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RESEARCH ARTICLE

Neuroticism and extraversion mediate the association between loneliness and the dorsolateral prefrontal cortex

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Abstract Loneliness is an unpleasant and distressing feeling that a person experiences when he/she perceives that his/her social relationships are lacking in someway, either quantitatively or qualitatively; this can be linked to anxiety, depression, and suicide risk. Previous studies have found that certain personality traits (which are temporally stable and heritable) are predictors of loneliness. However, little empirical evidence is available on the brain structures associated with loneliness, as well as how personality traits impact the relationship between loneliness and brain structure. Thus, the current study used voxel-based morphometry to identify the brain structures underlying individual differences in loneliness (as measured by the UCLA Loneliness Scale) in a large sample, and then, applied multiple mediation analyses to explore the nature of the influence of personality traits on the relationship between loneliness and brain structure. The results showed that lonely individuals had greater regional gray matter volume in the left dorsolateral prefrontal cortex (DLPFC), which might reflect immature functioning in terms of emotional regulation. More importantly, we found that neuroticism and extraversion partially mediated the relationship between the left DLPFC and loneliness. In summary, through morphometric and multiple mediation analyses, this paper further validates the influence of both neuroticism and extraversion on loneliness.

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Introduction

Loneliness is an unpleasant and distressing feeling that a person experiences when he/she perceives his/her social relationships to be lacking in someway, either quantitatively or qualitatively (Perlman and Peplau 1981, 1982). Obviously, the definition emphasizes the affective character of loneliness. Specifically, loneliness involves many emotional aspects such as sorrow, sadness and feelings of frustration, shame, and desperation (Shute and Howitt 1990). Loneliness is a common phenomenon in contemporary societies (Putnam 2000; McPherson et al. 2006; Kanai et al. 2012). Some surveys have reported that 15–30 % of people experience persistent feelings of loneliness (Sermat and Hartog 1980; Andersson 1982). In addition, loneliness very frequently occurs during earlier developmental periods (Peplau and Perlman 1982; Perlman and Landolt 1999). For example, in a large-scale investigation, Parlee (1979) found that 79 % of subjects aged younger than 18 years and 71 % of 18- to 24-year-olds reported feeling lonely sometimes or often. Although loneliness can be a normative experience, it can also be pathological (Asher and Paquette 2003). Numerous researchers have confirmed that loneliness is linked to anxiety, depression, and suicide risk (Moore and Schultz 1983; Koenig et al. 1994; Roberts et al. 1998; Lau et al. 1999; Johnson et al. 2001; Lasgaard 2007).

Moreover, many studies have investigated the relationship between loneliness and personality traits and found that neuroticism, extraversion, and psychoticism might be the predictors of loneliness (Hojat 1982; Stokes 1985;

Saklofske and Yackulic 1989; Halamandaris and Power 1999; Cheng and Furnham 2002; Atak 2009). It is well known that neuroticism and extraversion are the most important and frequently studied traits of personality and are correlated with emotional experience (Williams 1990; Kardum and Hudek-Knežević 1996; Furnham and Cheng 1999). For example, neurotic individuals are typically described with negative emotional terms such as depression and anxiety, whereas extraverted individuals are typically described with positive emotional terms such as excitement and enthusiasm (Eysenck and Eysenck 1991). At the same time, psychoticism is proposed to indicate a predisposition toward coldness, aggressiveness, egocentrism, impersonality and antisocial nature, lack of empathy, creativity, impulsivity, and tough-mindedness (Eysenck and Eysenck 1985); thus, it is a trait which encompasses relatively powerful emotional content (Zuckerman 1989). These personality traits (neuroticism, extraversion, and psychoticism) are good candidates for research because their temporal stability and heritability make them likely to have an impact on function throughout the life cycle (Loehlin and Martin 2001; Birley et al. 2006; Bratko and Butkovic 2007; Ivkovic et al. 2007; Wray et al. 2007). However, so far, little empirical evidence is available on how personality impacts the relationship between loneliness and brain structure.

As of now, there are few neuroimaging studies about the neural processes related to loneliness. For example, Eisenberger et al. (2003) indicated that the anterior cingulate cortex (ACC; related to increased distress after social exclusion) and right ventral prefrontal cortex (PFC; correlated with diminished distressing after social exclusion) were active during the social pain participants felt during an episode of social exclusion. At the same time, some neuroimaging studies have revealed that neuroticism and extraversion were also significantly correlated with the lateral PFC and ACC (Canli et al. 2001; Eisenberger et al. 2005). Kross et al. (2011) also found that the secondary somatosensory cortex and dorsal posterior insula became active when participants thought about being rejected by their ex-partner. In a recent voxel-based morphometry (VBM) study, Kanai et al. (2012) showed that those who are more prone to loneliness had less gray matter volume (GMV) in the left posterior superior temporal sulcus (pSTS), which may reflect deficiencies in processing social cues (social perception plays a crucial role in shaping an individual's experience of loneliness). Moreover, they also found that social network size, anxiety, and empathy independently contributed to loneliness. However, they did not explore the relationship between personality and loneliness. In addition, the development of top-down prefrontal regions during adolescence is immature relative to the development of bottom-up striatal regions implicated in the detection of salient cues in the environment (Somerville and Casey 2010); that is, characteristics of adolescence, such as susceptibility to social rejection or isolation from others, are associated with deficiencies in the development in these brain areas (e.g., PFC, pSTS), which can in turn lead to loneliness. More studies are needed to explore these brain structures and their functional roles. The current study was conducted with the aim of bridging these gaps in the literature.

The current study aimed to explore the relationship between brain structures and loneliness (measured by the UCLA Loneliness Scale) (Russell 1996) in a relatively large sample of normal Chinese young adults ($N = 308$). We used VBM to identify the brain structures underlying individual differences in loneliness. Moreover, even though it is believed that personality traits (neuroticism, extraversion and psychoticism) are predictors of loneliness (Hojat 1982; Stokes 1985; Saklofske and Yackulic 1989; Halamandaris and Power 1999; Cheng and Furnham 2002; Atak 2009), the nature of the influence of personality on the relationship between loneliness and brain structure is unclear. Thus, we further tried to explore whether personality mediated the relationship between brain structure and loneliness. Specifically, we hypothesized that: (1) loneliness is correlated with certain personality traits (neuroticism, extraversion, and psychoticism); (2) individual differences in loneliness are associated with the regional gray matter volume (rGMV) in the brain regions responsible for emotion (e.g., PFC) and social perception (e.g., pSTS); and (3) personality traits (neuroticism, extraversion, and psychoticism) mediate the relationship between specific brain regions (identified using VBM) and loneliness. It was thought that the use of morphometric results combined with a multiple mediation analysis could further validate the influence of personality traits on loneliness.

Materials and methods

Participants

A total of 308 right-handed, healthy volunteers (167 females; age range 18–27 years, mean ± SD 19.94 ± 1.27) participated in this study, which was conducted as a part of our ongoing project to examine the association between brain imaging, creativity, and mental health. All participants were undergraduate or postgraduate students from Southwest University, China. All participants completed the University of California Los Angeles (UCLA) Loneliness Scale (Russell 1996) and the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eysenck 1969), which has emerged as an important psychometric theory in the field of personality. None of the participants had a history of neurological or psychiatric illness. This study was approved by the local ethics committee of Southwest China

University and by the Institutional Human Participants Review Board of Southwest University Imaging Center for Brain Research. All participants provided written informed consent prior to taking part in the study.

Assessment of loneliness

The UCLA Loneliness Scale was designed to assess subjective feelings of loneliness or social isolation. The scale comprises 20 items, which are scored on a four-point Likert-type scale, where 1 = Never and 4 = Always; the total scores range from 20 (low level of loneliness) to 80 (high level of loneliness). An example statement is, "How often do you feel that there is no one you can turn to?" Items are counterbalanced to account for social desirability. The scale has adequate internal consistency and test–retest reliability (Russell 1996) and was shown to have a high level of internal consistency (Cronbach's $\alpha = 0.83$) in our sample.

Assessment of EPQ

The EPQ is a self-report questionnaire on three different personality dimensions— neuroticism, extraversion, and psychoticism—and a validity dimension—lie (Eysenck and Eysenck 1969; Chen 1983). Participants are required to respond with "true" or "false" in response to each of the 85 statements. Gender-specific normative data were used to calculate the *t*-scores for neuroticism, extraversion, and psychoticism, which were the main variables of interest. The EPQ has demonstrated adequate reliability and validity (Chen 1983). In addition, the scale has shown satisfactory internal consistency for neuroticism (Cronbach's $\alpha = 0.82$), extraversion (Cronbach's $\alpha = 0.80$), and psychoticism (Cronbach's $\alpha = 0.72$) in our sample.

MRI data acquisition

MRI scans were acquired on a 3.0T Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany). High-resolution T1-weighted anatomical images were acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time = 1,900 ms; echo time = 2.52 ms; inversion time = 900 ms; flip angle = 9°; resolution matrix = 256 × 256; slices = 176; thickness = 1.0 mm; voxel size = 1 × 1 × 1 mm).

Image processing for VBM

MRI scans were processed using the Statistical Parametric Mapping software (SPM8; Welcome Department of Cognitive Neurology, London, UK [www.fil.ion.ucl.ac/spm]) implemented in MATLAB 7.8 (MathWorks Inc., Natick, MA, USA). First, MRI scans were assessed by manual inspection for artifacts or gross anatomical abnormalities. For better registration, the reorientation of the images was manually set to the anterior commissure. Second, the images were segmented into three distinct tissue classes—gray matter, white matter, and cerebrospinal fluid—using the new segmentation tool in SPM8. Third, diffeomorphic anatomical registration through exponentiated lie (DARTEL) algebra was used for registration, normalization, and modulation (Ashburner and Friston 2005; Ashburner 2007). Fourth, to ensure that regional differences in the absolute amount of gray matter were conserved and to preserve the volume of tissue from each structure after warping, gray matter voxel values were modulated by multiplying the Jacobian determinants derived from the normalization (Good et al. 2002). The registered images were then transformed to Montreal Neurological Institute (MNI) space. Finally, the normalized, modulated gray matter images were smoothed with a 10-mm full-width at half-maximum Gaussian kernel to increase the signal-to-noise ratio.

Statistical analysis of VBM

Statistical analyses of GMV data were performed using SPM8. For whole-brain analyses, we performed multiple linear regression analysis with loneliness as the independent variable and voxel-wise GMV as the dependent variable. Loneliness was used as the variable of interest in the multiple linear regression analyses. Age and gender were treated as nuisance variables because both of them may affect brain structure (Good et al. 2002; Sowell et al. 2003), and total GMV (tGMV) was entered as a nuisance variable due to differences in head size (Bendfeldt et al. 2009). We also applied explicit masking with a population-specific optimal threshold using the masking toolbox in SPM8 to restrict the search volume within gray matter and white matter (http://www0.cs.ucl.ac.uk/staff/g.ridgway/masking/). This approach reduced the risk of false negatives caused by overly restrictive masking (in comparison with the use of absolute or relative threshold masking), as potentially interesting voxels were excluded from the statistical analysis (Ridgway et al. 2009). For all analyses, multiple comparison correction was carried out on the whole-brain data using the voxel-level family-wise error (FWE) approach and the corrected threshold was set at $P < 0.05$.

Furthermore, to examine the correlation between loneliness and regional brain volume, regions of interest (ROIs) were defined by a sphere with a radius of 6 mm, centered on the peak coordinate of the cluster obtained in the above analysis. The correlation between loneliness and the mean GM volume of the ROI was calculated while controlling for age, gender, and tGMV.

Table 1 Participant demographics ($N = 308$; males = 141, females = 167)

Measure	Mean (SD)	Range	1	2	3	4	5	6
Age	19.94 (1.27)	18–27	–					
UCLA loneliness	41.70 (7.87)	24–62	–	–				
EPQ (*t*-score)								
Extraversion	57.55 (10.21)	33–77	–	−0.45**	–			
Neuroticism	51.55 (10.42)	31–78	–	0.44**	−0.23**	–		
Psychoticism	51.33 (7.82)	32–73	–	0.17**	−0.03	0.24**	–	
Left DLPFC	–	–	–	0.27**	0.21**	−0.13*	0.03	–

Pearson's bivariate correlations, shown are *r*-values

N number, *SD* standard deviation, *UCLA Loneliness scale* University of California Los Angeles Loneliness scale, *EPQ* Eysenck Personality Questionnaire, *left DLPFC* left dorsolateral prefrontal cortex

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

Multiple mediation analyses

To test how personality impacts the relationship between loneliness and individual differences in brain structures, we employed a multiple mediation model using the SPSS macros for bootstrapping (Preacher and Hayes 2008). Multiple mediation models comprise two parts: (1) investigating the total indirect effect, namely whether the set of mediators (personality traits) transmit the effect of X (brain structures) to Y (loneliness); (2) testing hypotheses regarding individual mediators in the context of a multiple mediator model (i.e., investigating the specific indirect effect associated with each putative mediator). The total effect (c) of the independent variable on the dependent variable is the sum of the direct effect (c') and all of the specific indirect effects ($a_1.b_1 + a_2.b_2 + \cdots$), namely, $c = c' + a_1.b_1 + a_2.b_2 + \cdots$. The total indirect effect can also be calculated as $c–c'$. Estimates of all paths are computed using ordinary least squares (OLS) regression. An indirect effect was considered to be significant if its 95 % bootstrap confidence intervals from 2,000 bootstrap samples did not include zero. The indirect, direct, and total effects of the brain structures on loneliness were calculated while controlling for age, gender, and tGMV effects.

Results

Descriptive data analysis

Age, gender, UCLA loneliness scores, and EPQ *t*-scores for this sample are shown in Table 1. The results revealed that loneliness was positively correlated with neuroticism ($r = 0.44$, $P < 0.001$) and psychoticism ($r = 0.17$, $P < 0.01$), and negatively related to extraversion ($r = -0.45$, $P < 0.001$).

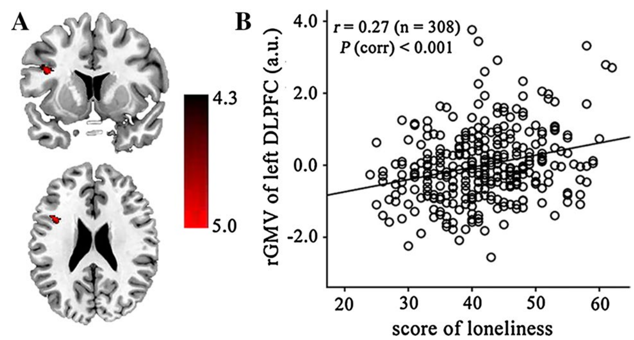

Fig. 1 Correlation between regional gray matter volume (rGMV) and loneliness, as measured by the UCLA Loneliness Scale. **a** The left dorsolateral prefrontal cortex (DLPFC) exhibited significant positive correlation with loneliness ($n = 308$). The results are shown with a threshold of P[FWE-corr] = 0.007. **b** A *scatter plot* showing the correlation between loneliness and the rGMV of left DLPFC adjusted for age, gender, and total GMV (shown for illustrative purposes only)

VBM analysis

After controlling for age, gender, and tGMV, the results revealed a positive correlation between loneliness and the rGMV of a cluster, which mainly included areas in the left DLPFC ($r = 0.27$; cluster size = 76; $t = 4.94$; Brodmann areas, 9; MNI coordinates: −41, 12, 23; $P = 0.007$ corrected for multiple comparisons using the voxel-level FWE at the whole-brain level; see Fig. 1) (Benson et al. 2008; Causse et al. 2013). There were no negative correlations between loneliness and the rGMV of any brain area ($P > 0.05$, FWE corrected).

Neuroticism and extraversion mediate the association between the left DLPFC and loneliness

To examine whether personality mediates the relationship between the brain structures identified in the

Table 2 Indirect effects of the left DLPFC on loneliness through neuroticism and extraversion

	Point estimate	Boot	SE	*df*	Bootstrapping BC 95 % CI	
					Lower limit	Upper limit
Total	0.1425	0.1424	0.0411	301	0.0635	0.2294
Neuroticism	0.0871	0.0866	0.0275		0.0398	0.1513
Extraversion	0.0555	0.0557	0.0253		0.0098	0.1105
C_1	0.0316	0.0309	0.0331		−0.0276	0.1048

C_1 Difference between the indirect effects of neuroticism and extraversion, *SE* standard error, *df* degree of freedom, *BC* bias corrected confidence intervals, 2,000 bootstrap samples

aforementioned VBM study and loneliness, we conducted multiple mediation analyses. Table 1 provides Pearson's correlations for the measures of EPQ (neuroticism, extraversion and psychoticism), loneliness, and the rGMV of left DLPFC identified in the VBM analysis. In addition, after controlling for age, gender, and tGMV effects, the correlations of the left DLPFC with loneliness, neuroticism, extraversion, and psychoticism were calculated. The correlations revealed that loneliness was significantly positively correlated with neuroticism ($r = 0.44$, $P < 0.001$) and psychoticism ($r = 0.17$, $P < 0.01$), and negatively associated with extraversion ($r = -0.45$, $P < 0.001$). Moreover, the rGMV of left DLPFC was positively correlated with neuroticism ($r = 0.14$, $P < 0.05$) and negatively correlated with extraversion ($r = -0.12$, $P < 0.05$). However, there was no correlation between the left DLPFC and psychoticism ($P > 0.05$) and the prerequisite for mediation was not satisfied, so it was concluded that psychoticism was not a mediator.

The total effect of the left DLPFC on loneliness was significant ($c = 0.3381$, $P < 0.0001$). After adjusting for the indirect effects of the mediators, the direct effect of the left DLPFC on loneliness was attenuated but remained significant ($c' = 0.1983$, $P = 0.0009$). While these results suggest a partial mediation scenario, more recent statistical research suggests the importance of examining the indirect effects separately, given that the total effect is not necessary for mediation to occur (MacKinnon et al. 2000; Shrout and Bolger 2002; Preacher and Hayes 2008). Table 2 contains the parameter estimates for the total and specific indirect effects on the association between the left DLPFC and loneliness as mediated by neuroticism and extraversion. The total indirect effect and the indirect effects of neuroticism and extraversion were significant, as evidenced by the confidence intervals that did not contain zero. As illustrated in Fig. 2, the left DLPFC was significantly related to the two mediators, which in turn were significantly related to loneliness. Finally, there were no significant contrasts between the mediators, indicating that no mediator had a significantly greater indirect effect than other mediators on loneliness.

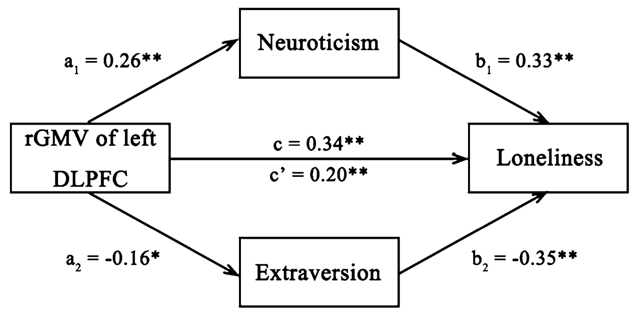

Fig. 2 Paths linking the rGMV of left DLPFC to loneliness via neuroticism and extraversion. $^*P < 0.05$, $^{**}P < 0.01$

Discussion

This study investigated the association between brain structures and individual loneliness in a large sample and tried to explore which personality trait would be able to mediate the relationship between brain structure and loneliness. Our results showed that more lonely individuals had greater rGMV in the left DLPFC. Out of particular interest, we found that neuroticism and extraversion partially mediated the relationship between the left DLPFC and loneliness. The role of rGMV variations within the left DLPFC and the implication of the relationship between loneliness, the left DLPFC, and neuroticism (or extraversion) are discussed below.

Previous studies have indicated that the DLPFC plays a crucial role in working memory (Smith et al. 1998; Daskalakis et al. 2008; Hoppenbrouwers et al. 2013), executive functioning (Wagner et al. 2001), and emotion regulation (Banks et al. 2007; Rilling et al. 2007; Ruocco et al. 2013). The DLPFC is one of the brain regions implicated in emotional processing, particularly during down-regulation of negative emotional conditions (Davidson et al. 2000). For instance, certain aspects of emotional regulation have been associated with increased activity in prefrontal regions, which include the DLPFC and dorsomedial PFC (DMPFC) (Albaugh et al. 2013). Increased activity in the DLPFC was reported in an fMRI study during the processing of positive emotional stimuli in comparison with the processing of neutral and negative ones (Dolcos et al. 2004). Further, Ruocco et al. (2013) found bilateral reduction in activation within the DLPFC in bipolar disorder patients relative to control subjects, which likely reflects a diminished capacity for cognitive control in the modulation of subjectively experienced negative emotions. Furthermore, a number of studies using electrophysiological and/or functional neuroimaging techniques have reported consistently increased activity in the DLPFC under reappraisal conditions (modifying the intensity of emotional stimuli using cognitive strategies) (Ochsner et al. 2002; Kim and Hamann 2007). With regard to the involvement of the DLPFC in higher order cognitive functions such as working memory (Smith et al. 1998; Daskalakis et al. 2008), the findings of the previous studies suggest that lower working memory capacity is associated with less control over emotional responses and reduced emotional self-regulation following negative feedback (Schmeichel et al. 2008; Schmeichel and Demaree 2010). In brief, it is suggested that increased rGMV in the left DLPFC may contribute to loneliness through "inefficient emotion regulation" functions that are associated with this region (Dronkers et al. 2004; Binder et al. 2009; Turken and Dronkers 2011).

Recently, several studies have indicated that "the larger the volume, the better the function" premise does not always hold true (Kanai and Rees 2011; Takeuchi et al. 2011). For example, one of these studies reported an association between lower rostrolateral PFC volume and stronger self-referential ability, and a relationship between greater volume in the dorsal part of the ACC and increase in negative mood (Takeuchi et al. 2014b). Further, Kanai and Rees (2011) found that lower cortical volume can sometimes be associated with better task performance. Indeed, there is evidence that the gray matter of brain regions (e.g., prefrontal regions) can thin over time during the course of normal development (Sowell et al. 2003; Decety et al. 2004; Amodio and Frith 2006; Buckner et al. 2008; Schulte-Rüther et al. 2011). For instance, there is a decrease in GMV in the prefrontal regions during adolescence, which might represent more effective synaptic and/or neuronal pruning processes (i.e., the process of removing inefficient synapses and neurons over a lifetime) (Kanai and Rees 2011; Takeuchi et al. 2014a). Based on these findings, we think that the increased rGMV in the left DLPFC within prefrontal regions may be reflective of neuronal immaturity, which is mainly due to brain maturation characterized by cortical thinning such as effective synaptic pruning. Therefore, increased DLPFC volume is linked to more negative moods (inefficient emotion regulation), which in turn enhances an individual's feeling of loneliness.

Interestingly, the current study found that neuroticism and extraversion partially mediated the relationship between the left DLPFC and loneliness. However, this mediation effect was not observed for psychoticism, which was also correlated with loneliness. The result might suggest that psychoticism contributes to loneliness, but its association with loneliness might be independent of the left DLPFC structure. Many previous papers have reported that neuroticism and extraversion show temporal stability and heritability (Birley et al. 2006; Bratko and Butkovic 2007; Ivkovic et al. 2007; Wray et al. 2007) and are strongly associated with loneliness (Stokes 1985; Saklofske and Yackulic 1989; Halamandaris and Power 1999; Atak 2009). In fact, our behavioral data also showed that the *t*-scores for neuroticism and extraversion were significantly related to loneliness. However, the nature of the influence of neuroticism and extraversion on the relationship between loneliness and brain structure is unclear. Based on the above discussion, we think that increased DLPFC volume is linked to more negative moods (inefficient emotion regulation); thus, a lack of inhibitory control (disrupted synaptic or neuronal pruning of the DLPFC) might facilitate the development of neuroticism and inhibit the development of extraversion, which is likely to exacerbate feelings of loneliness (e.g., negative thinking, social rejection, and isolation). Although we cannot determine the direction of causation among neuroticism (or extraversion), loneliness, and left DLPFC involvement, we hypothesize that the left DLPFC predicts neuroticism (or extraversion), which in turn influences and predicts loneliness.

Conclusions

The present study used VBM to examine the structural correlates of individual loneliness. We found a positive correlation between the rGMV of left DLPFC and loneliness. This finding indicated that inefficient emotional regulation may lead an individual to develop vulnerability to social rejection or isolation, thereby enhancing loneliness. In addition, we found that neuroticism and extraversion partially mediated the relationship between the left DLPFC and loneliness, that is, higher neuroticism or lower extraversion might be associated with increased rGMV in the left DLPFC, which may in turn be linked to individual loneliness. Neuroticism and extraversion might therefore play important roles in shaping an individual's feeling of loneliness. In summary, through morphometric and multiple mediation analyses, this paper further validates the influence of both neuroticism and extraversion on loneliness. The implementation of longitudinal or intervention studies may further help to elucidate the complex relationships between loneliness, brain structure, and personality.

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Conflict of interest The authors declare no competing interests.

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