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Invited Article

Genetics

A potential ethnic difference in the association between 5-HTTLPR polymorphisms and the brain default mode network

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Abstract The serotonin-transporter-linked polymorphic region (5-HTTLPR) is associated with mood disorders. This association is thought to be due to amygdala hyper-responsiveness to negative emotional stimuli as a result of reduced frontal cortical control. In Caucasians, the short form is associated with this effect, but in Han Chinese we recently found that the long form is involved. Serotonin receptors have rich expression in default mode network (DMN) regions and the recent studies have found an association between the short form of the 5-HTTLPR and DMN functional connectivity (FC) in Caucasians. The present study has investigated whether there may also be an ethnic difference in this influence of 5-HTTLPR on the DMN. We recruited 233 young Han Chinese subjects and calculated the resting-state default-network FC. Our study found that the L carriers had decreased FC in the bilateral medial prefrontal cortex, right parahippocampal gyrus, left middle temporal gyrus, and increased FC in left precuneus (Pcu) compared to SS. The PCC-Pcu FC in L carriers was significantly negatively correlated with the depression scores. Our findings, therefore, suggest that there is also a difference between Caucasian and Han Chinese subjects in the association between the different forms of the 5-HTTLPR and DMN functional connectivity.

Keywords 5-HTTLPR · Default mode network · Ethnic difference · Resting-state functional connectivity

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1 Introduction

The serotonin-transporter-linked polymorphic region (5-HTTLPR), which affects 5-HTT gene transcription and modulates the serotonergic activity, comprises two variants: the long (L, 16 copies of a 20–23 base pair repeat unit) and the short (S, 14 copies) allele, and is an important candidate gene for understanding the gene mechanism of mood disorders [1, 2]. A number of studies have presented an important role of ethnic background on the effects of the short and long forms of 5-HTTLPR. These studies have shown that firstly in Asians, the L allele of 5-HTTLPR confers a higher risk for depression and is also associated with a reduced response to antidepressant drugs [3–6], whereas in Caucasians, it is the S rather than that the L allele which exhibits this link [7–11]. Secondly, there exists an ethnic difference in the allele distribution of

5-HTTLPR with the S allele frequency being significantly higher in Asians than that in Caucasians [9]. Thirdly, whereas the S allele is associated with amygdala hyperactivation in Caucasian subjects during a classical emotional processing task [12–14], in Asian subjects, this same 5-HTTLPR effect is associated with the L allele [15, 16]. The amygdala-frontal neural network is important for understanding the pathogenesis of mood disorders and our previous study found that the effect of 5-HTTLPR on the amygdala-PFC functional and structural coupling was also varied across racial or ethnic groups, decreased coupling observed with L allele carriers in HAN Chinese [17], but S allele ones in Caucasian/heterogeneous subjects [18, 19]. To date, the studies have mainly focused on the limbic-prefrontal cortex system and it is not clear whether there are also different effects of 5-HTTLPR on the other neural networks associated with mood disorders.

The brain default mode network (DMN), a fundamental resting-state network, shows high activity during rest and internally directed thoughts but becomes deactivated during tasks involving externally directed attention [20, 21]. This so called 'task-negative' intrinsic network has been implicated in self-referential and introspective processing, such as during rumination, personal future planning and episodic memory [20–22]. The DMN includes medial prefrontal cortex (mPFC), lateral parietal cortex, posterior cingulate cortex (PCC), parahippocampal gyrus (PHG), and retrosplenial and inferior temporal cortex [22–24]. Based on its important role in emotion processing and the heritability of the functional connectivity (FC) in DMN [25], it has been considered as a plausible endophenotype to link gene polymorphisms and mental disorders [20, 21]. Serotonin receptors are highly expressed in the DMN [26] and recently, a study in Caucasian subjects has reported that S allele homozygotes of 5-HTTLPR had the weakest resting-state FC between the posterior hub of the DMN (PCC) and mPFC [27]. However, it is currently unclear whether this is also the case with Asian subjects or whether a similar ethnic difference exists for 5-HTTLPR effects on DMN as has been found for amygdala-frontal connections.

The current study therefore investigated the association between DMN FC and 5-HTTLPR in a large population of Han Chinese using resting-state functional magnetic resonance imaging (rsfMRI). We chose the PCC as the seed region and calculated the functional connectivity of the PCC with other DMN regions. Based on the previous studies, we hypothesized that the 5-HTTLPR alleles would be associated with different strengths of FC in the DMN and that in Han Chinese subjects, in contrast to Caucasians, it would be the L allele which would be linked with reduced FC between PCC and some other DMN regions. In addition, until now, many studies, including our previous research, have shown that the 5-HTTLPR variants were associated with anxiety-related scores and depression [6, 7, 11, 17]. In light of the link between the anxiety/depression measures and functional connectivity [18, 28–31] and the heritability of DMN FC [25], it seems interesting to study whether the association between anxiety/depression scores and FC in DMN was moderated by 5-HTTLPR genotypes. We expected to find the distinct correlation between behavior scores and DMN FC in different genotypes of 5-HTTLPR variants.

2 Materials and methods

2.1 Subjects

All participants in this study were Han Chinese and were recruited by advertisement. Written informed consent was signed by all the subjects. The study was approved by the local Medical Research Ethics Committee of the Tianjin Medical University. Before the formal experiment, we carefully asked the subjects to insure that they had no family history of psychiatric disorder, drug or alcohol abuse, psychiatric or neurological illness, head trauma, and no contraindications to MRI scanning, although no clinical tools (SCID) were used to screen. The Beck Depression Inventory-II (BDI-II) was used to measure depression levels, while the State-Trait Anxiety Inventory (STAI) and the Self-Rating Anxiety Scale (SAS) were used to measure anxiety. This study included 239 participants, and the details for the participants' inclusion had been described in our previous study [17].

2.2 Genotyping

Genomic DNA was extracted from whole blood by using the EZgeneTM Blood gDNA Miniprep Kit (Biomiga Inc, San Diego, CA, USA). Then, the PCR and ligation detection reaction (LDR) methods [32, 33] were used to genotype the 5-HTTLPR polymorphisms for each participant. The PCR primer sequences of 5-HTTLPR were as follows: forward: 5′-AACCCCTAATGTCCCTACTGC-3′ and reverse: 5′-GGAGATCCTGGGAGAGGTG-3′. PCR was carried out in 20 μL volume samples that contained 1 μL genomic DNA, 0.4 μL primer mixture, 2 μL dNTPs, 0.6 μL Mg^{2+}, 2 μL buffer, 4 μL Q-Solution, and 0.3 μL Taq DNA polymerase. The amplification protocol consisted of an initial denaturation and enzyme activation phase at 95 °C for 15 min followed by 35 cycles of denaturation at 94 °C for 30 s, annealing at 62 °C for 5-HTTLPR for 1 min and 30 s, extension at 72 °C for 1 min, and then a final extension at 72 °C for 7 min. The PCR products were verified in 3 % agarose gels that had been stained with ethidium bromide to regulate the amount of DNA that was added to the LDR. The polymorphisms of

5-HTTLPR could be obtained by the PCR products. Six subjects were excluded for failure of genotyping.

2.3 MRI acquisition

MRI data were acquired on a 3.0 T GE scanner (General Electric; Milwaukee, WI, USA). During rsfMRI, the volunteers were instructed to lie quietly without falling asleep and to keep their eyes closed. A single-shot, gradient-echo, echo-planar-imaging sequence was used to collect the fMRI data with 180 volumes, and every volume included 40 slices. The repetition time (TR) and echo time (TE) for the rsfMRI scanning were 2,000 and 30 ms, respectively. Other parameters included the slice thickness (4 mm), the flip angle (90°), the FOV (240 mm × 240 mm), and the matrix (64 × 64). T1-weighted images were obtained by using a brain volume sequence with the following parameters: TR/TE = 8.1/3.1 ms, flip angle = 13°, matrix = 256 × 256, FOV = 256 mm × 256 mm, 176 sagittal slices, and slice thickness = 1 mm.

2.4 fMRI preprocessing

First, two experienced radiologists checked the raw fMRI data, blind to any gene polymorphism information and excluded the subjects whose raw data had serious signal loss or interslice motion artifacts (nine subjects). The preprocessing process was then carried out using DPARSF (http://www.restfmri.net/forum/DPARSF). The first ten volumes were discarded and a slice-timing correction was applied. A correction for head motion was then performed, which excluded participants who had maximum displacements along the x, y, or z direction greater than 2 mm, or maximum rotations greater than 2° around the x, y, or z axis (11 subjects). Subsequent preprocessing included spatial normalizing to the Montreal Neurological Institute (MNI) space and smoothing using a 4-mm Gaussian Kernel. Linear regression was then conducted to avoid the potential effects of head motion, linear drift, white matter, cerebrospinal fluid, and global signal. Finally, the fMRI data were temporally filtered with a band-pass filter of 0.01–0.08 Hz.

2.5 DMN definition

We chose the PCC which is a hub in the DMN [34] as the seed region and defined it as a 6 mm cubic volume at the central MNI coordinate: $(x, y, z) = (0, -52, 30)$ as in the previous studies [35]. Then, the average time series for the seed region was calculated by averaging the time series in the PCC, and the correlation coefficients were calculated between this and the time series in the other voxels. Fisher r-to-z transformation was used to transform resulting correlation maps to Z values. A one sample t test was performed on the resulting Z maps for all subjects to obtain the DMN at the threshold of $P < 0.05$, with a family-wise error correction.

2.6 Statistical analysis

Based on the previous studies in the Asian population [15] and the genotype distribution of 5-HTTLPR in our subjects, we divided the subjects into two groups (L carriers (LL + LS) and SS homozygotes). Then a two sample t test was carried out to find the difference in the FC of PCC between the L carriers and S homozygotes in a voxel-wise manner, with age and gender as covariates. A Monte Carlo simulation was used for multiple comparisons correction and results were obtained which survived under a corrected $P < 0.05$ (the parameters for AlphaSim program in REST, http://www.restfmri.net/forum/, where: P value at each voxel = 0.005, cluster connection radius r mm = 5, FWHM = 4 mm, number of Monte Carlo simulations = 5000, with a mask from one sample t test on the resulting Z maps). Two sample t tests were also conducted to compare the BDI-II, SAS, STAI-state, and STAI-trait scores between the different groups of 5-HTTLPR. Correlations between scores on the depression and anxiety questionnaires and functional connectivity between DMN regions were carried out using *Pearson* tests in the two different genotype groups.

3 Results

In the current study, 233 participants were included in the final gene behavior analysis and 213 participants were included in the final functional connectivity analysis. The 233 subjects (132 females, mean age: 22.76, age range: 18–29 year old) were divided into two groups: L carriers (LL: 15 and LS: 85) and S homozygotes (SS: 133). As our previous study has reported [17], the 5-HTTLPR variants significantly influenced the state anxiety ($P = 0.032$) of STAI measure and tended to influence the trait anxiety ($P = 0.063$) of the STAI measure. However, the 5-HTTLPR polymorphisms showed no influence on the SAS score ($P = 0.629$) and BDI-II score ($P = 0.307$). Specifically, the L carriers of 5-HTTLPR had significantly higher state anxiety scores (L carriers: mean ± SD 31.94 ± 6.06; SS: 30.05 ± 6.27) and tended to have higher trait anxiety (L carriers: 35.67 ± 6.48; SS: 33.93 ± 6.28) than S homozygotes. In addition, two genotypes showed no significant differences for age and gender.

Resting-state FC analysis showed that the PCC was positively correlated with the regions involved in DMN, such as mPFC, superior frontal cortex, orbitofrontal cortex, PHG, inferior and medial temporal gyri, retrosplenial and lateral parietal cortices, and cerebellum [24], as shown in Fig. 1a. There was also a significant impact of 5-HTTLPR

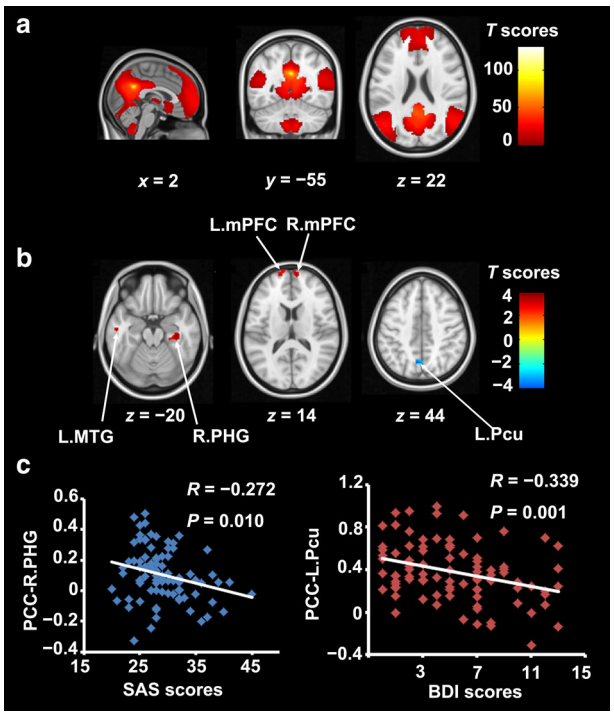

Fig. 1 The DMN pattern obtained from rsfMRI and the results for resting-state functional connectivity analysis. **a** The default-network functional connectivity. **b** The alterations in default-network functional connectivity between two genotypes of 5-HTTLPR. The *warm color* indicated the regions showing decreased connectivity and the *cool color* indicated the regions showing increased connectivity in L carriers than S homozygotes. **c** The association between the PCC-R.PHG coupling and the SAS scores and between the PCC-L.Pcu link and BDI scores in L carriers. *L* left, *R* right. *SAS* Self-Rating Anxiety Scale, *BDI* Beck Depression Inventory-II

on DMN functional connectivity. The L carriers (LL: 15 and LS: 75) of 5-HTTLPR showed significantly reduced functional connectivity in the bilateral mPFC, the right PHG and left middle temporal gyrus (MTG) compared with the S homozygotes (SS: 123). On the other hand, the L carriers exhibited greater functional connectivity in left precuneus (Pcu) than the S homozygotes (Table 1, Fig. 1b).

Correlation analysis between scores on behavioral tests and functional connectivity between the PCC and the left and right mPFC, right PHG, left MTG, and left Pcu revealed a significantly (corrected threshold $P = 0.05/20$, Bonferroni correction for multiple testing) negative association between BDI-II scores and the PCC-Pcu ($P = 0.001$) only in L carriers (see Table 2; Fig. 1c). In addition, the SAS scores tended to be correlated with the PCC-PHG ($P = 0.01$) in L carriers.

4 Discussion and conclusions

The current study investigated the impact of 5-HTTLPR gene polymorphisms on the functional connectivity of DMN in Han Chinese subjects and generally confirmed our hypothesis that 5-HTTLPR L allele carriers would have reduced DMN functional connectivity compared to S allele homozygotes. In particular, the L carriers showed decreased functional connectivity between the PCC and the bilateral mPFC, left MTG and right PHG, but increased FC between the PCC and left Pcu. Altered functional connectivity between these DMN regions occurred frequently in mood disorders [20, 21, 36, 37] and we found that in L carriers, but not in S homozygotes, the strength of functional connections between the PCC and the left Pcu was significantly negatively correlated with depression scores and the PCC-L.Pcu connectivity tended to be correlated with anxiety scores.

The inhibitory 5-HT_{1A} receptor is highly expressed in the frontal, parietal, and temporal cortices [26], which are core regions within the DMN, and there is also an association between 5-HT_{1A} receptor binding and DMN during resting-state and task-dependent activity [35]. The previous research in healthy volunteers has found that 5-HTTLPR variants influenced 5-HT_{1A} receptor binding potential in widespread brain regions, including the frontal cortex, temporal lobe, and parietal cortex [38]. On the other hand, the research has also shown the evidence for widespread binding of the excitatory 5-HT_{2A} receptor in frontal, parietal, and temporal DMN regions [26] and the recent study has found that the hallucinogen, psilocybin, which is a 5-HT_{2A} receptor antagonist, reduced functional connectivity between ventromedial prefrontal cortex and PCC [39]. Other studies which used acute tryptophan depletion to modulate the 5-HT level in healthy participants have also reported reduced fractional amplitude of low-frequency fluctuation in the mPFC and PCC [40]. Functional connectivity between the mPFC and PCC/Pcu is altered in a number of psychiatric disorders during both the resting-state and self-processing tasks [41]. Thus, 5-HTTLPR polymorphisms may influence 5-HT concentrations and interact with both inhibitory and excitatory receptors to influence mood and self-processing via the cortical midline components of the DMN. However, in the current study, we did not find a significant correlation between the PCC-mPFC functional connection and anxiety in L carriers.

Our results also showed that the L allele of 5-HTTLPR was associated with reduced functional connectivity between the PCC and PHG and MTG but increased connectivity with the Pcu. For the PCC functional connection with the PHG, there was a negative trend of correlation with self-rated anxiety (SAS score) in the L carriers but not in the S homozygotes, although this correlation could not survived under an overall strict corrected $P = 0.0025$. Thus, higher anxiety scores were associated with weaker functional connection strength in this PCC-PHG link. The PHG plays an important role in emotion regulation and memory [36] and novelty detection [42] and along with the

Table 1 Default-network functional connectivity in the different 5-HTTLPR genotypes

Brain regions	K	*T*	*Z*	MNI coordinates			Genotypes, mean (SD)	
				x	*y*	*z*	L carriers	S homozygotes
SS > L carriers								
L.mPFC	77	3.20	3.16	−10	72	16	0.27 (0.26)	0.39 (0.22)
R.mPFC	42	3.21	3.17	6	68	16	0.33 (0.31)	0.46 (0.27)
R.PHG	158	3.87	3.80	34	−26	−18	0.11 (0.17)	0.19 (0.14)
L.MTG	28	3.22	3.18	−54	−14	−18	0.37 (0.28)	0.49 (0.27)
L carriers > SS								
L.Pcu	58	3.91	3.83	−6	−64	44	0.38 (0.27)	0.23 (0.29)

All regions survived under the corrected threshold of $P < 0.05$. *K* cluster size (the number of voxels), *mPFC* medial prefrontal cortex, *PHG* parahippocampal gyrus, *MTG* middle temporal gyrus, *Pcu* precuneus, *L* left, *R* right, *SD* standard deviation

Table 2 Correlations between altered PCC functional connectivity and behavior scores for L carriers and S homozygotes

	BDI *R* value (*P* value)		SAS *R* value (*P* value)		STAI_state *R* value (*P* value)		STAI_trait *R* value (*P* value)	
	L carriers	S homozygotes	L carriers	S homozygotes	L carriers	S homozygotes	L carriers	S homozygotes
L.mPFC	−0.052	−0.040	−0.072	−0.004	−0.058	−0.136	0.018	−0.081
	(0. 632)	(0.664)	(0.504)	(0.965)	(0.590)	(0.127)	(0.867)	(0.375)
R.mPFC	−0.139	−0.003	−0.153	0.070	−0.086	0.021	−0.093	0.001
	(0.196)	(0.971)	(0.154)	(0.447)	(0.428)	(0.821)	(0.389)	(0.994)
R.PHG	−0.108	0.033	−0.272	−0.040	−0.106	0.014	0.036	0.051
	(0.316)	(0.721)	(0.010)	(0.661)	(0.326)	(0.881)	(0.739)	(0.578)
L.MTG	−0.126	0.021	0.156	−0.114	−0.044	−0.146	0.075	−0.145
	(0.242)	(0.821)	(0.148)	(0.214)	(0.683)	(0.111)	(0.489)	(0.112)
L.Pcu	−0.339	−0.058	−0.101	0.030	−0.030	0.068	0.075	0.024
	(0.001)	(0.531)	(0.351)	(0.747)	(0.785)	(0.456)	(0.488)	(0.798)

A *P* value of <0.0025 was considered significant (i.e. corrected for multiple tests)

amygdala and hippocampus shows increased responses to emotional stimuli in panic disorder [43, 44] and specific phobias [45]. Thus, the reduced functional connectivity between the PCC and PHG in L carriers may represent an increased susceptibility to anxiety disorders and associated emotional and cognitive dysfunction.

The increased functional connectivity between the PCC and left Pcu in L carriers was strongly negatively correlated with depression scores. Thus, the higher depression scores were associated with weaker functional connectivity in this PCC-Pcu link. The PCC-Pcu is considered to play an important role in the DMN and interacts strongly with all other regions within it [46]. The Pcu is involved with a range of behavioral functions, including emotion responses, working memory, and self-processing [47], and both PCC and Pcu are activated during autobiographical memory retrieval [48]. Two recent studies on Asian subjects have reported altered functional connectivity between PCC and Pcu in depression patients [49, 50]. Thus, our current findings suggest that the L carriers of the 5-HTTLPR may have a greater susceptibility to depression related changes in this core area of the DMN, although we did not find the overall evidence for L carriers having higher depression scores than S homozygotes.

Our study also found evidence of reduced PCC to left MTG functional connectivity in L carriers, although this was not correlated with either anxiety or depression scores. The MTG is also associated with the serotonin system [51, 52] and has been implicated in emotional perception and emotional regulation [53, 54]. Both schizophrenia and depression patients had smaller gray matter volume in the MTG and abnormal MTG–DMN functional connectivity which may relate to negative thoughts in relation to self [55, 56].

Overall our results in Han Chinese subjects have shown that L carriers of the 5-HTTLPR had decreased functional connectivity within the DMN, with the exception of the PCC-Pcu. However, these findings were contrary to those of the recent report that the S allele of 5-HTTLPR was associated with the reduced functional connectivity between posterior DMN and mPFC in Caucasians [27]. We have found similar evidence for this ethnic difference in 5-HTTLPR for amygdala-frontal connectivity, with again the L carriers exhibiting reduced functional and structural connectivity compared with S homozygotes in Han Chinese subjects [17]

but with the S carriers showing this pattern in Caucasian subjects [18]. Thus, our current study suggests that the ethnic difference between the influence of the short and long forms of the 5-HTTLPR may extend to multiple brain systems associated with emotional and cognitive processing as well as psychiatric disorders. Another recent study on Chinese subjects has found greater activity in the mPFC of Han Chinese subjects with the S allele of 5-HTTLPR, although this correlated with higher levels of distressed feelings [57]. This suggests that the L allele in Han Chinese subjects is associated with both reduced mPFC activity and functional connectivity with the PCC, although the link with different emotional traits is less clear at this point. Clearly, further confirmation of an ethnic difference of 5-HTTLPR on DMN activity and functional connectivity between Han Chinese and Caucasian subjects is required, along with the behavioral consequences. The previous study on Caucasian subjects was also considered as a preliminary research on the DMN with a relatively small number of subjects including adolescents [27]. As far as we know, the ethnic difference in the effect of 5-HTTLPR polymorphisms between the Asians and the Caucasians is common and reflects in the association with the depression disorder [6, 7], the response to antidepressant treatment [3, 10], the amygdala activation to the emotional stimuli [12, 15], and the neural circuit related to the emotional processing [17, 18]. The different allele distribution of 5-HTTLPR, the genetic background, environmental, and culture factors, might give rise to such ethnic difference. However, until now, we have been unsure what actually causes this ethnic difference in the impact of 5-HTTLPR genotypes. Our work was an initial study and found the different effect of 5-HTTLPR on the default mode network between the Han Chinese and the Caucasian, further micro and macro researches are needed to identify the biochemical mechanism and environmental effect for the ethnic difference.

In summary, we found potential evidence that in Han Chinese subjects reduced functional connectivity occurring in a number of DMN regions was associated with the long allele of the 5-HTTLPR, whereas the short allele may be involved with this same effect in Caucasian subjects. This is in agreement with a similar ethnic difference for functional connectivity involving the amygdala and frontal cortex and therefore suggests a potential widespread different impact of these 5-HTTLPR polymorphisms on brain function in Han Chinese and Caucasian populations. These differences may reflect altered functional interactions between serotonin signaling and emotional and cognitive function in Han Chinese and Caucasian populations with potential implications for pharmacological treatments of mood disorders. The functional consequences of this ethnic difference in the effects of 5-HTTLPR are clearly an important area for further investigation.

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