, 2000; Saxe and Kanwisher, 2003), causal attribution of physical attributes (mPFC, cerebellum, Han *et al.*, 2011), etc. Similarly, previous research found that neural responses to neutral words were modulated by 5-HTTLPR polymorphism in multiple brain regions such as the superior parietal lobule, superior temporal gyrus, inferior frontal gyrus, precentral gyrus and cingulate (Canli *et al.*, 2005). Life stress also interact with 5-HTTLPR polymorphism to modulate the resting activity in multiple brain regions including the ACC, middle frontal cortex, caudate nucleus, etc (Canli *et al.*, 2006). Given that different brain regions in the social brain network contribute to distinct (e.g. cognitive and affective) components of social cognition, it may be speculated that the 5-HTTLPR may play a broad role in moderation of the relationship between self-construals and multiple processes of social cognition (e.g. reflection on the self and mother in the current work).

Third, our findings suggest that the effect of gene × culture interaction on human brain activity may vary across different tasks. The current study observed the moderator effects only in the brain activity during judgments on mental attributes of the self and mother but not during judgments on the physical and social attributes. Thus it appears that the neural substrates underlying self-reflection on mental attributes are vulnerable to gene × culture interaction. Alternatively, since only the words used in the mental judgment have clear negative or positive emotional values, it is possible that the gene × culture interaction might be more sensitive to emotion-related self-referential processing. This account is consistent with previous findings that the effect of 5-HTTLPR mainly focused on emotional processes, such as mood disorders (Lesch *et al.*, 1996; Sen *et al.*, 2004; Munafò *et al.*, 2005), amygdala reactivity to emotional stimuli (Hariri *et al.*, 2002; Canli *et al.*, 2005) and dACC/insular activity related to negative self-reflection (Ma, Li, *et al.*, 2014).

Forth, our findings suggest a possible way of gene × culture interaction on human brain and mind. Gene-culture coevolution theory (Boyd and Richerson, 1985) proposes that culture influences environments in which genetic selection occurs. In support of this theory, it has been shown that a cultural trait can influence the spread of a gene in a specific sociocultural environment (see Laland *et al.*, 2010 for a review). In addition, cultures interact with genes to influence human behaviors such that self-reported emotional support seeking behaviors show opposite patterns of genetic variation in Western and East Asian cultures (Kim *et al.*, 2010, 2011). While recent research suggests that genes are changing as a result of cultural variations and cultural evolution often plays the leading role during human evolution (Richerson *et al.*, 2010), the current study suggests another way of gene × culture interaction, that is, individual differences in the association between a cultural trait and brain activity underlying social cognition are constrained by a specific genetic polymorphism. Such a pattern of gene × culture interaction may provide a biological basis of the assumption that genetic polymorphism influence the probability that a particular cultural trait will be adopted by individuals (Feldman and Laland, 1996).

Our findings also raise a few interesting questions for future research. We found evidence for genetic moderation of the association between interdependence of self-construals and the social brain

network only in Chinese participants. Previous research has shown that the s allele frequency is different across different cultural groups, being much higher in Asian than Caucasian populations (Kunugi *et al.*, 1997). The interdependence of self-construals dominates East Asian populations whereas the independence of self-construals is encouraged in Western populations (Markus and Kitayama, 1991). Given these biological and cultural differences among populations, future research should address whether the genetic moderation effect observed in our work also exists in Western cultural contexts.

The current work reported the association between self-construals and brain activity during reflection on the self and mother but did not address why the correlation between interdependence of self-construal and neural activity was positive in some brain regions but negative in other brain regions in l/l allele carriers. It is likely that the distinct patterns of associations between a cultural trait and neural activity in the social brain network may reflect the fact that a specific cultural trait may facilitate one neural strategy but inhibit another neural strategy related to social cognition. This may be tested in future research.

Finally, the previous research found that depressive symptoms in s allele carriers are more sensitive to life experiences (e.g. Caspi *et al.*, 2003), whereas the current work reported evidence for the association between a cultural trait and neural activity in the social brain network in l/l but not s/s carriers. There are at least two possible reasons for these different observations. One possibility is that s/s carriers in Chinese population adopt the interdependence to a strong degree such that s/s genotype individuals showed little variation of the association between interdependent self-construals and the social brain network activity. However, this may not be the case because self-report interdependence did not differ significantly between s/s and l/l carriers (the mean rating scores of interdependence was even higher in l/l than s/s carriers). Alternatively, it is possible that l/l carriers as a minority in Chinese population might be more sensitive to a cultural trait (i.e. interdependence) than s/s carriers and thus showed greater variations of the association between interdependent self-construals. This implicates that life experiences associated with an individual and cultural traits linked to a population may interact with genes in different fashions. This speculation may be clarified in future research.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

Conflict of Interest

None declared.

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