

The functional connectome predicts feeling of stress on regular days and during the COVID-19 pandemic

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ABSTRACT

Although many studies have explored the neural mechanism of the feeling of stress, to date, no effort has been made to establish a model capable of predicting the feeling of stress at the individual level using the resting-state functional connectome. Although individuals may be confronted with multidimensional stressors during the coronavirus disease 2019 (COVID-19) pandemic, their appraisal of the impact and severity of these events might vary. In this study, connectome-based predictive modeling (CPM) with leave-one-out cross-validation was conducted to predict individual perceived stress (PS) from whole-brain functional connectivity data from 817 participants. The results showed that the feeling of stress could be predicted by the interaction between the default model network and salience network, which are involved in emotion regulation and salience attribution, respectively. Key nodes that contributed to the prediction model comprised regions mainly located in the limbic systems and temporal lobe. Critically, the CPM model of PS based on regular days can be generalized to predict individual PS levels during the COVID-19 pandemic, which is a multidimensional, uncontrollable stressful situation. The stability of the results was demonstrated by two independent datasets. The present work not only expands existing knowledge regarding the neural mechanism of PS but also may help identify high-risk individuals in healthy populations.

1. Introduction

Coronavirus disease 2019 (COVID-19) has presented humanity with one of the greatest health and economic crises of the 21st century. It is characterized by enormous uncertainty, life-threatening conditions, and intense loss; therefore, it has become an uncontrollable stressor for many individuals (Gruber et al., 2020). Although individuals may be confronted with this multidimensional stressor, their appraisal of the impact and severity of these events might vary. The impact of objectively stressful events is determined by their perception of stressfulness (Cohen et al., 1983). The subjective measure of event-specific stress levels can be defined with perceived stress (PS), which refers to the degree to which situations in one's life are appraised as stressful, unpredictable and uncontrollable (Cohen et al., 1983; Phillips, 2012). High PS increases the risk of physical problems, such as cardiovascular disease,

hypertension, and stroke (Aggarwal et al., 2014; Chrousos, 2009; Ostwald et al., 2009), and some psychiatric disorders such as depression, anxiety and addiction disorder (Andrews and Wilding, 2004; Baghurst and Kelley, 2014; Chrousos, 2000; Faravelli et al., 2012; Gress-Smith et al., 2015; Johnson et al., 1992). Considering that stress levels have increased dramatically during COVID-19 (Brooks et al., 2020), it is valuable to identify neurobiological markers of PS that can predict the feeling of stress at the individual level.

Early studies on the neural mechanism of PS identified the involvement of localized brain regions such as the limbic systems and prefrontal cortex (Hermans et al., 2014; McEwen and Morrison, 2013; Menon, 2011; Pruessner et al., 2008; Seo et al., 2011; Sinha et al., 2004; Van Oort et al., 2017). Many studies have demonstrated that some limbic regions belonging to the default model network (DMN), such as the hippocampus and parahippocampus (PHG), are involved in stress

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processes (Albert et al., 2015; Boehringer et al., 2015; Chang and Yu, 2019; Li et al., 2014; McEwen and Gianaros, 2011; Ploghaus et al., 2001; Sinha et al., 2004). Some regions of the salience network (SN), such as the amygdala, insula, and thalamus, that engage in detecting salient internal and external events are also important in stress-related processes (Dedovic et al., 2014; Hermans et al., 2014; Li et al., 2014; Seo et al., 2011; Sinha et al., 2004; Wang et al., 2005). The prefrontal cortex, which is associated with cognitive and emotion regulation processes, are also associated with stress processes (Li et al., 2014; Maron-Katz et al., 2016; Wang et al., 2019; Wu et al., 2018). In addition to localizing stress to some specific regions, some work has tried to identify the functional brain connectivity of stress with task-based and resting-state data (Hermans et al., 2011, 2014; Quaedflieg et al., 2015a,b; Vaisvaser et al., 2013, 2016; Van Oort et al., 2017; Zhang et al., 2019, 2020). One meta-analysis indicated three networks, i.e., the SN, the DMN and the central executive network (CEN), that are involved in experimentally induced stress responses (Van Oort et al., 2017). In sum, previous studies showed that the stress response was associated with alterations of multiple brain regions organized into functional networks.

Although previous neuropsychological studies have advanced our understanding of the neural basis of stress, to the best of our knowledge, no study has used resting-state functional connectivity (rsFC) to predict PS at the individual level for healthy people. Intrinsic rsFCs are closely associated with underlying anatomical connections (Greicius et al., 2009) and can be better used to explore relatively stable personal characteristics and their individual differences (Biswal et al., 1995; Crossley et al., 2013; Finn et al., 2015; Fornito et al., 2012). One advantage of resting-state data over task-based data is that they are much easier to record and are not influenced by task difficulty (Kable and Levy, 2015; Nash et al., 2015). Considering that a secondary crisis after the outbreak of COVID-19 is mental health problems (Gruber et al., 2020), models that can be used to predict high PS at the individual level may help identify high-risk individuals in healthy populations. These models may provide some insight for clinical diagnosis in the future. Moreover, predicting PS during the COVID-19 pandemic with whole-brain rsFC would provide some insight into the neural mechanism of PS (Cole et al., 2014; Krienen et al., 2014; Petersen and Sporns, 2015) because the stress process is known to induce large-scale network reorganization (Hermans et al., 2014). Most of the previous studies of the neural mechanisms of PS focused on some localized brain regions or specific functional connectivity with stress processes and had inconsistent results because of differences in experimental design and contrast (Van Oort et al., 2017). Network-based approaches provide whole-brain rsFC in individual participants and are particularly well suited to address the complex interplay of multiple neurocognitive processes in perceived stress.

Recently, a novel approach—connectome-based predictive modeling (CPM)—has been used to explore the association between functional connectivity in the brain and meaningful psychological traits. CPM was employed to identify networks consisting of the functional connectivity most associated with observed trait scores and uses these networks to generate models that predict trait scores in novel individuals (Beatty et al., 2018; Fountain-Zaragoza et al., 2019; Hsu et al., 2018; Lu et al., 2019; Rosenberg et al., 2016, 2020). CPM has been employed to predict attention (Rosenberg et al., 2016, 2020; Yoo et al., 2018), personality traits (Hsu et al., 2018), and creative ability (Beatty et al., 2018). In this study, we implemented a CPM to test whether a whole-brain connectome based on rsFC can reliably predict PS in novel participants within this dataset. Moreover, we also examined whether the psCPM built on regular days can predict individual PS levels during the COVID-19 pandemic, a multidimensional stressor situation. Because perceived stress is commonly considered a personality style (Cohen et al., 1983; Phillips, 2012), individuals with a high level of PS may tend to feel more stressed during the COVID-19 pandemic than others. We hypothesized that psCPM based on regular days tracked the degree of perceived stress in the full spectrum. Although stress levels during the

COVID-19 pandemic were shown to be significantly elevated, brain networks that register stress levels remained the same networks. Therefore, the psCPM built with regular days can predict individuals' stress levels during the COVID-19 pandemic. To assess the predictive power of this neural model, external validation analyses were conducted with two independent datasets.

2. Methods

2.1. Participants

Three datasets that included a total of 817 participants were used in this study. All participants were recruited from Southwest University in Chongqing, China. Dataset 1 was used as the discovery dataset with 673 participants (491 females) from our Gene-Brain-Behavior (GBB) project, which was conducted from 2015 to 2017 and aimed to explore the neural and genetic basis underlying complex human behavior and mental health. The recruitment program and exclusion criteria are detailed in our previous publications (Liu et al., 2017). All the participants completed brain imaging scanning from September to December 2016. A total of 673 participants from the GBB project who completed the PS scale in 2016 were used in the following data analysis. Dataset 2 consisted of 87 participants (69 females), and dataset 3 consisted of 57 participants (47 females). These two datasets were used as the external validation dataset. All the participants in dataset 2 and dataset 3 completed an online questionnaire survey from February 21 to 28, 2020, and brain imaging scanning from June to September 2019 and March 2018, respectively. All the participants were right-handed and had no history of neurological or psychiatric disorders. This study was approved by the Southwest University Brain Imaging Center Institutional Review Board, and written informed consent was obtained from all participants.

2.2. Perceived stress measurements

The participants' PS levels were measured with the PS scale, which was designed to measure the extent to which situations in one's life could be appraised as stressful during the past month (e.g., 'In the last month, how often have you felt nervous and 'stressed'?') (Cohen et al., 1983). This inventory consisted of 14 items, and participants were asked to rate their opinion on each item on a 5-point scale from "never" (0) to "very often" (4). High scores indicated elevations in perceived stress. Previous studies have shown that the PS scale has high reliability and validity and is a sensitive measure of subjective stress levels in clinical and nonclinical samples (Cohen et al., 1983, 1993; Ng, 2013). In this study, the PS scale showed high internal consistency, $\alpha = 0.844$.

2.3. fMRI data acquisition and analysis

2.3.1. Image protocols and preprocessing

Resting-state fMRI scanning of dataset 1 and dataset 3 was performed on a 3T Trio scanner (Siemens Medical Systems, Erlangen, Germany) at Southwest University Brain Imaging Center. During scanning, participants were asked to close their eyes and remain awake. A total of 242 vol lasting for 8 min were acquired using a gradient echo-planar imaging (EPI) sequence with the following parameters: echo time [TE] = 30 ms, repetition time [TR] = 2000 ms, slices = 32, thickness = 3 mm, matrix size = 64×64 , flip angle = 90° , field of view [FOV] = $220 \times 220 \text{ mm}^2$, and voxel size = $3.4 \times 3.4 \times 4 \text{ mm}^3$.

Brain imaging data of dataset 2 were collected on a 3T Prisma Siemens Trio MRI scanner (Siemens Medical Systems, Erlangen, Germany) using a 32-channel brain coil at Southwest University Brain Imaging Center. Resting-state scanning contained 240 vol, and data were obtained with a gradient EPI sequence: TR = 2000 ms, TE = 30 ms, FOV = 224×224 , FA = 90° , slices = 62, thickness = 2 mm, slice gap = 0.3 mm, and voxel size = $2 \times 2 \times 2 \text{ mm}^3$. All participants were asked to close their eyes and rest but not to fall asleep.

The resting-state fMRI data were preprocessed using the Data Processing & Analysis of Brain Imaging toolbox (DPABI; Version 3.1) (Yan et al., 2016). The first 10 functional volumes were discarded to decrease signal instability. The remaining volumes of each participant underwent subsequent preprocessing, including slice timing and realignment. Data from participants whose mean framewise displacement was greater than 0.2 mm were excluded from further processing (Jenkinson et al., 2002). The functional volumes were then spatially normalized to standard Montreal Neurological Institute (MNI) space with a $3 \times 3 \times 3$ mm³ voxel resolution. Afterwards, the linear trends of time courses were removed, and bandpass filtering (0.01–0.1 Hz) was applied to reduce low-frequency drift and high-frequency physiological noise. Subsequently, the images were spatially smoothed with a Gaussian filter to decrease spatial noise (4 mm full width at half maximum in each direction). Finally, common nuisances were regressed out, including signals related to the whole brain signal, ventricular signal, white matter signal, and any effects of head motion using the 24 head motion parameters procedure (6 motion parameters, 6 temporal derivatives, and their squares) (Friston et al., 1996).

2.3.2. Functional network construction

After data preprocessing, the whole-brain rsFC matrix was constructed with the Human Brainnetome Atlas, which consisted of 210 cortical and 36 subcortical ROIs. This atlas provides a new framework for connectome analysis that integrates multimodal information and overcomes several drawbacks of previous parcellation schemes (Fan et al., 2016). For each participant, the blood oxygenation level-dependent time course of each node was extracted by taking the mean across voxels, and a 246×246 correlation matrix was calculated between time courses of node pairs with Pearson correlation followed by Fisher's z transformation. Thus, each connection (or 'edge') in the matrix represents the FC strength between two nodes.

2.3.3. Connectome-based predictive modeling

We used CPM, a recently developed technique, to predict individuals' PS scores based on whole-brain rsFC (Finn et al., 2015; Rosenberg et al., 2016; Shen et al., 2017) in dataset 1 (discovery dataset) composed of 673 participants. A detailed protocol and scripts of CPM are available in Shen et al. (2017). First, to obtain networks used in the prediction, a Pearson correlation was made between individuals' PS scores and every edge in the connectivity matrix of each participant. A commonly used threshold ($p < 0.01$) in the CPM protocol (Jangraw et al., 2018; Rosenberg et al., 2016; Shen et al., 2017) was applied to remove most weak connections and retain significantly correlated edges. Edges that were significantly positively related to PS scores made up the positive prediction network, and edges that were significantly negatively related to PS scores made up the negative prediction network. We then calculated each participant's positive and negative network strength (a single summary statistic) by summing the edge strength within the positive network and the negative network separately. For each participant, we also computed combined network strengths by summing the edges from both the positive and negative networks. Summing the strength of connections within a given network for each participant provides a quantitative summary statistic of the overall strength of functional connectivity that has been identified to correlate with the outcome measure of interest (i.e., PS scores).

Next, a predictive model was built that fit a linear regression between each participant's network strengths and the observed PS scores (Beatty et al., 2018; Finn et al., 2015; Rosenberg et al., 2016). The model was then applied to new participants in a leave-one-out cross validation (LOOCV) procedure. Briefly, the predictive model was trained on $N-1$ participants' connectivity matrices and PS scores and subsequently tested on the left-out participant. After all the LOOCV folds were completed, we obtained the predicted scores of each participant.

The predictive power of the model was assessed by the magnitude and statistical significance of Pearson's correlation between actual and

predicted behavioral values. If actual and predicted PS scores were significantly positively related, this would suggest that the model was successful in its prediction. Permutation testing was used to assess the significance of the prediction results. Specifically, we randomly shuffled the label between observed PS scores and rsFC matrices each time and reran the above LOOCV prediction procedure. The 1000 Pearson correlations between observed and predicted scores composed null distributions of r values. The number of null r values was greater than or equal to the observed r value plus one and then divided by 1001, providing an estimated p value.

2.3.4. Control analyses

To avoid potential confounding effects of sex, age and head movements in prediction, control analyses were conducted in addition to the main, non-controlled results. We built new predictive networks that uniquely predicted PS scores when controlling for these covariates.

2.3.5. External generalizability

To test the external validity of the psCPM identified in the discovery dataset, we tested whether these edges were significantly predictive of PS in two independent datasets. Specifically, we applied the positive and negative PS brain networks and the model parameters derived from the discovery dataset to the external validation datasets. Model performance using external datasets was assessed by correlating the predicted and actual PS scores.

3. Results

3.1. Behavioral results

Based on case data from the National Healthy Commission of the People's Republic of China (<http://www.nhc.gov.cn/>), the number of existing confirmed COVID-19 cases (58,016 cases) peaked on February 17, 2020. The epidemic remained severe during our online questionnaire collection period from February 21 to 28, 2020 (the number of existing confirmed cases ranged from 39,919 to 54,965). The mean and standard deviation of the PS scores in the three datasets are described in Table 1. The PS scores reported during the COVID-19 pandemic period (Feb 2020) for datasets 2 and 3 were significantly larger than the PS scores reported in 2016 for Dataset 1, $t(815) = -4.837$, $p = 0.000$, Hedges' $g = 0.4437$. Because participants in dataset 3 had PS scores on regular days and during the COVID-19 pandemic, we also performed a paired-sample t -test for the PS scores in this dataset. The results also showed that participants' PS scores during the COVID-19 pandemic were also significantly higher than those on regular days, $t(56) = -2.221$, $p = 0.030$, Hedges' $g = 0.2971$. Demographic information for all datasets is presented in Table 1.

3.2. CPM results

3.2.1. Predicting individualized PS scores

For predicting individual PS on regular days, the results showed that the positive model and negative model had significant predictive power for PS scores: positive network, $r = 0.360$, $p < 0.001$; negative network, $r = 0.431$, $p < 0.001$, Fig. 1A; combined network: $r = 0.444$, $p < 0.001$. P_{perm} values were based on 1000 permutation tests. After controlling for head motion, age, and sex, all three networks still significantly predicted

Table 1
Demographic information.

Data set	Age (SD)	PSS (SD)
Dataset 1	19.46 (1.46)	25.32 (6.35)
Dataset 2	19.38 (0.63)	28.97 (7.72)
Dataset 3	18.58 (0.65)	27.09 (6.79)

Abbreviations: PSS, Perceived Stress Score; SD, Standard Deviation.

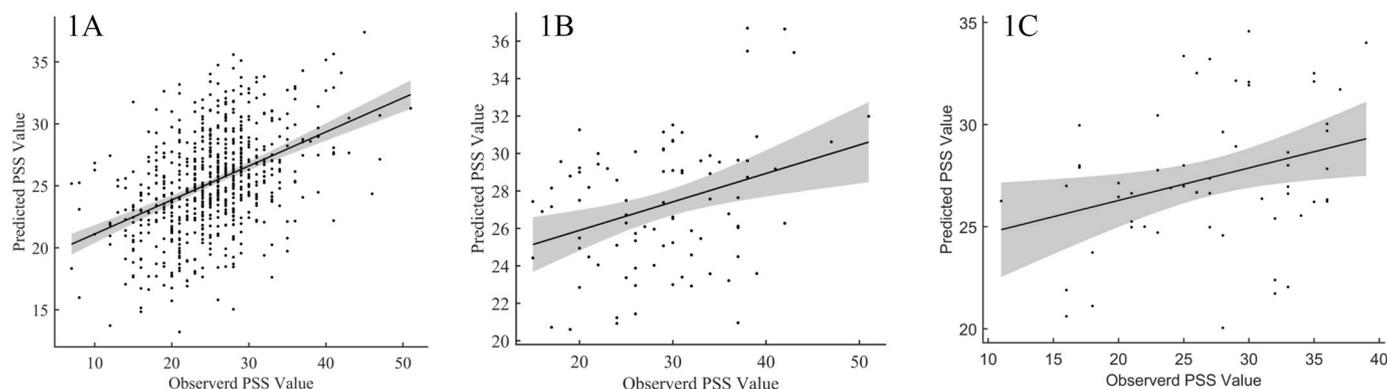


Fig. 1. (A) Scatter plots showing the correlation between the actual and predicted perceived stress scores (PSS) generated using CPM based on the negative networks in dataset 1. (B) and (C) The built predictive model of PSS generalized to the external validation datasets (dataset 2 and dataset 3) and showed a positive correlation between the actual PSSs and the predicted scores.

PS scores: positive network: $r_{\text{partial}} = 0.379, p < 0.001$; negative network: $r_{\text{partial}} = 0.451, p < 0.001$; combined network: $r_{\text{partial}} = 0.468, p < 0.001$.

We next assessed whether the networks that predicted PS on regular days in the discovery dataset generalized to two other datasets separately. Edges identified in the discovery dataset as significantly related to observed PS scores were extracted from dataset 2 and then the FC strength was directly input into the final CPM to obtain the predicted PS scores and to calculate its correlation with the actual scores. The results showed a significant prediction of PS scores for the negative network [$r_{\text{partial}} = 0.336, p = 0.001$, Fig. 1B] and combined network [$r_{\text{partial}} = 0.271, p = 0.011$] but not the positive network [$r = 0.080, p = 0.462$]. The validation analysis from dataset 3 showed the same results. The CPM built with negative network strength and combined network

strength reliably predicted novel participants' PS scores (negative network: $r_{\text{partial}} = 0.309, p = 0.020$, Fig. 1C; combined network: $r_{\text{partial}} = 0.389, p = 0.003$) but not the positive network ($r_{\text{partial}} = 0.251, p = 0.060$). Because we only found a successful prediction of PS during the COVID-19 pandemic using negative network strength, the following discussion focused on the connections within the negative network. The connections within the positive network are presented in the supplementary information (Supplementary Fig. 1 and Supplementary Table 1).

3.2.2. Network anatomy

For PS scores, the negative network (consisting of edges included in negative predictions in every iteration of the leave-one-out procedure)

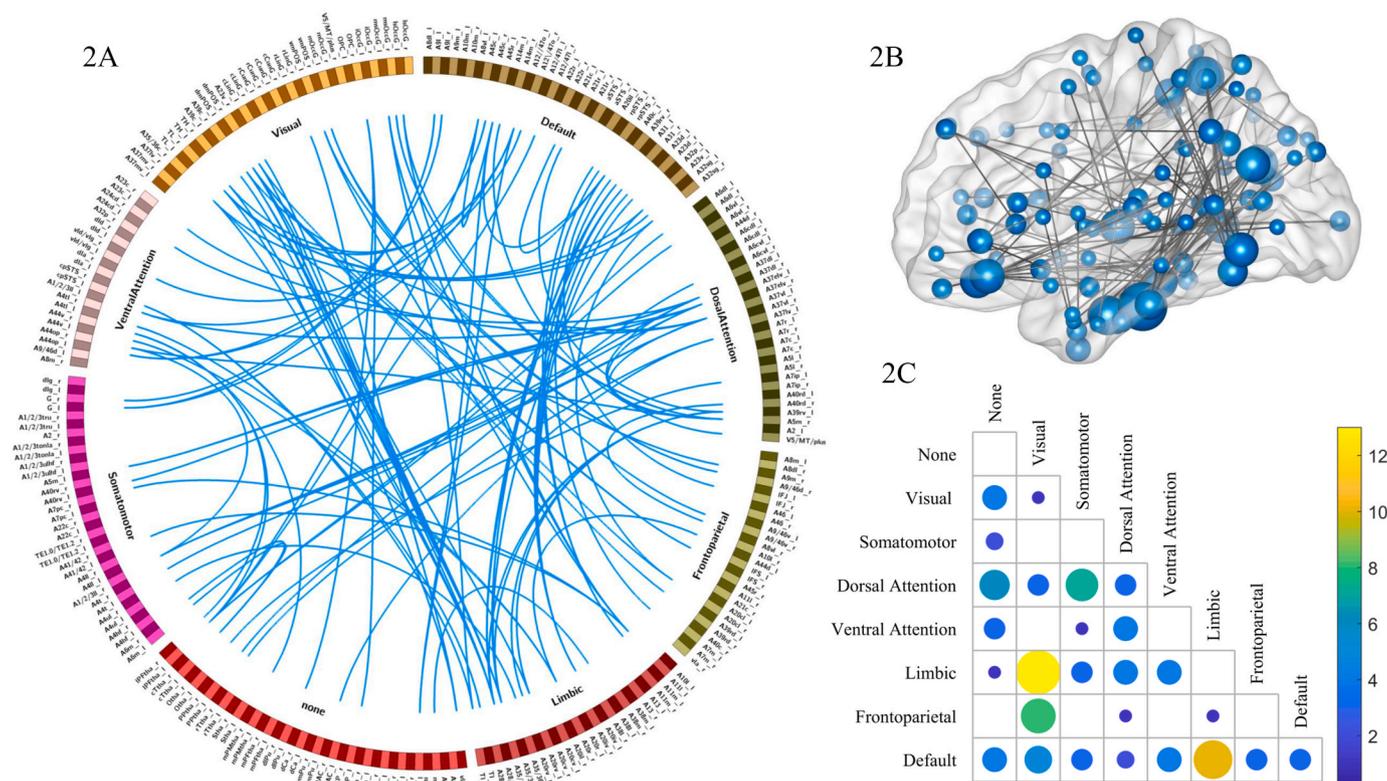


Fig. 2. (A) The functional connectivity sets of the negative network that connected 246 nodes in the circle plot. (B) We mapped the functional connectivity of the negative network to the surface, and the node size represented the degree. (C) The 246 nodes are grouped into canonical functional networks, and the connection number between brain networks is shown in the matrix (larger spheres indicate more connections).

contained 103 edges (0.34% of all possible edges) (Fig. 2A). At a macroscale level, connections distributed in the temporal lobe, frontal lobe, parietal lobe, limbic system and subcortical lobe made the greatest contribution to the prediction of individual differences in PS (Fig. 2A and B). The nodes with the highest degrees for the negative network included nodes that belong to the DMN (e.g., the parahippocampal gyrus, precuneus, and orbital gyrus) and salience network (e.g., the thalamus) (Fig. 2A and C, Table 2).

4. Discussion

The present study first used CPM to predict individual PS scores in novel healthy participants with whole-brain rsFC data. The results showed that inter-individual differences in PS were primarily predicted by rsFC located within and between the domain general large-scale network-DMN (e.g., the PHG, precuneus, and orbital gyrus) and SN (e.g., the thalamus), for which neural activity has been previously associated with stress processing (Hermans et al., 2014; Van Oort et al., 2017). The external validity of the functional networks of PS was tested with two independent datasets. Critically, the results demonstrated successful generalizability of the psCPM based on regular days to a multidimensional stressor situation—the COVID-19 pandemic—even though the stress levels during the COVID-19 pandemic were significantly elevated; this finding suggests that psCPM tracked the degree of perceived stress in the full spectrum of stressful days. Taken together, this finding provided the first evidence that the subjective feeling of stress across situations can be reliably predicted from an individual's unique rsFC profile.

Our results showed that the greatest number of significantly correlated functional connections corresponded to the hubs of the DMN, such as the PHG, precuneus, and orbital gyrus (see Table 2). Previous studies have shown that DMN regional activity and connectivity between the DMN and other brain regions are associated with stress processes (Boehringer et al., 2015; Chang and Yu, 2019; Dedovic et al., 2014; Hermans et al., 2014; Koric et al., 2012; Lederbogen et al., 2011; Maron-Katz et al., 2016; Quaedflieg et al., 2015a,b; van Oort et al., 2017). Abnormal DMN connectivity was associated with stress-related

psychopathologies, such as posttraumatic stress disorder (Bluhm et al., 2009; Rabinak et al., 2011) and depression (Greicius et al., 2007). The DMN is associated with self-referential processing and emotion regulation (Andrews-Hanna et al., 2014; Buckner et al., 2008; Leech and Sharp, 2014). Connectivity between a core region of DMN regions and the SN was found to be enhanced after stress induction and suggests a top-down regulation of amygdala activity. This connectivity in the recovery phase after stress might be associated with resilience to stress (Veer et al., 2011). The interaction between the DMN and SN in the stress process is critical for the generation and regulation of emotional reactions in response to stressful situations (Van Oort et al., 2017). One study found that rsFC between the SN and DMN may underlie the individual tendency and dynamics of subjective stress recovery (Maron-Katz et al., 2016). The current study showed that the connection between the DMN and SN is also critical in predicting individual stress feeling in daily life and during the COVID-19 pandemic.

The current study showed that some regions of the SN were critical in predicting individual PS, such as the thalamus. Previous task-based studies demonstrated the important role of the SN regions in the stress process (Li et al., 2014; Menon, 2011; van Oort et al., 2017). The rsFC between the thalamus and some nodes of the DMN was found to be involved in post-stress rsFC alterations (Maron-Katz et al., 2016; Vaisvaser et al., 2013). The thalamus is critical in arousal regulation and in mediating the interaction of attention and arousal in humans (Portas et al., 1998; Schiff, 2008). The SN is engaged in orienting attention to salient information in the external or internal environment (Menon, 2011). Previous studies have suggested that increased connectivity between the SN and visual system promotes a state of hypervigilance during stressful situations (Liston et al., 2009). In this study, some sensory areas were important in predicting individual PS. The connection between the SN and the vision network is also critical in the negative psCPM network (see Fig. 2C). The SN may also orient attention to salient and emotional information in the internal environment, which is supported by connectivity with the DMN (Maron-Katz et al., 2016; Quaedflieg et al., 2015a,b; Vaisvaser et al., 2013; Van Oort et al., 2017). Based on previous studies, the SN may interact with sensory areas and the DMN to orient attention to salient information in the external or internal environment. This connectivity may support a hypervigilant state that improves threat detection and promotes survival (Hermans et al., 2014; van Marle et al., 2009; van Oort et al., 2017).

An interesting result from this study is that the CPM model of PS based on regular days can be generalized to predict the PS level in the COVID-19 pandemic situation, which is a multidimensional, uncontrollable stressful situation. The stability of this result was tested by two independent datasets. The behavior results were consistent with those of previous studies (Brooks et al., 2020) and showed that individual PS scores in the COVID-19 pandemic were higher than those on regular days. Although stress levels during the COVID-19 pandemic were significantly elevated, psCPM based on regular days can also predict inter-individual differences in PS levels. It should be noted that the positive model of PS built on data from regular days could not separately predict individual PS levels in the COVID-19 pandemic. This might suggest that the positive network of PS can be influenced by the situation and that the negative network of PS is more stable in predicting individual stress levels in the full spectrum of stressful days. In the positive network of PS, the critical rsFCs included the connection between the DMN and visual network. This suggests that the connectivity between the visual and somatomotor networks is more heavily influenced by the situation and is not suitable for predicting individual stress in the full spectrum of stressful days. Our study first provided evidence that the subjective feeling of stress across situations can be reliably predicted from an individual's unique rsFC profile. Considering that the increased stress during the COVID-19 pandemic had both physical and psychological aspects (Andrews and Wilding, 2004; Baghurst and Kelley, 2014; Chrousos, 2000; Faravelli et al., 2012; Gress-Smith et al., 2015; Johnson et al., 1992), the CPM of PS would be an objective neuromarker to help

Table 2

Top ten nodes with highest degree in the negative network.

Degree	Gyrus	Lobe	Hemisphere	Label	MNI (x, y, z)
8	Parahippocampal Gyrus	Temporal Lobe	Left	111	-25, -25, -26
6	Parahippocampal Gyrus	Temporal Lobe	Left	115	-19, -12, -30
6	Precuneus	Parietal Lobe	Right	150	7, -47, 58
6	Precuneus	Parietal Lobe	Left	151	-12, -67, 25
5	Orbital Gyrus	Frontal Lobe	Left	43	-36, 33, -16
5	Orbital Gyrus	Frontal Lobe	Left	45	-23, 38, -18
5	Middle Temporal Gyrus	Temporal Lobe	Right	86	60, -53, 3
5	Inferior Temporal Gyrus	Temporal Lobe	Left	97	-55, -60, -6
5	Parahippocampal Gyrus	Temporal Lobe	Right	114	30, -30, -18
5	Thalamus	Subcortical Lobe	Left	245	-11, -14, 2

Note. The template information was extracted from the Human Brainnetome Atlas.

identify high-risk individuals during the COVID-19 pandemic. Predicting high PS at the individual provides a novel perspective for the early identification of high-risk individuals, and it also provides some insight for clinical utility in terms of diagnosis and prognosis in the future. Moreover, a better understanding of the neural mechanism of PS with rsFC with respect to health may ultimately lead to a better understanding of how stress contributes to psychopathology in vulnerable individuals.

There are several limitations in the present study. First, we only recruited healthy participants given that the aim of this study was early identification in a subclinical population. Future studies should test whether the psCPM can be generalized to psychological patients who are characterized by higher PS levels. Second, we only recruited college students as participants because these young adults have high levels of stress (Abouerie, 1994; Lupien et al., 2009). The generality of the psCPM should be tested with other adults and older healthy participants, and some individuals with psychologic problems induced by high levels of stress. Third, one recent study used a fMRI-based sustained exposure paradigm and demonstrated that stressor-modulated hippocampal networks can predict individual stress (Goldfarb et al., 2020). Therefore, future studies can also use task-fMRI to predict individual PS levels in the COVID-19 pandemic and compare neural markers based on rsFC and task FC. In addition, recent studies found that the white matter (WM) functional connectome offers a novel applicable neuromarker to explore brain-behavior relationships, such as fluid intelligence (Li et al., 2020; Liao et al., 2020). Future studies should explore whether the WM functional connectome could predict individual PS levels.

5. Conclusion

In conclusion, we established a brain connectivity-based model that was able to predict PS in novel individuals. The results showed that the functional interplay between the DMN and SN network associated with emotion regulation and salience attribution was crucial for predicting individual differences in PS. Critically, this model can be generalized to a novel situation, the COVID-19 pandemic, a severely stressful situation. This suggests that psCPM appears to provide a robust neuromarker that can be useful in making predictions in severely stressful situations despite the presence of situation-related changes in behavior. This study not only provides some insight into the neural mechanism of PS but also has important implications for the early identification of individuals enduring high PS levels in nonclinical populations.

Declaration of conflicting interests

The authors declared that there were no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ynstr.2020.100285>.

Author contributions

P. Liu, W. Yang and J. Qiu developed the study concept. P. Liu and K.

Zhuang analyzed and interpreted the data under the supervision of J. Qiu. P. Liu and W. Yang drafted the manuscript, and J. Qiu, R. Yu, X. Huang and D. Wei provided critical revisions. All authors approved the final version of the manuscript for submission.

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