Genetic and neural correlates of romantic relationship satisfaction

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Abstract

Romantic relationship satisfaction (RRS) is important for mental/physical health but varies greatly across individuals. To date, we have known little about the biological (genetic and neural) correlates of RRS. We tested the hypothesis that the serotonin transporter promoter polymorphism (5-HTTLPR), the promoter region of the gene SLC6A4 that codes for the serotonin transporter protein, is associated with individuals' RRS. Moreover, we investigated neural activity that mediates 5-HTTLPR association with RRS by scanning short-short (s/s) and long-long (l/l) homozygotes of 5-HTTLPR, using functional MRI, during a Cyberball game that resulted in social exclusion. l/l compared with s/s allele carriers reported higher RRS but lower social interaction anxiety. l/l compared with s/s carriers showed stronger activity in the right ventral prefrontal cortex (RVPFC) and stronger functional connectivity between the dorsal and rostral ACC when being excluded from the Cyberball game. Moreover, the 5-HTTLPR association with RRS was mediated by the RVPFC activity and the 5-HTTLPR association with social interaction anxiety was mediated by both the dorsal–rostral ACC connectivity and RVPFC activity. Our findings suggest that 5-HTTLPR is associated with satisfaction of one's own romantic relationships and this association is mediated by the neural activity in the brain region related to emotion regulation.

Key words: 5-HTTLPR; fMRI; functional connectivity; romantic relationship satisfaction; ventral prefrontal cortex

Introduction

Mutually voluntary interactions between romantic partners constitute one of the most important interpersonal relationships in humans. Psychology and medical care research has shown that higher romantic relationship satisfaction (RRS) is associated with greater relationship stability and lower rates of relationship dissolution (Gottman and Levenson, 1992). Higher RRS also predicts higher levels of well-being and mental/physical health (Prigerson *et al*., 1999). It is thus of wide interests to investigate what psychological traits influence RRS. Meta-analyses have revealed that greater RRS is associated with higher emotional stability, agreeableness, conscientiousness, extraversion and openness (Heller *et al*., 2004) and higher levels of emotional intelligence (Malouff *et al*., 2014). Higher levels of personality traits in one partner are also associated with higher levels of relationship satisfaction in the other partner (Malouff *et al*., 2010).

Despite the significance of RRS for well-being and health, to date, we have known little about the biological (genetic and neural) correlates of subjective feelings of one's own romantic relationships among young adults. This study tested the potential association between RRS and the serotonin transporter promoter polymorphism (5-HTTLPR)—the promoter region of the gene SLC6A4 that codes for the serotonin transporter protein. The 5-HTTLPR has a short and a long variant with the short variant producing less serotonin transporter mRNA and protein than the long variant, leading to higher concentrations of serotonin in the synaptic cleft, greater association anxiety-related personality traits and higher risk for affective spectrum disorders (Lesch *et al*., 1996; Greenberg *et al*., 2000; Caspi *et al*., 2003; Canli and Lesch, 2007). Functional magnetic resonance imaging (fMRI) studies also reported evidence for enhanced neural responses to negative emotions in brain regions such as the amygdala, dorsal anterior cingulate cortex (dACC) and anterior

Received: 2 May 2015; **Revised:** 13 August 2015; **Accepted:** 14 September 2015

insula (AI) in the short than the long variant of 5-HTTLPR (Hariri *et al.*, 2002; Canli *et al.*, 2005; Heinz *et al.*, 2005; Ma *et al.*, 2014).

Recent behavioral research has suggested an association between the 5-HTTLPR and individuals' affective responses related to marital partners. For example, Schoebi *et al.* (2012) asked married young couples with mean ages of 26.4 (wives) and 27.9 (husbands) years to report their affective states before and after marital discussions. It was found that, relative to spouses with the long-long (l/l) allele of the 5-HTTLPR, spouses carrying the short alleles of the 5-HTTLPR were more responsive to their partner's pre-interaction positive affect and anxiety. Of more relevance to this work, Haase *et al.* (2013) investigated whether the 5-HTTLPR moderates the association between negative and positive emotional behavior and changes in marital satisfaction over time in middle-aged and older adults aged between 40 and 70 years. They found that, for short-short (s/s) homozygotes of 5-HTTLPR but not l/l allele carriers, higher negative and lower positive emotional behavior at Time 1 predicted declines in marital satisfaction over time. Although these findings suggest that the 5-HTTLPR plays a role in marital satisfaction and related affective response in married adults, it is unclear whether the 5-HTTLPR is also associated with subjective feelings of the romantic relationships in unmarried young adults. Furthermore, it remains unknown whether and how the association between the 5-HTTLPR and feelings of one's own romantic relationships is mediated by emotion-related brain activity.

Building on the previous studies, this study had two goals. First, we tested a possible association between 5-HTTLPR and RRS. Given the fact that the short compared with long allele carriers of the 5-HTTLPR showed greater anxiety-related personality traits and higher risk for affective spectrum disorders (Lesch *et al.*, 1996; Greenberg *et al.*, 2000; Caspi *et al.*, 2003; Canli and Lesch, 2007) whereas the long compared with short allele carriers of 5-HTTLPR reported greater life satisfaction (De Neve, 2011), we hypothesized that the long compared with short allele carriers are more satisfied with their own romantic relationships. This hypothesis was tested by collecting self-report of romantic relationships in s/s and l/l allele carriers of the 5-HTTLPR who were in a romantic relationship but unmarried when being tested.

The second goal of this work was to investigate whether and how the difference in RRS between short and long variants of 5-HTTLPR, if any, is mediated by emotion-related brain activity. Besides the findings of increased emotional responses in the amygdala and dACC/AI in the short compared with long allele carriers (e.g. Hariri *et al.*, 2002; Canli *et al.*, 2005; Heinz *et al.*, 2005; Ma *et al.*, 2014, 2015), there has been evidence for the 5-HTTLPR genotype difference in emotion regulation. Walderhaug *et al.* (2010) reported behavioral evidence that the short compared long allele carriers of the 5-HTTLPR were more impulsive in a continuous performance test. Firk *et al.* (2013) showed brain imaging evidence that, during passive perception of negative emotional pictures, l/l compared with s/s allele carriers of the 5-HTTLPR showed greater activity in the lateral prefrontal cortex, a brain region that is engaged in emotion regulation (Ochsner and Gross, 2005). These findings, together with the fact that both anxiety-related trait and emotion regulation were associated with subjective well-being (Costa and McCrae, 1980; Gross and John, 2003), inspired us to test two competing hypotheses, i.e. either the brain activity related to emotional responses in the amygdala and dACC/AI or the brain activity related to emotion regulation in the lateral prefrontal cortex plays a key role in mediating the 5-HTTLPR association with RRS.

We adopted a social rejection paradigm (Eisenberger *et al.*, 2003) to test these competing hypotheses for a couple reasons. First, behavioral research has shown that the sensitivity to rejection by familiar and unfamiliar others is negatively correlated with satisfaction in relationships but positively associated with depressive symptoms (Ayduk *et al.*, 2001; Downey *et al.*, 1999). Therefore, emotional and neural responses induced by social rejection can be used as objective measures of sensitivity to rejection that influences romantic relationships (e.g. Downey *et al.*, 1999). Second, the previous fMRI studies have shown that social rejection activates a neural network in which the AI and rostral ACC (rACC) are related to distressed feelings due to social rejection (Eisenberger *et al.*, 2003; Eisenberger and Lieberman, 2004; Masten *et al.*, 2009; Way *et al.*, 2009; DeWall *et al.*, 2010; Masten *et al.*, 2011), the dACC is linked to both conflict monitoring and distress (Lieberman, 2007; Shackman *et al.*, 2011; Luo *et al.*, 2014, 2015), and the right ventrolateral prefrontal cortex (RVPFC) is involved in regulation of negative affective responses to social or painful threats (Eisenberger *et al.*, 2003; Wager *et al.*, 2004; Lieberman, 2007). Moreover, the functions of these brain regions are highly related to romantic relationships. For instance, adolescents in romantic relationships reported experiencing more conflict than other adolescents (Laursen, 1995). A romantic break-up is one of the main triggers of a major depressive disorder (Davila *et al.*, 2004; Harper and Welsh, 2007), and better self-regulation ability predicts greater relationship outcomes (Luchies *et al.*, 2011). Therefore, to record brain activity during social rejection allowed us to test whether the AI/dACC and RVPFC activity that has different functional significance mediates the association between the 5-HTTLPR and individuals' feelings of their own romantic relationships.

Using fMRI, we scanned a Chinese sample of s/s and l/l homozygotes of 5-HTTLPR whose dACC, AI and amygdala showed distinct responses to negative emotion (Ma *et al.*, 2014, 2015). We adopted a Cyberball game from the previous research (Eisenberger *et al.*, 2003; Masten *et al.*, 2011), in which participants were initially included in ball tossing with two unfamiliar individuals and were excluded at a later stage of the game. Previous studies have shown that being excluded from the Cyberball game induced distressed feelings and activated the emotion-related brain regions such as the dACC/rACC, AI and RVPFC (Eisenberger *et al.*, 2003; Eisenberger and Lieberman, 2004; Masten *et al.*, 2009, 2011). We asked participants to report their RRS before fMRI scanning. Brain activity in response to rejection by unfamiliar others during the Cyberball game was used to estimate participants' general sensitivity to social rejection. We were particularly interested in whether s/s and l/l allele carriers of 5-HTTLPR showed distinct neural responses to social rejection during the Cyberball game and which brain regions activated by social rejection mediate the difference in RRS between the two genotyped groups. To clarify these issues helps us to understand whether and how genetic influences on RRS are mediated by negative emotional responses (e.g. distress) or emotion regulation.

Materials and methods

Participants

A genotyped sample of 1532 Chinese university students were screened regarding their romantic relationships and other information 1–3 months before this fMRI study. All participants were neither married nor cohabiting. Forty-eight participants were randomly selected from those who reported to be in a romantic

relationship for the current fMRI experiment, including 24 homozygotes for the l allele (l/l genotype group) and 24 homozygotes for the s allele (s/s genotype group). All were screened again regarding their romantic relationships before fMRI scanning and 6 participants reported to be out of romantic relationships. Thus, the final behavioral and fMRI data analyses include 21 l/l and 21 s/s carriers. All participants were right handed, had normal or corrected-to-normal vision, and reported no abnormal neurological history. Gender, age and self-esteem did not differ significantly between s/s and l/l groups (see Table 1 for details). Informed consent was obtained from all participants before scanning. This study was approved by a local ethics committee.

DNA isolation and analysis

We used a PCR method (Ota *et al*., 2007) to determine the genotypes of 5-HTTLPR. In a total volume of 50 μl, about 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′-GCATCCCCCATTAT CCCCCCCT-3′ and reverse 5′-AGGCTTGGAGGCCGGGATGC-3′) at final concentration of 200 nM. Thermal cycling consisted of a 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, the 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.

Stimuli and procedure

Before fMRI scanning, participants were asked to complete the Interaction Anxiousness Scale (IAS, Leary and Kowalski, 1993) and the Relationship Assessment Scale (RAS, Hendrick, 1988) to estimate their social interaction anxiety and satisfaction with romantic relationships, respectively. Participants also completed the Rosenberg Self-Esteem Scale (Rosenberg, 1965), the Satisfaction with Life Scale (Diener *et al*., 1985) and the Life Orientation Test (Scheier and Carver, 1985) to estimate their self-esteem, life satisfaction and optimism.

An fMRI-adapted version of the Cyberball game was used to assess neural activity in response to social exclusion. Similar to the previous studies (Eisenberger *et al*., 2003; Masten *et al*., 2011), participants were told prior to scanning that their 'mental visualization' ability was tested by playing a game of 'catch' over the internet with two other players, though participants actually played with a preset computer program. As part of the 'mental visualization' exercise, participants were instructed to imagine the experience as real as possible. In the first scan, the participant watched the other 'players' play the Cyberball game. During the first scan participants were told that they

Trust Centre for Neuroimaging, London, UK). In order to compensate for delays associated with acquisition time differences between slices during the sequential imaging, the functional data were first time-corrected. Then the functional images were 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 $2 \times 2 \times 2\,mm^3$. Functional images were smoothed using a Gaussian filter with the full-width/half-maximum parameter set to 8 mm. The event-related neural activity was modeled using a canonical hemodynamic response function.

Fixed effect analyses were first performed to estimate effects at each voxel and to compare regionally specific effects in individual participants using linear contrasts. To define social exclusion specific neural activations, the contrast of exclusion *vs* inclusion was calculated. Random effect analyses were then conducted across all participants based on statistical parameter maps from each individual participant to allow population inference. A threshold of $P < 0.05$ (family-wise error (FWE) corrected) was used to define social exclusion specific neural activations. To assess the difference in the neural activity related to social exclusion between s/s and l/l groups, we defined ROIs based on the results of the previous research of social exclusion (MNI coordinates: ACC: x/y/z = 8/20/40, RAI: x/y/z = 42/16/1, RVPFC: x/y/z = 37/50/1, Eisenberger *et al.*, 2003). The ROIs were defined as spheres with radii of 5 mm centered at the peak voxel of activated clusters using MarsBar toolbox in SPM8. To further confirm the difference between s/s and l/l groups during social exclusion, a two sample whole brain analysis was performed and significant differences between s/s and l/l groups were defined using a threshold of $P < 0.05$ (FWE corrected).

Original effect size (ES) and standardized ES (Cumming, 2014) were also calculated to test our hypothesis. As we assumed a social exclusion activity, the original ES of social exclusion was defined as the increased beta values during social exclusion relative to those during social inclusion. The standardized ESs were computed using the partial eta-square (η^2_p) method. Confidence interval (CI) reported along with the ES referred to 95% CI.

A psychophysiological interaction (PPI) analysis (Friston *et al.*, 1997) was performed to identify brain regions that showed significantly different covariation (i.e. functional connectivity) with dACC activity between social inclusion and exclusion. The coordinates of the peak voxel from the random effect analysis were used as a landmark for the individual seed voxels. An ROI of a sphere with a radius of 5 mm in the dACC was defined around the peak voxel. The time series of each ROI was then extracted and the PPI regressor was calculated as the element-by-element product of the mean-corrected activity of this ROI and a vector coding for the differential effect of social inclusion *vs* social exclusion. The PPI regressors reflected the interaction between psychological variable (social inclusion *vs* exclusion) and the activation time course of dACC. The individual contrast images reflecting the effects of the PPI between dACC and other brain areas were subsequently subjected to one-sample *t*-tests. The results of the group analysis identified brain regions in which the activity systematically showed increased and decreased correlation with dACC activity during social exclusion. The threshold at the cluster level was set to $P < 0.05$ (FWE corrected) for the identification of brain areas that showed significantly different functional connectivity with the seed ROIs.

Hierarchical regression analysis

We entered the variables predictive of RRS into a stepwise linear regression to identify the most important predictive variables. The stepwise methodology used $P = 0.05$ to enter a variable into each step and $P = 0.1$ to remove. This method is preferable to classical multiple regression when correlation between factors is suspected. Bootstrap analyses (1000 iterations) were used to explore the mediation relationship between the 5-HTTLPR, RVPFC activity, social interaction anxiousness and RRS (Preacher and Hayes, 2008). An observation of zero outside the 95% CI would indicate that the indirect (or mediated) effect was significantly different from zero at $P < 0.05$.

Results

Behavioral results

Table 1 shows the results of questionnaire measures of psychological traits, mood, life satisfaction and RRS in the two genotype groups. s/s and l/l allele carriers of 5-HTTLPR did not differ significantly in rating scores of self-esteem and optimism. s/s compared with l/l allele carriers tended to report slightly higher anxiety during social interaction but lower life satisfaction, though the difference did not reach significance. More interestingly, l/l compared with s/s allele carriers reported significantly greater RRS. A stepwise linear regression analysis was conducted to examine the specific association between 5-HTTLPR and individuals' RRS. Six predictor variables were entered into a model with RRS as the dependent variable: (i) 5-HTTLPR genotype; (ii) optimism; (iii) self-esteem; (iv) life satisfaction; (v) gender; and (vi) age. This model predicted RRS ($R^2 = 0.29$, $P < 0.05$, Table 2). Stepwise linear regression showed that only 5-HTTLPR genotype ($\beta = 0.38$, $P < 0.01$) and optimism ($\beta = 0.32$, $P < 0.05$) made a significant contribution to self-report of RRS (significance R^2 change, $P > 0.1$ for the other variables).

The social exclusion questionnaire after fMRI scanning confirmed that being excluded during the Cyberball game elicited distress feelings in our participants. The average response to each question was 2.73. The mean ± SE of the total score on this questionnaire was 32.73 ± 1.17, which was significantly greater than the minimum score of 12 that indicates no exclusion-related distress ($t(47) = 17.76$, $p < 0.001$). This score was slightly greater in s/s than l/l groups, but the difference did not reach significance (s/s *vs* l/l groups: 33.83 ± 1.81 *vs* 31.63 ± 1.48, $t(1,46) = 0.95$, $P = 0.35$, $\eta^2 = 0.02$).

Neuroimaging results

We first conducted whole-brain analyses to identify neural activity in response to social exclusion (*vs* inclusion) across all participants. This contrast revealed increased activations in the dACC/MPFC), bilateral AI, middle frontal gyrus, superior temporal sulcus (STS), temporoparietal junction (TPJ), caudate and cerebellum (Figure 1A, Table 3). Separate analyses of fMRI data from the two genotype groups showed similar patterns of brain activations when s/s and l/l allele carriers were excluded from the game (Table 4). ROI analyses were conducted to estimate the association between these brain activations and participants' emotional distress due to social exclusion. Self-reported distress was positively correlated with both the dACC and right AI (RAI) activities across all participants (dACC: x/y/z = 4/24/20, $r = 0.32$, $P < 0.05$; RAI: x/y/z = 30/24/−8, $r = 0.40$, $P = 0.01$, Figure 1B), suggesting that stronger dACC and RAI activations predicted greater distressed feelings after being excluded from the

Table 2. Results of stepwise linear regression analyses examining the association between relationship satisfaction and the 5-HTTLPR genotype

Criterion variable	Predictor variables	B	95% CI	β	t	P-value
Relationship satisfaction	5-HTTLPR genotype	4.59	[1.27,7.91]	0.42	2.80	0.008**
	Optimism	0.25	[−0.03,0.53]	0.34	1.79	0.08
	Gender	−1.80	[−5.51,1.90]	−0.16	−0.99	0.33
	Life satisfaction	−0.73	[−2.72,1.26]	−0.15	−0.74	0.46
	Self-esteem	0.08	[−0.45,0.61]	0.06	0.30	0.77
	Age	−0.04	[−1.21,1.14]	−0.01	−0.06	0.95
Stepwise						
Relationship satisfaction	5-HTTLPR genotype	4.22	[1.16,7.29]	0.38	2.79	0.008**
	Optimism	0.23	[0.03,0.43]	0.32	2.35	0.02*

*$P < 0.05$; **$P < 0.01$.

Fig. 1. Illustration of the fMRI results. (A) Social exclusion *vs* inclusion activated the dACC/MPFC, bilateral AI, bilateral STS and thalamus across all participants. (B) Positive correlations between the dACC and RAI activities with participants' self-reported distress in response to social exclusion. dACC/MPFC, dorsal anterior cingulate/medial prefrontal cortex; AI, anterior insula; STS, superior temporal sulcus.

game. We also conducted whole-brain interaction analyses to examine distinct patterns of neural activity to social exclusion and social inclusion in the two genotype groups. This revealed that the contrasts of exclusion *vs* inclusion disclosed stronger activation in the RVPFC (x/y/z = 44/52/14) in l/l compared with s/s carriers (Figure 2A), suggesting a reliable genotype difference in the neural activity in the brain region that is associated with emotion regulation.

Next we estimated whether the neural activity in the brain regions related to distressed feeling (e.g. RAI), conflict monitoring (e.g. dACC) and emotion regulation (e.g. RVPFC) can predict individuals' RRS. We first extracted parameter estimates of signal intensity from all participants in the ROIs of the dACC, RAI and RVPFC that were defined independently based on the previous study of social exclusion (Eisenberger *et al.*, 2003). Repeated measure analyses of variance (ANOVAs) with Engagement (Exclusion *vs* Inclusion) as a within-subjects variable and Genotype (s/s *vs* l/l carriers) as a between-subjects variable were then conducted on the signal intensity in these brain regions. ANOVAs of dACC and AI activities first confirmed increased activations during social exclusion compared with social inclusion (dACC: $F(1,40) = 8.16$, $P < 0.01$, ES = 0.21, 95% CI: [0.14, 0.29], $\eta^2 = 0.17$; RAI: $F(1,40) = 23.75$, $P < 0.001$, ES = 0.38, 95% CI: [0.30, 0.46], $\eta^2 = 0.37$). However, the exclusion-related dACC and AI activities did not differ significantly between the two genotype groups [dACC: $F(1,40) = 0.51$, $P = 0.48$, $\eta^2 = 0.01$; RAI:$F(1,40) = 2.56$,

Table 3. Brain activations during social exclusion *vs* inclusion session across all participants

Brain region			MNI coordinate		
	k	*t* value	x	y	z
RAI/IFG	3988	8.67	50	32	−8
RAI		7.67	36	26	−6
Right MFG		6.65	42	18	40
Left AI	3319	7.75	−28	16	−16
Left TPJ		7.62	−42	−54	28
Left STS		7.34	−58	−18	−14
Right STS	3666	9.28	52	−20	−10
Right TPJ		7.85	46	−48	24
dACC/MPFC	6995	9.12	2	46	32
dACC		5.94	14	32	24
Left MFG		7.48	−40	8	52
PCC	755	7.19	−6	−48	40
Right caudate	769	7.79	12	12	0
Left caudate	309	6.08	−20	14	12
Left cerebellum	657	8.00	−18	−84	−28
Right cerebellum	252	7.28	18	−78	−38

dACC/MPFC, dorsal anterior cingulate/medial prefrontal cortex; AI, anterior insula; IFG, inferior frontal cortex; MFG, middle frontal gyrus; STS, superior temporal sulcus; TPJ, temporoparietal junction; PCC, posterior cingulate cortex.

Table 4. Increased activities during social exclusion *vs* inclusion in the two genotype groups

Brain region	s/s homozygote				l/l homozygote			
	t value	x	y	z	*t* value	x	y	z
ACC/dMPFC	7.75	2	48	22	9.39	10	44	40
Left AI	4.47	−28	6	−16	8.43	−28	18	−16
RAI	4.59	36	28	−4	7.44	40	22	−16
Left IFG	4.34	−54	24	10	7.23	−46	18	−2
Right IFG	6.06	50	32	−10	8.43	50	32	−4
Left caudate	4.08	−16	0	4	5.36	−10	10	0
Right caudate	5.45	12	10	−2	7.19	8	12	0
Left thalamus	4.05	−18	−4	6	7.22	−18	−2	10
Right thalamus	4.16	16	0	4	8.35	12	−6	16
Left TPJ	5.28	−36	−54	20	8.80	−52	−62	24
Right TPJ	6.53	46	−50	26	5.43	54	−38	44
Left STS	6.13	−50	−12	−14	6.35	−48	−24	−10
Right STS	5.40	50	−20	−10	8.64	54	−20	−10
Left MFG					8.16	−38	10	40
Right MFG	5.17	44	12	34				
Right hippocampus					8.39	24	−34	−12
Left hippocampus					6.16	−30	−26	−4
Right cerebellum					7.60	12	−82	−36
Left cerebellum	6.04	−22	−84	−26	6.67	−8	−80	−24

ACC/dmPFC, anterior cingulated cortex/dorsal medial prefrontal cortex; AI, anterior insula; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; TPJ, temporoparietal junction; STS, superior temporal sulcus.(voxel threshold: $P = 0.001$; cluster threshold: $P = 0.05$ FWE corrected).

$P = 0.12$, $\eta^2 = 0.06$, Figure 2B]. ANOVAs of the RVPFC activity revealed greater activation during social exclusion than social inclusion [$F(1,40) = 10.83$, $P < 0.005$, ES = 0.35, 95% CI: [0.24, 0.46], $\eta^2 = 0.21$]. Moreover, the RVPFC activity related to social exclusion was significantly stronger in l/l compared with s/s carriers [$F(1,40) = 5.50$, $P = 0.02$, $\eta^2 = 0.12$, Figure 2B].

To investigate whether the RVPFC activity due to social exclusion mediated the genotype difference in RRS, we first conducted a regression analysis with individuals' RRS as the criterion variable and the RVPFC activity as predictor variables across all participants. The results indicated that the RVPFC activity significantly predicted self-report RRS [$r(42) = 0.62$, $P < 0.001$, Figure 2C], suggesting that individuals with a stronger RVPFC activity were more satisfied with their romantic relationships. Similar analyses failed to identify any association between dACC/AI activities and RRS (*Ps* > 0.05). Next we conducted a mediation regression analysis, where both 5-HTTLPR genotype and the RVPFC activity were included as predictors of RRS to test the mediating role of the RVPFC activity in the association between genotype and RRS. We found that the RVPFC activity remained a reliable predictor ($\beta = -0.56$, $P < 0.001$), whereas the effect of 5-HTTLPR genotype decreased significantly (from $\beta = -0.41$ to $\beta = 0.09$; Figure 2D). We conducted a bootstrap analysis to further confirm that the RVPFC activity was a significant mediator variable of the relationship between 5-HTTLPR genotype and RRS. This analysis found that the difference between the mediated and unmediated RVPFC activity effects on RRS was estimated to lie between 1.4543 and 6.0856 with 95% CI (based on procedures recommended by Preacher and Hayes, 2008). The fact that zero is not in the 95% CI indicates that the indirect (or mediated) effect was significantly different from zero at $P < 0.05$. This suggests that the 5-HTTLPR effect on RRS was reduced by adjusting the influence of the RVPFC activity. A similar bootstrap analysis was conducted to asses an alternative interpretation that RRS mediates the relationship between 5-HTTLPR genotype and emotion regulation as indexed by the RVPFC activity. This analysis, however, found that the indirect (or mediated) effect was not significantly different from zero at $P < 0.05$[95% CI:(−1.0249, 1.3055)], suggesting that the RRS did not mediate the relationship between 5-HTTLPR and the RVPFC activity.

Similar analyses were also conducted to examine whether the RVPFC activity mediated the genotype difference in social interaction anxiety. A regression analysis first revealed that the RVPFC activity significantly predicted individuals' social interaction anxiety across all participants [$r(48) = -0.54$, $P < 0.001$, Figure 2E], suggesting that individuals with a stronger RVPFC activity showed lower social interaction anxiety. Moreover, an analysis of regression of mediation with both 5-HTTLPR genotype and the RVPFC activity included as predictors of social interaction anxiousness showed that the RVPFC activity remained a reliable predictor ($\beta = -0.56$, $P < 0.001$, Figure 2F), whereas the effect of 5-HTTLPR genotype decreased significantly (from $\beta = -0.25$ to $\beta = 0.05$; Figure 2F). We conducted the bootstrap analysis to confirm that RVPFC activity was a significant mediator variable of the relationship between 5-HTTLPR genotype and social interaction anxiety. This analysis found that the difference between the mediated and unmediated 5-HTTLPR effects on social interaction anxiety was estimated to lie between −8.1918 and −2.1404 with 95% CI, indicating that the 5-HTTLPR effect on social interaction anxiety was reduced by adjusting the influence of the RVPFC activity.

Next we examined whether the functional connectivity between the key nodes of the neural circuit activated by social exclusion can predict RRS and social interaction anxiety across all participants. This analysis uncovered significant results only when the dACC was used as the seed for the PPI analysis. The coordinates of the peak voxel around dACC from the random effect analysis were used as a landmark of the seed voxel (x/y/z = 2/46/32, Figure 3A). Social inclusion *vs* exclusion led to

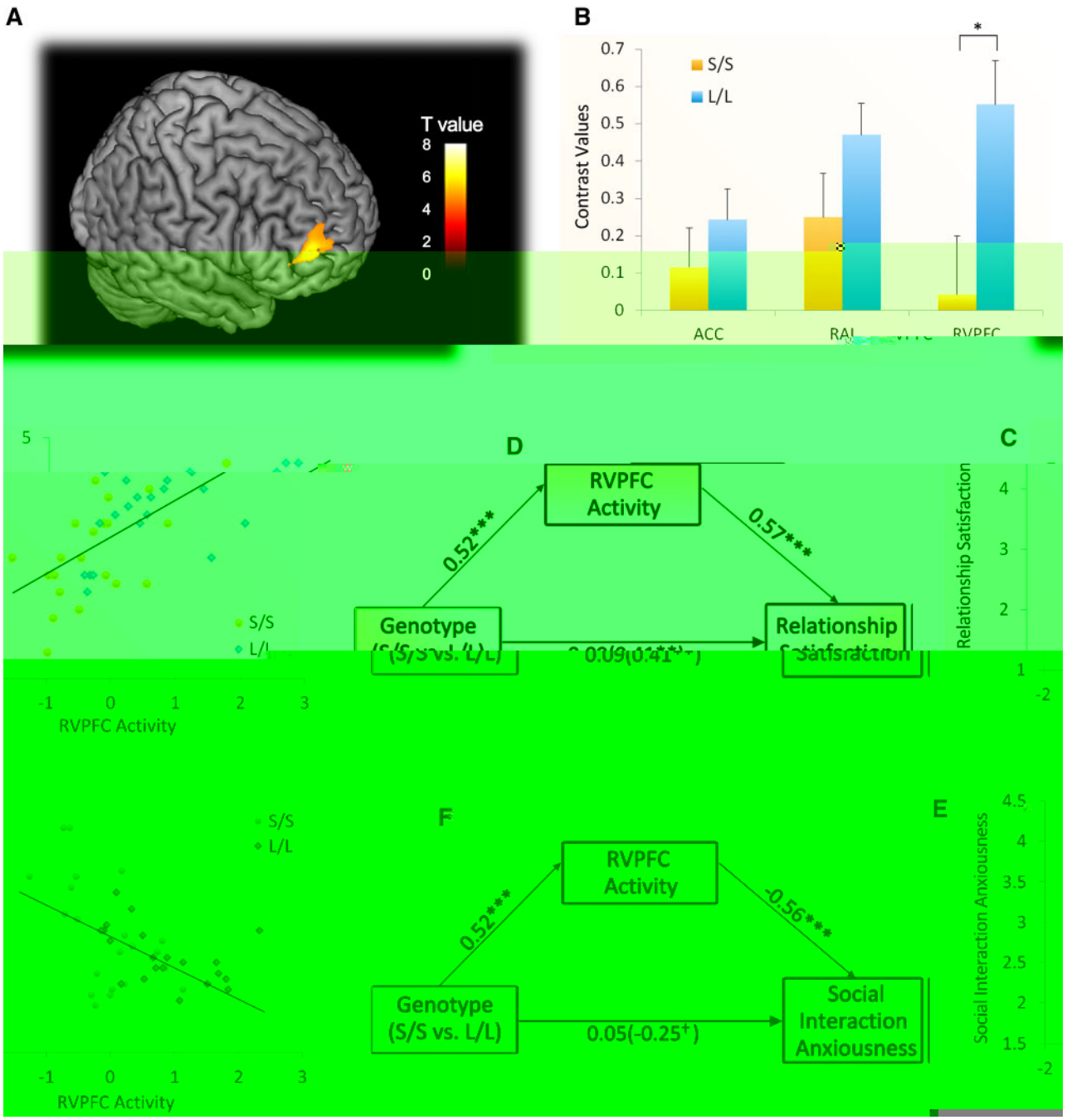

Fig. 2. Genetic differences in the RVPFC activity. (A) The whole-brain analysis revealed stronger RVPFC activity in response to social exclusion in l/l than in s/s allele carriers. (B) The results of ROI analyses. (C) The RVPFC activity during social exclusion predicted individuals' RRS. (D) Illustration of the mediation effect. The effect of genotype on relationship satisfaction was significantly reduced when the RVPFC activity during social exclusion was included in the regression model. (E) The RVPFC activity during social exclusion predicted individual's social interaction anxiety. (F) Illustration of the mediation effect. The effect of genotype on social interaction anxiousness was significantly reduced when the RVPFC activity during social exclusion was included in the regression model.

increased functional connectivity between the dACC and pre-/post-central gyrus (x/y/z = 18/−20/74, Z = 4.29; x/y/z = 26/−42/74, Z = 3.81; Figure 3B), suggesting greater involvement of the sensory and motor cortices when being included in the game. In contrast, relative to social inclusion, social exclusion increased functional connectivity between the dACC and bilateral STS (right STS: x/y/z = 58/−50/26, Z = 4.31; left STS: x/y/z = −64/−48/12, Z = 4.00) and between the dACC and left cerebellum (left cerebellum: x/y/z = −24/−76/−20, Z = 4.09, Figure 3C).

A two-sample analysis of the contrast of exclusion *vs* inclusion further revealed stronger functional connectivity between the dACC and rACC (x = 12, y = 48, z = 4, Z = 3.81) in l/l than in s/s carriers (Figure 3D). To assess whether the dACC-rACC connectivity during social exclusion predicted individuals' RRS and social interaction anxiety, we conducted a regression analysis with RRS and social interaction anxiety as the criterion variable and the dACC-rACC connectivity as predictor variables. The dACC-rACC connectivity only significantly predicted

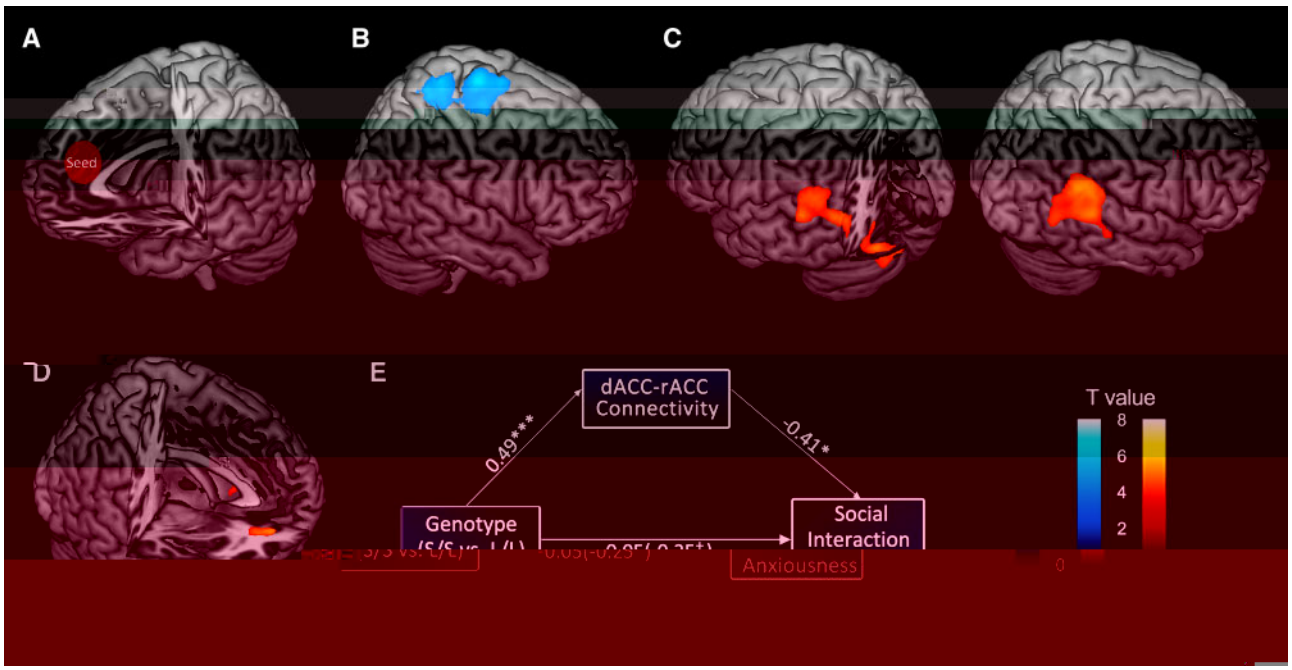

Fig. 3. Results of PPI (A) Illustration of the location of the dACC seed for the PPI -nalysis. (B) Increased functional connectivity between the dACC -nd right pre/postcentral gyrus during social inclusion *vs* exclusion. (C) Increased functional connectivity between the dACC -nd bilateral STS -nd left cerebellum during social exclusion *vs* inclusion. (D) l/l compared with s/s allele carriers showed stronger functional connectivity between the dACC -nd rACC during social exclusion *vs* inclusion. (E) Illustration of the effect. The effect of genotype on social interaction anxiousness was significantly reduced when thea2 connectivity between the dACC -nd rACC during social exclusion was included in the regression model.

individuals' social interaction anxiety [$r(48) = -0.43$, $P < 0.003$], individuals with a stronger dACC-rACC connectivity showed lower social interaction anxiety. To further test whether the dACC-rACC connectivity mediated the association between genotype and social interaction anxiety, we conducted a mediation regression analysis where both 5-HTTLPR genotype and dACC-rACC connectivity were included as predictors of social interaction anxiety. We found that the dACC-rACC connectivity remained a reliable predictor ($\beta = -0.41$, $P < 0.02$) whereas the 5-HTTLPR effect decreased significantly (from $\beta = -0.25$ to -0.05; Figure 3E). We also conducted the bootstrap analysis to confirm that dACC-rACC connectivity was a significant mediator variable of the relationship between 5-HTTLPR genotype and social interaction anxiety. There was a significant reduction in the direct relation between 5-HTTLPR genotype and social interaction anxiety (95% CI: −7.5373 to −0.1294; $P < 0.05$, as tested by a bias-corrected bootstrapping procedure). A similar regression of mediation on 5-HTTLPR genotype, dACC-rACC connectivity and RRS revealed that, although there was a significant correlation between RRS and dACC-rACC connectivity [$r(42) = 0.41$, $P < 0.01$], the 5-HTTLPR association with RRS did not change significantly when dACC-rACC connectivity was included (from $\beta = 0.41$ to 0.27). The bootstrap analysis failed to find significant reduction in the direct relation between 5-HTTLPR genotype and individuals' RRS (95% CI: −0.0351 to 3.7044; $P > 0.05$).

Finally, we conducted a multiple regression analysis to assess the specificity of the association between the RVPFC activity and RRS. Seven predictor variables were entered into the model with RRS as the dependent variable: (i) RVPFC activity, (ii) dACC-rACC connectivity, (iii) optimism, (iv) self-esteem, (v) life satisfaction, (vi) gender and (vii) age. This model predicted RRS across all participants ($R^2 = 0.50$, $P = 0.001$, Table 5). Stepwise linear regression showed that only the RVPFC activity ($\beta = 0.62$, $P < 0.001$) made a significant contribution (significance change, $P > 0.1$ for the other variables). A similar multiple regression analysis with social interaction anxiety as the criterion variable was conducted to determine the specificity of the association between dACC-rACC connectivity and individyr 0 TdC social interaction anxiety. This model predicted social interaction anxiety ($R^2 = 0.43$, $P = 0.001$, Table 6). Stepwise linear regression showed both the RVPFC activity ($\beta = -0.44$, $P = 0.001$) and dACC-rACC connectivity ($\beta = -0.28$, $P < 0.$ bution to social interaction anxi $P > 0.1$ for the other variables).

Discussion

This work investigated genetic associations with RRS and whether such associations are mediated by the neural activity related to negative emotional responses or emotion regulation in a context of social rejection. We tested s/s and l/l allele carriers of 5-HTTLPR who were identified in the previous studies with distinct anxiety/depression (Lesch *et* ., 1996; Greenberg *et a* ., 2000; Caspi *et a* ., 2003; Canli Lesch, 2007) distinct brain responses to negative emotions (Hariri *et* ., 2002; Ma *et a* ., 2015). The two genotype groups in our study were matched in psychological traits such as self-esteem and optimism. Self-report measures in this study showed a tendency of higher anxiety related to social interaction lower life satisfaction in s/s than l/l allele carriers. These are consistent with the behaviorals of the previous research (Lesch *et* ., 1996; Caspi 2003; De Neve, 2011). Most interestingly, we found l/l compared with s/s allele carriers reported significantly greater satisfaction of their romantic relationships. The distinction between 5-HTTLPR and RRS was confirmed when psychological traits, life satisfaction, gender age were controlled as covariants. These behavioral results were surprising because our sample size that was determined for fMRI scanning

Table 5. Results of stepwise linear regression analyses examining the association between RVPFC activity, dACC-rACC connectivity and relationship satisfaction

Criterion variable	Predictor variables	*B*	95% CI	β	*t*	*P*-value
Relationship satisfaction	RVPFC activity	3.33	[1.33,5.34]	0.48	3.37	0.002**
	dACC-rACC connectivity	7.62	[−0.01,15.24]	0.29	2.03	0.05
	Life satisfaction	−1.32	[−3.06,0.43]	−0.27	−1.53	0.13
	Optimism	0.19	[−0.07,0.44]	0.26	1.50	0.14
	Gender	−1.92	[−5.07,1.24]	−0.17	−1.23	0.23
	Self−esteem	0.14	[−0.32,0.59]	0.10	0.61	0.54
	Age	−0.14	[−1.14,0.87]	−0.04	−0.27	0.79
Stepwise						
Relationship satisfaction	RVPFC activity	4.26	[2.52,5.99]	0.62	4.96	<0.001***

**P < 0.01; ***P < 0.001.

Table 6. Results of stepwise linear regression analyses examining the association between RVPFC activity, dACC-rACC connectivity and interaction anxiety

Criterion variable	Predictor variables	*B*	95% CI	β	*t*	*P*-value
interaction anxiety	RVPFC activity	−4.47	[−7.36, −1.59]	−0.43	−3.13	0.003**
	dACC−rACC connectivity	−12.91	[−22.90,−2.91]	−0.36	−2.61	0.01*
	Life satisfaction	2.65	[0.15,5.16]	0.37	2.14	0.04*
	Optimism	−0.21	[−0.57,0.16]	−0.19	−1.13	0.26
	Self-esteem	−0.24	[−0.87,0.38]	−0.13	−0.79	0.43
	Gender	1.09	[−3.41,5.59]	0.07	0.49	0.63
	Age	−0.29	[−1.65,1.07]	−0.05	−0.43	0.67
Stepwise						
Interaction anxiety	RVPFC activity	−4.56	[−7.21,−1.91]	−0.44	−3.46	0.001**
	dACC-rACC connectivity	−9.86	[−19.04,−0.68]	−0.28	−2.16	0.04*

*P < 0.05; **P < 0.01.

was much smaller than the previous behavioral studies (Lesch *et al.*, 1996; Caspi *et al.*, 2003; De Neve, 2011). These behavioral results indicate high consistency across individuals in each genotype group and support our hypothesis of the association between 5-HTTLPR and RRS. The distinct patterns of differential anxiety and RRS in s/s and l/l allele carriers observed here are congruent with the previous findings of a negative association between anxiety-related trait and subjective well-being (Costa *et al.*, 1980).

Our fMRI results identified brain activations in response to social rejection during the Cyberball game in the regions related to social cognitive and affective processing such as the dACC, AI, RVPFC, STS and TPJ. These activations replicated the previous fMRI findings of social rejection using the same game (Eisenberger *et al.*, 2003; Masten *et al.*, 2009, 2011; Sebastian *et al.*, 2011; Bolling *et al.*, 2011; Moor *et al.*, 2012). We also found that the dACC and RAI activities were specifically correlated with self-report of distress due to exclusion from the game, suggesting the functional role of dACC and RAI in representing distressed feelings during social rejection. The two genotype groups reported comparable distressed feelings linked to social rejection during the Cyberball game. Consistent with this, our fMRI results showed comparable dACC/AI activity during social exclusion between s/s and l/l allele carriers of 5-HTTLPR.

More interestingly, we found that, relative to s/s allele carriers of 5-HTTLPR, l/l allele carriers exhibited stronger RVPFC activity in response to social rejection. The previous research has shown that the RVPFC was activated during both social rejection (Eisenberger *et al.*, 2003; Masten *et al.*, 2009, 2011) and physical pain (Petrovic *et al.*, 2000). Moreover, the RVPFC activation was negatively associated with the dACC activity during social and physical pain (Lorenz *et al.*, 2003; Eisenberger *et al.*, 2003) and with the amygdala activity during perception of emotional faces (Hariri, 2000). Because early brain imaging findings verified the functional role of the RVPFC in different kinds of emotion regulation processes (Lévesque *et al.*, 2003; Phan *et al.*, 2005; Harenski and Hamann, 2006; Kim and Hamann, 2007; Ochsner and Gross, 2008), the RVPFC has been suggested to play a key role in regulation of distress produced by social and physical pain (Eisenberger *et al.*, 2003; Eisenberger and Lieberman, 2004). Thus the distinct patterns of the RVPFC activity in the two genotype groups observed in this work suggest stronger engagement of emotion regulation when experiencing social exclusion in l/l than s/s allele carriers. More closely related to our hypothesis, our correlation analyses revealed that the RVPFC activity positively predicted individuals' self-report of RRS. In addition, the bootstrap analyses confirmed that the difference in RRS between s/s and l/l allele carriers was mediated by the activity in the RVPFC but not in dACC and AI. These results support the proposal that emotion regulation rather than distress feelings mediates the genotype difference in subjective feelings of one's own romantic relationships. Our bootstrap analyses further ruled out the possibility that RRS mediates the relationship between 5-HTTLPR genotype and emotion regulation. Taken together, while the previous behavioral studies suggested associations between RRS and personality traits/emotional intelligence (Heller *et al.*, 2004; Malouff *et al.*, 2014), our current brain imaging findings provide the evidence for genetic and neural correlates of subjective feelings of one's own romantic relationship.

Interestingly, the RVPFC activity did not specifically mediate the association between 5-HTTLPR and RRS. We also found that the RVPFC activity negatively predicted self-report of social interaction anxiety and was a reliable predictor of the association between 5-HTTLPR and individuals' disposition related to social anxiety. Thus it is likely that the neural activity in the brain region related to emotion regulation plays a general role in mediating genetic (e.g. 5-HTTLPR) influences on human affective states related to romantic relationships, though the patterns of the mediation effects could be different depending on affective valence (e.g. satisfaction *vs* anxiety). The previous research reported both increased amygdala activity in response to negative environmental stimuli (Hariri *et al*., 2002; Canli *et al*., 2005; Heinz *et al*., 2005; Ma *et al*., 2015) and increased dACC/AI activity in response to one's own negative personality traits in s/s allele carriers than l/l carriers (Ma *et al*., 2014). There was also evidence for increased functional connectivity between the medial prefrontal cortex and amygdala but decreased functional coupling between the ventral ACC and amygdala in s allele carriers than l/l carriers (Heinz *et al*., 2005; Pezawas *et al*., 2005). These findings have been used to interpret genetic differences in susceptibility for anxiety and depression. Our findings complement the previous findings by suggesting that the increased RVPFC—a brain region typically involved in regulation of emotion (Ochsner and Gross, 2005)—may contribute to l/l carriers' low risk for mood disorder during social interactions. In addition, as the RVPFC activity mediated the 5-HTTLPR associations with both RRS and trait anxiety, this brain region may play a general functional role in mediating the association between emotion regulation and individuals' well-being (Gross and John, 2003).

Our fMRI results found that the RVPFC was the only neural mediator of the association between 5-HTTLPR and RRS but was not the only neural mediator of the 5-HTTLPR association with individuals' deposition of social anxiety. We found evidence for increased functional connectivity between dACC and rACC during social exclusion in l/l compared with s/s allele carriers. In addition, the dACC-rACC connectivity negatively predicted individuals' social interaction anxiety and was demonstrated to be a mediator of the association between 5-HTTLPR and social anxiety. The associations between social interaction anxiety and the RVPFC activity/dACC-rACC connectivity was also verified when individuals' traits and gender/age were controlled. Early imaging studies suggest that the dACC and rACC are involved in cognitive (e.g. action and conflict monitoring) and affective dimensions of multiple tasks (Bush *et al*., 2000), respectively. More recent findings indicate that the dACC constitutes a hub where information about negative affect, pain and cognitive control is linked to motor centers responsible for expressing affect and executing goal-directed behavior ua(to)-469z-319(ict)-37n11 1 Tf16.5394.505 22.8815(et)-272.4 (49gniti/T10 1 Tf1.8973 HT)1 48

a long-lasting task engaged in negative emotion, the 5-HTTLPR influence was more salient in the RVFC activity related to emotion regulation rather than transient emotion responses in the ACC/insula or amygdala. Together, these findings suggest that different experimental paradigms tackled different aspects of the s/s and l/l genotype difference in emotion-related activity.

In conclusion, this work provided preliminary behavioral evidence for the association between 5-HTTLPR and self-reported RRS. Our fMRI findings suggest that better ability of emotion regulation as indexed by the greater RVPFC activity in response to social rejection predicts high level of RRS. More importantly, our fMRI findings revealed a mediator role of the RVPFC in connecting the 5-HTTLPR and RRS, suggesting a possible neurocognitive mechanism underlying 5HTTLPR impact on subjective feelings of one's own romantic relationship. In addition, both the RVPFC activity and dACC-rACC connectivity mediated the association between 5-HTTLPR and self-report of trait anxiety. Thus the emotion regulation underpinned by the RVPFC may play a general role in mediating the 5-HTTLPR effects on human affective state and well-being.

Acknowledgements

We thank Yina Ma, Bingfeng Li, Chenbo Wang, Yi Liu, Xiaoyang Li, Chao Jiang for research assistance.

Funding

This work was supported by the National Natural Science Foundation of China (Projects 31421003, 31470986, 91332125, 91224008) and the Ministry of Education of China (Project 20130001110049).

Conflict of interest. None declared.

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