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 , 2002; Zhu , 2007; Heatherton , 2006; Han , 2008, 2010; Ma and Han, 2011, Jenkins and Mitchell, 2011; Sul , 2012; Ma, Bang , 2014). Attributing mental states such as desires and beliefs to others engages the dorsal medial prefrontal cortex (dmPFC), TPJ and precuneus (Gallagher , 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 , 2011; Falk , 2010).

cognition and behaviors such as emotional support seeking (Kim , 2010, 2011) and willingness to volunteer for prosocial causes (Sasaki , 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, , 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- celebrity-judgments) or of one's mother (defined in the contrast of mother- 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 , 2012; Ma, Bang, , 2014). The TPJ is engaged during self-reflection on social roles (Sul , 2012; Ma, Bang, , 2014) and the precuneus, superior temporal sulcus and cerebellum are involved in self-reflection on physical attributes (Jenkins and Mitchell, 2011; Ma, Bang , 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 , 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 , 2014) and genetic (Ma, Li , 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 , 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

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 , 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: ,. , ; 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

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. 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-celebrity-judgments in the bilateral insula, mPFC, and bilateral middle/superior frontal cortex (Table 3). The measure of interdepend-

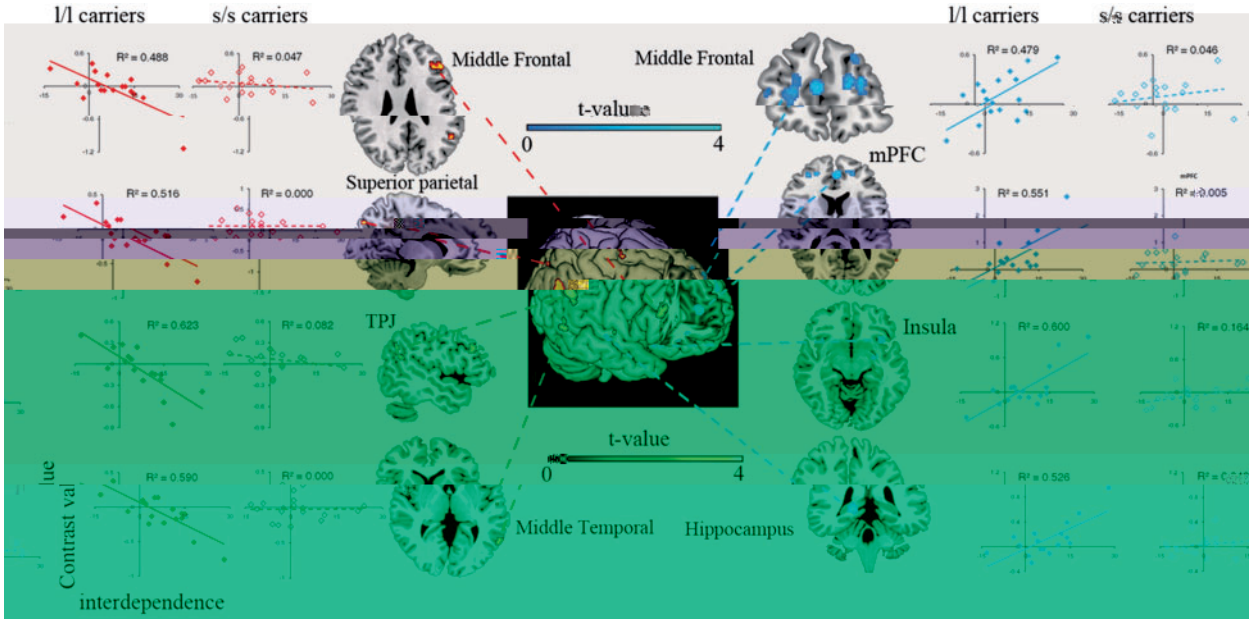

Fig. 1 Genotype differences in the association between the measure of interdependence and neural activity related to judgments of mental attributes of the self. The middle panel shows the brain regions in which the association between interdependence of self-construals and brain activity related to self- *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 , 2009; TPJ in Ma, Bang , 2014) can be associated with a cultural trait (e.g. interdependence). The results of our simple regression analyses suggest that the

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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 , 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 , 2002; Zhu , 2007; Han , 2008; 2010; Wang , 2012), episodic memory (e.g. hippocampus, Tulving and Markowitsch, 1998; Cavanna and Trimble, 2006), mental attribution of others (e.g. mPFC and TPJ, Gallagher , 2000; Saxe and Kanwisher, 2003), causal attribution of physical attributes (mPFC, cerebellum, Han , 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 , 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 , 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).

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 , 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 , 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 online.

Conflict of Interest

None declared.

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