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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.

: 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

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)

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 relation-

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

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/z¾44/52/14) 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 24.3m4.9ie-306.5 (in)-m reg-272.3isendur]

P¼0.12, η^2¼0.06, Figure 2B]. ANOVAs of the RVPFC activity revealed greater activation during social exclusion than social inclusion [F(1,40)¼10.83, P < 0.005, ES¼0.35, 95% CI: [0.24, 0.46], η^2¼0.21]. Moreover, the RVPFC activity related to social exclusion was significantly stronger in l/l compared with s/s carriers [F(1,40)¼5.50, P¼0.02, η^2¼0.12, 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)¼0.62, P < 0.001, Figure 2C],

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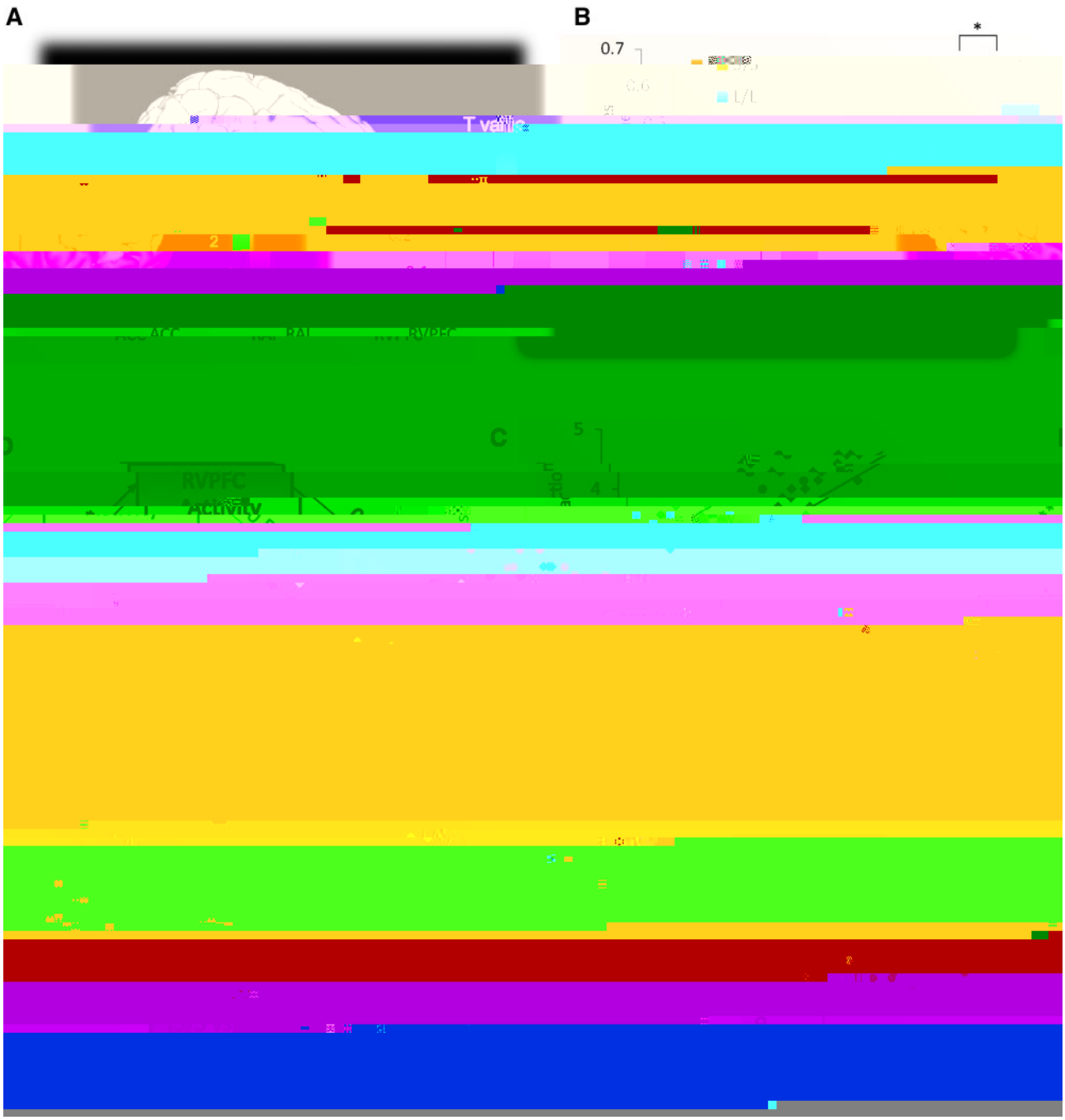

. 2. Genetic differences in the RVPFC activity. (A) The whole-brain analysis revealed stronger RVPFC activity in response to social exclusion in l/l than in s/s allele carriers. (B) The results of ROI analyses. (C) The RVPFC activity during social exclusion predicted individuals' RRS. (D) Illustration 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/z¼18/□20/74, Z¼4.29; x/y/z¼26/□42/74, Z¼3.81; 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/z¼58/□50/26, Z¼4.31; left STS: x/y/z¼□64/□48/12, Z¼4.00) and between the dACC and left cerebellum (left cerebellum: x/y/z¼□24/□76/□20, Z¼4.09, Figure 3C).

A two-sample analysis of the contrast of exclusion vs inclusion further revealed stronger functional connectivity between the dACC and rACC (x¼12, y¼48, z¼4, Z¼3.81) 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

individuals' social interaction anxiety [r(48)¼□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 (β¼□0.41, P < 0.02) whereas the 5-HTTLPR effect decreased significantly (from β¼□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)¼0.41, P < 0.01], the 5-HTTLPR association with RRS did not change significantly when dACC-rACC connectivity was included (from β¼0.41 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 as-

was much smaller than the previous behavioral studies (Lesch et al., 1996; Caspi et al., 2003; De Neve, 2011).19se

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 ne6o3 (v(26.8 (mediator)34(332n338.1ywiS)-2.5 (5-HT)-a24.8 (l/l)so5(0 rg[(med24.8(traie)-375.1 (mediating)-3medd24.8 rg)8 (onlr)-3medegfor

a long-lasting task engaged in negative emotion, the 5-HTTLPR

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