Regional gray matter volume is associated with rejection sensitivity: Avoxel-based morphometry study

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Abstract Rejection sensitivity (RS) can be defined as the disposition that one tends to anxiously expect, readily perceive, and intensely react to rejection. High-RS individuals are more likely to suffer mental disorders. Previous studies have investigated brain activity during social rejection using different kinds of rejection paradigms and have provided neural evidence of individual differences in response to rejection cues, but the association between individual differences in RS and brain structure has never been investigated. In this study, voxel-based morphometry (VBM) was used to investigate the relationship between gray matter volume (GMV) and RS in a large healthy sample of 150 men and 188 women. The participants completed the RS Questionnaire and underwent an anatomical magnetic resonance imaging scan. Multiple regression was used to analyze the correlation between regional GMV and RS scores, adjusting for age, sex, and total brain GMV. These results showed that GMV in the region of the posterior cingulate cortex/precuneus was negatively associated with RS, and GMV in the region of the inferior temporal gyrus was positively correlated with RS. These findings suggest a relationship between individual differences in RS and GMV in brain regions that are primarily related to social cognition.

Keywords Rejection sensitivity · Voxel-based morphometry · Posterior cingulate cortex/precuneus · Social cognition

Faculty of Psychology, Southwest University, No.2, TianSheng RoadBeibei district Chongqing 400715, China e-mail: zhangql@swu.edu.cn e-mail: qiuj318@swu.edu.cn Belongingness or inclusion is a basic need for individuals (Pickett, Gardner, & Knowles, 2004). If this goal is not satisfied, a feeling of exclusion or rejection will be present. Being rejected or devalued from others is regarded as a painful experience (Eisenberger, 2012; MacDonald & Leary, 2005). Expressions like "broken hearted" and "painful" after ending a relationship, "hurt feelings" after a person has been excluded from a circle of friends, or "a slap in the face" after a kind invitation has been rejected, testify to the pain of rejection by others (Eisenberger, 2012; Premkumar, 2012; Rosenbach & Renneberg, 2011).

Differences in parenting styles, life experiences, and personal dispositions engender different levels of sensitivity to rejection. Some people maintain equanimity under rejection, whereas greater cortisol response levels (Dickerson & Kemeny, 2004) and more negative affect (Nezlek & Plesko, 2001) may be experienced by others. RS was described by Downey and his colleagues as a disposition characterized by anxious expectation, ready perception, and intense reaction during social interactions (Downey & Feldman, 1996; Downey, Feldman, & Ayduk, 2000). Both theoretical and empirical work has suggested that RS is derived from early ignored and rejected experiences with significant others, including caregivers and close friends (Downey & Feldman, 1996). Such experiences lead individuals to anxiously expect rejection in social interactions (Brennan, Clark, & Shaver, 1998; Yoo et al., 2005). Thus, high-RS individuals display a heightened attentiveness to social cues that may result in rejection, tend to attribute ambiguous stimuli to a form of rejection, and always feel insecure and dissatisfied in romantic relationships (Downey & Feldman, 1996; Downey, Freitas, Michaelis, & Khouri, 1998). As a relatively stable characteristic (Rosenbach & Renneberg, 2011), RS has been found to be associated with various mental disorders, primarily including social anxiety, depressive symptoms, neuroticism, and borderline personality disorders (Beeri & Lev-Wiesel, 2012;

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Downey & Feldman, 1996; Parker et al., 2002; Rosenbach & Renneberg, 2011).

Given that RS plays an important role in mental health, it is important to consider the methods that may be appropriate to explore the neural basis of individual differences in RS. Both functional and anatomical approaches can been used to examine the neural basis of individual differences in RS (Kanai & Rees, 2011; Kane & Engle, 2002). As compared with functional imaging (fMRI) studies, structural imaging is not limited to specific tasks, such as the Cyberball task, the social evaluation task, or tasks involving stimuli such as pictures conveying rejection or acceptance information (Eisenberger et al., 2003; Kross, Egner, Ochsner, Hirsch, & Downey, 2007). A recent review focusing on fMRI studies under different rejection paradigms revealed that paradigms of social exclusion and rejection scenes do better at evoking rejection-related neural responses, whereas paradigms of presenting rejection cues may give a greater opportunity to explore how individuals differ in downregulating their responses to the rejections they perceive (Premkumar, 2012). Premkumar also observed that the different paradigms may produce inconsistent results. In addition, macroscopic alterations in gray matter measured by voxel-based morphometry (VBM) may be contributed to by changes in synaptic bulk, neurite, glial, and neuronal cells (Draganski et al., 2004; May & Gaser, 2006; Mechelli, Price, Friston, & Ashburner, 2005). In clinical populations, the morphometric changes that are associated with cell loss and/or atrophy may represent the pathophysiology of mood disorders (Manji, Moore, Rajkowska, & Chen, 2000). Furthermore, although few studies have examined the relationship between volumetric and functional abnormalities, neurochemical studies may support the overlap between structure and function. Recently, Hsu et al. (2013) found a positive correlation between trait resiliency and μ -opioid activation in the amygdala, subgenual anterior cingulate cortex (ACC), and periaqueductal gray matter during rejection, suggesting that these areas may be involved in decreasing the severity of painful experiences. Mood disorders displaying abnormalities in limbic and prefrontal cortex (PFC) brain structures also show blood flow and metabolic rate abnormalities in the same areas (Drevets, 2000; Manji et al., 2000). Moreover, prior research has already revealed that individual differences in personality traits and temperament are reflected in structural variances in specific brain areas (e.g., DeYoung et al., 2010; Gardini, Cloninger, & Venneri, 2009; Takeuchi et al., 2014). Therefore, a structural imaging study of individual differences in RS can contribute to a comprehensive understanding of the neural substrates of social rejection and RS-related mental disorders.

Previous brain imaging studies have offered insights into the potential neural mechanisms underlying RS. Functional MRI studies have determined the associations between social rejection and activities in several human brain regions, primarily including the ACC, posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), and ventrolateral prefrontal cortex (VLPFC) (Bolling, Pitskel, Deen, Crowley, McPartland, & Pelphrey, 2011; Eisenberger, Lieberman, & Williams, 2003; Onoda et al., 2010; Somerville, Heatherton, & Kelley, 2006). Recent reviews have also confirmed the involvement of these regions in processing exclusion-related information (Eisenberger, 2012; Premkumar, 2012). For example, Kross et al. (2007) found that rejection images induced more activity in the regions of the dorsal ACC, PCC, and mPFC than did acceptance images. Furthermore, RS was positively correlated with activation in regions of the dorsal ACC and precuneus (Prec) in adults, when comparing exclusion with inclusion in the Cyberball task (Masten et al., 2009). In another study, selfreported social distress was positively correlated with activation of the brain regions responsible for dealing with rejection experiences, such as the dorsal ACC, and negatively associated with activation of the brain regions responsible for emotion regulation, such as the ventromedial PFC (Premkumar, 2012). Although a large number of functional imaging studies have concerned social rejection/exclusion, the structural basis of individual differences in RS is still not very clear. Previous studies have reported an association between RS-related mental disorders and structural variations. For example, a structural MRI study showed that higher anxiety ratings were associated with reduced gray matter volume (GMV) in regions including the PFC, ACC, and PCC in healthy participants (Spampinato, Wood, De Simone, & Grafman, 2009). Panic disorders were also found to be related to decreased GMV in regions of the bilateral putamen, right Prec, and other cortical areas, in comparison with healthy controls (Yoo et al., 2005). Furthermore, patients with bipolar disorder and borderline personality disorder were found to have reduced GMV in the PCC and ACC relative to healthy controls (Hazlett et al., 2005; Nugent et al., 2006). Both the functional and structural studies suggested that brain regions such as the ACC, PCC, and mPFC might underlie deficits in social cognition related to RS.

On the basis of the aforementioned research findings, we hypothesized that individual differences in RS might be associated with GMV in the ACC, PCC, and mPFC, which have been demonstrated to be associated with rejection-related psychological processes and RS-related mental disorders. To test this hypothesis, we explored how individual differences in RS were correlated to GMV using VBM in a large sample of healthy participants. The RS of individuals was assessed using the self-report Rejection Sensitivity Questionnaire (RSQ; Downey & Feldman, 1996).

Method

Participants

The participants were college students from our ongoing project examining the associations among brain imaging, creativity, and mental health. They were recruited from Southwest University, China. The exclusion criteria included a history of manic episodes, psychotic features, neurological illness, and lefthandedness. A total of 338 right-handed, healthy volunteers (150 males and 188 females; mean age= 19.98 years, *SD*= 1.30) completed the RSQ (Downey & Feldman, 1996). None of them had a history of neurological or psychiatric illness. The study was approved by the Southwest University Brain Imaging Center Institutional Review Board. In accordance with the Declaration of Helsinki (1991), written informed consent was obtained from all participants.

Assessment of rejection sensitivity

To assess individual differences in RS, participants completed the RSQ. The RSQ asked participants to read 18 separate hypothetical situations in which rejection was possible (e.g., "Asking your friend to do you a big favor"). For each situation, participants were asked to assess the level of anxiety that they would experience in relation to the outcome of the situation on a six-point scale (1 = very unconcerned, 6 = very*concerned*), as well as the likelihood of acceptance (1 = verv)*unlikely*, 6 = very likely). To compute the total RS scores, the acceptance expectancy scores were reversed to indicate expectations of rejection, and subsequently multiplied by the level of anxiety experienced in each situation. The sum of the products across all of the situations was divided by the number of situations. The reliability for this measure in the present study was acceptable (α = .82). The RSQ has been widely used in behavioral and neuroimaging studies (Downey et al., 1998; Kross et al., 2007; Staebler, Helbing, Rosenbach, & Renneberg, 2011) and has been shown to have a unique predictive utility for personality constructs such as depression, neuroticism, adult attachment, social avoidance, self-esteem, and social anxiety (Downey & Feldman, 1996).

Assessment of trait anxiety

The State–Trait Anxiety Inventory (STAI) was used (Spielberger, 1983) to obtain trait anxiety (TA) scores. This is a 20-item self-report questionnaire that measures TA (e.g., "I feel nervous and uneasy"). The STAI has been used widely to measure trait anxiety and has been demonstrated to be reliable and valid (Comeau, Stewart, & Loba, 2001; Zahn-Waxler, Klimes-Dougan, & Slattery, 2000). Items are rated on a four-point scale ($1 = hardly \ ever$ to 4 = always), with higher total scores indicating higher levels of trait anxiety. The internal consistency of this measure in the present study was .80.

Assessment of neuroticism

The self-report Eysenck Personality Questionnaire (EPQ) was used to assess neuroticism (Chen, 1983). Participants were

asked to respond "True" or "False" in answer to 85 items. Gender-specific normative data were used to calculate t scores. The EPQ has been demonstrated to be both reliable and valid (Chen, 1983; Eysenck & Eysenck, 1975). In addition, the internal consistency for this measure in the present sample (participants who completed the RSQ, TA, and EPQ) was .81.

MRI data acquisition

A 3.0-T Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany) was used to obtain MR images. A magnetization-prepared rapid gradient echo (MPRAGE) sequence was used to acquire high-resolution T1-weighted anatomical images (repetition time= 1,900 ms, echo time= 2.52 ms, inversion time= 900 ms, flip angle= 9 deg, resolution matrix= 256×256 , slices= 176, thickness= 1.0 mm, voxel size= $1 \times 1 \times 1 \text{ mm}^3$).

Preprocessing of structural data

The MR images were processed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK; www.fil. ion.ucl.ac.uk/spm) implemented in MATLAB 7.8 (MathWorks Inc., Natick, MA, USA). Each MR image was displayed in SPM8 to screen for artifacts or gross anatomical abnormalities. To attain better registration, the reorientation of the images was manually set to the anterior commissure. Segmentation of the images into gray matter (GM), white matter (WM), and cerebrospinal fluid was performed through the new segmentation toolbox in SPM8. Subsequently, we performed diffeomorphic anatomical registration through exponentiated Lie (DARTEL) algebra in SPM8 for registration, normalization, and modulation (Ashburner, 2007). To ensure conservation of regional differences in the absolute amounts of GM, the image intensity of each voxel was modulated by the Jacobian determinants. The registered images were transformed to Montreal Neurological Institute (MNI) space. Finally, the normalized modulated images (GM and WM images) were smoothed with a 10-mm full-width-at-halfmaximum Gaussian kernel to increase the signal-to-noise ratio.

Statistical analyses

Statistical analyses of the brain imaging data were performed using SPM8. In the whole-brain analysis, multiple regression analysis was used to explore the association between GMV and individual differences in RS as measured by the RSQ. The RSQ score was used as the variable of interest. Total brain GMV, age, and sex were entered as covariates of no interest to control for the possible effects of these variables. To minimize GM/WM boundary effects, absolute voxel signal intensity threshold masking of 0.2 was used; that is, voxel signal intensity values lower than 0.2 were excluded. The voxel-level family-wise error (FWE) method was used at the whole-brain level. The significance threshold was set at p<.05 and corrected for multiple comparisons.

Furthermore, small-volume correlation (SVC) was performed in the areas with a strong a priori hypothesis. The regions of interest (ROIs) were chosen because previous structural and functional imaging studies had revealed that they might play an important role in social rejection. The Wake Forest University (WFU) Pick Atlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) was used to define the areas of the PCC, ACC, and mPFC. Specific ROIs were examined at a corrected threshold of p < .05, using the FWE method for multiple comparisons.

Results

Demographics

The demographic information and behavioral data of all participants are presented in Table 1. The range of RSQ scores for the present study was 2.50 to 16.06 (M= 7.24, SD= 2.69), which is consistent with previous research in college student samples. For example, the RSQ scores of two previous studies ranged from 2.16 to 18.4 and from 2.83 to 15.5 (Kross et al., 2007; Powers, Somerville, Kelley, & Heatherton, 2013). We found no significant difference (p> .05) in RSQ scores between the sexes.

Correlation between GMV and RSQ scores

In whole-brain analysis, multiple regression analysis revealed that the RSQ scores were significantly and negatively correlated with GMV in a cluster that primarily included areas in the PCC, Prec, and calcarine sulcus (FWE-corrected p < .05; see Fig. 1A and Table 2), and significantly and positively correlated with GMV in a cluster that was primarily in the right inferior temporal gyrus (FWE-corrected p < .05; Fig. 1B and Table 2).

Table 1 Demographic and behavioral data

Items	Total Participants
No. of participants	338
Males/females	150/188
Age (years)	19.98±1.30 (18-27)
RSQ score	7.24± 2.69 (2.50–16.06)
TA score	41.18±7.2 (25–62)

SVC analysis revealed a significant negative correlation between GMV in the left PCC and RSQ scores [MNI (9, -60, 14), cluster size= 1,254, t= 5.16, p<.05, corrected for FWE]. However, no significant relationships were observed in the ACC and mPFC.

We also found that the GMV of the PCC/Prec was negatively related to ITG (r=-.165, p<.01) when controlling for total brain GMV, sex, and age (Seeley, Crawford, Zhou, Miller, & Greicius, 2009; Zhang et al., 2011). However, when controlling for RS, total brain GMV, sex, and age, the correlation became marginally significant (r=-.098, p=.073).

Analyses investigating the effects of trait anxiety and neuroticism

To examine whether these results were affected by anxiety and neuroticism, which have been found to be closely associated with RS (Downey & Feldman, 1996; Rosenbach & Renneberg, 2011), additional analyses examining RS's associations with GMV were explored with TA and neuroticism scores as covariates. Several participants failed to complete the EPO; therefore, only the 304 of 338 participants who completed all questionnaires remained for this further analysis. RSQ scores were positively correlated with TA (r=.412, p < .001) and neuroticism (r=.306, p < .001). TA and neuroticism were added as covariates of no interest with age, sex, and total brain GMV. The results pertaining to the restricted sample of 304 participants were similar to those for all 338 participants (Table 3). All associations remained significant, both when controlling for the effects of TA and neuroticism separately and when controlling for both of them together (Table 3). Although we found small variations in cluster size, the significant regions were consistent with those identified in initial analyses after correcting for multiple comparisons.

To test whether the observed relationships between RS and GMV in brain structures only reflected indirect effects through anxiety or neuroticism, mediation analyses were performed using the PROCESS macro designed for SPSS (Preacher & Hayes, 2008). This macro uses bootstrapped sampling to estimate the indirect mediation effect. In this analysis, 5,000 bootstrapped samples were drawn, and bias-corrected 95% bootstrap confidence intervals (CI) were reported. CIs that do not include zero indicate a significant indirect effect of the independent variable on the dependent variable through the mediators (Preacher & Hayes, 2008). In the present study, the average GMV within the above-mentioned two statistically significant regions was extracted and used as the dependent variable, whereas RS scores were used as an independent variable, and TA scores or neuroticism scores were used as proposed mediators. These results showed no significant indirect effects of RS on the PCC/Prec [CI: -.0011, .0014] or the ITG [CI: -.0014, .0020] through anxiety. No significant



Fig. 1 Anatomical correlations with Rejection Sensitivity Questionnaire (RSQ) scores. (A)Gray matter volume (GMV) was negatively correlated with individual RS in the right PCC/Prec, and (B)GMV was positively related to individual RS in the right inferior temporal gyrus. The results

indirect effect of RS was apparent for the PCC/Prec [CI: -.0009, .0011] or ITG [CI: -.0010, .0015] through neuroticism, either.

Similar analyses were repeated in the sample composed of 338 participants who had both RS scores and TA scores, to examine the potential effect of TA on the correlation between RS and specific brain areas. When TA scores were added to

 Table 2
 Regional gray matter volumes show significant correlations with RSQ scores

Brain regions	Brodmann Areas	Cluster Size (voxels)	Peak t Values	Peak Coordinates in MNI (<i>x</i> , <i>y</i> , <i>z</i>)
Positive Correlation Right ITG	BA37	87	5.32*	47, -57, -10
Negative Correlation Right PCC/Prec/ Calcarine sulcus	BA23/30/31	296	-5.16*	9, -60, 14

PCC, posterior cingulate cortex; Prec, precuneus; ITG, inferior temporal gyrus. *p < .05, corrected by FWE.

are shown with p< .0001 uncorrected, for visualization purposes. The corresponding partial-correlation scatterplots between RS and brain areas, to the right of panels A and B, are adjusted for age, sex, and total GMV and are shown for illustration purposes only.

control for the potential effect, similar results were obtained [ITG: MNI (47, -57, -12), cluster size= 9, t= 4.5; PCC/Prec: MNI (9, -63, 15), cluster size= 133, t= -4.90]. Mediation analysis showed no significant indirect effects of RS on brain areas through TA [PCC/Prec, CI= -.0011, .0014; ITG, CI= -.0011, .0022].

Discussion

In the present study, we aimed to reveal the structural basis underlying individual differences in RS using VBM and RSQ. Consistent with our hypothesis, the results showed that individual differences in RS were negatively correlated with GMV in a cluster that primarily included the regions of the PCC, Prec, and calcarine sulcus. In addition, we also found a positive correlation between RS and GMV in the region of the posterior ITG, which is associated with face cognition (Rossion et al., 2003). These results were still significant after controlling for the effects of anxiety and neuroticism. Mediation analysis also excluded the possibility of significant indirect effects of RS on the PCC/Prec and ITG through trait anxiety or neuroticism. These findings suggest an association

Brain Regions	Cluster Size (voxels)	Peak t Values	Peak Coordinates in MNI (<i>x</i> , <i>y</i> , <i>z</i>)	Covariates
Positive Correlation				
Right ITG Negative Correlation	62	5.02*	48, -59, -12	age, sex, total gray matter volume
Right PCC/Prec/Calcarine sulcus	31	-4.56*	9, -63, 17	
Positive Correlation Right ITG	10	4.54*	47, -59, -12	age, sex, total gray matter volume, trait anxiety
Negative Correlation				
Right PCC/Prec/Calcarine sulcus	44	-4.65^{*}	11, -66, 18	
Positive Correlation Right ITG	21	4.64*	48, -59, -12	age, sex, total gray matter volume, neuroticism
Negative Correlation				
Right PCC/Prec/Calcarine sulcus	38	-4.57^{*}	9, -63, 15	
Positive Correlation Right ITG	4	4.48*	47, -59, -12	age, sex, total gray matter volume, neuroticism, trait anxiety
Negative Correlation				
Right PCC/Prec/Calcarine sulcus	43	-4.63*	11, -66, 18	

 Table 3
 Regional gray matter volumes in the 304 participants who completed all questionnaires show significant correlations with RSQ scores when controlling different covariates

PCC, posterior cingulate cortex; Prec, precuneus; ITG, inferior temporal gyrus. * p < .05, corrected for family-wise errors.

between individual differences in RS and GMV in the PCC/ Prec as well as the ITG, which is involved in social cognition.

The present study revealed that the variance in GMV in the PCC/Prec (related to social cognition) was correlated to individual differences in RS. Functional MRI studies have consistently shown that social exclusion evokes greater activation in the regions of the PCC and Prec related to social inclusion. For example, the PCC showed more activity under the condition of social exclusion, relative to fair play, during the game of Cyberball (Bolling, Pitskel, Deen, Crowley, McPartland, et al., 2011; Onoda et al., 2009). Structural changes in the PCC have also been observed in RS-related mental disorders. Structural imaging studies of social anxiety observed reduced GMV in the PCC/Prec (Syal et al., 2012). As compared with healthy controls, young people with generalized anxiety disorders also have smaller GMVs in the left PCC (Strawn et al., 2013). A study of trait anxiety in nonclinical participants revealed that GMV in the PCC was negatively associated with STAI scores (Spampinato et al., 2009). Patients with borderline personality disorder and bipolar disorder, who display deficits in interpersonal relationships, also showed reduced GMV in the region of the PCC, relative to healthy controls (Hazlett et al., 2005; Nugent et al., 2006). Furthermore, a longitudinal study showed increased GM concentration in participants' PCCs after a long time of mindfulness training, which has been demonstrated to be effective in ameliorating the symptoms of mental disorders (Holzel et al., 2011; Roemer, Orsillo, & Salters-Pedneault, 2008). Both structural and functional findings have given rise to the notion that the PCC plays an important role in social interactions. Thus, reduced GMV may partially explain why individuals with high levels of RS have difficulty with dealing with interpersonal problems and are vulnerable to psychological disorders (Beeri & Lev-Wiesel, 2012; Rosenbach & Renneberg, 2011).

In addition, previous studies have shown that the PCC/Prec is a central component of the neural systems for "mentalizing" (Gobbini, Koralek, Bryan, Montgomery, & Haxby, 2007; Mar, 2011). Mentalizing is the ability to explain and predict the behavior of others by attributing intentions and mental states to them (Fletcher et al., 1995; Gallagher & Frith, 2003). As a basic social skill, mentalizing enables individuals to flexibly deal with problems in social interactions (Heatherton & Wagner, 2011). Slaughter, Dennis, and Pritchard (2002) reported that popular children exhibited higher scores on mentalizing tasks than did those classified as rejected. A recent study also revealed that rejection by peers in children is related to poor mentalizing (Caputi, Lecce, Pagnin, & Banerjee, 2012). Individuals with high levels of RS exhibited greater activity in the brain areas implicated in mentalizing when anticipating positive feedback (Kross et al., 2007; Powers et al., 2013). Perhaps the ability to mentalize of high-RS individuals with decreased GMV in the region of the PCC/Prec was impaired, and thus caused them to perceive more rejection in social interactions. Identifying the exact relationships between mentalizing, RS, and the PCC/Prec should be an important goal of future studies.

Likewise, increased GMV in the region of the ITG was found in higher-RS individuals in the present study. ITG is a core part of the occipito-temporal regions that are sensitive to human faces (Haxby, 2001; Rossion et al., 2003). Facial expressions work as a comunication signal and have a pivotal effect in social interactions (Adolphs, 1999; de Gelder, 2009). An fMRI study revealed that the activation of this area was related to social exlcusion (Bolling, Pitskel, Deen, Crowley, Mayes, & Pelphrey, 2011). The ITG was observed to be more activated for negative than for neutral stimuli in a high-anxiety group (Engels et al., 2007). Moreover, increased gray matter in occipito-temporal areas was consistently observed in participants with bipolar disorder (Adler, Levine, DelBello, & Strakowski, 2005; Lochhead, Parsey, Oquendo, & Mann, 2004). Sturctural studies about patients with social anxiety disorder also showed significantly increased cortical thickness in the ITG relative to healthy controls (Frick et al., 2013). Given its enhanced sensitivity to disapproving facial expressions and structural changes in RS-related mental disorders, greater GMV in the right ITG for high-RS individuals may suggest increased sensitivity in the processing of rejectionrelated facial expressions (Burklund, Eisenberger, & Lieberman, 2007). Nevertheless, more research about the role that the ITG plays in RS will be needed in the future.

In the present study, the GMV of the PCC/Prec was negatively related to ITG. When controlling for RS, their correlation became marginally significant. The PCC/Prec and ITG may work together in RS, and the GMVs between the PCC/ Prec and ITG may have a tendency to be related in some way beyond RS. Further studies concerning the structural correlation network may reveal how specific brain areas may be directly linked to the GM structure of other brain regions (Seeley et al., 2009).

This study has some limitations. One is the use of college students. Although it is common to choose college students as participants (He, Xue, Chen, Lu, & Dong, 2013; Jung et al., 2010), the narrow age range made it difficult to examine the effect of age on RS and the developmental trajectory of RS, and it also certainly limits the generalizability of the results. However, the effect of age on individual brain volume was adjusted for by including age as a covariant in the correlation analyses. Much wider age ranges and larger samples will be needed to explore the developmental trajectory of RS in the future. Another is that one may think that RS likely overlaps with individuals' lifetime experiences of rejection. Thus, the results in the present study may be related to past rejection experiences. According to Downey and Feldman (1996), RS is a cognitive-affective processing disposition to anxiously expect, readily perceive, and intensely react to rejection. RS derives from early-onset and prolonged experiences of rejection by significant caregivers or close friends. To some extent, RS is linked to attentional and perceptual processes that underlie the processing of social information and is regarded as a relatively stable characteristic (Romero-Canyas, Downey, Berenson, Ayduk, & Kang, 2010). Rejection experiences are

more like episodic memories and have short-term negative consequences. The sensitivity to rejection can be enhanced by experiences of rejection (Rosenbach & Renneberg, 2011). Therefore, future studies should be designed to explore the effects of rejection experiences on the neural basis of RS.

This is the first study to have explored the associations between GMV structures and individual differences in RS. Previous functional imaging studies had investigated rejection-related brain activation. Our study investigated the anatomical basis of the individual differences in RS and found that structural variations that occur in the PCC/Prec and ITG underlie RS. The results indicate that brain areas involved in social cognition are associated with RS.

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References

- Adler, C. M., Levine, A. D., DelBello, M. P., & Strakowski, S. M. (2005). Changes in gray matter volume in patients with bipolar disorder. *Biological Psychiatry*, 58, 151–157. doi:10.1016/j.biopsych.2005. 03.022
- Adolphs, R. (1999). Social cognition and the human brain. *Trends in Cognitive Sciences*, *3*, 469–479. doi:10.1016/S1364-6613(99) 01399-6
- Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, 38, 95–113. doi:10.1016/j.neuroimage.2007.07.007
- Beeri, A., & Lev-Wiesel, R. (2012). Social rejection by peers: A risk factor for psychological distress. *Child and Adolescent Mental Health*, 17, 216–221. doi:10.1111/j.1475-3588.2011.00637.x
- Bolling, D. Z., Pitskel, N. B., Deen, B., Crowley, M. J., Mayes, L. C., & Pelphrey, K. A. (2011a). Development of neural systems for processing social exclusion from childhood to adolescence. *Developmental Science*, 14, 1431–1444. doi:10.1111/j.1467-7687. 2011.01087.x
- Bolling, D. Z., Pitskel, N. B., Deen, B., Crowley, M. J., McPartland, J. C., Mayes, L. C., & Pelphrey, K. A. (2011b). Dissociable brain mechanisms for processing social exclusion and rule violation. *NeuroImage*, 54, 2462–2471. doi:10.1016/j.neuroimage.2010.10. 049
- Brennan, K. A., Clark, C. L., & Shaver, P. R. (1998). Self-report measurement of adult attachment: An integrative overview. In J. A. Simpson & W. S. Rholes (Eds.), *Attachment theory and close relationships* (pp. 46–76). New York, NY: Guilford Press.
- Burklund, L. J., Eisenberger, N. I., & Lieberman, M. D. (2007). The face of rejection: rejection sensitivity moderates dorsal anterior cingulate activity to disapproving facial expressions. *Social Neuroscience*, 2, 238–253. doi:10.1080/17470910701391711

- Caputi, M., Lecce, S., Pagnin, A., & Banerjee, R. (2012). Longitudinal effects of theory of mind on later peer relations: the role of prosocial behavior. *Developmental Psychology*, 48, 257–270. doi:10.1037/ a0025402
- Chen, Z.-G. (1983). Item analysis of Eysenck Personality Questionnaire tested in Beijing-district. Acta Psychologica Sinica, 15, 85–92.
- Comeau, N., Stewart, S. H., & Loba, P. (2001). The relations of trait anxiety, anxiety sensitivity, and sensation seeking to adolescents' motivations for alcohol, cigarette, and marijuana use. *Addictive Behaviors*, 26, 803–825.
- de Gelder, B. (2009). Why bodies? Twelve reasons for including bodily expressions in affective neuroscience. *Philosophical Transactions of the Royal Society B*, 364, 3475–3484. doi:10.1098/rstb.2009.0190
- DeYoung, C. G., Hirsh, J. B., Shane, M. S., Papademetris, X., Rajeevan, N., & Gray, J. R. (2010). Testing predictions from personality neuroscience. Brain structure and the big five. *Psychological Science*, 21, 820–828. doi:10.1177/0956797610370159
- Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. *Psychological Bulletin*, 130, 355–391. doi:10.1037/0033-2909.130.3.355
- Downey, G., & Feldman, S. I. (1996). Implications of rejection sensitivity for intimate relationships. *Journal of Personality and Social Psychology*, 70, 1327–1343.
- Downey, G., Feldman, S., & Ayduk, O. (2000). Rejection sensitivity and male violence in romantic relationships. *Personal Relationships*, 7, 45–61.
- Downey, G., Freitas, A. L., Michaelis, B., & Khouri, H. (1998). The selffulfilling prophecy in close relationships: Rejection sensitivity and rejection by romantic partners. *Journal of Personality and Social Psychology*, 75, 545–560.
- Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Neuroplasticity: Changes in grey matter induced by training. *Nature*, 427, 311–312. doi:10.1038/427311a
- Drevets, W. C. (2000). Neuroimaging studies of mood disorders. Biological Psychiatry, 48, 813–829.
- Eisenberger, N. I. (2012). The pain of social disconnection: Examining the shared neural underpinnings of physical and social pain. *Nature Reviews Neuroscience*, 13, 421–434. doi:10.1038/nrn3231
- Eisenberger, N. I., Lieberman, M. D., & Williams, K. D. (2003). Does rejection hurt? An fMRI study of social exclusion. *Science*, 302, 290–292. doi:10.1126/science.1089134
- Engels, A. S., Heller, W., Mohanty, A., Herrington, J. D., Banich, M. T., Webb, A. G., & Miller, G. A. (2007). Specificity of regional brain activity in anxiety types during emotion processing. *Psychophysiology*, 44, 352–363. doi:10.1111/j.1469-8986.2007. 00518.x
- Eysenck, H. J., & Eysenck, S. B. G. (1975). Manual of the Eysenck Personality Questionnaire (junior and adult). London, UK: Hodder & Stoughton.
- Fletcher, P. C., Happé, F., Frith, U., Baker, S. C., Dolan, R. J., Frackowiak, R. S. J., & Frith, C. D. (1995). Other minds in the brain: A functional imaging study of "theory of mind" in story comprehension. *Cognition*, 57, 109–128. doi:10.1016/0010-0277(95)00692-R
- Frick, A., Howner, K., Fischer, H., Eskildsen, S. F., Kristiansson, M., & Furmark, T. (2013). Cortical thickness alterations in social anxiety disorder. *Neuroscience Letters*, 536, 52–55. doi:10.1016/j.neulet. 2012.12.060
- Gallagher, H. L., & Frith, C. D. (2003). Functional imaging of "theory of mind. *Trends in Cognitive Sciences*, 7, 77–83. doi:10.1016/S1364-6613(02)00025-6
- Gardini, S., Cloninger, C. R., & Venneri, A. (2009). Individual differences in personality traits reflect structural variance in specific brain regions. *Brain Research Bulletin*, 79, 265–270. doi:10.1016/j. brainresbull.2009.03.005

- Gobbini, M. I., Koralek, A. C., Bryan, R. E., Montgomery, K. J., & Haxby, J. V. (2007). Two takes on the social brain: a comparison of theory of mind tasks. *Journal of Cognitive Neuroscience*, 19, 1803– 1814. doi:10.1162/jocn.2007.19.11.1803
- Haxby, J. V. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science*, 293, 2425–2430. doi:10.1126/science.1063736
- Hazlett, E. A., New, A. S., Newmark, R., Haznedar, M. M., Lo, J. N., Speiser, L. J., & Buchsbaum, M. S. (2005). Reduced anterior and posterior cingulate gray matter in borderline personality disorder. *Biological Psychiatry*, 58, 614–623. doi:10.1016/j.biopsych.2005.04.029
- He, Q., Xue, G., Chen, C., Lu, Z. L., & Dong, Q. (2013). Decoding the neuroanatomical basis of reading ability: A multivoxel morphometric study. *Journal of Neuroscience*, 33, 12835–12843. doi:10.1523/ jneurosci.0449-13.2013
- Heatherton, T. F., & Wagner, D. D. (2011). Cognitive neuroscience of self-regulation failure. *Trends in Cognitive Sciences*, 15, 132–139. doi:10.1016/j.tics.2010.12.005
- Holzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., & Lazar, S. W. (2011). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research*, 191, 36–43. doi:10.1016/j.pscychresns.2010.08.006
- Hsu, D. T., Sanford, B. J., Meyers, K. K., Love, T. M., Hazlett, K. E., Wang, H., & Zubieta, J. K. (2013). Response of the µ-opioid system to social rejection and acceptance. *Molecular Psychiatry*, 18, 1211–1217.
- Jung, R. E., Segall, J. M., Bockholt, H. J., Flores, R. A., Smith, S. M., Chavez, R. S., & Haier, R. J. (2010). Neuroanatomy of creativity. *Human Brain Mapping*, 31, 398–409. doi:10.1002/hbm.20874
- Kanai, R., & Rees, G. (2011). The structural basis of inter-individual differences in human behaviour and cognition. *Nature Reviews Neuroscience*, 12, 231–242. doi:10.1038/nm3000
- Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomic Bulletin & Review*, 9, 637–671. doi:10.3758/BF03196323
- Kross, E., Egner, T., Ochsner, K., Hirsch, J., & Downey, G. (2007). Neural dynamics of rejection sensitivity. *Journal of Cognitive Neuroscience*, 19, 945–956. doi:10.1162/jocn.2007.19.6.945
- Lochhead, R. A., Parsey, R. V., Oquendo, M. A., & Mann, J. J. (2004). Regional brain gray matter volume differences in patients with bipolar disorder as assessed by optimized voxel-based morphometry. *Biological Psychiatry*, 55, 1154–1162. doi:10.1016/j.biopsych. 2004.02.026
- MacDonald, G., & Leary, M. R. (2005). Why does social exclusion hurt? The relationship between social and physical pain. *Psychological Bulletin*, 131, 202–223. doi:10.1037/0033-2909.131.2.202
- Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlasbased interrogation of fMRI data sets. *NeuroImage*, 19, 1233–1239.
- Manji, H. K., Moore, G. J., Rajkowska, G., & Chen, G. (2000). Neuroplasticity and cellular resilience in mood disorders. *Molecular Psychiatry*, 5, 578–593.
- Mar, R. A. (2011). The neural bases of social cognition and story comprehension. *Annual Review of Psychology*, 62, 103–134. doi: 10.1146/annurev-psych-120709-145406
- Masten, C. L., Eisenberger, N. I., Borofsky, L. A., Pfeifer, J. H., McNealy, K., Mazziotta, J. C., & Dapretto, M. (2009). Neural correlates of social exclusion during adolescence: understanding the distress of peer rejection. *Social Cognitive and Affective Neuroscience*, 4, 143– 157. doi:10.1093/scan/nsp007
- May, A., & Gaser, C. (2006). Magnetic resonance-based morphometry: A window into structural plasticity of the brain. *Current Opinion in Neurology*, 19, 407–411.
- Mechelli, A., Price, C. J., Friston, K. J., & Ashburner, J. (2005). Voxelbased morphometry of the human brain: methods and applications. *Current Medical Imaging Reviews*, 1, 105–113.

- Nezlek, J. B., & Plesko, R. M. (2001). Day-to-day relationships among self-concept clarity, self-esteem, daily events, and mood. *Personality and Social Psychology Bulletin, 27*, 201–211. doi:10. 1177/0146167201272006
- Nugent, A. C., Milham, M. P., Bain, E. E., Mah, L., Cannon, D. M., Marrett, S., & Drevets, W. C. (2006). Cortical abnormalities in bipolar disorder investigated with MRI and voxel-based morphometry. *NeuroImage*, 30, 485–497. doi:10.1016/j.neuroimage.2005.09.029
- Onoda, K., Okamoto, Y., Nakashima, K., Nittono, H., Ura, M., & Yamawaki, S. (2009). Decreased ventral anterior cingulate cortex activity is associated with reduced social pain during emotional support. *Social Neuroscience*, *4*, 443–454. doi:10.1080/ 17470910902955884
- Onoda, K., Okamoto, Y., Nakashima, K., Nittono, H., Yoshimura, S., Yamawaki, S., & Ura, M. (2010). Does low self-esteem enhance social pain? The relationship between trait self-esteem and anterior cingulate cortex activation induced by ostracism. *Social Cognitive* and Affective Neuroscience, 5, 385–391. doi:10.1093/scan/nsq002
- Parker, G., Roy, K., Mitchell, P., Wilhelm, K., Malhi, G., & Hadzi-Pavlovic, D. (2002). Atypical depression: a reappraisal. *American Journal of Psychiatry*, 159, 1470–1479.
- Pickett, C. L., Gardner, W. L., & Knowles, M. (2004). Getting a cue: The need to belong and enhanced sensitivity to social cues. *Personality* and Social Psychology Bulletin, 30, 1095–1107.
- Powers, K. E., Somerville, L. H., Kelley, W. M., & Heatherton, T. F. (2013). Rejection sensitivity polarizes striatal-medial prefrontal activity when anticipating social feedback. *Journal of Cognitive Neuroscience*, 25, 1887–1895. doi:10.1162/jocn a 00446
- Preacher, K. J., & Hayes, A. F. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior Research Methods*, 40, 879–891. doi:10. 3758/BRM.40.3.879
- Premkumar, P. (2012). Are you being rejected or excluded? Insights from neuroimaging studies using different rejection paradigms. *Clinical Psychopharmacology and Neuroscience*, 10, 144–154. doi:10.9758/ cpn.2012.10.3.144
- Roemer, L., Orsillo, S. M., & Salters-Pedneault, K. (2008). Efficacy of an acceptance-based behavior therapy for generalized anxiety disorder: Evaluation in a randomized controlled trial. *Journal of Consulting* and Clinical Psychology, 76, 1083–1089. doi:10.1037/a0012720
- Romero-Canyas, R., Downey, G., Berenson, K., Ayduk, O., & Kang, N. J. (2010). Rejection sensitivity and the rejection–hostility link in romantic relationships. *Journal of Personality*, 78, 119–148. doi:10. 1111/j.1467-6494.2009.00611.x
- Rosenbach, C., & Renneberg, B. (2011). Rejected, excluded, ignored: The perception of social rejection and mental disorders—A review. *Verhaltenstherapie*, 21, 87–98. doi:10.1159/000328839
- Rossion, B., Caldara, R., Seghier, M., Schuller, A. M., Lazeyras, F., & Mayer, E. (2003). A network of occipito-temporal face-sensitive

areas besides the right middle fusiform gyrus is necessary for normal face processing. *Brain, 126*, 2381–2395. doi:10.1093/brain/awg241

- Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L., & Greicius, M. D. (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron*, 62, 42–52. doi:10.1016/j.neuron.2009.03.024
- Slaughter, V., Dennis, M. J., & Pritchard, M. (2002). Theory of mind and peer acceptance in preschool children. *British Journal of Developmental Psychology*, 20, 545–564.
- Somerville, L. H., Heatherton, T. F., & Kelley, W. M. (2006). Anterior cingulate cortex responds differentially to expectancy violation and social rejection. *Nature Neuroscience*, 9, 1007–1008. doi:10.1038/ nn1728
- Spampinato, M. V., Wood, J. N., De Simone, V., & Grafman, J. (2009). Neural correlates of anxiety in healthy volunteers: a voxel-based morphometry study. *Journal of Neuropsychiatry and Clinical Neurosciences*, 21, 199–205. doi:10.1176/appi.neuropsych.21.2.199
- Spielberger, C. D. (1983). Manual for the State–Trait Anxiety Inventory (STAI, Form Y, "Self-Evaluation Questionnaire"). Palo Alto CA: Consulting Psychologists Press.
- Staebler, K., Helbing, E., Rosenbach, C., & Renneberg, B. (2011). Rejection sensitivity and borderline personality disorder. *Clinical Psychology and Psychotherapy*, 18, 275–283. doi:10.1002/cpp.705
- Strawn, J. R., Wehry, A. M., Chu, W.-J., Adler, C. M., Eliassen, J. C., Cerullo, M. A., & DelBello, M. P. (2013). Neuroanatomic abnormalities in adolescents with generalized anxiety disorder: A voxelbased morphometry study. *Depression and Anxiety*, 30, 842–848. doi:10.1002/da.22089
- Syal, S., Hattingh, C. J., Fouché, J.-P., Spottiswoode, B., Carey, P. D., Lochner, C., & Stein, D. J. (2012). Grey matter abnormalities in social anxiety disorder: A pilot study. *Metabolic Brain Disease*, 27, 299–309. doi:10.1007/s11011-012-9299-5
- Takeuchi, H., Taki, Y., Nouchi, R., Sekiguchi, A., Kotozaki, Y., Miyauchi, C. M., & Kawashima, R. (2014). Regional gray matter density is associated with achievement motivation: Evidence from voxel-based morphometry. *Brain Structure and Function*, 219, 71– 83. doi:10.1007/s00429-012-0485-3
- Yoo, H. K., Kim, M. J., Kim, S. J., Sung, Y. H., Sim, M. E., Lee, Y. S., & Lyoo, I. K. (2005). Putaminal gray matter volume decrease in panic disorder: An optimized voxel-based morphometry study. *European Journal of Neuroscience*, 22, 2089–2094. doi:10.1111/j.1460-9568. 2005.04394.x
- Zahn-Waxler, C., Klimes-Dougan, B., & Slattery, M. J. (2000). Internalizing problems of childhood and adolescence: Prospects, pitfalls, and progress in understanding the development of anxiety and depression. *Development and Psychopathology*, 12, 443–466.
- Zhang, Z., Liao, W., Zuo, X. N., Wang, Z., Yuan, C., Jiao, Q., & Liu, Y. (2011). Resting-state brain organization revealed by functional covariance networks. *PLoS ONE*, *6*, e28817. doi:10.1371/journal. pone.0028817