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Published in:
Cerebral Cortex

DOI:
[10.1093/cercor/bhaa407](https://doi.org/10.1093/cercor/bhaa407)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Wang, Z., Goerlich, K. S., Ai, H., Aleman, A., Luo, Y.-J., & Xu, P. (2021). Connectome-Based Predictive Modeling of Individual Anxiety. *Cerebral Cortex*, 31(6), 3006-3020. <https://doi.org/10.1093/cercor/bhaa407>

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ORIGINAL ARTICLE

Connectome-Based Predictive Modeling of Individual Anxiety

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Abstract

Anxiety-related illnesses are highly prevalent in human society. Being able to identify neurobiological markers signaling high trait anxiety could aid the assessment of individuals with high risk for mental illness. Here, we applied connectome-based predictive modeling (CPM) to whole-brain resting-state functional connectivity (rsFC) data to predict the degree of trait anxiety in 76 healthy participants. Using a computational “lesion” approach in CPM, we then examined the weights of the identified main brain areas as well as their connectivity. Results showed that the CPM successfully predicted individual anxiety based on whole-brain rsFC, especially the rsFC between limbic areas and prefrontal cortex. The prediction power of the model significantly decreased from simulated lesions of limbic areas, lesions of the connectivity within limbic areas, and lesions of the connectivity between limbic areas and prefrontal cortex. Importantly, this neural model generalized to an independent large sample ($n = 501$). These findings highlight important roles of the limbic system and prefrontal cortex in anxiety prediction. Our work provides evidence for the usefulness of connectome-based modeling in predicting individual personality differences and indicates its potential for identifying personality factors at risk for psychopathology.

Key words: anxiety, computational lesion, connectome-based predictive modeling (CPM), limbic system, resting-state functional connectivity

Introduction

Anxiety, a personality dimension in healthy individuals, is a universal negative emotion that entails avoidance behaviors such as worrying, irritability, difficulty to relax, and a tendency to interpret ambiguous situations as threatening (Spielberger 2010; Grachev and Apkarian 2000; Eysenck et al. 2007). Although anxiety has valuable adaptive benefits, individuals enduring high trait anxiety may be at risk to develop mental disorders (Pezawas et al. 2005; Sandi and Richter-Levin 2009; Cremers et al. 2010). It has been estimated that an alarming 28.8% of the general population suffer from an anxiety-related disorder at some point in their lifetime (Kessler et al. 2005). Identifying neurobiological markers signaling high trait anxiety could aid the assessment of high-risk individuals, especially those with difficulty expressing their feelings to others (Eisenberger et al. 2005; Drysdale et al. 2017).

Anxiety is a complex emotion that is associated with mutual inhibition between subcortical and cortical areas of the brain (Tovote et al. 2015; Xu et al. 2019). Particularly, the limbic system and the prefrontal cortex are highly engaged in the balance of these mutually inhibitory relationships (Hofmann et al. 2012). The limbic system has long been considered crucial for emotion processing (Fuchs and Flügge 2003), and the prefrontal cortex plays an important role in top-down regulation of limbic activity (Mochcovitch et al. 2014). Regarding to anxiety disorders, an emotion dysregulation model has been proposed that is characterized by an imbalance of prefrontal regulation over limbic activity (Behar et al. 2009; Manber Ball et al. 2013; Mochcovitch et al. 2014). Specifically, it has been suggested that patients with anxiety disorders experience chronic hyper-arousal in the limbic circuitry (Kim et al. 2011). This fatigues the top-down regulation system in the prefrontal cortex, resulting in ineffective control particularly of negative emotions (Manber Ball et al. 2013). With regard to trait anxiety as a personality dimension in nonclinical samples, it has been demonstrated that anxiety-prone individuals require greater engagement of prefrontal regions to down-regulate negative emotions (Campbell-Sills et al. 2011). However, no effort has been made as yet to predict anxiety at the individual level based on the whole-brain connectivity. Individualized prediction of anxiety would advance our understanding of the underlying neural mechanism and facilitate early identification of proneness to clinical anxiety.

Recently, connectome-based predictive modeling (CPM) has been tested to account for inter-individual variability in brain functional networks. CPM is a novel data-driven approach for developing predictive models of brain-behavior relationships that can detect individual variability more accurately ("functional connectome fingerprinting"; Finn et al., 2015) by extracting and summarizing the most relevant features from resting-state functional connectivity (rsFC) using full cross-validation (Shen et al. 2017). Despite testing a specific hypothesis, CPM provides more holistic measures with whole-brain analyses. This approach has successfully been used to predict individual personality traits and aspects of functional cognition, such as fluid intelligence (Finn et al. 2015), sustained attention (Rosenberg et al. 2015), and creative ability (Beatty et al. 2018). Moreover, a computational lesion based on CPM can reveal brain regions that are important in individualized prediction (Feng et al. 2018). The computational lesion approach allows for the computational manipulation of brain regions to be "lesioned," and thus represents a noninvasive method simulating the effect of lesions in particular brain regions on aspects of neuropsychological functioning.

The aim of current study was to predict individual levels of trait anxiety in healthy participants by applying CPM and the computational lesion approach to whole-brain resting-state functional magnetic resonance imaging (fMRI) data. We hypothesized that CPM would successfully predict anxiety at the individual level. Based on the emotion dysregulation model (Behar et al. 2009) and the computational lesion approach in CPM (Feng et al. 2018), we expected that both the limbic system and prefrontal cortex would significantly contribute to the identification of individual levels of trait anxiety.

Materials and Methods

Participants

A total of 88 healthy undergraduate students took part in MRI scanning. All the participants had no history of neurological and psychiatric disorders or head injury. After excluding excessive head motion (10 participants, exceeding 2.5 mm maximum translation, 2.5° rotation or 0.2 mm mean frame-wise displacement [FD; Yan et al., 2013; Power et al., 2014]) and outliers in Beck Anxiety Inventory scores (BAI: 2 participants, out of mean $\pm$ 2.5 standard deviation [SD]), the final sample consisted of 76 participants (38 females; age = 21.34 ± 1.76). The study was approved by the local Ethics Committee at Beijing Normal University and written informed consent was obtained from all participants.

Anxiety Assessment

To assess anxiety, we used the Chinese version of the BAI (Beck et al. 1988). This inventory consists of 21 items, each answer being scored on a 4-point Likert scale of 1 (not at all) to 4 (severely). Participants also completed the Chinese version of the Zung self-rating depression scale (SDS; Zung, 1965). In the Chinese version, the normative scores of the BAI were calculated as rounding $1.19 \times$ raw total scores to the nearest integers towards zero (Cheng et al. 2002), whereas the normative scores of the SDS were calculated as rounding $1.25 \times$ raw total scores to the nearest integers (Wang and Chi 1984). In the Chinese version of BAI, individuals scoring higher than 38 in raw scores (45 in normative scores) were regarded as slightly anxious (Pang et al. 2019). With this cutoff, 9 of 76 participants in our sample reached the level of slight anxiety. Based on the Chinese SDS manual, those scoring 40–47 in the raw scores (50–59 in the normative scores) were classified as mildly depressed, 48–55 in the raw scores (60–69 in the normative scores) as having moderate-to-marked depression, and higher than or equal to 56 in the raw scores (70 in the normative scores) as having severe depression (Wang et al. 2014). In the current sample, 10 of 76 participants reached mild depression level, 5 of 76 participants reached the level of moderate-to-marked depression, and 1 of 76 participants reached severe depression. Therefore, it should be noted that the sample may not be entirely healthy, though none of them reported any history of psychiatry or mental disorders. We used raw scores for analysis since raw and normative scores were highly correlated (BAI: $r_{(74)} = 0.9993$; SDS: $r_{(74)} = 0.9996$ for the 76 participants).

Image Acquisition

MRI data were acquired with a Siemens Trio 3T scanner powered with Total Imaging Matrix technique at the Imaging Center for Brain Research at Beijing Normal University. Both the fMRI and high-resolution 3D structural brain data were

obtained using a 12-channel phased-array head coil with implementing a parallel imaging scheme that generalized autocalibrating partially parallel acquisitions (Griswold et al. 2002). The fMRI data were acquired with a gradient-echo echo-planar imaging sequence with the following parameters: repetition time (TR)=2000 ms, echo time (TE)=30 ms, 33 transversal slices, slice thickness 3.5 mm with gap 0.7 mm, flip angle=90°, field of view (FOV)=224 × 224 mm, data matrix=64 × 64, 240 volumes scanned in 8 min, and spatial coverage (3.5 + 0.7) mm/slice × 33 slices ≈ 139 mm. Additionally, the 3D structural brain images (1 mm³ isotropic) were acquired for each participant using a T1-weighted 3D magnetization-prepared rapid gradient echo sequence with the following parameters: TR/TE=1900 ms/3.44 ms, flip angle=9°, data matrix=256 × 256, FOV=256 × 256 mm, BW=190 Hz/pixel, 176 image slices along the sagittal orientation, obtained in about 6 min. During resting-state scanning, all participants were instructed to keep still, close their eyes, remain awake, and think of nothing in particular. No participant reported to be asleep during the scan.

Preprocessing

Functional MRI data were preprocessed with DPABI (<http://rfmri.org/dpabi>; Yan et al. 2016), a software package based on SPM12 (version no.7219; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). It comprised the following steps: 1) discarding the first 10 volumes to decrease the signal's instability; 2) correcting slice timing; 3) realignment; 4) co-registering the T1-weighted image to the corresponding mean functional image; 5) segmenting into gray matter, white matter and cerebrospinal fluid by DARTEL; 6) regressing common nuisance out by CompCor (Behzadi et al. 2007), including the white matter signal, the cerebrospinal fluid signal, 24 movement regressors, and global signal. The 24 movement regressors included autoregressive models of motion incorporating 6 head motion parameters, 6 head motion parameters one time point before, and the 12 corresponding squared items (Friston et al. 1996; Yan et al. 2013). Note that we conducted global signal regression (GSR) given that GSR effectively reduced noise in fMRI data, including head motion and respiratory as well as cardiorespiratory artifacts (Power et al. 2015; Ciric et al. 2017, 2018; Murphy and Fox 2017). Moreover, the use of GSR has been demonstrated to improve the performance of CPM as compared with CPM without GSR (Greene et al. 2018); 7) detrending; 8) normalizing to the standard Montreal Neurological Institute space (MNI template, resampling voxel size 3 × 3 × 3 mm³); 9) smoothing with a Gaussian kernel of 4 mm full width at half maximum; and 10) filtering (0.01–0.1 Hz).

Functional Network Construction

After preprocessing, we constructed the static whole-brain rsFC matrices. Specifically, we employed a 268-node functional atlas that was derived from a group-wise spectral clustering algorithm. This group-wise optimization approach ensures functional homogeneity within each subunit, and time-course consistency of the network nodes at the group level, resulting in improved reliability and sensitivity of the network analyses (Shen et al. 2010, 2013). In light of previous studies (Shen et al., 2013; Feng et al., 2018), nodes were further divided into 10 lobes, including prefrontal lobe (46 nodes), motor lobe (21 nodes), insula 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; Fig. 3g). After Fisher's Z transformation, the resulting 268 × 268 symmetric matrices represented edges from the rsFC profile.

Connectome-Based Predictive Modeling

Based on the whole-brain rsFC, we used CPM to predict the degree of anxiety individually. In light of 10 simple rules for applying predictive modeling to rsFC data (sample size < 200; Scheinost et al., 2019) and to be consistent with past work employing CPM (Finn et al. 2015; Rosenberg et al. 2015; Beaty et al. 2018), we performed leave-one-out cross-validation (LOOCV). That is, in each iterative analysis, the predictive model was built based on $n - 1$ participants (training set) and then the score of the remaining participant (test set) was predicted. In this study, we ran it 76 times. Steps were as follows (Fig. 1). 1) Data preparation, preparing rsFC matrices, and BAI scores of all participants. 2) Edge selection, performing Pearson correlations between each edge in rsFC matrices and BAI scores in the training set and selecting only the most significantly correlated edges as predictive edges. The threshold was set at $P < 0.01$ (Dosenbach et al. 2010; Rosenberg et al. 2015; Takagi et al. 2018). 3) Network construction, a positive network (i.e., positive correlation within selected edges), and a negative network (i.e., negative correlation within selected edges). 4) Network strengths, summing the values of all edges in the rsFC matrix in the positive network, and the negative network separately for each participant. 5) Model building, fitting the linear model between BAI scores and network strengths across the training set for both the positive network, and the negative network to build the positive model and the negative model, respectively. 6) Individual prediction, applying models to predict the BAI score according to the network strengths in the test set (the excluded participant). Notably, normalization on each edge across the training set was performed and parameters (i.e., mean and SD) from the training set were applied to the test set (Feng et al. 2018, 2019). Specifically, the mean and SD on each edge were computed across the training set; normalization on each edge was then calculated as the difference between edge value and the mean divided by the SD [(Edgez – mean)/SD]. During the testing procedure, edge strength was normalized using the parameters obtained from the training set (Feng et al. 2018, 2019). This group-based normalization kept strict separation of training and testing data.

Internal Validation: Model Assessments

After LOOCV, the model validity was evaluated by Pearson correlation coefficient (r) between real BAI scores and predicted BAI scores for the positive and negative model, respectively. For significant effect(s) of parametric statistics, we further performed nonparametric permutation tests by running LOOCV 999 times. Specifically, during each permutation, we randomly shuffled real BAI scores to generate predictive networks and predicted BAI scores from LOOCV and then calculated the correlation coefficient between real BAI scores and predicted BAI scores. The 1000 (999 plus the true one) correlation coefficients composed null distributions of r -values. The nonparametric P -values were calculated as the number of permutations that generated r -values equal to or larger than the true r -values/1000.

Figure 1. The schematic flow of connectome-based predictive modeling.

This permutation approach was used to calculate the nonparametric P -value(s) for all r -values between real and predicted scores in main prediction analyses. For lesion analyses and confound analyses (see Computation Lesion Prediction and Control Analyses), we re-ran permutation tests to evaluate the significance of nonparametric P -values. Please note that the reported P -values are calculated from nonparametric permutation testing except if otherwise noted.

Computational Lesion Prediction

Because the obtained networks were slightly different in each iteration, we intersected networks within the training procedure across each iteration (i.e., overlaps of all the negative networks) to construct the common network and then categorized them into 10 macroscale lobes. After that, lesion prediction analyses were performed to examine the weights of the limbic lobe and the prefrontal lobe as well as their connectivity. For example, after excluding edges in the limbic lobe (36 nodes), the remaining 232×232 rsFC matrices were used to predict individual anxiety (Feng et al., 2018). Finally, we contrasted whole-brain prediction

with lesion prediction in terms of predictive power by Steiger's Z (Steiger 1980).

Control Analyses

To avoid potential confounding effects of head movements, gender and age, control analyses were conducted. We repeated our analyses by implementing scrubbing with the criterion of an FD above 0.2 mm (Jenkinson et al. 2002; Yan et al. 2013). Additionally, partial Pearson correlation analyses were conducted with mean FD of head motion (Jenkinson et al. 2002), gender and age as co-variables in edge selection and final correlation, separately.

Replication of Predictive Model in an Independent Dataset of Trait Anxiety

To examine whether the current predictive model of BAI is specific for trait or state anxiety, we replicated the current predictive model to an independent dataset of 37 participants, including resting-state fMRI data and scores of the Trait subscale of the State-Trait Anxiety Inventory (STAI-T; Shek,

1988). See [Supplementary Material](#) for details about the dataset. Except slice timing, the same preprocessing, functional network construction, criteria for head motion and outlier in questionnaires, and reciprocal transformation (100/scores; [Box and Cox, 1964](#)) were performed in the independent dataset. Note that we did not correct slice timing for this multiband dataset. The final sample for replication consisted of 34 participants (19 females; age = 21.38 ± 2.49 ; STAI-T = 39.12 ± 8.16). The cut-off value of STAI-T for the Chinese version was 45 ([Pang et al. 2019](#)). In our sample, 7 of 34 participants reached this level, indicative of anxiety and mood disorders. Given that limiting feature selection to the specified network during the CPM pipeline has been demonstrated to be sensitive to predictive power ([Goldfarb et al. 2020](#)), we ran the CPM pipeline within the common network obtained from the BAI predictive model. These replication analyses could also examine whether anxiety features measured by the BAI corresponded to trait anxiety as assessed by the STAI-T ([Creamer et al., 1995](#)).

External Validation Using the Human Connectome Project

To ensure robustness and avoid overfitting ([Yarkoni and Westfall 2017](#)), we additionally tested the here identified predictive networks of anxiety in a large dataset from the Human Connectome Project (HCP) 900 Subject Release (see [Van Essen et al., 2012](#) for dataset details). For simplicity, we only used the unprocessed HCP S900 3T resting data of the first run with phase encoding in a right-to-left (RL) direction. Further, anxiety scores adjusted for gender and age were used from the Achenbach Adult Self-Report (ASR) Diagnostic and Statistical Manual (DSM)-Oriented Scales ([Achenbach 2009](#)). The inclusion criteria for the HCP S900 dataset are shown in [Supplementary Figure S1](#). Except slice timing, the same preprocessing, functional network construction, criteria for head motion, and outliers in questionnaires as well as reciprocal transformation (100/scores; [Box and Cox, 1964](#)) was performed in this HCP S900 dataset. Note that we did not correct slice timing for this multiband dataset. The final sample for external validation consisted of 501 participants (276 females; age = 28.51 ± 3.62 ; DSM-based anxiety scores = 52.32 ± 3.71). We defined the common network from internal validation as the predictive network for this external validation. In line with previous CPM studies performing external validation ([Rosenberg et al. 2015](#); [Beatty et al. 2018](#)), we calculated the network strength in each of the 501 participants, followed by calculation of correlations between individual network strengths and anxiety scores.

Distinct Brain Networks between Anxiety and Depression

Although anxiety was highly correlated with depression ([Stavrakaki and Vargo 1986](#); [Clark and Watson 1991](#)), it has also been widely shown that there are distinct neural circuitries between anxiety and depression ([Oathes et al. 2015](#); [Pannekoek et al. 2015](#)). Therefore, we explored distinct brain networks for anxiety versus depression in this module ([Fig. 2](#)). After excluding 2 participants (out of mean ± 2.5 SD) in BAI scores, 46 high anxious participants were selected from the criteria of the top 55% in BAI scores, and 44 high depressive participants were selected from the top 55% in SDS scores. To maximize the sample size in each specific group, we used a cutoff at top 55% for scores of anxiety/depression (see [Supplementary Table S1](#)). A total of 11 anxiety-specific participants and 9 depression-specific

participants were identified for further explorative contrast analyses after excluding 35 anxiety participants comorbid with depression (for raw and normative score of BAI and SDS in each group, see [Supplementary Table S2](#)).

In line with [Takagi et al. \(2018\)](#), we used the same approach to explore distinct brain networks for anxiety and depression ([Fig. 2](#)). In a LOOCV manner, we conducted two-sample t-tests for each edge in rsFC matrices across the training set between anxiety-specific participants and the depression-specific participants. Based on the significance threshold $P < 0.01$ ([Dosenbach et al., 2010](#); [Rosenberg et al., 2015](#); [Takagi et al., 2018](#)), edges in anxiety-specific participants that were significantly higher than edges in depression-specific participants across the training set were selected to construct the “anxiety > depression” network. Likewise, edges in depression-specific participants that were significantly higher than edges in anxiety-specific participants across the training set were selected to construct the “depression > anxiety” network. Next, “network strength” of the remaining participants (test set) for the “anxiety > depression” network was defined summing rsFCs of the “anxiety > depression” network; “network strength” for the “depression > anxiety” network was calculated correspondingly. After LOOCV, a two-sample t-test validated the difference of network strength between the “anxiety > depression” and “depression > anxiety” networks. Please note that 2 values for each participant were generated across LOOCV: one represents network strength for the “anxiety > depression” network, another represents network strength for the “depression > anxiety” network. It is true that “anxiety > depression” and “depression > anxiety” networks are definitely different, but their network strengths are not necessarily significantly different from each other if the current model was invalid (for more details, see [Takagi et al., 2018](#)). Lastly, we intersected networks within the training procedure across each iteration (i.e., overlaps of all “anxiety > depression” networks and overlaps of all “depression > anxiety” networks) to construct common networks and then divided them into 10 macroscale lobes.

To ensure the robustness of the distinctive networks between anxiety and depression, we tested the external validation in the HCP S900 dataset. Depression scores adjusted for gender and age were used from the ASR DSM-Oriented Scales ([Achenbach 2009](#)). The same grouping criteria (top 55%) for anxiety scores and depression scores were used. Then, 76 anxiety-specific participants and 85 depression-specific participants were identified for external validation analyses. Specifically, we calculated the network strength of “anxiety > depression network” and “depression > anxiety network” in each participant, followed by calculation of two-sample t-tests to validate the difference of network strength.

Results

Normality Test

BAI scores were not normally distributed according to the Kolmogorov-Smirnov Test of Normality (BAI, $Z = 1.695$, parametric $P = 0.006$, [Fig. 3a](#); raw BAI scores, range = 21–44, mean $\pm$ SD = 27.78 ± 6.21 ; normative BAI scores, range = 24–52, mean $\pm$ SD = 32.53 ± 7.46 ; SDS, $Z = 0.788$, $P = 0.564$; raw SDS scores, range = 20–57, mean $\pm$ SD = 34.34 ± 7.89 ; normative SDS scores, range = 25–71, mean $\pm$ SD = 43.05 ± 9.86). Therefore, we performed reciprocal transformation (100/scores; [Box and Cox, 1964](#)) to normalize BAI scores ($Z = 1.312$, $P = 0.064$; mean $\pm$ SD = 3.75 ± 0.70 ; [Fig. 3b](#)

Figure 2. The schematic flow for identifying distinct brain networks between anxiety and depression.

and c). Note that we performed reciprocal transformation at the individual level before LOOCV.

CPM Assessments of Anxiety

LOOCV revealed that the negative model, but not the positive model, had significant prediction power for anxiety scores

[positive model, $r_{(74)} = -0.01$, parametric $P = 0.939$, Fig. 3d; negative model, $r_{(74)} = 0.33$, parametric $P = 0.004$, Fig. 3e]. Given that the significant parametric result was only found in the negative model, we performed permutation tests only for the negative model. Permutation tests (1000 times) revealed that this result was expected above chance ($P = 0.036$, Fig. 3f). Thus, subsequent analyses focused on the negative model. Please note that the

Figure 3. Prediction models and contributing connections. (a) Distribution of raw BAI scores. (b) Distribution of transformed BAI scores. (c) The cumulative count of a function of transformed BAI scores. In (a)–(c) dark color represents high anxiety severity, whereas light color represents low anxiety severity. Correlations between real BAI score and predicted BAI scores in (d) positive model and (e) negative model. (f) Permutation distribution of correlations in the negative model. Please note that the negative model indicates positive correlations between rsFC and levels of anxiety due to reciprocal transformation. (g) Whole-brain parcellation with 10 lobes. (h) Common edges contributing to anxiety prediction. (i) and (j) Division of anxiety network into 10 lobes and the contribution of each lobe to anxiety prediction. Abbreviations: Mot, motor; Ins, insula; Par, parietal; Tem, temporal; Occ, occipital; Lim, limbic; Cer, cerebellum; Sub, subcortical; Bsm, brainstem. R: right; L, left.

negative model indicated positive correlations between rsFC and levels of anxiety due to reciprocal transformation.

Across iterations of 76 times, the number of edges, common edges, and generated networks within CPM of anxiety are shown in Table 1 and Figure 3h. The number of edges in each lobe from common networks is shown in Figure 3i and j. Figure 3i (Fig. 5b and c) shows the similar pattern after correcting for the size of

lobe × lobe pairs (for details, see Supplementary Fig. S4). These corrected matrices showed similar patterns with the original uncorrected matrix patterns (see Supplementary Fig. S4), indicating that localization results were not driven by lobe-lobe size differences. Furthermore, the top 10 connected brain nodes were located in the ventral anterior cingulate cortex (vACC), ventral-lateral prefrontal cortex (vlPFC), posterior cingulate cortex (PCC),

Table 1 The number of edges, common edges and generated networks across LOOCV in CPM of anxiety, “anxiety > depression” network, and “depression > anxiety” network

	CPM of anxiety	Anxiety-specific networks	Depression-specific networks
Edges [min, max]	[130, 169]	[108, 197]	[93, 179]
Common edges	58	54	40
Networks ^a	76	20	20

^aNote: The number of networks equals the number of iterations since the obtained networks were slightly different in each iteration.

Table 2 Results of prediction analyses with specific lesions

Lesion	Predictive power		Difference from the whole-brain model	
	<i>r</i>	<i>P</i>	Steiger's <i>Z</i>	Parametric <i>P</i>
Lim	0.16	0.243	−2.38	0.017
PFC	0.24	0.118	−1.44	0.149
Tem	0.17	0.218	−2.24	0.025
Lim–Lim	0.29	0.052	−3.06	0.002
Lim–PFC	0.28	0.054	−2.03	0.042
Lim–Tem	0.29	0.052	−1.21	0.227
PFC–PFC	0.33	0.034	0	0.997
PFC–Tem	0.32	0.044	−0.36	0.716
Tem–Tem	0.34	0.025	1.87	0.062

Note: Abbreviations: Lim, limbic; PFC, prefrontal cortex; Tem, temporal.

medial superior parietal gyrus (mSPG), inferior temporal gyrus (ITG), and middle temporal gyrus (MTG; see [Supplementary Fig. S3](#)).

Computational Lesion Prediction

In addition to simulated lesions of the limbic lobe and the prefrontal lobe, we also conducted prediction analyses with the simulated lesion of the temporal lobe, because the number of common edges in the temporal lobe was almost as high as for the limbic lobe and the prefrontal lobe ([Fig. 3j](#)). To correct for differences in lobe size (number of nodes in that lobe), we also calculated the relative number of each lobe contributing to the common network (the number of common edges in each lobe/lobe size). Results consistently showed that the limbic lobe, the prefrontal lobe and the temporal lobe were top 3 lobes contributing to the common edges (see [Supplementary Fig. S2](#)). As shown in [Table 2](#) and [Figure 4](#), these results suggested that the anxiety prediction power of the model decreased dramatically from lesions to the limbic or temporal lobes, to lesioned connectivity within the limbic lobe, and to lesioned connectivity between the limbic and the prefrontal lobe.

Control Analyses

After controlling for nuisance variables in edge selection and final correlation, and for scrubbing in preprocessing, the predictive models remained (marginally) significant ([Table 3](#)). However, the prediction power decreased significantly when controlling for gender in the edge selection (see [Supplementary Table S3](#)).

Replication of the Predictive Model in an Independent Dataset of Trait Anxiety

For replication in the STAI-T dataset, the result within the common network showed a significant predictive power and good statistical power [$r_{(32)} = 0.45$, $P = 0.023$, $1 - \beta = 0.86$], suggesting

that the common network is sufficiently sensitive to STAI-T prediction. This prediction remained significant when controlling for head motion, gender and age in the stage of final correlation ([Table 4](#)). However, the prediction power again decreased significantly when controlling for gender in the edge selection (see [Supplementary Table S3](#)). These results replicated the predictive network in an independent sample of trait anxiety.

External Validation from HCP S900 Dataset

We observed a significant negative correlation between network strength and anxiety scores in 501 participants of the HCP S900 dataset [$r_{(499)} = -0.10$, $P = 0.017$]. This prediction remained significant when controlling for head motion [$r_{(498)} = -0.10$, $P = 0.009$] as well as scrubbing [$r_{(499)} = -0.10$, $P = 0.013$]. Given that the current scores were adjusted for gender and age, we did not conduct control analysis for age and gender. In sum, these replication and external validation analyses corroborated the robustness of the identified anxiety prediction network.

Distinct Brain Networks between Anxiety and Depression

Despite strong correlation between (reciprocally transformed) BAI scores and SDS scores [$r_{(74)} = -0.73$, parametric $P < 0.001$, [Fig. 5a](#)], the two-sample t-test revealed a significant difference in network strengths between the “anxiety > depression” and “depression > anxiety” networks [$t_{(38)} = -4.15$, parametric $P < 0.001$, Cohen's $d = -1.857$, [Fig. 5d](#)], validating the distinctiveness of the 2 networks. Across iterations of 20 times, the number of edges, common edges, and generated networks within “anxiety > depression” and “depression > anxiety” networks were shown in [Table 1](#), [Figure 5b–f](#). Consistent with model assessment from 20 participants, results of external validation in the HCP S900 dataset also showed that network strength in “anxiety > depression network” was significant lower

Figure 4. Lesion predictions. (a) Lesion lobe predictions. (b) Lesion connectivity predictions. Abbreviations: Lim, limbic; Tem, temporal. *, parametric $P < 0.05$; **, parametric $P < 0.01$.

Table 3 Control analyses in internal validation with head motion, age and gender as covariates in edge selection and final correlation, as well as scrubbing of head motion

	Control at edge selection	Control at final correlation
Head motion	$r = 0.31, P = 0.018$	$r = 0.33, P = 0.033$
Age	$r = 0.24, P = 0.068$	$r = 0.30, P = 0.047$
Gender	$r = 0.22, P = 0.082$	$r = 0.32, P = 0.039$
Scrubbing	$r = 0.28, P = 0.040$	

Table 4 Control analyses in replication dataset with head motion, age and gender as covariates in edge selection and final correlation, as well as scrubbing of head motion

	Control at edge selection	Control at final correlation
Head motion	$r = 0.44, P = 0.024$	$r = 0.46, P = 0.020$
Age	$r = 0.40, P = 0.033$	$r = 0.45, P = 0.024$
Gender	$r = 0.36, P = 0.038$	$r = 0.46, P = 0.020$
Scrubbing		$r = 0.47, P = 0.021$

than that in “depression > anxiety network” [$t_{(320)} = -15.41, P < 0.001$, Cohen’s $d = -1.717$]. The two-sample t -tests also showed significant group differences between anxiety-specific versus depression-specific participants in network strength of “anxiety > depression” and “depression > anxiety” common networks for both our sample of 20 participants and the HCP dataset (161 participants), supporting distinctive networks for anxiety and depression. Specifically, the strength of “anxiety > depression” network was stronger in anxiety-specific compared with depression-specific participants [$t_{(18)} = 23.08, P < 0.001$, Cohen’s $d = 10.375$], whereas the strength of “depression > anxiety” network was stronger in depression-specific than in anxiety-specific participants [$t_{(18)} = 11.58, P < 0.001$, Cohen’s $d = 5.205$] based on our sample of 20 participants. For the HCP dataset, there was a greater network strength for “anxiety > depression” in anxiety-specific than in depression-specific participants [$t_{(159)} = 9.91, P < 0.001$, Cohen’s $d = 1.564$], whereas there was a greater network strength for “depression > anxiety” in depression-specific than in anxiety-specific participants: [$t_{(159)} = 13.26, P < 0.001$, Cohen’s $d = 2.093$] (for details, see [Supplementary Material](#)).

Discussion

In this study, we employed CPM, a data-driven, full cross-validation approach, to predict levels of anxiety in healthy participants from whole-brain rsFC. We demonstrated that anxiety could be predicted by individual functional connectivity patterns, especially those from the limbic system and prefrontal cortex. Specifically, “lesion prediction” revealed that connectivity within the limbic system as well as connectivity between the limbic system and prefrontal cortex dominantly contributed to the prediction of individual anxiety. We also showed preliminary evidence for distinctive brain networks between anxiety and depression. Importantly, all these findings could be replicated in independent datasets.

We found that the CPM could robustly predict individual anxiety from the negative network in healthy adults, which is of importance given the high incidence of subclinical anxious traits. Recent studies have provided increasing evidence for individual predictions based on CPM. For example, fluid intelligence could be predicted by CPM from both positive and negative networks (Finn et al. 2015) or from a combined

Figure 5. Distinctive anxiety-specific and depression-specific brain networks. (a) Distribution of anxiety scores and depression scores in 76 participants. (b) anxiety > depression network. (c) depression > anxiety network. (d) Model assessment using 2 sample t-test in network strengths between the “anxiety > depression” and “depression > anxiety” networks. (e) Division of “anxiety > depression” network into 10 lobes. (f) Division of “depression > anxiety” network into 10 lobes. The color bar reflects the number of selected edges belonging to each lobe pair. Abbreviations: Mot, motor; Ins, insula; Par, parietal; Tem, temporal; Occ, occipital; Lim, limbic; Cer, cerebellum; Sub, subcortical; Bsm, brainstem. R: right; L: left. ***, parametric $P < 0.001$.

network (Greene et al. 2018). Interestingly, Greene et al. (2018) suggested that, from a neurobiological perspective, the positive and negative networks may in fact, belong to a single network by calculating the correlation of degree vectors between positive and negative networks. Furthermore, Rosenberg et al. (2015) observed that predictions from the combined network were not more accurate than predictions from the positive or negative network, although all of them successfully predicted individual attentional performance. These results indicated that the positive and negative networks provided redundant information (Rosenberg et al. 2015), reflecting “the single network” idea to some extent. However, several studies provided evidence for the alternative opinion—that the positive and negative networks represent different functions and are disproportionately located at different functional networks (Finn et al. 2015; Shen et al. 2017; Beaty et al. 2018; Feng et al. 2019). For instance, when predicting individual fluid intelligence by CPM, positive network were located in the frontoparietal networks, whereas negative networks lay in the default-mode network (Finn et al. 2015). Consistent with previous studies revealing that personality traits (narcissism and loneliness) could only be predicted by one tail network (Feng et al. 2018, 2019), in the current study we observed that the negative network rather than the positive network successfully predicted anxiety. These 2 competing opinions thus require further investigation.

Using a computational lesion method, our CPM-based approach suggested that the anxiety-predictive power of the model significantly decreased with 1) lesion of the limbic system; 2) lesion of the connectivity within the limbic system;

and 3) lesion of the connectivity between the limbic system and prefrontal cortex. These results, except increased prefrontal-limbic connectivity, are consistent with the emotion dysregulation model (Behar et al. 2009). Anxiety is commonly associated with emotional hyper-arousal, which may be accompanied by hyper-connectivity within the limbic system (Kim et al. 2011). However, interpretations of the observed prefrontal-limbic hyper-connectivity are less straightforward. In anxiety-related disorders, attenuated prefrontal responses (Manber Ball et al. 2013) to over-responsiveness of the limbic system (Etkin et al., 2004; Qin et al., 2014; Bishop, 2007) have been observed. A nonclinical study has shown that anxiety-prone individuals were as successful as controls to reduce negative their emotions, but required greater engagement of lateral and medial PFC for successful down-regulation of negative emotions (Campbell-Sills et al. 2011). The increased prefrontal-limbic connectivity at rest in the current study might thus reflect more effort to regulate emotions in daily life in participants with higher degrees of anxiety.

Among the top 10 nodes, the ventral attention network (including the vlPFC and MTG), default mode network (including the PCC and ITG), and cingulo-opercular network (including the vACC) contributed to the anxiety-predictive model (Sylvester et al. 2012). The ventral attention network is involved in bottom-up attentional and affective processing of emotion-laden stimuli (Sylvester et al. 2012). The default mode network has been implicated in top-down emotion regulation specifically in trait anxiety (Sylvester et al. 2012; Xu et al. 2019). The cingulo-opercular network plays a crucial role in cognitive control

(Dosenbach et al. 2008). The involvement of these networks in the prediction of anxiety in the current study might reflect the neural underpinning of successful emotion regulation in healthy individuals with nonclinical levels of anxiety. Please note that caution is needed in the interpretation of these functional networks based on reverse inference (Poldrack 2011). We agree that one cannot directly infer emotion regulation, based on resting-state fMRI measurements. On the other hand, there is evidence to attest the relevance of these networks for emotion regulation. For example, Morawetz et al. (2016) examined brain activation during an emotion regulation task and resting state networks in the same study and observed common connected regions involved in emotion regulation. Reviews of published studies have also established the relevance of default mode network in emotion regulation alterations in anxiety (e.g., Sylvester et al., 2012). It is noteworthy that the amygdala was not shown in the top 10 connected brain nodes. It has long been acknowledged that the amygdala exerts a significant role in anxiety and emotion regulation (Whalen et al., 2002; Somerville et al., 2004; Sylvester et al., 2012; Grupe and Nitschke, 2013; Tovote et al., 2015; Xu et al. 2013, 2019). Despite this, previous hypothesis-driven studies may over-represent the amygdala. Specifically, the significant diagnostic effect of the amygdala in region-of-interest (ROI) studies disappeared when whole-brain studies were also considered in a meta-analysis for mental disorders (including anxiety disorders; Sprooten et al., 2017). Another reason for failure to find the amygdala might be that it was difficult to infer the specific involvement of the amygdala in the 268-node functional atlas, because the averaged size of the amygdala (1.24 cm³) is smaller than the average size of the other nodes (4.8 cm³; Brabec et al., 2010; Hsu et al., 2018). Studies are necessary to account for such differences in the average size of relevant brain regions.

The neural model from anxiety prediction measured by the BAI significantly predicted trait anxiety measured by the STAI-T, suggesting that the predictive network of individual anxiety in the current study is indeed significantly related to trait anxiety. It recently has been shown that state anxiety, rather than trait anxiety, could be predicted based on the cortical connectivity (Duan et al. 2020), suggesting that distinctive connectivity patterns might be involved in prediction of state anxiety and trait anxiety. Although this does not exclude a potential involvement of transient anxious mood states, this result demonstrates that the BAI scores used in this study are predictive of anxiety as a trait. In addition, although the anxiety-predictive model held when controlling for potential confounds, model performance significantly decreased when controlling for gender (both for internal validation and replication). This suggests differences in rsFC for anxiety prediction between genders. Indeed, rsFC can be predictive of gender (Zhang et al. 2018), and gender effects were observed in previous applications of CPM for fluid intelligence (Greene et al. 2018). Future studies should thus test the predictive power of rsFC-based CPM separately in female and male samples to reveal gender differences in anxiety prediction.

It is important to note that anxiety and depression were highly correlated in this study (a common finding) and that CPM failed to predict levels of anxiety when controlling depressive scores. Anxiety in this study may therefore be considered as referring to an anxious-depressed trait. Such close connection is not surprising given that anxiety and depression in real life are highly correlated (Stavrakaki and Vargo 1986; Clark and Watson 1991), which may share symptoms, psychological processes, and neural processes (Clark and Watson 1991; Kendler

1992). It has been demonstrated that anxiety-prone individuals require more engagement of the prefrontal cortex to accomplish down-regulation of negative emotion (Campbell-Sills et al. 2011), which has also been found in depressed individuals (Johnstone et al. 2007). Altered neuropsychological mechanisms of emotion regulation, especially the prefrontal-limbic connectivity, may thus be common characteristics in both anxiety and depression (Campbell-Sills et al. 2011).

However, it has also been widely shown that there are distinct neural circuitries between anxiety and depression (Oathes et al. 2015; Pannekoek et al. 2015). Therefore, one can hypothesize that there might be both common and distinctive neural pathways between anxiety and depression. We found that the “anxiety > depression” networks were mainly centered in the prefrontal cortex, connecting with the insula, subcortical lobes and cerebellum, whereas the “depression > anxiety” networks were mainly observed within the cerebellum and between the limbic system and brainstem, supportive of distinctive brain networks between anxiety and depression. These anxiety-specific connections are possibly associated with estimating the value and probability of uncertain threat (Geng et al. 2018) and detecting salient changes in the environment (Mchaffie et al. 2005). Therefore, anxiety-specific networks may confirm that anxious arousal is probably more central to anxiety (Oathes et al. 2015). Cerebellum lesions have been associated with personality changes (Stoodley and Schmahmann 2010). For example, cerebellum took part in individual prediction of neuroticism (Hsu et al. 2018), which may reflect that depression-specific networks are associated with personality-related factors. Deficiency in the limbic system has been constituted as vulnerability factor to long-term trajectory and state-dependent changes of depression (Ai et al. 2015, 2019), as well as generic effect of anxiety (van Tol et al. 2010). The brain stem central noradrenergic system has been proposed as stress circuitry that related to both anxiety and depression (Ito and Sugimoto 2010). Adding to these, our limbic-brainstem connectome finding indicates the distinctive role of this stress network on depression. In sum, the current data supports the idea by providing not only a common predictive model but also revealing distinctive networks between anxiety and depression.

The present work represents advances in neuroscience to advocate the applications of rsFC in a cross-validation manner (Shen et al. 2017). The advantages of this approach are 4-fold. First, resting-state data is easy to collect relative to task-dependent experiments (Rosazza and Minati 2011). Despite being task-free, rsFC can track individual cognitive performance (Scheinost et al. 2019), even higher-order functions such as trust (Lu et al. 2019). Importantly, rsFC is stable (even across 3 years; Horien et al. 2019) and unique (functional connectome “fingerprinting”; Finn et al. 2015). Second, compared with standard group comparisons between high-anxious and low-anxious individuals, the present model is more sensitive for the assessment of aspects of neuropsychological functioning in the individual brain (Gabrieli et al. 2015; Dubois and Adolphs 2016). Although studies with correlation or regression models also used the term “prediction,” such in-sample prediction incurs over-fitting (Gabrieli et al. 2015; Dubois and Adolphs 2016; Yarkoni and Westfall 2017). Third, instead of ROI or seed-based rsFC studies, we were able to obtain an objective picture of whole-brain rsFC networks in individual participants, eliminating the risk of over-representation of certain ROIs (Sprooten et al. 2017). In this way, our findings were still meaningful, conforming to emotion regulation network regarding “emotion dysregulation model” (Behar et al. 2009;

Manber Ball et al. 2013; Mochcovitch et al. 2014). Finally, the approach of implementing computational (“virtual”) lesions may have advantages above noninvasive neurostimulation methods, for instance, transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), which can cause some discomfort to participants. Although the causal explanatory power of neurostimulation techniques is stronger, they have significant drawbacks, the most important one being that they can only target superficial cortical regions as the depth of stimulation is very limited. A combination of the strength of both methods can also be indicative. Indeed, the computational lesion approach might provide potential neurostimulation targets (i.e., network-guided TMS; Fox et al. 2012) for future studies to reduce the tension of anxiety.

Several limitations of the present study are worth mentioning. First, we used a group-level atlas in the individualized prediction of anxiety, which might overlook subtle brain-behavior associations if they are highly variable. It has been documented that individualized prediction with the group-level atlas has a weaker predictive power than that with the individualized template (Wang et al. 2018). Second, for the purpose of early identification in subclinical population, we only recruited healthy participants. Given the asymmetric mechanisms between patients and healthy participants (Liao et al. 2010; Xu et al. 2020), however, whether the current predictive model could be used for early identification in anxiety disorders remains unknown. Future studies could test our model in patients with anxiety disorders.

To conclude, we established a brain connectivity-based model that was able to predict anxiety in novel individuals. In line with emotion dysregulation models, networks relevant for emotion regulation were of importance for individual anxiety prediction in healthy people. We also provide preliminary evidence for distinct networks in the classification of anxiety and depression. The current work may have important implications for the early identification of individuals enduring high trait anxiety in nonclinical populations.

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

Funding

The National Natural Science Foundation of China (31920103009, 31530031, 31871137, 31700959, 31671133, and 31500920); Young Elite Scientists Sponsorship Program by China Association for Science and Technology (YESS20180158); Guangdong International Scientific Collaboration Project (2019A050510048); Guangdong Key Basic Research Grant (2018B030332001); Guangdong young Innovative Talent Project (2016KQNCX149); Guangdong Pearl River Talents Plan Innovative and Entrepreneurial Team grant (2016ZT06S220); Guangdong University Innovation Team Project (2015KCXTD009); Guangdong Basic and Applied Research Major Project (2016KZDXM009); Shenzhen-Hong Kong Institute of Brain Science-Shenzhen Fundamental Research Institutions (2019SHIBS0003); Shenzhen Science and Technology Research Funding Program (JCYJ20180507183500566, CYJ20170412164413575, and JCYJ20180305124819889); and Shenzhen Peacock Program (827-000235, KQTD2015033016104926).

Notes

Conflict of Interest: None declared.

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