Authors' response

We thank the reviewers for their enthusiasm and positive evaluation of our manuscript. We also appreciate their thoughtful and constructive comments and have revised the manuscript to address every point made. We feel that the revisions have strengthened our manuscript and hope that the reviewers feel that it is now ready for publication.

Reviewer # 1

1. The authors cited one paper (Mounce, Keogh, and Eccleston 2010) as a justification for extracting a general negative emotion score. While this paper indeed used a similar approach and obtained a general distress component, I would like to see more supporting literature, especially theoretical ones clarifying the meaning of the core negative emotion score. Also, these citations should be added to the main manuscript.

Response:

Previous studies have suggested the multidimensional structure of negative emotion (Stokes and Levin 1990; Watson and Clark 1984) and provide evidence that it is highly related to the symptoms and diagnosis of both anxiety and depression (Brown et al. 1997; Clark and Watson 1991; Watson and Clark 1984). Lovibond et al. (1995) developed the depression anxiety stress scales to measure the general negative affective syndromes (Lovibond and Lovibond 1995) . Brown et al. (1997) have suggested that the subscales of the DASS may measure the three dimensions specified in the tripartite model of negative affect: low positive affect (Depression), physiological hyperarousal (Anxiety), and negative affect (Stress) (Brown et al. 1997). Based on these evidences, it's reasonable to use PCA to extract core negative emotion scores based on the raw measures of depression, anxiety and stress.

We also added these citations in the main manuscript. Please see section 2.4, line 16-21.

2. I do not find the authors' response to this question: "Second, since the PCA was performed on the whole sample, there was also a data leakage problem similar to the sCCA".

Response:

We apologize for not describe our revision clearly. PCA and SCCA only performed on the training dataset, and the testing dataset were obtained based on the component coefficients extract form PCA and SCCA process.

The detail of the prediction pipeline was as follows: the whole dataset was divided into 10 subsets. Then 9 of the subsets were used as training sample, and the remaining one was used as the testing sample. 2, PCA was performed on the training data to obtain individual's negative emotion score, the negative emotion of testing data

were obtained based on the raw measures and the component coefficients of PCA. Then PCA was used to reduce the dimension of the raw FC matrix in the training dataset, keeping only the top 300 PCs as the neural profile matrix. The neural profile matrix of the testing dataset were obtained based on the raw FC matrix and the component coefficients of PCA. 3, SCCA were applied to extract psychological meaningful neural patterns based on the training data， the neural patterns of the testing data were obtained based on the neural profile matrix and the unmixing matrices of SCCA. 4, The predictive model was trained using Lasso regression algorithm.

We also revised these details in the manuscript, please see section 2.4 line 16-23, section 2.5, line 16-28. Section 2.6.1, paragraph 2, line 10-14.

3. About the correlations between the predicted and actual scores in Table 2 of the response letter, did the authors train a new model for each of the indicators (e.g., depression, anxiety)? If so, I would like to see the procedure to be reported in more detail and added to the main manuscript or as supplementary information.

Response:

We apologize for not describe our revision clearly. As the reviewer suggested, we trained a new model for each of the indicators, including depression, anxiety and stress, using the same prediction pipeline in the manuscript. We also present the results in the supplementary information eMethods 4, eResults 2 and eTable 6.

eTable 6 Correlations between predicted scores and actual scores in the BBP sample

	r	p	MAE	MAPE
Depression	0.18	1.89×10^{-5}	8.94	0.18
Anxiety	0.26	4.66×10^{-10}	8.31	0.20
Stress	0.31	6.12×10^{-14}	6.25	0.23

Reference:

Brown, Timothy A., Bruce F. Chorpita, William Korotitsch, and David H. Barlow. 1997. “Psychometric Properties of the Depression Anxiety Stress Scales (DASS) in Clinical Samples.” *Behaviour Research and Therapy* 35(1):79–89.

Clark, Lee Anna, and David Watson. 1991. “Tripartite Model of Anxiety and Depression: Psychometric Evidence and Taxonomic Implications.” *Journal of Abnormal Psychology* 100(3):316.

Lovibond, Peter F., and Sydney H. Lovibond. 1995. “The Structure of Negative Emotional States: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories.” *Behaviour Research and Therapy* 33(3):335–43.

Stokes, Joseph P., and Ira M. Levin. 1990. “The Development and Validation of a Measure of Negative Affectivity.” *Journal of Social Behavior and Personality* 5(2):173.

Watson, David, and Lee A. Clark. 1984. “Negative Affectivity: The Disposition to Experience Aversive Emotional States.” *Psychological Bulletin* 96(3):465.

A neural predictive model of negative emotions for COVID-19

Yu Mao, Dongtao Wei, Wenjing Yang, Qunlin Chen, Jiangzhou Sun, Yaxu Yu, Yu Li, Kaixiang Zhuang, Xiaoqin Wang, Li He, Tingyong Feng, Xu Lei, Qinghua He, Hong Chen, Shaozheng Qin, Yunzhe Liu and Jiang Qiu

Abstract—The long-lasting global pandemic of Coronavirus disease 2019 (COVID-19) has changed our daily life in many ways and put heavy burden on our mental health. To safeguard the mental health of the public, a predictive model of negative emotions during COVID-19 is of great importance for identifying potential risky population. To establish a neural predictive model achieving both good interpretability and predictivity, we have collected a large-scale (n=542) longitudinal dataset, alongside two independent samples for external validation. The whole-brain resting-state neural activity and social-psychological profile of the subjects were obtained from Sept. to Dec. 2019 (Time 1). Their negative emotions were tracked and re-assessed twice, on Feb 22 (Time 2) and Apr 24 (Time 3), 2020, respectively. We built a predictive model based on psychological meaningful resting state neural activities. We first applied canonical correlation analysis on both the neural profiles and psychological profiles collected on Time 1, this step selects only the psychological meaningful neural patterns for later model construction. The two most important neural patterns are associated with self-control and social interaction. We then trained the neural predictive model using those identified features on data obtained on Time 2. It achieved a good prediction performance with-in sample ($r = 0.44$, $p = 8.13^{-27}$). This study established an effective neural prediction model of negative emotions, achieving good interpretability and predictivity. It may be useful for identifying potential risky population of emotional disorders during COVID-19.

Index Terms—predictive model, negative emotions, COVID-19

1 Introduction

In this global pandemic of Coronavirus disease 2019 (COVID-19), our life experienced radical changes. Around the world, most of us, have been put in lockdown at least once, and even till today, social distancing is a requirement in most of the countries. This major life stress events is likely to have enduring influence on our emotional wellbeing and mental health.[1] Surging increase of depression and anxiety disorders[2], [3] is recognized as one of possible consequences. It is therefore crucial to establish neural predictive models of psychological vulnerability to such stressful life events, which will help us to identify potential risky population before they develop emotional disorders. One prominent feature of neural predictive model is its objectivity compared with self- report approaches. Moreover, neural predictive models are useful for understanding the neurophysiological bases underlying individual differences in vulnerability of emotional disorders under stress. So far, the most common approach for finding such neural markers is by correlating psychophysiological symptoms with neuroimaging data.[4] However, the low interpretability of the neural markers and the high homogeneity of the data used both in feature selection and prediction against the exploration of the potential social-psychological and neurobiological risk for emotional disorders.[5], [6] Furthermore, lack of independent dataset to facilitate the external validation hinder the generalization of the predictive model in some degree.[7]

People differ in both social-environmental and individual-trait like factors, [8], [9] both of which are shown to have a neural basis in their intrinsic functional connectivity during rest [10], [11] and proved to be robust protective/risk factors for emotion disorders. [12]–[14] Thus in this study, we opt to build an emotion predictive model by combining both their neural and social-psychological profiles (in a large sample size, n = 542, longitudinal design, see details in Methods), the approaches which were expected to generate interpretable neural markers and robust prediction performance. To be predictive, those profiles were taken before COVID-19 (Time 1: September to December 2019), their psychopathological states (focusing on negative emotions) were tracked twice during the COVID-19 (Time 2: February 22, Time 3: April 24, 2020). We have also collected another independent dataset (n = 90) to test the out-of-sample generalizability of the model.

We have constructed a predictive model for negative

- *Jiang Qiu Author is with Key Laboratory of Cognition and Personality of the Ministry of Education, Faculty of Psychology, Southwest University. Beibei District, Chongqing 400715, China. E-mail: qiuj318@swu.edu.cn*
- *Yunzhe Liu Author is with State Key Laboratory of Cognitive Neuroscience and Learning, IDG/McGovern Institute for Brain Research, Beijing Normal University. Beijing Normal University, 19 Xinjiekouwai Street, Beijing 100875, China. E-mail: yunzhe.liu@bnu.edu.cn*
- *Yu Mao Author is with College of Computer and information Science School of Software, Southwest University. Beibei District, Chongqing 400715, China.*
- *Dongtao Wei, Wenjing Yang, Qunlin Chen, Jiangzhou Sun, Yaxu Yu, Yu Li, Kaixiang Zhuang, Xiaoqin Wang, Li He, Tingyong Feng, Xu Lei, Qinghua He, Hong Chen, are with Key Laboratory of Cognition and Personality of the Ministry of Education, Faculty of Psychology, Southwest University. Beibei District, Chongqing 400715, China.*
- *Shaozheng Qin Author is with State Key Laboratory of Cognitive Neuroscience and Learning, IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing Normal University, 19 Xinjiekouwai Street, Beijing 100875, China.*

This article has been accepted for publication in IEEE Transactions on Affective Computing. This is the author's version which has not been fully edited and content may change prior to final publication. Citation information: DOI 10.1109/TAFFC.2022.3181671

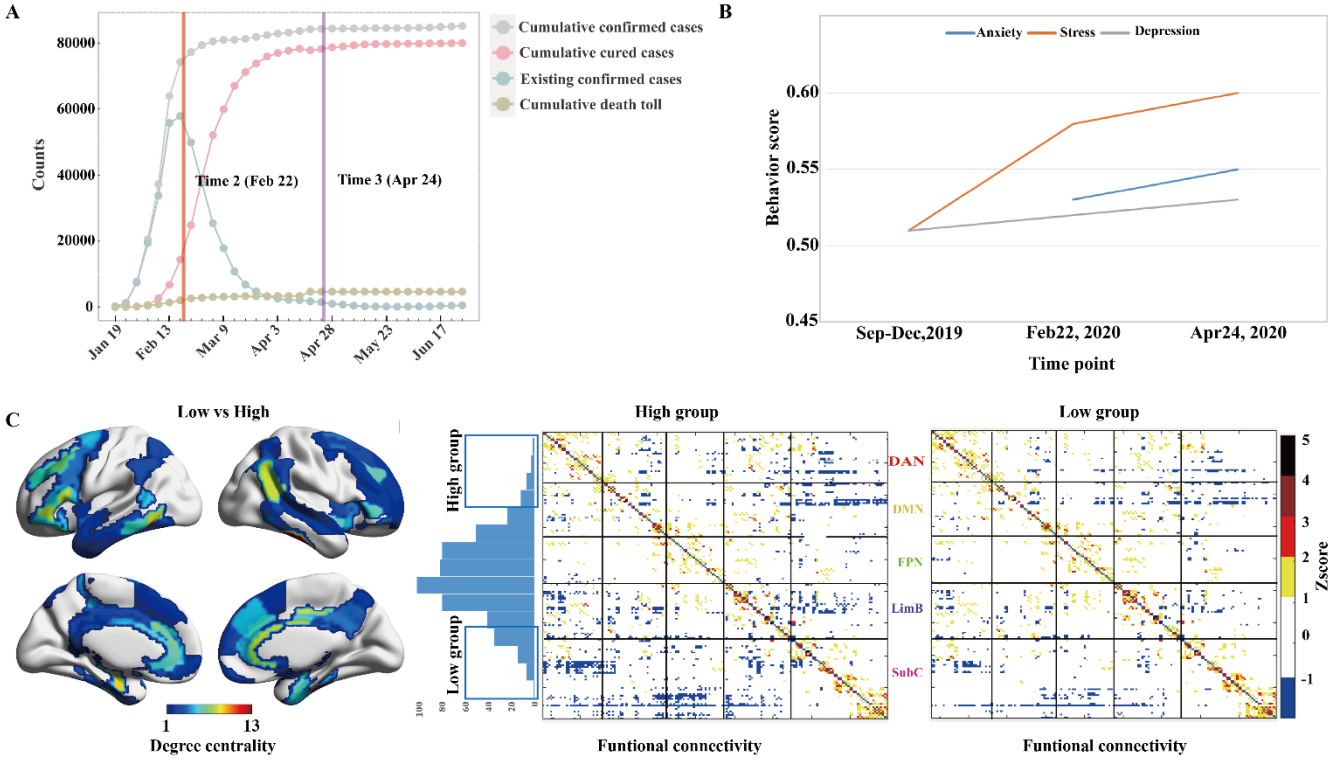

Fig. 1. Descriptive information of COVID-19 and corresponding emotional changes. (A) The figure presented the number of cumulative confirmed cases (grey line), cumulative cured cases (pink line), existing confirmed cases (blue line) and cumulative death toll (green line) in China from Jan 19 to Jun 27, 2020. After the rapid growth from Jan 19 to Feb 19, the existing confirmed cases began to fall, and less than 3000 in early April. The orange line indicated second time point (Feb 22, 2020) of the psychopathological assessment, around the turning point of the pandemic. The purple line indicated the third time point (Apr 24, 2020) of the psychopathological assessment, the time when existing cases in China is close to 0. (B) Anxiety (only collected data in Time 2 & 3), stress and depression surge as COVID-19 evolves over time. For each domain, individual's scores divided by the maximum value of the observed scores and the mean values were obtained within each time point. Significant increase can be visually observed across time on anxiety, stress and depression. In addition, LME also indicated a significant effect of time on individual's emotion state (eTable 2, Supplement). (C) The different FC patterns of subject with high (highest 10%) vs. low (lowest 10%) negative emotions in Time 1 can be visually observed in the connectivity matrix, especially the FC between SubC, DAN, DMN and FPN. Furthermore, the brain map demonstrated difference of the degree centrality between 2 groups. Note that absolute value of the difference of the degree centrality between 2 groups were used to generate the figure. DAN, dorsal attention network; DMN, default mode network; FPN, frontoparietal network; SubC, subcortical network;

emotions under COVID-19, however, whether these neural predictors were specific to COVID-19, rather than negative emotions in daily life is unclear. Compared with negative life events in daily life, such as failing an exam, this global crisis with long-term of self-isolation might be associated with more intense and chronic negative emotions. Thus, we applied this predictive model on another longitudinal sample without COVID-19 and expected a relatively poor predictive performance. We also trained a predictive model for daily life negative emotions, which allowed us to capture the different predictive patterns for negative emotions under COVID-19 and daily life.

2 MEHTODS

2.1 Participants

This is a large scale, longitudinal study aiming to find a predictive neural model of negative emotions to the major life stress events - COVID-19. 901 College students were registered for this study (273 males, age 17-26 years). Among them, 604 subjects (177 males, age 17-26 years) completed MRI scans and a comprehensive assessment of their social-psychological profile between September 17, - December 11, 2019 (Time 1). On February 22, 2020 (Time 2) and April 24, 2020 (Time 3), the subjects were tested on their psychopathological states, focusing on negative emotions. The specific testing date of Time 2 and 3 were selected based on the evolving situation of COVID-19 in China. Time 2 is around the turning point (peak of existing cases) of the pandemic, and from this time onwards, the pandemic is relatively under control. On Time 3 (and onward), the existing cases in China is below 1500, with a daily increase less than 150 (Fig. 1A). After matching the MRI data on Time 1 and the behavior data on Time 1 and Time 2, We have 542 subjects remained (164 males, age 17-26 years). The data of these subjects were used to conduct feature selection and model training. On Time 3, 456 of these subjects (133 males, age 17-26 years) completed another round of psychopathological assessment. The data of these 456 subjects were used to conduct model validation and prediction within-samples. In design, this is part of an ongoing program - Behavioral Brain Research Pro-

ject of Chinese Personality (BBP). We will refer to this dataset BBP throughout.

In addition to BBP, we have collected another independent dataset (n = 90, 18 males, age 18-21 years) for model validation and predictions out-of-samples. These subjects completed the MRI scans between June 3, - September 8, 2019, followed by psychopathological assessment on February 22, 2020. It should be noted that both BBP sample and validation sample consisted with healthy subjects not being infected by COVID-19. Moreover, we also adopted a sample (n = 101, 24 males, age 18-20 years) without COVID-19 to prove the specificity of the COVID-based predictive model. These subjects completed the MRI scans and psychopathological assessment between March 13, - April 29, 2018, followed by 3 psychopathological assessments (average interval = 1 month).

All participants were healthy, without a history of psychiatric or neurological illnesses prior to admitting to the project. All participants provided the information consent document before the experiment and were compensated with money at the end of the study. The ethical approval of this study was granted by the Ethics Committee of Southwest University, and all procedures involved were in accordance with the sixth revision of the Declaration of Helsinki.

2.2 Neuroimaging Data Acquisition & Preprocessing

All neuroimaging data were acquired on a 3T Prisma Siemens Trio scanner, using a 32-channel head coil. Resting-state fMRI scans (8 mins) were collected using a gradient echo-planar imaging (EPI) sequence: TR = 2000 ms, TE = 30 ms, flip angle = 90 °, FOV = 224 × 224 mm^2， resolution matrix = 112 × 112, slices = 62, thickness = 2.0 mm, slice gap = 0.3 mm, voxel size = 2× 2×2 mm^3. Structural scans were acquired using a T1-weighted structural images were acquired using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence: TR = 2530 ms, TE = 2.98 ms, flip angle = 7°, FOV = 224 × 256 mm^2, resolution matrix = 448 × 512, slices = 192, thickness = 1.0 mm, inversion time = 1100 ms, voxel size = 0.5 × 0.5 × 1 mm^3.

The preprocessing procedure was identically performed for GGBBP dataset and the other validation samples using Statistical Parametric Mapping (SPM) and the Data Processing & Analysis of Brain Imaging toolbox (DPABI). [15], [16] The processing procedure included the following steps: removal of the first 10 EPI scans, correction of slice timing and head motion, spatial normalization, nuisance signal regression, data scrubbing, spatial smoothing and band-pass filtering. More details are available in eMethods 1 in the Supplement.

2.3 Social-psychological Profile: Environmental Factors & Psychological Traits

The assessment of social-psychological profile focus on two parts: environmental factors and psychological traits, both of which are assumed to be stable across a long time-scale.[8], [17]–[22] The environmental factors include socioeconomic status, social relationship, and childhood trauma, etc. The psychological traits include emotion regulation ability, resilience ability and coping flexibility, etc. The details of these questionnaires are available in eTable 1 in the Supplement. There were 236 questionnaire measurements in total for each subject, forming a social-psychological profile matrix - S_raw (subjects x items). To avoid potential confounds from sex and age-related difference, [23], [24] we regressed out their influence on each column of S_raw, and used the resulting residual matrix - S for future analyses. This social-psychological profile matrix will be used later to select relevant neural features for the prediction model.

2.4 Emotional Assessments

The mental health problems during the pandemic, especially those related to emotion disorders, are the current focus. We therefore tracked their depression, anxiety and perceived stress levels, both during (Time 2) and after (Time 3) the worst COVID-situation in China (Fig. 1B). In the BBP sample, they were measured by self-depression scale, [25] state anxiety inventory [26] and perceived stress scale. [27] In the validation sample, they were measured by beck depression inventory, [28] state anxiety inventory, [26] perceived stress scale, [27] positive affect and negative affect scale, [29] and post-traumatic stress disorder scale. [30] In the independent sample without COVID, they were measured by beck depression inventory, [28] state anxiety inventory, [26] perceived stress scale. [27] In BBP sample, the predictive model was trained with 10-fold cross validation. Condiering the multidimencional construct of negative emotion, principle component analysis (PCA) was performed on the training dataset and we took the first principle component (PC) of their emotional state measurements representing the core negative emotion scores [31]–[33]. The core negative emotion in the testing dataset were obtained based on the raw scores of the measures and the principal component coefficients. In the validation sample, the first PC derived from PCA was used as the core negative emotion. The core negative emotion scores will be used as the dependent variable (D) in both training and validation of the neural prediction model.

2.5 Multivariate Neural Profile

To build the neural prediction model, we chose to use the whole-brain multivariate functional connectivity pattern as model features. This is because emotion related disorders were shown to be more related to the deficits in the connections across brain regions than activation within a region. [34], [35] First, we parcellated the whole brain into 246 nodes based on Human Brainnetome Atlas [36] (excluding low-level sensory regions like visual cortex and sensorimotor areas). Then, the blood-oxygenation-level-dependent (BOLD) activity were averaged across voxels within each region, resulting in BOLD time series of 179 nodes. After that, a pairwise functional connectivity matrix was constructed for each subject by taking the fisher-z transformed correlation score between nodes. Given this matrix is symmetrical, we only kept left

diagonal values (15931 edges), this gives us a neural profile matrix - N_raw (487x15931, subjects x edges). To control potential confounds from age, sex and mean framewise displacement (FD) power [37], [38], we regressed out their influences on each column of N_raw, resulting in the functional connectivity (FC) matrix N_r. To reduce the dimensionality of the data, we performed PCA on the FC pattern dimension of N_r, keeping only the top 300 PCs (explaining around 91% of variance). We obtained the final neural profile matrix - N (487×300) for model training. The neural profile matrix for the model testing were obtained based on the raw functional connectivity data and the principal component coefficients.

2.6 Model Construction

2.6.1 Feature Selection (n = 487)

For the sake of interpretability, which is paramount in psychiatry research, [39], [40] we selected the neural features that can be linked to social-psychological profile. The social-psychological profiles are assumed to be stable, [8], [21], [22] we expect its related neural features to also be robust, thereby offering a good generalization and prediction ability when testing either in a later time within-sample or generalize across-samples (to an independent dataset, detailed later).

The predictive model was trained with nested cross-validation, as the outer 10 F-CV loop estimating the generalizability of the model, and the inner loop determining the optimal parameter for the LASSO regression model. In the outer 10 F-CV, the sample were divied into 10 subsets and we used sparse canonical correlation analysis (sCCA) to align the neural and social-psychological profiles on the 9 subsets (training dataset). The data matrix S (social-psychological profile) and N (multivariate neural profile) were fed into sCCA to identify the relationships between the two sets of multidimensional variables (Fig. 2 A: Step 1). This is done by finding two sets of respect tive linear transformation (i.e., canonical coefficients), such such that the correlation between two projected vari

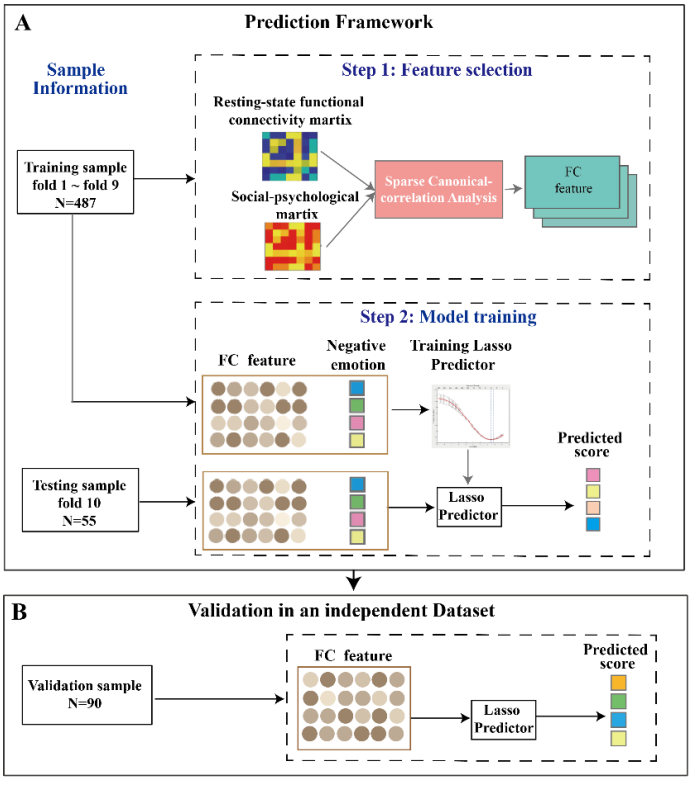

Fig. 2. Schematic overview of the prediction framework. (A) the prediction framework on BBP sample. The whole sample was divided into 10 subsets, 9 of which were used as the training sample and the the remaining one was used as the testing sample. Step1: Feature selection was performed on training sample and sparse canonical correlation analysis (sCCA) was used to identify FC features, which will be used as predictors in the predictive model. Step2: Model training was performed on training sample, least absolute shrinkage and selection operator (LASSO) regression algorithm were used to train the predictive model. To avoid overfitting and ensure the generalizability of the model, the dataset was randomly resampled 100 times, 70% of the training sample were used as training set and 30% as testing set. The model with best prediction performance was used in the subsequent analysis. (B) Prediction in an independent dataset. To test the generalizability of the predictive model, it was applied to predict the negative emotions in the validation sample. The FC features were generated using the same principal component coefficients and unmixing matrices obtained in the BBP sample. Similarly, principal component analysis was used to obtain the core scores of negative emotions. This figure was inspired by fig. 1 reported in the study by Wang et al. (2018)[41] and fig. 1 reported in the study by Cui et al. (2018).[42]

-ables) is maximized. L1 regularization was used in the process to encourage sparsity [43] so that a small set of dominate modes can be identified. [41], [44]

The hyperparameters of L1 penalty were tuned in cross-validation (eFig. 1), the value that yielded the highest canonical correlation of the first mode was fixed on the whole sample to conduct the feature selection analysis. The sCCA method was implemented with R package from CRAN (penalized multivariate analysis, PMA). [43] sCCA estimates unmixing matrices A (300 x 236) and B (236 × 236) in order to find latent modes with the highest correlations between U (U=N×A) and V (V=S×B). U represent the combination of the FC edges and were used as predictors in the neural prediction model. The neural predictors of the testing data were obtained based on the neural profile matrix and the unmixing matrices (A). For visualization purpose, the unmixing matrices and the principal component coefficients of N_r were used to generate the loading of the original FC edges and project the sCCA modes (U) back to the original FC space (Nr)

2.6.2 Model Training & Validation

We obtained the neural predictors of interest (U, obtained in Time 1) and dependent variable (D) - core negative emotion scores (obtained in Time 2). The job was to build a model among the columns of U to predict D. To achieve this, we trained a LASSO regression model with L1 regularization (Fig. 2A: Step 2). The L1 regularization was used here to avoid overfitting and improve the prediction accuracy [45], its hyperparameter is determined across 100 randomly resampled samples (70% of the original sample as training datasets and 30% as testing datasets). LASSO regression model was implemented using glmnet package. [46] The model performance was quantified by the Pearson correlation and mean absolute error (MAE) between the actual scores and the predicted scores in the cross-validation testing sets. The final neural prediction model was selected based on the best cross-validation performance and was used to estimate the overall predictive performance in Time 2.

2.7 Model Prediction in An Independent Dataset (n = 90)

To further test the generalizability of the trained model, we applied the model to predict the negative emotions in an independent dataset (Fig. 2B). In this dataset, we extracted the FC sets based on the same template in BBP dataset and constructed the FC matrix N_(v_r) (90 x 15931) in the same way as N_r. To ensure we capture the same neural features in this independent data set, we obtained the neural profile matrix - N_v (with analogy to N), based on the same 300 PCs from N_r, and construct the model predictors U_v (with analogy to U), using the same unmixing matrices A obtained in the BBP dataset. These predictors were entered in the prediction model with fixed parameters to predict their core emotion scores.

2.8 Prediction of Negative Emotions in Daily Life (n = 101)

We hypothesized that compare with negative emotions in daily life, the present prediction model is more sensitive to negative emotions under COVID-19. To confirm this hypothesis, we applied the COVID-based predictive model on the dataset without COVID. Moreover, to facilitate the comparation of the different prediction patterns for negative emotions under COVID-19 and daily life, we also trained a predictive model for negative emotions in daily life, using the same approach of BBP sample.

3 Results

3.1 Negative Emotions Surge as COVID-19 Involves Over Time

We first looked at the emotional state of the subjects, sampled before (Time 1, September-December 2019), during (Time 2, February 22, 2020) and after (Time 3, April 24, 2020) the worst situation of COVID-19 in China (Fig. 1A). To estimate the effect of time on individual's emotional state, while treating subject as random effect (eMethods 2, Supplement), we used linear mixed model (lme4 Package in R)[38]. We found significant increases of their depression ($p = 2 \times 10^{-16}$), stress ($p = 0.004$), and anxiety (only collected data in Time 2 & 3, $p = 5.55 \times 10^{-5}$) level over time (Fig. 1B, eTable 2 in the Supplement). However, there were no significant changes of negative emotions in another longitudinal sample (tracking for 3 times) without COVID (see eTable 3, Supplement).

3.2 Multivariate Brain Patterns During Rest were Qualitatively Different in Subjects with High vs. Low Negative Emotions

The surge of negative emotions, perhaps, is not surprising given the far-reaching influence of this pandemic to everyone. It is intriguing to see if such emotion changes can be predicted from neural activities before the pandemic. We used whole-brain resting-state functional connectivity (FC) as a fingerprint of their neural activities given the robustness of resting state networks, and their wide relevance to mental disorders. [47]–[49] First, we investigated whether the brain patterns during rest differ in subjects with high vs. low negative emotions. For visualization purpose, we contrasted the FC pattern of subject with high (top 10%) vs. low (lowest 10%) negative emotion scores in Time 1 (Fig. 1C). Differences can be observed in subcortical system (SubC), dorsal attention network (DAN), default mode network (DMN) and frontoparietal network (FPN). Those brain regions are known to be involved in emotional processing, [50], [51] mentalizing, [52], [53] executive control, [54], [55] with wide implications in emotion disorders, like depression and anxiety. [56]–[59] [48] In addition to comparing changes in FC strength directly, we can also look for changes in the hub of resting-state networks (i.e., centrality), we observed differences of the degree centrality between the two groups in DMN, limbic and subcortical systems, suggesting an organizational change in their neural fingerprint. [60] These results suggest emotional states differences can be mapped to their multivariate brain patterns: a logic prior for building neural prediction model of negative emotions.

This article has been accepted for publication in IEEE Transactions on Affective Computing. This is the author's version which has not been fully edited and content may change prior to final publication. Citation information: DOI 10.1109/TAFFC.2022.3181671

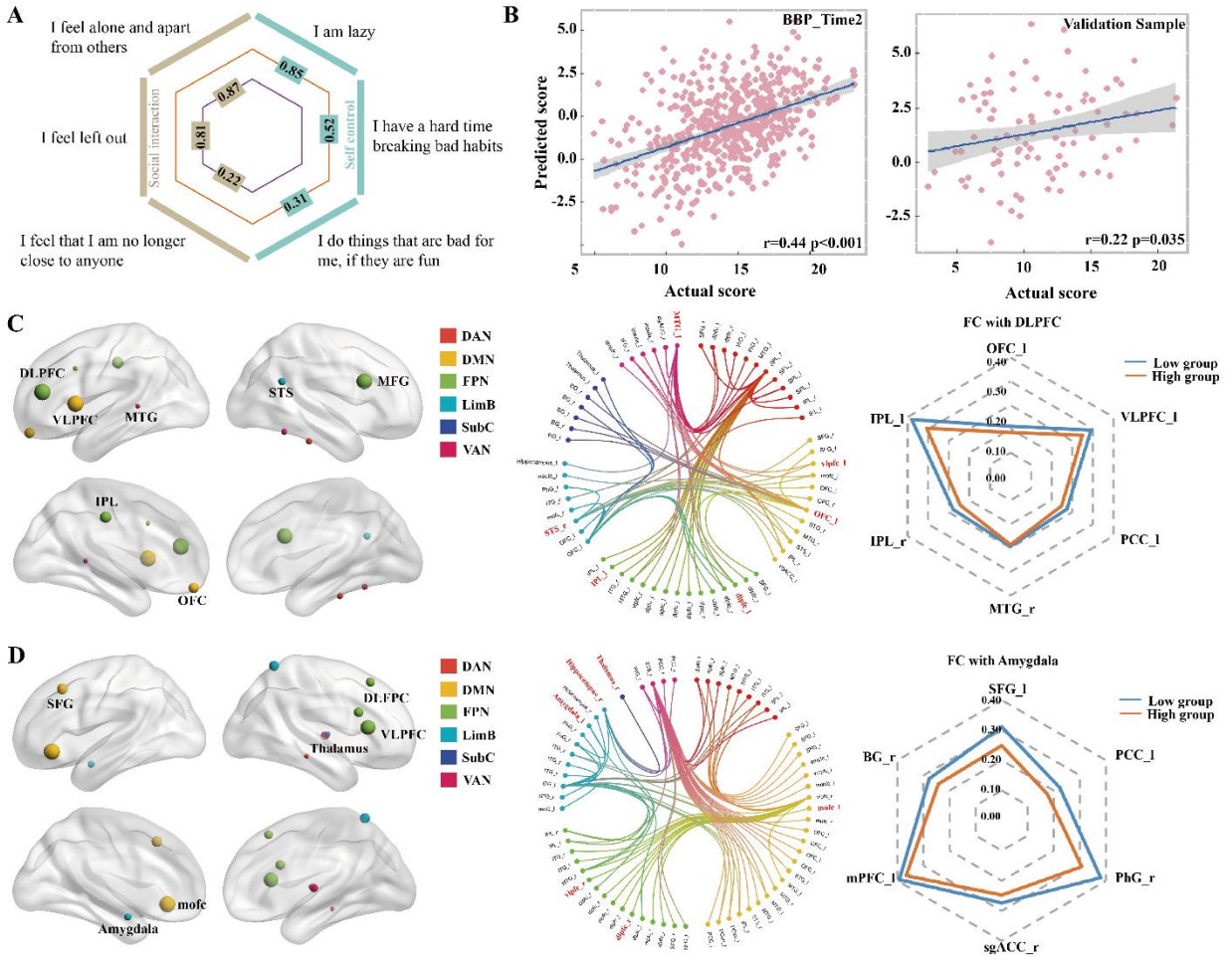

Fig. 3. Social-psychological implications and FC patterns of the robust neural predictors. (A) We present the social-psychological dimension of top 2 neural predictors (self-control and social interaction) with strongest predict power. The radar map presents items from different social-psychological domains. Numbers in the inner lines represent loadings for each item in their respective dimension. M1 (orange line) represents the self-control dimension and M2 (purple line) represents the social interaction dimension. (B) Prediction performance of the trained model. The correlations between predicted scores and actual scores for the BBP sample in Time 2 and validation sample were presented by the scatter plot. (C-D) The neuroanatomical locations of the nodes with the strongest loadings and their corresponding FC patterns of the top 2 neural predictors (B for M1 and C for M2). we summarized the absolute loadings at nodal level and present the top 10 nodes in each pattern. The FC links of these 10 nodes are thresholded at the 1% according to their absolute loadings in each pattern and then presented with the chord diagram. We also present the differences of FC patterns between high group (highest 10%) and low group (lowest 10%) of negative emotions on Time 2 with the radar map. To aid visualization, we choose the FC pattern of DLPFC (M1) and amygdala (M2) as examples. DAN, dorsal attention network; DMN, default mode network; FPN, frontoparietal network; LimB, limbic network; SubC, subcortical network; VAN, ventral attention network; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; OFC, orbitofrontal cortex; IPL, inferior parietal lobule; MTG, middle temporal gyrus; MFG, middle frontal gyrus; SFG superior frontal gyrus; STS, superior temporal sulcus; PCun, precuneus; ITG, inferior temporal gyrus; Thal, thalamus; Amyg, amygdala; mofc, medial orbitofrontal cortex, PCC, posterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; BG, basal ganglia; mpfc, medial prefrontal cortex.

3.3 Neural Prediction Model Predicts Negative Emotion Development within BBP

To achieve a robust predictive model for negative emotions, LASSO regression algorithm was performed on BBP sample in Time 2, with nested CV. The results revealed a strong association between actual value and predicted value of negative emotions ($r_{cv} = 0.33$, $p_{cv} = 8.88 \times 10^{-16}$, MAE = 14.43). Then, the trained model was applied on BBP sample in Time 2 ($r = 0.44$, $p = 8.13^{-27}$, MAE = 14.58, Fig. 3B), confirming the reliability of the model.

3.4 Social-psychological Implication of The Neural Predictors

We used the constructed predictive model to decipher decipher social-psychological implication and functional connectivity pattern of the neural predictors. sCCA algorithm assign each sCCA mode with a specific pattern that relates a weighted set of subjective measures to a weighted set of functional connections. Thus, we can deduce the social-psychological implication of the neural predictors through its associated subjective measures.

The predictive model revealed five neural predictors (derived from 4 sCCA modes), which were respectively associated with social-psychological dimensions including self-control, social interaction, emotional support and stressful life events (see Fig. 4). Here we presented the detailed subjective items corresponding to two neural predictors with the strongest predictive weight in Fig. 3A. The self-control mode was driven by items corresponding to the poor self-control ability in keeping healthy habits, including "I am lazy", "I have a hard time breaking bad habits", "I am doing things that are bad for me, if they are fun". [61] The social interaction mode contained items quantifying the degree of the negative social interaction with others, including "I feel alone and apart from others", "I feel left out" "I feel that I am no longer close to anyone". [62] These connectivity-guided social-psychological dimensions emphasized the vital role of self-control and social interaction in coping with stressful life events.

3.5 Functional Connectivity Patterns of The Neural Predictors

Next, we decoded the neural patterns of the top two predictors (i.e., the self-control mode and the social interaction mode). To extract key information from the high-dimensional connectivity data, we calculated the loading of the original FCs for each neural predictor, then summarized the absolute loadings for each brain node. Higher value indicates a stronger involvement of such node in a specific neural predictor? We presented the anatomical distribution of the top 10 most important (based on the absolute loading) brain regions (Fig. 3C for self-control mode and Fig. 3D for social interaction mode, details of the 10 nodes are available in eTable 4 in the supplement).

We also presented the FC patterns with a chord diagram thresholded at the top 1% according to the absolute loading of the FC. The FC pattern of the self-control mode was associated with nodes including dorsal lateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), orbitofrontal cortex (OFC), inferior parietal lobule (IPL), middle temporal gyrus (MTG), and superior temporal sulcus (STS), regions commonly implicated in cognitive control. [63]–[66] The FC pattern of social interaction mode was associated with VLPFC, medial orbitofrontal cortex (MOFC), IPL, amygdala and thalamus, all of which have been implicated in emotional regulation. [51], [67] To aid the interpretation of the results, we further split the FC patterns of subjects with high (top 10%) vs. low (lowest 10%) negative emotion scores in Time 2. We choose the FC pattern of DLPFC (self-control mode) and amygdala (social interaction mode) as examples (Fig. 3C-D: radar map), given their wide implications and reported involvement in emotional disorder. [68]–[70]

3.6 Neural Prediction Model Generalizes Well Out-of-samples

To test the generalizability of the model out-of-samples, an external validation was performed on an independent dataset experienced COVID-19. The BBP-based predictive model were then applied to an independent validation sample to generate the predicted scores of their negative emotions. The model performance was estimated by the Pearson correlation between the predicted scores and actual scores (r = 0.22, p = 0.035, MAE=3.23), which confirmed generalizability of the model and the practical value of these neural markers.

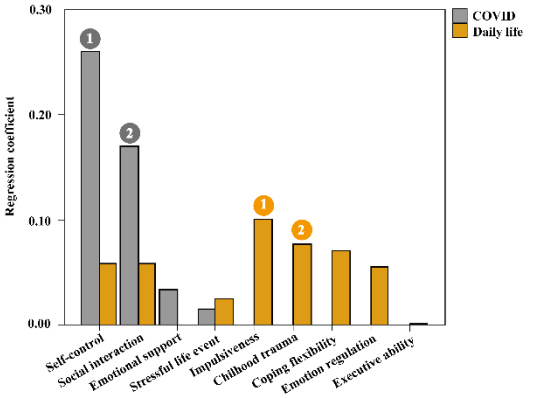

Fig. 4. Regression coefficients of the predictive model for negative emotions in COVID-19 and daily life. The predictive model for COVID-19 emphasized the self-control dimension and social interaction dimension, while the predictive model for daily life emphasized the impulsiveness dimension, childhood trauma dimension.

Moreover, to test whether the predictive model is more sensitive to negative emotions in COVID-19, rather than daily life, COVID-based predictive model were then applied to the dataset without COVID. The results revealed a marginal significance between predicted scores and actual scores (r = 0.162, p = 0.087, MAE=5.24), which supported the specificity of the COVID-based predictive model.

Finally, we trained a predictive model for negative emotions in daily life, using the same approach in BBP sample (see Fig. 4 and eResults 1 in the supplement). The predictive model worked well in this sample (r=0.44, p=4.4 x 10^{-6}, MAE=4.14), but not good in BBP sample (r=0.05, p=0.22, MAE=6.67). In summary, the prediction model for negative emotions under COVID-19 demonstrate 2 key predictors: self-control and the social interaction, while in the prediction model for daily life negative emotions emphasized the role of impulsiveness, childhood trauma and coping flexibility (see Fig. 4). This might imply different neural basis underlying the emotional response toward daily life stress versus COVID-19 related stress.

4 Discussion

Individual's mental health has been severely affected by this pandemic, [71] which implicate the urgency and sign ificance of exploring neural markers for negative emotions caused by COVID-19. The present study addressed this question by exploring the specific FC patterns that predict individual's negative emotions under stressful life events. We do this by applying LASSO regression algorithm to a large-scale dataset. LASSO is a particular case of the penalized least squares regression

with L1-penalty function. When there is high correlation in the group of predictors, LASSO chooses only one among them and shrinks the others to zero, which contribute to improve the prediction accuracy and produce easily interpretable models.[72] This dataset in the present is unique in that it contains longitudinal and multi-dimensional data from subject that suffering the same stressful life events (i.e., COVID-19). This dataset serves as a valuable resource for exploring neural markers of developmental course, and risk/protective factors for psychiatric symptom under a sudden public health accident.

Based on this dataset, we have established a predictive neural model using psychological-meaningful FC features (associated with social-psychological dimensions, like self-control, social interaction, etc.). We chose to only use these features because interpretability is just as important as predictivity (if not more) in real life setting. We show this model can predict negative emotions during COVID-19. We have also validated this model on an independent external dataset. The advantage of having a neural model is that it is free from subjectivity inherit in self report, and it does not require one to be self-aware of his own mental deficits. This makes it a more objective model. We hope it can be a useful tool for screening potential risky population in basic mental health care.

This model reveals two critical neural predictors for negative emotions under COVID-19. The first is associated with self-control ability, emphasizing the role of frontal and parietal cortex. [64], [73], [74] Items in self-control mode refers to the capacity to keep a healthy and disciplined life, which constitute the foundation of adaptive behaviors. [75], [76] The dysfunction of this system, manifested as inefficient deployment of cognitive resources for flexible, adaptive responses to a changing world, were shown to be associated with the symptoms of various mental disorders. [77]–[80] The second predictor was associated with social interaction. Consistent with previous studies, [81] our results suggested interpersonal emotion regulation was another effective coping strategy: seeking support from others to deal with stress. The neural pattern associated with social interaction demonstrated a significant involvement of frontal-limbic system, [82]–[84] especially the reciprocal PFC-amygdala relationship, which were previously reported to be the neural mechanism underlying emotion regulation. [85], [86] Abnormal FCs within this pattern might accompanied with deficits in emotion processing and regulation, which ultimately result in increased negative emotions under stress. Based on the aforementioned points, we speculate that, neural defects in cognitive control system and emotion regulation system might be the risk factors for the negative emotions under stress.

Unlike COVID-based model, the predictive model for daily life negative emotions supported that neural predictors associated with impulsiveness, childhood trauma and copying flexibility were important for temporary and mild negative emotions. However, facing with chronic and severe stress during COVID-19, self-control and positive social interaction might be more effective coping strategies, for example, eat, sleep, work and exercise regularly,[87], [88] keep interactions with family and friends. [89], [90]

The present study utilized the correlation structure between neural and psychological profiles to build a predictive model with good interpretability. We note all participants in the present study were healthy subjects, and their risk of being infected with COVID-19 is relatively low. This model is therefore intended to be applicable to general public, but not to clinical populations. It might be informative for policymakers, and mental health practitioners for identifying potential risky population of emotional disorder during COVID-19.

ACKNOWLEDGMENT

Jiang Qiu and Yunzhe Liu are the corresponding author of the paper.
The authors report no financial relationships with commercial interests.
Dr. Mao was supported by the Chongqing Social Science Planning Project (grants 2021BS093). Dr. Qiu was supported by the National Natural Science Foundation of China (grants 31771231 and 32071070), the Chang Jiang Scholars Program, the National Outstanding Young People Plan, and the Chongqing Talent Program. Dr. Wei was supported by the Natural Science Foundation of Chongqing (grant cstc2019jcyj-msxmX0520 and cstc2020jcyj-msxmX0299), the Fundamental Research Funds for the Central Universities (grant SWU119007), and the Social Science Planning Project of Chongqing (grant 2018PY80).

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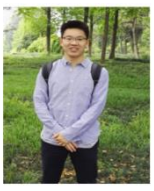
Yu Mao received the PhD degree from Soutwest university in China in 2021. She is She is currently a post-doctoral researcher in the College of Artificial Intelligence, Southwest University. Her main research interests include affective decoding and computing

Dongtao Wei received the PhD degree from Southwest university in China in 2014. He is currently an assistant professor in Faculty of Psychology, Southwest University. His main research interests include mental health and interoception.

Wenjing Yang received the PhD degree from Southwest university in China in 2015. She is currently an assistant professor in Faculty of Psychology, Southwest University. Her main research interest is the neural basis of memory.



Qunlin Chen received the PhD degree from Southwest university in China in 2016. He is currently an assistant professor in Faculty of Psychology, Southwest University. His main research interest is the neural basis of creativity.

Jiangzhou Sun received the PhD degree from Southwest university in China in 2017. She is She is currently a post-doctoral researcher in Faculty of Psychology, Southwest University. Her main research interest is the neural basis of verbal creativity.

Yaxu Yu received the PhD degree from Southwest university in China in 2021. She is currently a researcher in Neimeng Normal university. Her main research interest is the neural basis of Autism.

Yu Li received the PhD degree from Southwest university in China in 2021. She is currently a post-doctoral researcher in Faculty of Psychology, Southwest University. Her main research interest is mental health and personality,

Kaixiang Zhuang received the PhD degree from Southwest university in China in 2022. His current research interests include semantic network and creativity.

Li He received the PhD degree from Southwest university in China in 2022. His current research interests include semantic network and creativity.

Tingyong Feng received the PhD degree from Southwest university in China in 2007. He is currently a professor in Faculty of Psychology, Southwest University. His main research interests include social cognition and decision making.

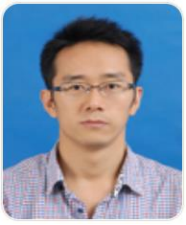
Xu Lei received the PhD degree from University of Electronic Science and Technology in China in 2011. He is currently a professor in Faculty of Psychology, Southwest University. His main research interests include the neural basis of sleep and sleep related disorder.

Qinghua He received the PhD degree from Beijing normal university in China in 2011. He is currently a professor in Faculty of Psychology, Southwest University. His main research interests include Neurophysiological basis and intervention of addiction

Hong Chen received the PhD degree from Southwest university in China in 1997. She is She is currently a professor in Faculty of Psychology, Southwest University. Her main research interests include Neurophysiological basis obesity.

Shaozheng Qin received the PhD degree from Southwest university in China in 2009. He is currently a principal investigator in State Key Laboratory of Cognitive Neuroscience and Learning, IDG/McGovern Institute for Brain Research, Beijing Normal University. His main research interests include the neural basis of memory and emtion,

Yunzhe Liu received the PhD degree from University College London in United Kingdom in 2021. He is currently a principal investigator in State Key Laboratory of Cognitive Neuroscience and Learning, IDG/McGovern Institute for Brain Research, Beijing Normal University. His main research interests include the neural basis of replay and computational psychiatry,



Jiang Qiu received the PhD degree from Southwest university in China in 2007. He is currently a professor in the Faculty of Psychology, Southwest University. His main research interests include the neural basis of creativity and mental disorder.