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Connectome-based individualized prediction of loneliness

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Abstract

Loneliness is an increasingly prevalent condition linking with enhanced morbidity and premature mortality. Despite recent proposal on medicalization of loneliness, so far no effort has been made to establish a model capable of predicting loneliness at the individual level. Here, we applied a machine-learning approach to decode loneliness from whole-brain resting-state functional connectivity (RSFC). The relationship between whole-brain RSFC and loneliness was examined in a linear predictive model. The results revealed that individual loneliness could be predicted by within- and between-network connectivity of prefrontal, limbic and temporal systems, which are involved in cognitive control, emotional processing and social perceptions and communications, respectively. Key nodes that contributed to the prediction model comprised regions previously implicated in loneliness, including the dorsolateral prefrontal cortex, lateral orbital frontal cortex, ventromedial prefrontal cortex, caudate, amygdala and temporal regions. Our findings also demonstrated that both loneliness and associated neural substrates are modulated by levels of neuroticism and extraversion. The current data-driven approach provides the first evidence on the predictive brain features of loneliness based on organizations of intrinsic brain networks. Our work represents initial efforts in the direction of making individualized prediction of loneliness that could be useful for diagnosis, prognosis and treatment.

Key words: loneliness; connectome-based predictive modeling; resting-state functional connectivity

Introduction

Loneliness is a negative emotional state induced by subjective perception of social isolation even when among other people (Weiss, 1973; Cacioppo and Cacioppo, 2018). Susceptibility to loneliness is a trait-like phenotype that is moderately heritable, stable across time and varied across individuals (McGuire and Clifford, 2000; Boomsma *et al.*, 2005; Boomsma *et al.*, 2007; Canli *et al.*, 2018). People high on loneliness experience less reward from daily social interactions, exhibit hypersensitivity

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to negative social information, show impaired social skills and have poor self-regulation (Jones *et al.*, 1982; Hawkley *et al.*, 2007; Bangee *et al.*, 2014; Yildiz, 2016; Cacioppo *et al.*, 2017). Loneliness has also been linked to big five personality dimensions, especially neuroticism and extraversion (Atak, 2009; Abdellaoui *et al.*, 2018a).

Loneliness is a risk factor for a variety of mental and physical health conditions (House *et al.*, 1988), ranging from depression and anxiety to Alzheimer's disease, cardiovascular disease and cancer (Antoni *et al.*, 2006; Cacioppo *et al.*, 2006; Wilson *et al.*, 2007; Cacioppo *et al.*, 2010; Hawkley *et al.*, 2010). Due to the increasing prevalence of loneliness and its detrimental effects in modern societies, many researchers have advocated the medical solution of loneliness as a public health problem (Holt-Lunstad *et al.*, 2017; Cacioppo and Cacioppo, 2018). In this context, models that can be used to predict loneliness severity at the individual level may provide clinical utility in terms of diagnosis and prognosis in future. The current work presents initial efforts in this direction by making individualized prediction of loneliness from intrinsic whole-brain functional connectivity.

Recent brain imaging studies on loneliness have demonstrated links between loneliness and changes in brain functions and structures important for affective, social and cognitive processing. First, loneliness has been linked to attenuated ventral striatum responses to positive social information (Cacioppo *et al.*, 2009; Inagaki *et al.*, 2015), and enhanced insular responses to negative social information (Lindner *et al.*, 2014), as well as aberrant fronto-limbic functional connectivity when processing negative stimuli (Wong *et al.*, 2016). Second, loneliness is associated with altered structural morphometry and integrity in brain regions that are important for social perception, particularly the posterior superior temporal sulcus (pSTS) and temporoparietal junction (TPJ; Kanai *et al.*, 2012; Nakagawa *et al.*, 2015). Lastly, altered gray matter volume in the prefrontal system [e.g. dorsolateral prefrontal cortex (dlPFC)] (Kong *et al.*, 2015) as well as its within- and between-network organizations have been associated with diminished self-regulation in lonely people (Tian *et al.*, 2014; Layden *et al.*, 2017; Tian *et al.*, 2017). Taken together, previous neuroimaging evidence indicates diverse manifestations of loneliness in multiple neuropsychological processes (Cacioppo and Hawkley, 2009; Cacioppo *et al.*, 2014). Intriguingly, preliminary evidence has shown that associations between loneliness and altered brain functions and structures are mediated by the neuroticism and extraversion (Kong *et al.*, 2015).

Building on recent brain imaging findings (Rosenberg *et al.*, 2016; Smith *et al.*, 2017; Beaty *et al.*, 2018; Hsu *et al.*, 2018), here we implemented a connectome-based predictive modeling approach (Shen *et al.*, 2017) to predict individual loneliness from whole-brain resting-state functional connectivity (RSFC). The RSFC allows for examining interplay between large-scale neural systems associated with loneliness (Braun *et al.*, 2018), which is a complex construct rooted in the functional and structural integrity of distributed networks (e.g. Tian *et al.*, 2014; Nakagawa *et al.*, 2015; Layden *et al.*, 2017; Smith *et al.*, 2017; Tian *et al.*, 2017; Smith *et al.*, 2018). Furthermore, the machine-learning approach typically implements cross-validation procedures to estimate the model with training samples and to test the performance of the model with independent samples (i.e. test samples). Therefore, the predictive model enables subject-specific predictions, which are of help in clinical practice where doctors require for individualized assessment of symptom severity (Paulus, 2015; Huys *et al.*, 2016; Paulus, 2017). Moreover, predictive models integrate all available brain features (i.e. RSFC in the present study) to predict outcomes (i.e. loneliness), which enhance statistical power and avoid multiple comparisons and provide more practical utility compared to commonly used group statistics (see also Woo *et al.*, 2017). Finally, predictive features adopted by the model implicate neural correlates of the loneliness (Rosenberg *et al.*, 2016; Cui *et al.*, 2018).

Based on previous findings, we expected that individual differences in loneliness would be predicted by characteristics of intrinsic connectivity across distributed networks, particularly those implicated in emotional (e.g. the amygdala, insula, striatum), social (e.g. the pSTS and TPJ) and cognitive (e.g. the dlPFC) processing. We also expected that both loneliness and associated network connectivity would be modulated by neuroticism and extraversion.

Material and methods

Participants

Seventy-five healthy right-handed college students from Beijing Normal University (62 males and 55 singles; age 21.88 ± 3.01 years) without history of neurological or psychiatric disorder were recruited. The study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments and was approved by the Ethics Committee of Beijing Normal University. Written informed consents were obtained from all participants.

Assessment of loneliness

Loneliness was assessed using the Revised UCLA Loneliness Scale (Russell, 1996), which is a well-validated measure of general feelings of loneliness. The scale consists of 20 items, and each item is scored on a 4-point Likert scale ranging from 1 (never) to 4 (always). The higher scores on the scale indicate higher levels of loneliness.

NEO personality inventory-revised

Personality was assessed by the NEO personality inventory-revised (Costa Jr and McCrae, 1992). The scale consists of 120 items and assesses the five different dimensions of personality: neuroticism, extraversion, openness, agreeableness and conscientiousness. Each item is rated on a 5-point Likert scale ranging from 'strongly disagree' to 'strongly agree'.

Image acquisition

Images were acquired on a Siemens 3-Tesla TRIO scanner at Beijing Normal University Imaging Center for Brain Research. The resting state scanning consisted of 150 contiguous echo-planar imaging (EPI) volumes using the following parameters: axial slices, 33; slice thickness, 3.5 mm; gap, 0.7 mm; repetition time (TR), 2000 ms; echo time (TE), 30 ms; flip angle, 90°; voxel size, $3.5 \times 3.5 \times 3.5$ mm^3 and field of view (FOV), 244×244 mm^2. In addition, high-resolution structural images were acquired through a 3D sagittal T1-weighted magnetization-prepared rapid acquisition with gradient-echo sequence, using the following parameters: sagittal slices, 144; TR, 2530 ms; TE, 3.39 ms; slice thickness, 1.33 mm; voxel size, $1 \times 1 \times 1.33$ mm^3; flip angle, 7°; and FOV, 256×256 mm^2.

All participants underwent a 5 min resting-state functional magnetic resonance imaging scanning, during which they

were instructed to close their eyes, keep still, remain awake and not to think about anything systematically (see also Nooner et al., 2012). Several approaches were implemented to reduce the possibility that participants might fall asleep during the scan: (i) participants were explicitly instructed to close their eyes but not fall asleep during the resting-state scan; (ii) experimenters communicated with each participant immediately after the scan, and all participants responded promptly, indicating that they did not fall asleep; and (iii) the current study implemented rigorous criteria (see also 'image preprocessing') to exclude participants from further analyses based on their head motion. Therefore, it is likely that participants sleeping during the scan (therefore, lower control of head movements) were excluded from analyses in the current study.

Image preprocessing

Neuroimaging data analyses were performed with the DPABI software package (Yan et al., 2016), which is a convenient software plug-in based on SPM12 (http://www.fil.ion.ucl.ac.uk/spm). The first 10 volumes of the functional images were discarded for signal equilibrium and participants' adaptation to scanning noise. The images were then realigned for head movement correction. Seven participants (6 males, 5 singles) were excluded from further analysis under the criteria of head motion exceeding 2.5 mm maximum translation, 2.5° rotation or mean framewise displacement exceeding 0.2 mm throughout the course of scans (Power et al., 2012; Yan et al., 2013). To normalize functional images, participants' structural brain images were first co-registered to their own mean functional images and were subsequently segmented. The parameters derived from segmentation were used to normalize each participant's functional images into the standard Montreal Neurological Institute space (MNI template, resampling voxel size was $3 \times 3 \times 3$ mm^3). Afterwards, the linear trends of time courses were removed, and a band-pass filtering (0.01–0 1 Hz) was applied to the time series of each voxel to reduce the effect of low-frequency drifts and high-frequency physiological noise (Biswal et al., 1995; Zuo et al., 2010). Subsequently, the images were spatially smoothed using a Gaussian filter to decrease spatial noise ($4 \times 4 \times 4$ mm^3 full width at half maximum). Finally, three common nuisance variables were regressed out, including the white matter signal, the cerebrospinal fluid signal (Fox et al., 2005; Snyder and Raichle, 2012) and 24 movement regressors including autoregressive models of motion incorporating six head motion parameters, six head motion parameters one time point before and the 12 corresponding squared items (Friston et al., 1996).

RSFC feature extraction

In the current study, network nodes were defined by using a functional brain atlas, derived from a graph theory-based parcellation algorithm that maximized the similarity of the voxel-wise time series within each node (Shen et al., 2010; Shen et al., 2013). The atlas includes 268 nodes spanning the whole brain including cerebellum and brainstem (Figure 2A). Notably, the 268-node atlas comprises nodes with more coherent time series than those defined by the automatic anatomic labeling atlas and thus represents an improvement over anatomical parcellation schemes because anatomical boundaries do not always match functional ones (Shen et al., 2013).

For each participant, the time course of each node was computed by averaging the blood oxygen level-dependent signal of all of its constituent voxels at each time point. Second, network edges were defined as functional connectivity between each pair of nodes, calculating as the correlation (Pearson's r) between time courses of each pair of nodes. Fisher's r-to-z transformation was then implemented to improve the normality of correlation coefficients, resulting in a 268×268 symmetric connectivity matrix that represented the set of edges/connections in each participant's resting-state connectivity profile (Finn et al., 2015; Rosenberg et al., 2016).

Exploratory correlation analysis

An exploratory correlation analysis was implemented across all participants to examine the relevance of RSFC to loneliness. Specifically, Pearson correlation between each edge in the connectivity matrices and loneliness scores was computed across participants. The resultant r values were forward to a threshold of $P < 0.05$ (Finn et al., 2015; Rosenberg et al., 2017; Rosenberg et al., 2018) and separated into a positive tail (i.e. positive correlation between strength of edge and loneliness scores) and a negative tail (i.e. negative correlation between strength of edge and loneliness scores). Therefore, connections in the positive tail (hereafter referred to as 'positive network') and negative tail (hereafter referred to as 'negative network') were selected by correlations with loneliness scores rather than positive or negative functional connections themselves (see also Rosenberg et al., 2016; Beaty et al., 2018; Hsu et al., 2018). Afterwards, a single aggregate metric of network strength was employed to characterize degree of connectivity in the positive and negative tails for each participant. That is, positive network strength was computed by summing the edge strengths (i.e. Z scores) for all the edges in the positive tail. Similarly, negative network strength was computed by summing the Z scores of all the edges in the negative tail. Lastly, the positive and negative network strengths were correlated with loneliness scores. Notably, results of this analysis were for display purpose, and no statistical tests were performed (Kriegeskorte et al., 2009; Kristensen and Sandberg, 2017). Furthermore, conclusions on the relationship between positive/negative network strengths and loneliness were not derived from this analysis, but instead were based on results from cross-validation detailed below. In other words, this analysis was conducted to illustrate an overview of data before formal prediction analysis (see also Rosenberg et al., 2016).

Prediction analysis using cross-validation

To determine whether network strength predicted loneliness in unseen individuals, a leave-one-out cross-validation (LOOCV) was used to evaluate the out-of-sample prediction performance. Specially, N-1 participants were used as the training set and the remaining one was used as the testing sample, where N is the number of the participants. During the training procedure, predictive networks were defined and employed for calculating positive and negative network strengths as described in the exploratory correlation analysis. Afterwards, simple linear models were constructed to respectively relate positive and negative network strengths to loneliness scores in the training set. During the testing procedure, each testing participant's strengths of positive and negative network was normalized using the parameters acquired during training procedure, and then the trained models were used to predict the testing participant's loneliness

score (Finn *et al.*, 2015; Rosenberg *et al.*, 2016; Shen *et al.*, 2017). The training and testing procedures were repeated *N* times such that each participant was used once as the testing participant.

Pearson correlation coefficient (*r*) and mean squared error (MSE) between actual and predicted loneliness scores were used to evaluate the accuracy of prediction. The permutation test was applied to determine whether the obtained metrics were significantly better than expected by chance. Specially, we permuted the loneliness scores across participants without replacement 1000 times, and each time re-applied the above LOOOCV prediction procedure. This resulted in a distribution of correlation (*r*) and MSE values reflecting the null hypothesis that the model did not exceed chance. The number of times the permuted value was greater than (or with respect to MSE values, less than) or equal to the true value plus one was then divided by 1001 providing an estimated *P*-value for both the correlation coefficient (*r*) and observed MSE.

Contributing network in the prediction of loneliness scores

To characterize the neural substrates of the contributing network, the network was defined as the set of edges that were present in the every iteration of the LOOCV described above. Afterwards, the 268 nodes were grouped into 10 macroscale brain regions, including the prefrontal lobe (46 nodes), motor lobe (21 nodes), insular lobe (7 nodes), parietal lobe (27 nodes), temporal lobe (39 nodes), occipital lobe (25 nodes), limbic lobe (36 nodes), cerebellum lobe (41 nodes), subcortical lobe (17 nodes) and brainstem lobe (9 nodes) (Finn *et al.*, 2015; Rosenberg *et al.*, 2016). The number of edges between each pair of macroscale regions was then calculated. Furthermore, the importance of individual nodes was measured as the number of their connections (Rosenberg *et al.*, 2016; Beaty *et al.*, 2018). The connectivity patterns of the top 20 most highly connected nodes were illustrated.

Validation analysis with different cross-validation schemes

Main results were further validated with different cross-validation schemes (i.e. 2-fold, 5-fold and 10-fold). Taken the 2-fold cross-validation as an example, all participants were divided into two subsets, in which one subset was used as the training set, and the remaining one was used as the testing set. Training set was normalized and used to train a linear prediction model, which then was used to predict scores of the normalized testing data. The normalization of testing data used the normalizing parameters acquired from training data. This procedure was repeated twice, so that each subset was used as testing set once. Finally, the correlation *r* and MSE between the true and predicted scores were calculated across all participants. As the full data set were randomly divided into two subsets, the performance might depend on the data division. Therefore, the 2-fold cross-validation was repeated 100 times, and the results were averaged to produce a final prediction performance. A 1000 times permutation test was applied to test the significance of the prediction performance.

Control analyses

Several control analyses were implemented to further examine the significance of predictions of our models despite potential confounds of age, gender, relationship status (single *vs* in a romantic relationship) and motion. In these analyses, new predictive networks were constructed by employing those edges whose partial Pearson correlation with loneliness scores while controlling for confounding variables (e.g. motion) passed the $P < 0.05$ threshold (see also Shen *et al.*, 2017; Hsu *et al.*, 2018). Finally, head motion was further controlled for in the data preprocessing, such that volumes with an $FD > 0.5$ mm, along with the immediately preceding volume and two subsequent volumes, were considered micromovement-containing volumes, and each of these volumes was modeled as a separate regressor in nuisance covariates regression (Yan *et al.*, 2013; Power *et al.*, 2014).

Relationship of personality with loneliness and associated network connectivity

The associations between loneliness and five personality dimensions (neuroticism, extraversion, openness, agreeableness and conscientiousness) were estimated with a linear regression, with the loneliness as the dependent variable and five personality dimensions as predictors. Since the regression analysis revealed reliable association of loneliness with neuroticism and extraversion (see also Results section), we examined whether networks contributing to the prediction of loneliness were capable of predicting neuroticism and extraversion. In these analyses, connectivity features selected by the prediction model of loneliness were forward to the predictive models for these personality scores. In other words, these analyses examined whether loneliness-related predictive networks were also associated with neuroticism and extraversion. Finally, control analyses were conducted to examine whether RSFC-based model could still predict loneliness after controlling for neuroticism and extraversion (for details, see also 'Control analyses' section).

Results

Exploratory correlation analysis

As expected, loneliness showed significant positive association with neuroticism ($\beta = 0.51$, $t = 3.99$, $P < 0.0005$) and negative association with extraversion ($\beta = -0.33$, $t = -3.28$, $P = 0.002$), but not with conscientiousness ($\beta = 0.06$, $t = 0.46$, $P = 0.65$), openness ($\beta = -0.06$, $t = -0.61$, $P = 0.55$) or agreeableness ($\beta = -0.18$, $t = -1.90$, $P = 0.06$). Additionally, loneliness scores were not significantly correlated with mean frame-to-frame head motion ($r = 0.0003$, $P = 1.00$) or age ($r = -0.04$, $P = 0.75$) and did not differ as a function of gender (males *vs* females: $t = -0.26$, $P = 0.80$) or relationship status (single *vs* in a romantic relationship: $t = 0.99$, $P = 0.33$).

Regarding the correlation between RSFC and loneliness scores, across all participants, the average *r* value was 0.298 (range: 0.241 ~ 0.3400) in the positive tail that comprised 14 edges. The average *r* value was −0.292 (range: −0.239 ~ −0.508) in the negative tail that comprised 8163 edges. Because limited number of edges in the positive tail could not provide reliable predictions, the following analyses focused on the negative network.

The edges in the negative network represented <25% of the whole-brain 35 778 total edges defined in the current atlas. The negative network strength, computed by summing the edge strengths for all the edges in the negative tail, were correlated with loneliness scores ($r = -0.488$). These findings implicated the validity of negative network strength as a summary statistic.

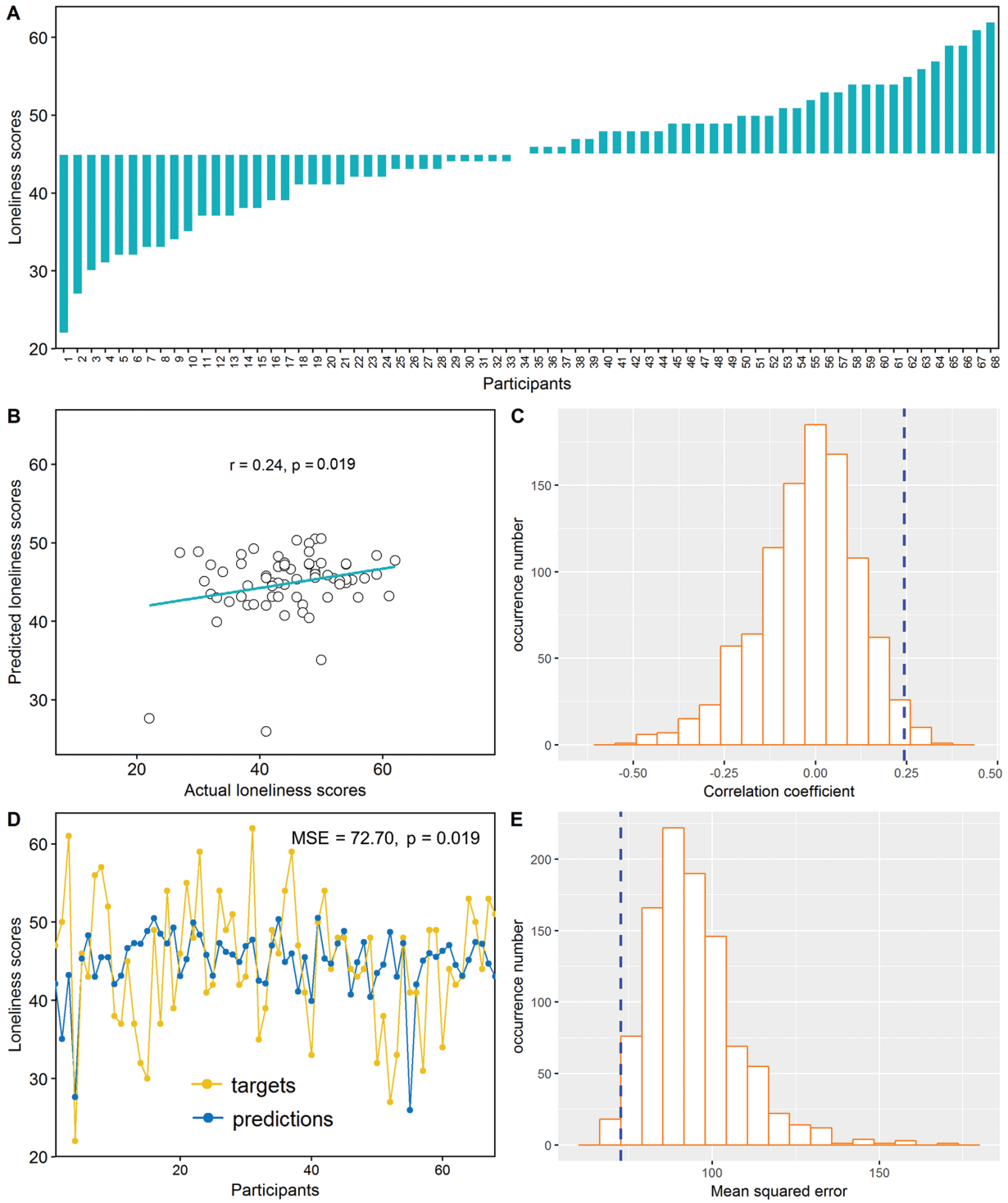

Fig. 1. Performance of the prediction model. (**A**) Scores of loneliness across participants. (**B**) Correlation between actual and predicted loneliness scores. (**C**) Permutation distribution of the correlation coefficient (r) for the prediction analysis. The value obtained using the real scores are indicated by the blue dash line. (**D**) Consistency between actual and predicted loneliness scores. (**E**) Permutation distribution of the mean squared error for the prediction analysis. The value obtained using the real scores are indicated by the blue dash line. $*P < 0.05$.

Prediction analysis using cross-validation

A LOOCV approach was implemented to examine whether the relevance between negative network strength and loneliness scores generalized to novel individuals. It was demonstrated that RSFC in the negative network was able to predict loneliness scores in the novel individuals (correlation between actual and predicted scores: $r = 0.244$, $P = 0.019$; MSE = 72.70, $P = 0.019$, permutatio tests, Figure 1). However, RSFC in the positive network could not reliably predict loneliness scores (correlation between actual and predicted scores: $r = -0.30$, $P > 0.05$; MSE = 97.72, $P > 0.05$).

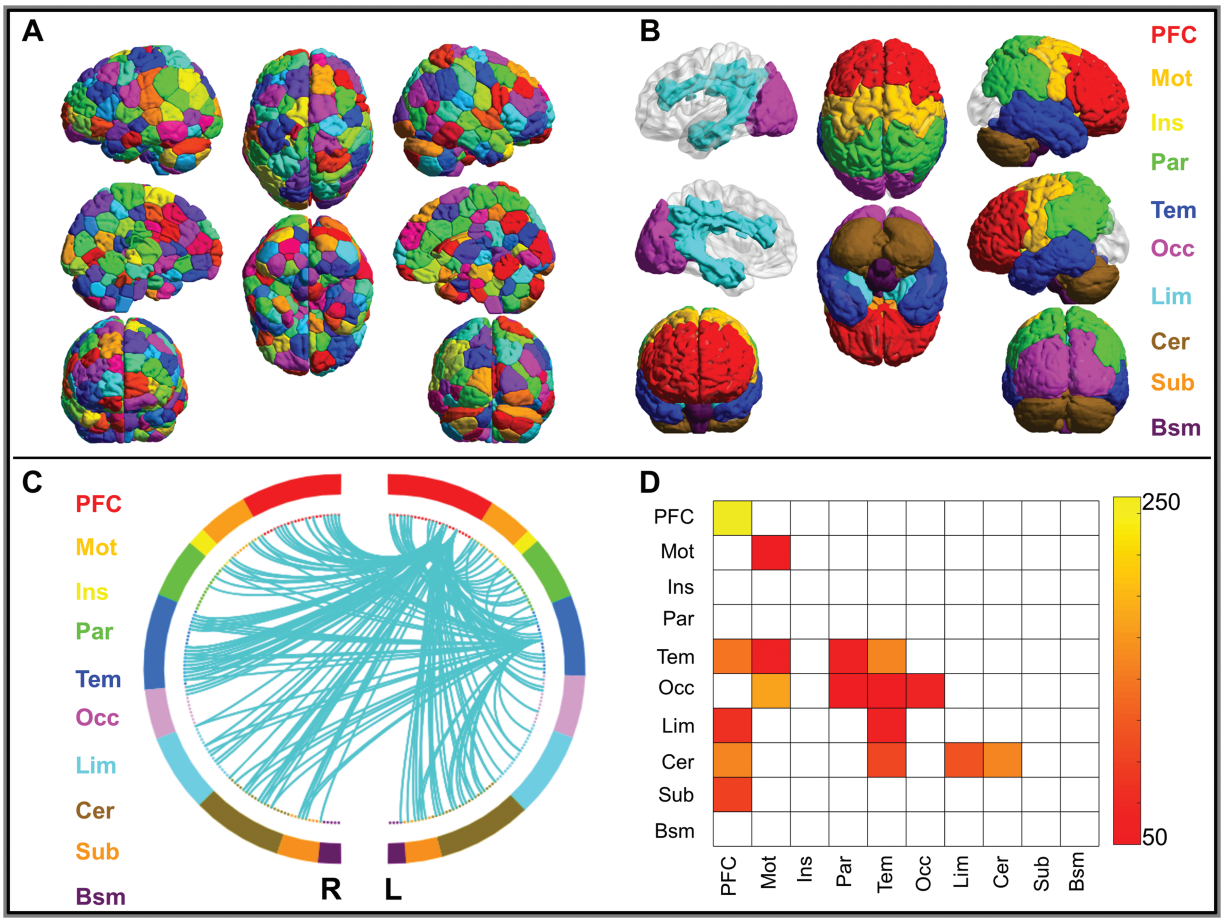

Fig. 2. Macroscale regions used for characterizing contributing connectivity. (**A**) The 268 nodes. (**B**) Twenty macroscale brain regions. (**C**) The connectivity patterns selected by the prediction model, plotted as number of connections within each macroscale regions. (**D**) Connections plotted as number of edges within and between each pair of macroscale regions. L, left; R, right; PFC, prefrontal; Mot, motor; Ins, insula; Par, parietal; Tem, temporal; Occ, occipital; Lim, limbic; Cer, cerebellum; Sub, subcortical; Bsm, brainstem.

Contributing networks in the prediction of loneliness scores

Across all folds of LOOCV, the numbers of edges that contributed to the prediction ranged from 2001 to 10 865. Notably, 1912 of these edges appeared in the every iterations of the LOOCV and were defined as the contributing network (Rosenberg *et al.*, 2016; Shen *et al.*, 2017).

Based on macroscale regions (Figure 2B), it was revealed that connections within prefrontal, temporal and occipital lobes; connections of the prefrontal lobe with subcortical, limbic and temporal lobes; and connections of the temporal with limbic, occipital and cerebellum lobes were primary predictors of loneliness scores (Figure 2C and D).

In addition, the top 20 most highly connected nodes were located in the dlPFC, lateral orbital frontal cortex (lOFC), ventromedial prefrontal cortex (vmPFC), caudate, amygdala, inferior temporal gyrus (ITG), middle temporal gyrus (MTG), supplementary motor area (SMA), precentral gyrus and cerebellum implicating the critical roles of these regions in predicting loneliness (Figure 3 and Table 1).

Validation with different cross-validation schemes

Using different cross-validation schemes, the performance of predication was re-estimated. The resultant correlation coefficients between actual and predicted loneliness scores remained significant (Table 2), thus validating the main findings.

Control analyses

After controlling for the potential confounds of head motion, age, gender, relationship state, head motion, neuroticism and extraversion, new predictive networks were constructed and used in the cross-validation schemes. These analyses indicated that predictive models could still significantly predict loneliness scores (i.e. correlation between actual and predicted loneliness scores remained significant), independent of age, gender, relationship state, head motion, neuroticism and extraversion (Table 2).

Personality prediction based on the loneliness-related network

To assess the association between personality (i.e. neuroticism and extraversion) and networks that contribute to the prediction of loneliness, we examined whether these networks were capable of predicting neuroticism and extraversion. It was demonstrated that the loneliness-related network was able to predict these personality scores in the novel individuals: neuroticism (correlation between actual and predicted scores:

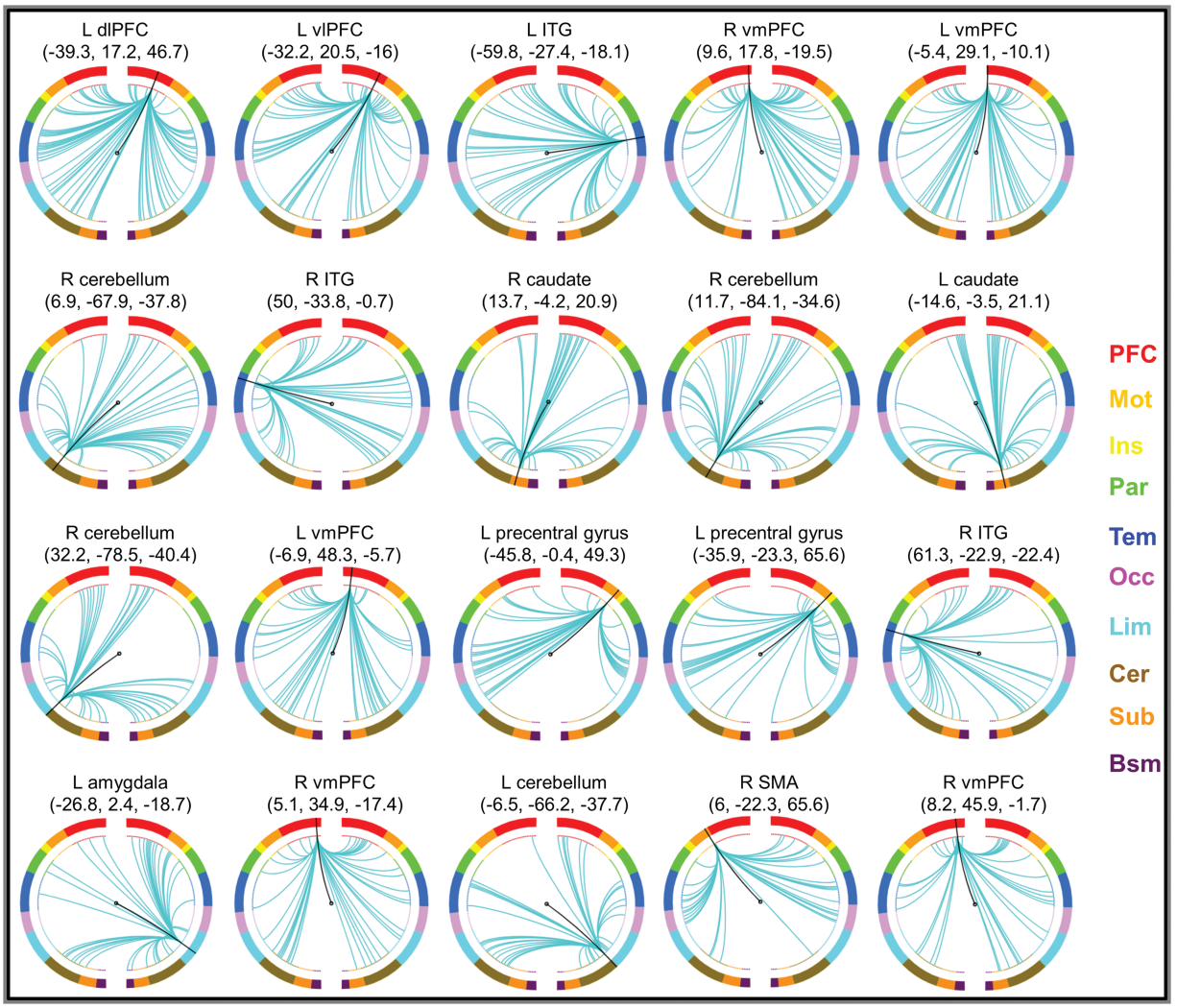

Fig. 3. Connectivity patterns of the top 20 nodes with the most connections. L, left; R, right; dlPFC, dorsolateral prefrontal cortex; lOFC, lateral orbital frontal cortex; ITG, inferior temporal gyrus; vmPFC, ventromedial prefrontal cortex; MTG, middle temporal gyrus; SMA, supplementary motor area; PFC, prefrontal cortex; Mot, motor; Ins, insula; Par, parietal; Tem, temporal; Occ, occipital; Lim, limbic; Cer, cerebellum; Sub, subcortical; Bsm, brainstem.

$r = 0.45$, $P = 0.001$; MSE = 143.01, $P = 0.001$, permutation tests, Figure 4A and C) and extraversion (correlation between actual and predicted scores: $r = 0.22$, $P = 0.004$; MSE = 110.10, $P = 0.001$, permutation tests, Figure 4B and D).

Discussion

Loneliness is an increasingly prevalent condition associated with enhanced morbidity and premature mortality. Despite the increased recognition of loneliness as an important risk factor for many mental and physical health and recent proposal on medicalization of loneliness (Holt-Lunstad *et al.*, 2017; Cacioppo and Cacioppo, 2018), so far no effort has been made to establish a model capable of predicting loneliness at the individual level. Such a model would be important for diagnosis and prognosis in future, and since the brain is thought to be the key organ of social connections and processes (Cacioppo *et al.*, 2014; Cacioppo *et al.*, 2015a), brain features provide promising candidates to establish predictive models. The current work utilized the intrinsic whole-brain functional connectivity in a machine-learning framework to establish a connectome-based model that is predictive of loneliness at the individual level. Notably, our findings further indicate that both loneliness and underlying neural substrates were modulated according to the levels of neuroticism and extraversion.

Our findings reveal intrinsic functional connectivity across multiple neural systems contributes to predicting individual loneliness. Specifically, inter-individual variations in loneliness were primarily accounted for by intrinsic functional connectivity within the prefrontal cortex as well as its connectivity with other networks, particularly the subcortical, limbic and temporal structures. The activity within these neural systems has been previously implicated in cognitive, affective and social components of loneliness (Cacioppo *et al.*, 2009; Inagaki *et al.*, 2015; Wong *et al.*, 2016; Canli *et al.*, 2018). In short, loneliness could be predicted by large-scale distributed functional network connectivity, suggesting that loneliness is characterized by interactive patterns across multiple brain systems. In line with this hypothesis, evidence from animal studies indicates that chronic social isolation has profound effects on brain chemistry and function across multiple neural systems (Zelikowsky *et al.*, 2018).

Table 1. Twenty nodes with the most connections selected by the prediction model

Node	MNI coordinates (mm)			Lobe	degree
L dlPFC	−39.3	17.2	46.7	Prefrontal	72
L lOFC	−32.0	20.5	−16.0	Prefrontal	54
L ITG	−59.8	−27.4	−18.1	Temporal	50
R vmPFC	9.6	17.8	−19.5	Prefrontal	48
L vmPFC	−5.4	29.1	−10.1	Prefrontal	47
R cerebellum	6.9	−67.9	−37.8	Cerebellum	44
R MTG	50.0	−33.8	−0.7	Temporal	43
R caudate	13.7	−4.2	20.9	Subcortical	41
R cerebellum	11.7	−84.1	−34.6	Cerebellum	41
L caudate	−12.5	11.6	8.7	Subcortical	41
R cerebellum	32.2	−78.5	−40.4	Cerebellum	40
L vmPFC	−6.9	48.3	−5.7	Prefrontal	40
L precentral gyrus	−45.8	−0.4	49.3	Motor	40
L precentral gyrus	−35.9	−23.3	65.6	Motor	39
R ITG	61.3	−22.9	−22.4	Temporal	39
L amygdala	−26.8	2.4	−18.7	Limbic	39
R vmPFC	5.1	34.9	−17.4	Prefrontal	39
L cerebellum	−6.5	−66.2	−37.7	Cerebellum	38
R SMA	6	−22.3	65.6	Motor	35
R vmPFC	8.2	45.9	−1.7	Prefrontal	35

L, left; R, right; dlPFC, dorsolateral prefrontal cortex; lOFC, lateral orbital frontal cortex; ITG, inferior temporal gyrus; vmPFC, ventromedial prefrontal cortex; MTG, middle temporal gyrus; SMA, supplementary motor area.

Table 2. Results of validation and control analyses

	r		MSE	
	r-value	P-value	MSE-value	P-value
Validation analyses				
2-fold	0.250	0.017	80.06	0.038
5-fold	0.248	0.014	74.36	0.019
10-fold	0.246	0.015	73.29	0.020
Control analyses				
age	0.243	0.020	72.85	0.019
gender	0.241	0.016	72.27	0.015
relationship status	0.243	0.018	7259	0.021
group motion regression	0.235	0.017	72.49	0.013
individual motion scrubbing	0.282	0.006	70.13	0.007
Neuroticism	0.254	0.014	73.46	0.021
Extraversion	0.247	0.016	71.80	0.013

MSE, mean squared error.
Note: the r and MSE values indicated the consistency between actual and predicted loneliness scores across different fold schemes in the validation analyses and after controlling for different confounding variables in the control analyses.

We demonstrate that the predictive model of loneliness consisted of key nodes associated with emotion processing, including the vmPFC, caudate and amygdala. On the one hand, the vmPFC and caudate have been frequently involved in positive social interactions, such as cooperating with others (Rilling *et al.*, 2002; Feng *et al.*, 2015a), being fairly treated (Tabibnia *et al.*, 2008; Feng *et al.*, 2015b) and communicating one's own thoughts and feelings to others (Tamir and Mitchell, 2012). Therefore, it is plausible that altered functional connectivity in these regions might underlie the diminished pleasure derived from social interactions among lonely people (Hawkley *et al.*, 2007). In line with our findings, loneliness is associated with lower striatal activation in response to positive social information (Cacioppo *et al.*, 2009) as well as differential transcriptome expression in the ventral striatum (Canli *et al.*, 2017). On the other hand, the amygdala is a key region in the limbic system associated with the encoding of threatening stimuli (LaBar *et al.*, 1998; Adolphs *et al.*, 2005; Adolphs, 2008). Accordingly, changes in functional connectivity of this region may be related to hypervigilance to negative social information and negative expectations of social interactions among lonely people (Yamada and Decety, 2009; Hawkley *et al.*, 2010; Cacioppo *et al.*, 2015b).

We further demonstrated MTG and ITG in the temporal lobe as key nodes of the predictive model of loneliness. These regions play critical roles in social perception, such as the processing

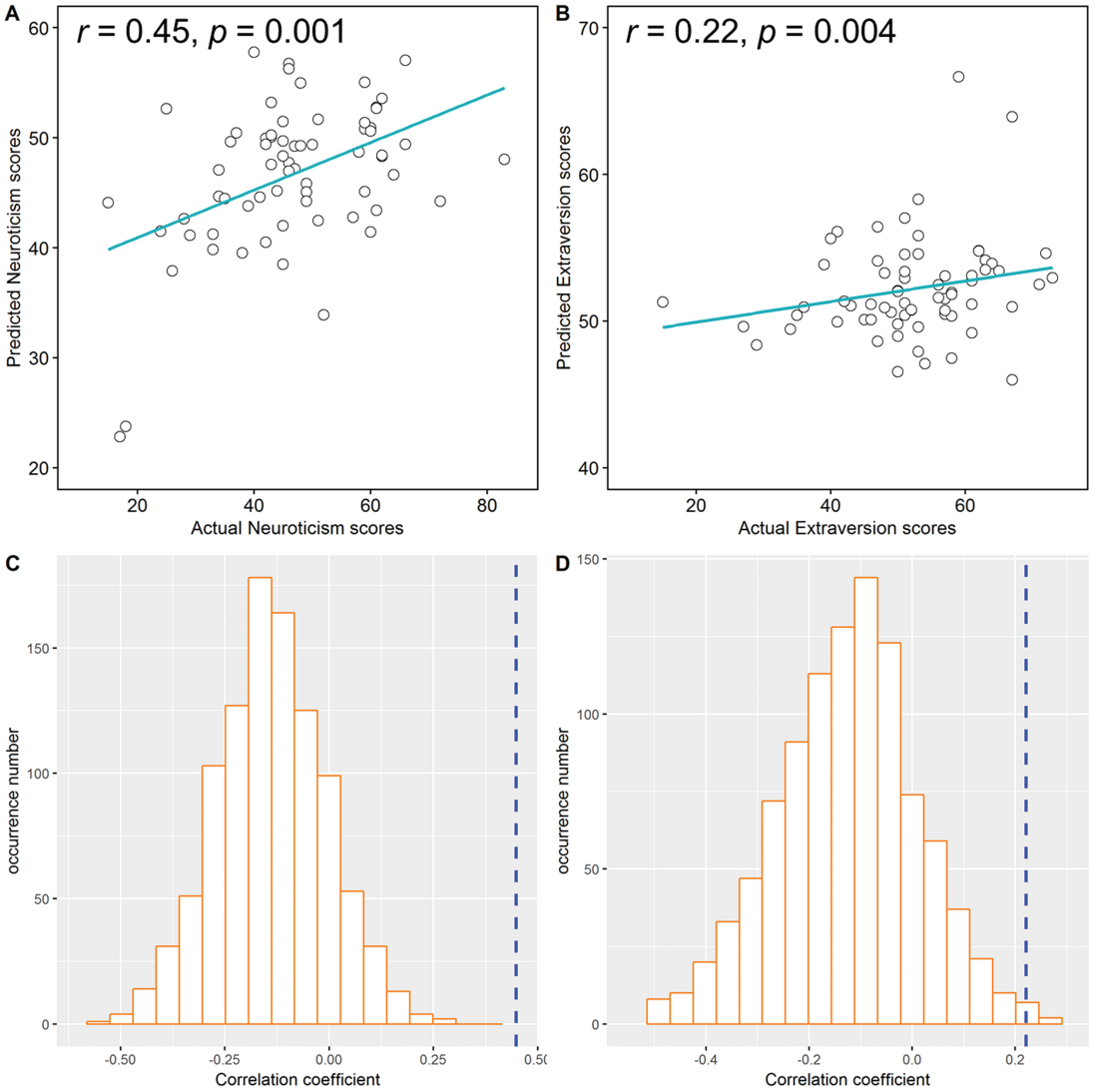

Fig. 4. Performance of the prediction model for personality scores. (**A**) Correlation between actual and predicted neuroticism scores. (**B**) Correlation between actual and predicted extraversion scores. (**C**) Permutation distribution of the correlation coefficient (*r*) for the prediction analysis of neuroticism scores. The value obtained using the real scores are indicated by the blue dash line. (**D**) Permutation distribution of the correlation coefficient (*r*) for the prediction analysis of extraversion scores. The value obtained using the real scores are indicated by the blue dash line.

of faces and eye gaze (Perrett *et al.*, 1985; Critchley *et al.*, 2000; Haxby *et al.*, 2002). Other studies have identified the activations of these regions in the empathy and theory of mind tasks (Farrow *et al.*, 2001; Völlm *et al.*, 2006). In light of previous findings, our results suggest that loneliness is involved in altered social perception and communication mediated by the temporal lobe. This conjecture aligns with two lines of evidence. First, high-lonely people compared to low-lonely people gave less attention to others during communication and were less accurate at encoding nonverbal communications, implicating social skill deficits among lonely people (Gerson and Perlman, 1979; Jones *et al.*, 1982). Second, loneliness was corrected with structural changes in the pSTS part of the temporal lobe, and the association was mediated by basic social perception skills (Kanai *et al.*, 2012).

We also revealed dlPFC and lOFC as key nodes in the prediction of loneliness. These regions have been implicated in many high-order control processes, ranging from task-set maintaining to long-term planning and response suppression and selection (Miller and Cohen, 2001; Cole and Schneider, 2007; Seeley *et al.*, 2007; Menon, 2011). Notably, they have also been involved in emotion regulation through modulations of limbic and subcortical regions (Wager *et al.*, 2008; Kober *et al.*, 2010; Lee *et al.*, 2012). Accordingly, the current findings provide a potential neural mechanism on the impaired self-regulation and cognitive functions among lonely people (Baumeister *et al.*, 2005; Campbell *et al.*, 2006; Hawkley *et al.*, 2009). In line with our findings, loneliness has been found related to changes in brain structures of the dlPFC (Kong *et al.*, 2015) and its functional connectivity with arousal systems (Layden *et al.*, 2017).

Taken together, the multiple neural systems identified in the current study might underlie the affective, social and cognitive processing deficits related to loneliness. Notably, our findings provide the first evidence showing that these seemingly distinct processes do not work separately, but extensively interact with each other to maintain loneliness. In this regard, the whole-brain functional connectivity approach provides more holistic measures of loneliness as a complex construct.

Our findings finally indicate that loneliness and associated neural substrates are modulated according to neuroticism and extraversion. These findings complement several lines of evidence. First, previous studies report the strongest correlations between loneliness and neuroticism or extraversion (Atak, 2009; Teppers *et al.*, 2013; Mund and Neyer, 2016), although several studies also identify correlations of loneliness with openness, agreeableness and conscientiousness (Lopes *et al.*, 2003; Abdellaoui *et al.*, 2018b). Second, loneliness and neuroticism exhibited a considerable genetic overlap measured by both genetic variants and familial relationships (Abdellaoui *et al.*, 2018a). Third, neuroticism and extraversion mediated the associations between loneliness and altered brain structures in the dlPFC (Kong *et al.*, 2015). These findings together indicate that loneliness and neuroticism/extraversion are highly relevant constructs, and they might share common underpinnings at both psychological and biological levels. In particular, neuroticism is characterized by enhanced sensitivity to aversive stimuli, whereas extraversion is characterized by increased sensitivity to positive social stimuli, and both personality characteristics are closely related to core features of loneliness (Cacioppo *et al.*, 2009; Cacioppo *et al.*, 2015b). Nevertheless, the current study revealed that the RSFC-based model could still predict individual loneliness scores after controlling for neuroticism and extraversion. These findings indicate that the predictive model can account for variance in loneliness that is not explained by the personality traits.

Notably, the current study represents advances in neuroscience advocating the applications of brain features in a machine-learning framework to establish neuroimaging-based predictions (Fu and Costafreda, 2013; Paulus, 2015; Woo *et al.*, 2017). This approach aims to reveal predictive brain features that can be used to facilitate diagnosis, prognosis and treatment of individual patients in clinical practice. Within this framework, an accumulating body of research has developed predictive models based on brain imaging features to discriminate patients from health controls or to predict symptom severity (for reviews, see also Fu and Costafreda, 2013; Woo *et al.*, 2017). In this regard, a potential application of the current approach would be the use of RSFC measures in predicting severity of loneliness either among general population or among patients (e.g. anxiety or mood disorder), considering that loneliness is a critical risk factor for many health problems.

Several limitations should be noted as they relate to the current study. First, although the current study controlled for potential major confounds such as age, gender, relationship status and motion, other measures of objective social isolation (e.g. the objective levels of social contact) should be collected and controlled for in future studies. Similarly, loneliness could be related to transient mood states and could be temporary, future studies may also consider controlling for those confounding factors. Second, one may not interpret the predictive network as a 'neuromarker' of loneliness, since the current study did not completely examine the specificity of the predictive model. Indeed, the relationship between RSFC and loneliness could be explained by their common associations with a third variable. Third, our prediction was obtained in a relatively small sample, and the generalization of the current findings requires further validation using an independent larger sample and other cross-validation methods. Fourth, it is noteworthy that the current prediction model of loneliness was based on the negative network (i.e. connections negatively associated with loneliness). The large negative but small positive predictive network of loneliness may reveal a dis-connectivity pattern as the increase of loneliness. Given the positive predictive model failed and was not stable, we should be cautious about drawing any conclusions based on the non-significant findings.

Despite these limitations, we first demonstrate that functional connectivity of distributed networks effectively predicts loneliness at the individual level. Notably, nodes and edges of the predictive network have been frequently implicated in affective, social and cognitive processing required by developing and maintaining social connections. The current data-driven approach provides a novel tool to characterize neural mechanisms of loneliness and might have potential applications in clinical practice.

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Author contributions

CF and PX designed the study. CF and LW performed the experiment. CF, LW, and TL analyzed the data. CF, PX, LW, and TL wrote the manuscript.

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