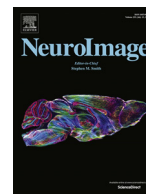




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COVID-19 vicarious traumatization links functional connectome to general distress

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ABSTRACT

As characterized by repeated exposure of others' trauma, vicarious traumatization is a common negative psychological reaction during the COVID-19 pandemic and plays a crucial role in the development of general mental distress. This study aims to identify functional connectome that encodes individual variations of pandemic-related vicarious traumatization and reveal the underlying brain-vicarious traumatization mechanism in predicting general distress. The eligible subjects were 105 general university students (60 females, aged from 19 to 27 years) undergoing brain MRI scanning and baseline behavioral tests (October 2019 to January 2020), whom were re-contacted for COVID-related vicarious traumatization measurement (February to April 2020) and follow-up general distress evaluation (March to April 2021). We applied a connectome-based predictive modeling (CPM) approach to identify the functional connectome supporting vicarious traumatization based on a 268-region-parcellation assigned to network memberships. The CPM analyses showed that only the negative network model stably predicted individuals' vicarious traumatization scores ($q^2 = -0.18$, $MSE = 617$, $r_{[\text{predicted}, \text{actual}]} = 0.18$, $p = 0.024$), with the contributing functional connectivity primarily distributed in the fronto-parietal, default mode, medial frontal, salience, and motor network. Furthermore, mediation analysis revealed that vicarious traumatization mediated the influence of brain functional connectome on general distress. Importantly, our results were independent of baseline family socioeconomic status, other stressful life events and general mental health as well as age, sex and head motion. Our study is the first to provide evidence for the functional neural markers of vicarious traumatization and reveal an underlying neuropsychological pathway to predict distress symptoms in which brain functional connectome affects general distress via vicarious traumatization.

1. Introduction

Coronavirus disease 2019 (COVID-19) spread around the world from February 2020, and with the emergence of new variants the pandemic remains a major public health crisis (Ray et al., 2021). There is growing concern not only about the burden of physical disease and disability, but also substantial long-lasting problems of population mental health (Pfefferbaum and North, 2020). Facing unprecedented threats, uncertainties and insecurities during the pandemic, individuals may be increasingly vulnerable to mental health problems including depression, anxiety and stress (Shanahan et al., 2022; Wu et al., 2021). These concerns have prompted researchers to seek factors that may influence individual susceptibility (de Figueiredo et al., 2021; Plomecka et al., 2020). Vicarious traumatization, a psychological construct closely related to

posttraumatic stress disorder (PTSD) and burnout (Tabor, 2011), is one such factor. Initially vicarious traumatization referred to the effects on therapists of working with traumatized clients (McCann and Pearlman, 1990; Pearlman and Ian, 1995), but the definition has been extended to other occupational group and the general populations; the key feature is stress resulting from the empathetic engagement with another's trauma (Lerias and Byrne, 2003; Sabin-Farrell and Turpin, 2003). Vicarious traumatization can negatively affect individuals' values, beliefs and feelings, as well as their cognitive, affective and social functioning, and their well-being (Lerias and Byrne, 2003; Whitton, 2018). Vicarious traumatization has been a common psychological response during the pandemic and is a risk factor for mental ill-health (Li et al., 2020b, 2020c; Liu and Liu, 2020; Serafim et al., 2020);

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however, vicarious traumatization has been very variable in the general public (Li et al., 2020c; Liu and Liu, 2020).

It is pertinent to ask what extent these differences may be explained by individual variation in intrinsic brain function, both to elucidate the pathophysiology, and because a neurobiological marker of susceptibility to vicarious traumatization could be useful in detecting particularly vulnerable individuals and targeting preventive measures or health care resource accordingly. In this study we sought, for the first time, to establish what extent these differences may be explained by individual variation in brain function as quantified using resting-state functional magnetic resonance imaging (RS-fMRI) (Biswal, 2012), analyzed in terms of functional connectivity. This approach, measuring associations of activity across different brain regions, can detect robust, unique patterns of brain activity that predict continuous phenotypic measures across individuals (Dubois and Adolphs, 2016; Rosenberg et al., 2018). Modeling the associations between phenotypic measures and functional brain organization helps establish the clinical utility of imaging data (Gao et al., 2019). The comprehensive map of functional connectivity is defined as “functional connectome” (Biswal et al., 2010), which can define individual differences towards psychological constructs and clinical symptoms (Dadi et al., 2019; Kelly et al., 2012).

In this study we set out to use RS-fMRI to examine the functional connectome of vicarious traumatization during the COVID-19 pandemic and define their relationships to subsequent development of general distress. What is already known about these mechanisms suggests which brain networks are likely to be important in vicarious traumatization: the activity and connectivity of the default mode network [DMN], frontoparietal network [FPN] and salience network [SN]) are core neural mechanisms in the response to acute and chronic stressors (Chang and Yu, 2019; Liu et al., 2021b; Wang et al., 2005); functional abnormalities in these networks are associated with stress-related mental ill-health in PTSD (Patel et al., 2012; Suo et al., 2020, 2022) and burnout syndrome (Durning et al., 2013; Tei et al., 2014); also, the DMN, FPN and SN are crucial for the development of general distress (e.g. in depression and anxiety) (Chahal et al., 2021; He et al., 2021; van Ettinger-Veenstra et al., 2020). We therefore sought a mediation link between functional connectome, vicarious traumatization and general distress by studying a cohort of university students, applied a well-validated and reliable connectome-based predictive modeling (CPM) method (Beaty et al., 2018; Finn et al., 2015; Shen et al., 2017; Taxali et al., 2021) to pre-pandemic RS-fMRI data in order to identify the neural networks prospectively encoding individual differences in vicarious traumatization related to the COVID-19 pandemic. Our first hypothesis was that individual variations of pre-pandemic functional connectome would predict the levels of vicarious traumatization, and that a few brain networks (notably DMN, FPN and SN) would dominate the connectome modeling. Then we used mediation analysis to test the hypothesis that the vicarious traumatization-related functional connectome can predict general distress, vicarious traumatization serving as a mediator between them. Finally, to assess the specificity of the findings, we carried out supplementary analyses controlling for confounding factors such as family socioeconomic status (SES), other stressful life events and general mental health.

2. Materials and methods

2.1. Participants

Fig. 1A gives an overview of the data collection. One hundred and fifty-one university students were recruited from an ongoing project examining the relation between neuroimaging and mental health in the general population. All participants were right-handed and had no history of psychiatric or neurological diseases as evaluated with two self-reported items (“Have you ever had any psychiatric diseases?”; “Have you ever had any neurological diseases?”) (Lai et al., 2022; Wang et al., 2019). They underwent multimodal MRI scanning and com-

pleted paper-based questionnaires from October 2019 to January 2020 (T1, prior to the outbreak of COVID-19 in China). Subsequently, all participants were contacted for COVID-related behavioral measurements during the initial outbreak and peak from February to April 2020 (T2) and for follow-up mental health evaluations from March to April 2021 (T3, post-peak period of the pandemic), both via an online survey. For the current experimental design, our primary goal was to recruit about 100 participants, given that at least 84 participants would be needed to detect medium-sized effects for conducting correlation analyses ($r = 0.3$, $\alpha = 0.05$, $1 - \beta = 0.80$) based on standard power analysis (Faul et al., 2007; Kong et al., 2020; Zhang et al., 2022; Zhang et al., 2021). Finally, a total of 115 participants responded and completed all the measures of T2 and T3. No participants at any point had COVID-19 confirmed by polymerase chain reaction testing. After excluding 10 participants with excessive head motion (see Section 2.3), data from 105 participants (45 males, 60 females, aged 19 to 27 years) were eligible for the final analyses. This study was approved by the Medical Research Ethics Committee of West China Hospital, Sichuan University, and informed written consent was obtained from all participants before the study.

2.2. Behavioral measures

Vicarious traumatization questionnaire (VTQ). At T2, vicarious traumatization was assessed with the 38-item VTQ (Li et al., 2020c), originally developed to study helpers in the Wenchuan earthquake. This uses qualitative interview methods and trauma-linked theory and measurement (Han, 2009), and includes 2 aspects: physiological reaction (11 items) and psychological reaction (5 items for cognitive reaction, 7 items for behavioral reaction, 9 items for emotional reaction and 6 items for life belief), with each item scored from 1 (never) to 5 (always). The total VTQ score is the sum across all items, and higher scores indicate greater vicarious traumatization. The VTQ has satisfactory reliability and validity (Han, 2009; Li et al., 2011), and has been used to assess COVID-related vicarious traumatization in both professional and general-public populations (Li et al., 2020c; Wang et al., 2021b). At T2, VTQ had Cronbach’s $\alpha = 0.95$, indicating excellent internal reliability.

Depression Anxiety Stress Scale-21 (DASS-21). DASS-21 was administered at T3. DASS-21 is a popular measure of general distress experienced in the preceding week (Lovibond and Lovibond, 1995; Zanon et al., 2021). It is a general distress construct combining 3 dimensions: depression, anxiety and stress (Lovibond and Lovibond, 1995; Zanon et al., 2021). Each dimension includes 7 items, and participants are asked to respond from 1 (not at all) to 4 (very much so). The total score is the sum across all items, and higher scores indicate greater general distress. The Chinese version of DASS-21 shows good reliability and validity among general populations (Chan et al., 2012; Lu et al., 2018; Wang et al., 2016; Yi et al., 2012). At T3, DASS-21 had Cronbach’s $\alpha = 0.94$, indicating excellent internal reliability.

Other controlling measures. Several other measures administered at T1 were used to exclude possible disturbing effects on the links between vicarious traumatization, distress and functional connectome: the Socioeconomic Status Scale (SSS), which assesses individuals’ family SES (Adler et al., 2000; Peng et al., 2021); the Self-Rating Life Events Checklist (SRLEC), which assesses the frequency and impact of stressful life events experienced in the preceding year (Liu et al., 1997, 2000); and the General Health Questionnaire-12 (GHQ-12), which assesses overall psychological health conditions (Li et al., 2009; Pan and Goldberg, 1990). SSS, SRLEC and GHQ-12 had Cronbach’s $\alpha = 0.72$, 0.90 and 0.85, respectively, indicating satisfactory internal reliability.

2.3. Image data acquisition and pre-processing

For each participant at T1, a total of 240 fMRI volumes were collected using a 3.0 T Siemens Trio (Erlangen, Germany) MRI scanner and 12-channel head coil, with the following scanning parameters: repetition time 2000 ms; echo time 30 ms; field of view $240 \times 240 \text{ mm}^2$;

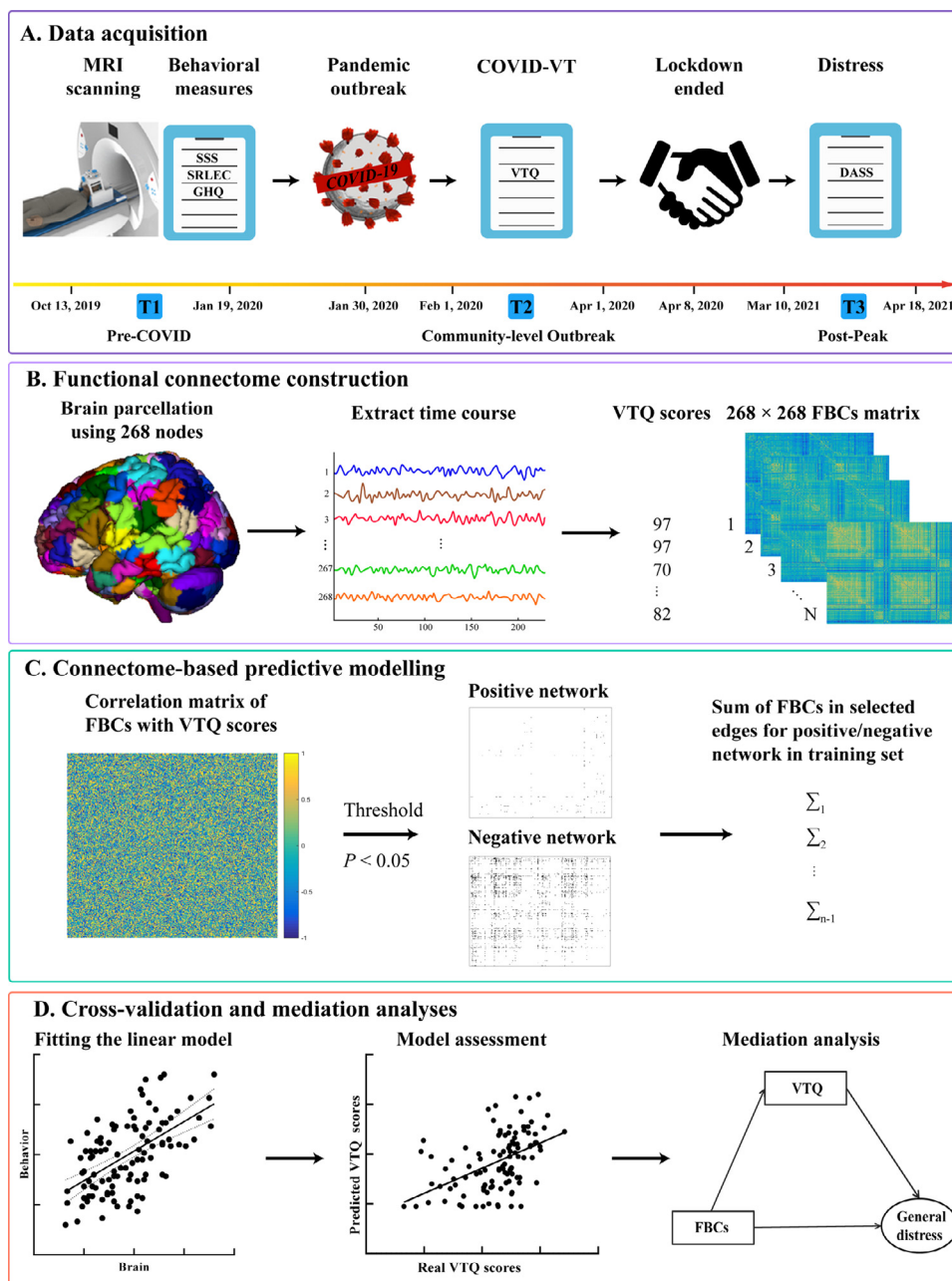


Fig. 1. The schematic flow of the study. Panel A shows the timing of data acquisition. Before the initial COVID-19 outbreak, from October 2019 to January 2020 (T1), participants underwent MRI scanning and completed paper-based questionnaires. During the initial outbreak and peak from February to April 2020 (T2), and for follow-up mental health evaluations during the post-peak period of the pandemic from March to April 2021 (T3), participants were re-contacted for behavioral measurement. Panel B shows the construction of the 268-region functional connectome for each subject (Shen et al., 2013), each element of which represents functional brain connection (FBC) strength between a pair of regions. Panel C illustrates connectome-based predictive modeling (CPM). The prediction models for individual VTQ scores, using the sum of the FBCs in the selected edges for positive/negative network in the training set, were built by a CPM approach with leave-one-subject-out cross-validation. Panel D illustrates the resulting prediction of individual VTQ scores from network strength (left sub-panel), the evaluation of its accuracy from the correlation between the predicted and actual behavioral scores (middle), and the exploration of the mediation relationship between FBCs, VTQ and general distress (right). Abbreviations: COVID-19, coronavirus disease 2019; MRI, magnetic resonance imaging; SSS, Socioeconomic Status Scale; SRLEC, Self-Rating Life Events Checklist; GHQ, General Health Questionnaire; DASS, Depression Anxiety Stress Scale; VTQ, Vicarious Traumatization Questionnaire; FBC, functional brain connection.

voxel size $3.75 \times 3.75 \times 5 \text{ mm}^3$; matrix size 64×64 ; flip angle 90° ; slice thickness 5 mm, no slice gap; and 30 axial slices per volume. Total scanning time was 480 s. Each subject was instructed to lie quietly with their eyes closed, not fall asleep, and not to think of anything during scanning.

SPM12 software (<http://www.fil.ion.ucl.ac.uk/spm>) was used for pre-processing. First, the initial 10 time points were deleted to establish magnetic tissue stabilization. Then slice timing correction was conducted to correct for intra-volume acquisition delay. The images were further realigned for the correction of head movement. To reduce the influences of head motion, a scrubbing method was performed, which deleted volumes with frame-wise displacement (FD) $> 0.5 \text{ mm}$ and volumes temporally close to the bad volumes (1 before and 2 after); on average, scrubbing was carried out on 13.1 vol per subject; mean FD was $0.139 \pm 0.045 \text{ mm}$. Images were normalized using echo-planar imaging templates (voxel size $[3 \times 3 \times 3]$). Linear trends in time series were removed. Nuisance signal (including the Friston 24-parameter head motion model, the white matter signal, and the cerebrospinal fluid signal) were regressed out. Finally, functional data were linearly detrended and

temporally bandpass (0.01–0.1 Hz) filtered to eliminate effects of high-frequency noise and low-frequency drift, and smoothed (Gaussian kernel with a full-width at half-maximum of 6 mm). Ten participants were excluded from further analysis due to excessive head motion (transformation distance $> 2 \text{ mm}$, rotation angle $> 2^\circ$, mean FD $> 0.30 \text{ mm}$).

2.4. Constructing the functional connectome

Fig. 1B summarizes the construction of the functional brain network. Using the GREYNA (<http://www.nitrc.org/projects/gretna/>) toolbox (Wang et al., 2015), the Shen brain atlas was applied to parcellate the brain into 268 regions of interest including the cortex, subcortex and cerebellum to define the network nodes (Shen et al., 2013), as in previous CPM studies (Beatty et al., 2018; Finn et al., 2015; Lake et al., 2019; Rosenberg et al., 2016; Yip et al., 2019). The mean time course was computed for each of the 268 nodes (i.e. average time course of all voxels within the node) for use in node-by-node pairwise Pearson's

correlations. The resultant r coefficients were transformed using Fisher's z -transformation to create symmetric 268×268 connectivity matrices in which each value of the matrix represents the connection strength between all pairs of nodes.

2.5. Connectome-based predictive modeling

Fig. 1C summarizes the process of connectome-based predictive modeling (CPM). Using validated and freely-available custom MATLAB scripts (Shen et al., 2017), CPM took brain connectivity data and behavioral measures (in this case, functional brain connectivity matrices and VTQ scores, respectively) as input to create a linear predictive model of VTQ using the connectivity matrices. Partial correlations with a statistical significance $p = 0.05$ threshold were calculated between edge weights and VTQ scores across the training participants to identify negative and positive predictive networks with age, sex, and mean FD as covariates. For the positive prediction network, edges were positively associated with behavioral measures, and negatively associated with behavioral measures for the negative prediction network; thus elements in the negative and positive prediction networks were defined by associations with VTQ scores rather than negative or positive functional connectivity themselves. While both networks were used for predicting the same variable, they were by definition independent, because a single edge was either a negative or a positive predictor (Shen et al., 2017). Individual summary values were calculated by summing the significant functional connectivity strength in each network and then applied to construct linear predictive models to estimate the relationships between network strength and VTQ scores. The resultant polynomial coefficients (including slope and intercept) were then used to predict levels of behavioral measures. Leave-one-out cross-validation (LOOCV) analysis was employed: the 'left-out' participant's predicted VTQ score was obtained by the predictive model trained on all other participants' data iteratively until all participants had a predicted score.

Model performance was assessed using cross-validated R^2 , mean square error (MSE), and Pearson correlations between the predicted and actual VTQ scores (Poldrack et al., 2020; Scheinost et al., 2019). To address the problem of non-independence of analyses in the leave-one-out folds, nonparametric permutation testing (rather than parametric testing) was performed to evaluate statistical significance. To obtain empirical null distributions for Pearson correlation coefficients, the correspondence between VTQ scores and connectivity matrices were randomly shuffled 5000 times and the CPM analysis was re-conducted using the shuffled data. The P-values for leave-one-out predictions were computed based on the null distributions as previously described (Shen et al., 2017).

To investigate the functional anatomy of the contributing elements, the distribution of nodes and edges were summarized. First, the 268 nodes were parcellated into ten previously-defined canonical networks (Barron et al., 2021; Lake et al., 2019): DMN, FPN, SN, medial frontal, visual (I, II, and association), motor, subcortical and cerebellum networks, and the number of connections between all pairs of canonical networks was computed. Next, the number of each node's connections were used to evaluate their importance (Beatty et al., 2018; Rosenberg et al., 2016); the functional connectivity patterns were then determined of the top 10 nodes with the most connections.

2.6. Validation analyses

Global signal. We planned not to use global signal regression, given the risk of inducing 'artefactual' anti-correlations (Murphy et al., 2009). However, whether global signals should be regressed out is the subject of ongoing research, and different choices likely yield complementary insights into brain functional organization (Murphy and Fox, 2017). Therefore, we also analyzed our data using global signal regression. **Feature selection threshold.** Though we reported the main results with a threshold of $p < 0.05$, we also examined the results with other thresholds

(0.01, 0.005, and 0.001). **Cross-validation strategy.** We used a commonly used LOOCV strategy to estimate the prediction accuracy in the main analysis. However, as this might generate some biased estimates, prediction results were also validated using different cross-validation schemes (5- and 10-fold) (Scheinost et al., 2019; Varoquaux et al., 2017). In brief, for 5/10-fold cross-validation, all subjects were divided into 5/10 subsets, in which one subset was used as the training set, the other as the testing set. **Parcellation strategies.** Given the strong influence of different parcellation methods on brain network analysis, we also constructed functional connectomes using two other brain parcellations, based on the Dosenbach atlas with 160 nodes (Dosenbach et al., 2010) and the Brainnetome atlas with 246 nodes (Fan et al., 2016), and then repeated the entire prediction procedure.

2.7. Mediation analyses

Fig. 1D summarizes the mediation analysis used to evaluate the indirect effect of brain functional connectivity on general distress via VTQ as a causal mediator. This used the SPSS macro PROCESS, incorporating a bootstrapping approach (Bolin, 2014). The sum of the brain functional connectivity was considered the independent variable (IV), VTQ scores were the mediator variable (MV), and general distress scores were the dependent variable (DV). We then estimated the indirect effect, referring to the product of path a (the relation between IV and MV) and path b (the relation MV and DV after adjusting for IV); the point estimates of the indirect effects were considered significant if the bootstrapped 95% confidence intervals (CIs) (5000 iterations) did not include zero.

3. Results

3.1. Behavioral characteristics of vicarious traumatization

Table 1 provides the descriptive statistics and bivariate correlations of the study variables. Participants differed widely in VTQ scores (Fig. 2A); the one-sample Kolmogorov-Smirnov (K-S) test showed that these scores were normally distributed (K-S = 0.06, $p = 0.200$). VTQ was not significantly correlated with participant age ($r = -0.003$, $p = 0.973$) or sex [$t(103) = 1.11$, $p = 0.269$], or with head motion (FD) during scanning ($r = -0.148$, $p = 0.131$).

3.2. Functional connectome of vicarious traumatization

In the CPM analysis, the RSFC in the negative network reliably predicted individual differences in VTQ ($q^2 = -0.18$, MSE = 617, $r_{[\text{predicted, actual}]} = 0.18$, $p = 0.024$; Fig. 2B and C). There was no significant association of VTQ with the RSFC in the positive network ($q^2 = -0.06$, MSE = 553, $r_{[\text{predicted, actual}]} = 0.017$, $p = 0.399$). It is worth noting that q^2 value was negative in our predictive model, suggesting that the performance of the current model was inferior to simply guessing the mean of the vicarious traumatization scores (Scheinost et al., 2019).

Across all folds of the LOOCV, 1308 edges (3.7% of the total 35,778 edges) in the negative network appeared in every iteration of the LOOCV and were defined as the contributing network (Fig. 3A). Dividing the 268 nodes into the 10 canonical networks, Fig. 3B shows the connectivity based on the number of connections within and between canonical networks for the negative network: this negative network included connections mainly in FPN, DMN, SN, medial frontal network and motor network, which were highly involved in the prediction.

The top 10 nodes with the most connections were located in the bilateral angular gyrus and inferior temporal gyrus, right temporal pole, fusiform gyrus, anterior prefrontal cortex, dorsal posterior cingulate cortex and brainstem, indicating the critical role of these nodes in predicting the COVID-related vicarious traumatization (Table 2 and Fig. 4).

To check the stability of the predictive model, we constructed new predictive networks and used them in cross-validation schemes by controlling for the potential confounds of age, sex, head motion, family

Table 1
Descriptive statistics and bivariate correlations of some study variables.

Variables (1–9)	Mean ± SD	Range	Bivariate correlation coefficients between variables (1–9)									
			1	2	3	4	5	6	7	8	9	
1. Sex ^a (T1)	–	–	–	–	–	–	–	–	–	–	–	–
2. Age (years) (T1)	22.3 ± 2.1	19.4–27.7	–0.126	–	–	–	–	–	–	–	–	–
3. FD (T1)	0.16 ± 0.05	0.05–0.29	–0.095	–0.138	–	–	–	–	–	–	–	–
4. Family SES (T1)	4.90 ± 1.47	1.5–9.0	0.022	0.001	–0.081	–	–	–	–	–	–	–
5. SRLEC-Number (T1)	12.7 ± 5.7	1–27	–0.046	–0.044	0.062	–0.193*	–	–	–	–	–	–
6. SRLEC-Impact (T1)	29.5 ± 16.7	2–77	0.044	–0.006	0.046	–0.199*	0.922***	–	–	–	–	–
7. GHQ (T1)	19.5 ± 4.8	12–36	0.166	0.118	–0.133	–0.261**	0.269**	0.279**	–	–	–	–
8. VTQ (T2)	74.2 ± 23.0	38–128	0.109	–0.003	–0.148	–0.212*	0.173	0.271**	0.252**	–	–	–
9. General distress (T3)	35.7 ± 10.7	21–59	–0.052	0.065	0.053	–0.176	0.240*	0.298**	0.447***	0.596***	–	–

Abbreviations: SD, standard deviation; FD, frame-wise displacement during scanning; SES, socioeconomic status; SRLEC, Self-Rating Life Events Checklist; GHQ, General Health Questionnaire; VTQ, Vicarious Traumatization Questionnaire; T1, sampling point October 2019 to January 2020; T2, February to April 2020; T3, March to April 2021. * $p < 0.05$

** $p < 0.01$

*** $p < 0.001$. ^a Male, 0; Female, 1.

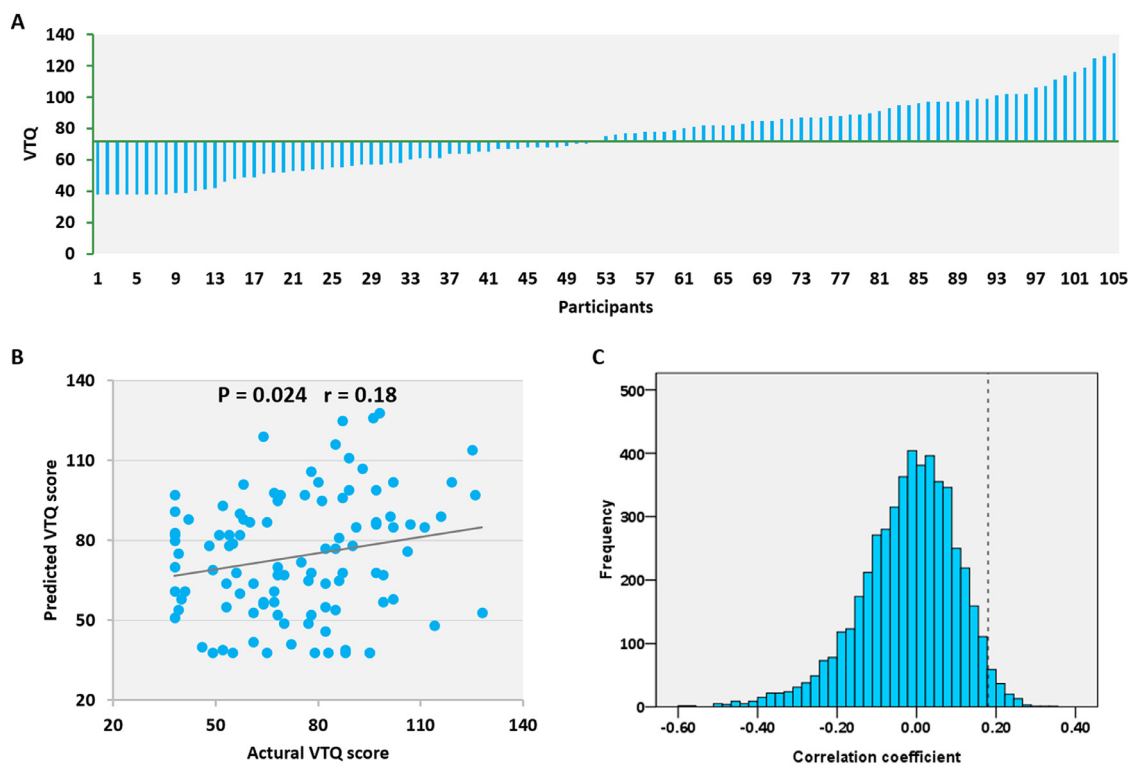


Fig. 2. VTQ scores distribution and performance of the prediction. (A) VTQ scores across all participants (horizontal line denotes the mean). (B) Correlation between VTQ predicted using RSFC in the negative network and actual VTQ. (C) Permutation distribution of the correlation coefficient (r) for the prediction analysis. Abbreviations: VTQ, Vicarious Traumatization Questionnaire.

Table 2
The ten nodes with the most connections selected by the prediction model.

No.	Node	MNI coordinate			Lobe	Degree
		x	y	z		
48	R Angular Gyrus (BA 39)	47.83	–61.58	34.71	Parietal	81
131	R Brainstem	5.96	–22.23	–42.26	Brainstem	64
196	L Inferior Temporal Gyrus (BA 20)	–51.76	–18.15	–28.79	Temporal	54
183	L Angular Gyrus (BA 39)	–51.38	–56.29	20.47	Parietal	52
70	R Fusiform Gyrus (BA 37)	60.79	–43.27	–17.64	Temporal	52
51	R Temporal Pole (BA 38)	27.18	11.56	–39.16	Temporal	46
6	R Anterior Prefrontal Cortex (BA 10)	14.56	64.73	3.64	Frontal	46
56	R Inferior Temporal Gyrus (BA 20)	54.50	–7.72	–31.53	Temporal	45
7	R Anterior Prefrontal Cortex (BA 10)	30.51	54.92	–3.52	Frontal	44
90	R Dorsal Posterior Cingulate Cortex (BA 31)	6.17	–57.36	38.15	Limbic	43

Abbreviation: L, left; R, right; BA, Brodmann area; MNI, Montreal Neurological Institute.

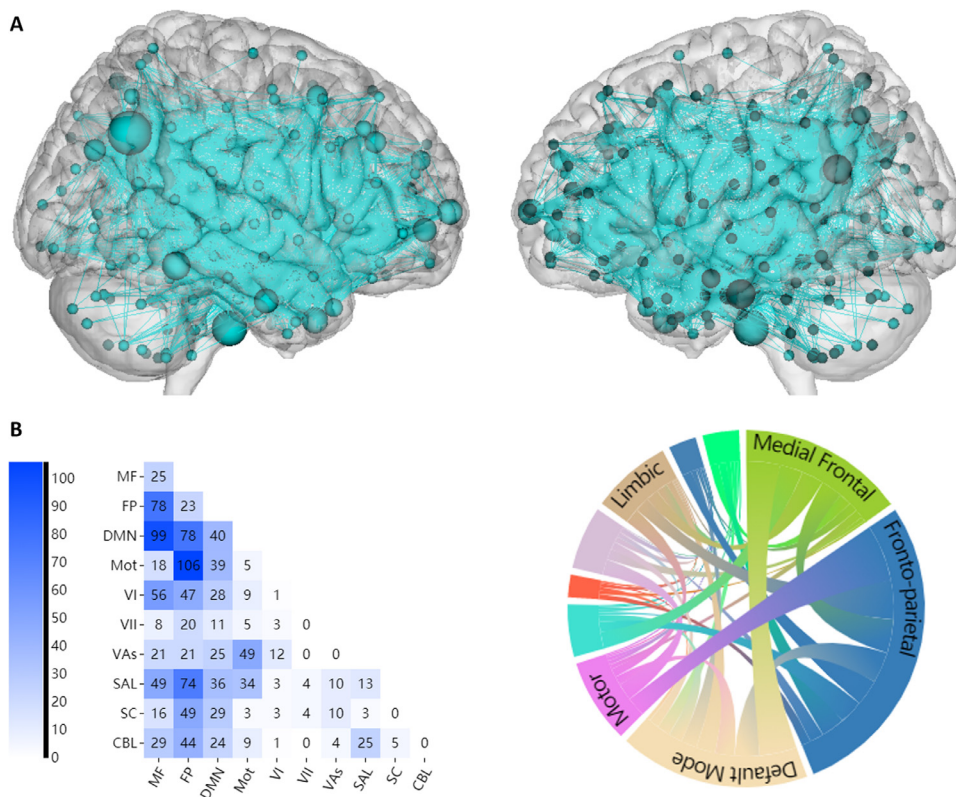


Fig. 3. Functional connections predicting VTQ scores. The results were visualized using BioImage Suite (<http://bioimagesuite.com/>). (A) Negative (blue) networks selected by the prediction model; for the negative network, decreased edge weights (i.e. decreased functional connectivity) predict higher VTQ scores. (B) Connections plotted as number of edges within and between each pair of canonical networks: on the left, cells represent the total number of edges connecting nodes within (and between) each canonical network, with darker colors indicating a greater number of edges; the connections are shown diagrammatically on the right. Abbreviations: MF, medial frontal; FP, frontoparietal; DMN, default mode network; Mot, motor cortex; VI, visual I; VII, visual II; VAS, visual association; SAL, salience; SC, subcortical; CBL, cerebellum.

SES, other stressful life events or general mental health, using different feature-selection thresholds, using 5/10-fold cross-validation, and using different brain parcellations. These alternative predictive models could still significantly predict VTQ (Table S1), and the contributing features to these new models were similar to those in the primary findings (Table S2). However, neither the negative network ($q^2 = -0.31$, $MSE = 684$, $r_{[\text{predicted, actual}]} = 0.05$, $p = 0.59$) nor the positive network ($q^2 = -0.28$, $MSE = 669$, $r_{[\text{predicted, actual}]} = -0.01$, $p = 0.50$) predictive model yielded significant prediction performance when global signal regression is applied.

Additionally, to explore sex differences in the association between vicarious traumatization and functional brain connectivity, a condition-by-covariate interaction analysis (Kong et al., 2014; Yamasue et al., 2008) was performed with sex as a condition, VTQ score as a covariate of interest and age and FD as covariates of no-interest. We found no sex differences in the association between vicarious traumatization and the functional connectivity.

3.3. Functional connectome linking vicarious traumatization and general distress

Having identified the brain functional connectome of vicarious traumatization, we investigated the underlying mechanisms linking VTQ, brain functional connectome and general distress. On the purely behavioral level, there was a significant positive correlation of vicarious traumatization with general distress ($r = 0.59$, $p < 0.001$); further regression analysis revealed that vicarious traumatization still explained significant additional variance in general distress after adjusting for sex, age and head motion ($\Delta R^2 = 38.3\%$, $\beta = 0.63$, $p < 0.001$). We then asked whether general distress could be predicted by the RSFC in the predictive network that was related to vicarious traumatization. There was a significant positive correlation of general distress with RSFC in the predictive network ($r = 0.33$, $p < 0.001$); further regression analysis revealed that RSFC in the predictive network still explained additional

variance in general distress after adjusting for sex, age and head motion ($\Delta R^2 = 11.5\%$, $\beta = 0.34$, $p < 0.001$).

Thus the functional connectome, vicarious traumatization and general distress are interrelated. To probe the nature of their relationships, a mediation analysis was performed to examine whether vicarious traumatization mediated the link of functional connectome to general distress (Fig. 5). There was a significant and full indirect effect of vicarious traumatization in the relation between the RSFC in the predictive network and general distress (indirect effect = 0.28, 95% CI = [0.18, 0.37], $p < 0.05$), and this remained even after adjusting for sex, age and head motion (indirect effect = 0.28, 95% CI = [0.19, 0.37], $p < 0.05$; Fig. 5). Thus the functional connectome may influence general distress via vicarious traumatization.

To examine the specificity of the relation between functional connectome, vicarious traumatization and general distress, we additionally controlled for several possible disturbing variables including family SES, other stressful life events and general mental health. The results remained after such adjustment, suggesting a substantial, degree of specificity (see Supplementary Results).

Additionally, to explore whether general distress can be predicted from functional connectome, we took the DASS scores and functional brain connectivity as input and repeated the CPM analysis. Neither the negative network ($q^2 = -0.26$, $MSE = 142$, $r_{[\text{predicted, actual}]} = 0.09$, $p = 0.19$) nor the positive network ($q^2 = -0.29$, $MSE = 145$, $r_{[\text{predicted, actual}]} = -0.21$, $p = 0.93$) model yielded significant prediction performance.

4. Discussion

In this prospective study, we collected behavioral data in the pre-pandemic, outbreak and remission periods on the mental health of a cohort of college students who had completed brain MRI scanning before the pandemic. Using a CPM approach, we constructed a functional connectome that stably predicted individual differences in vicarious traumatization; this principally involved the DMN, FPN, SN, medial

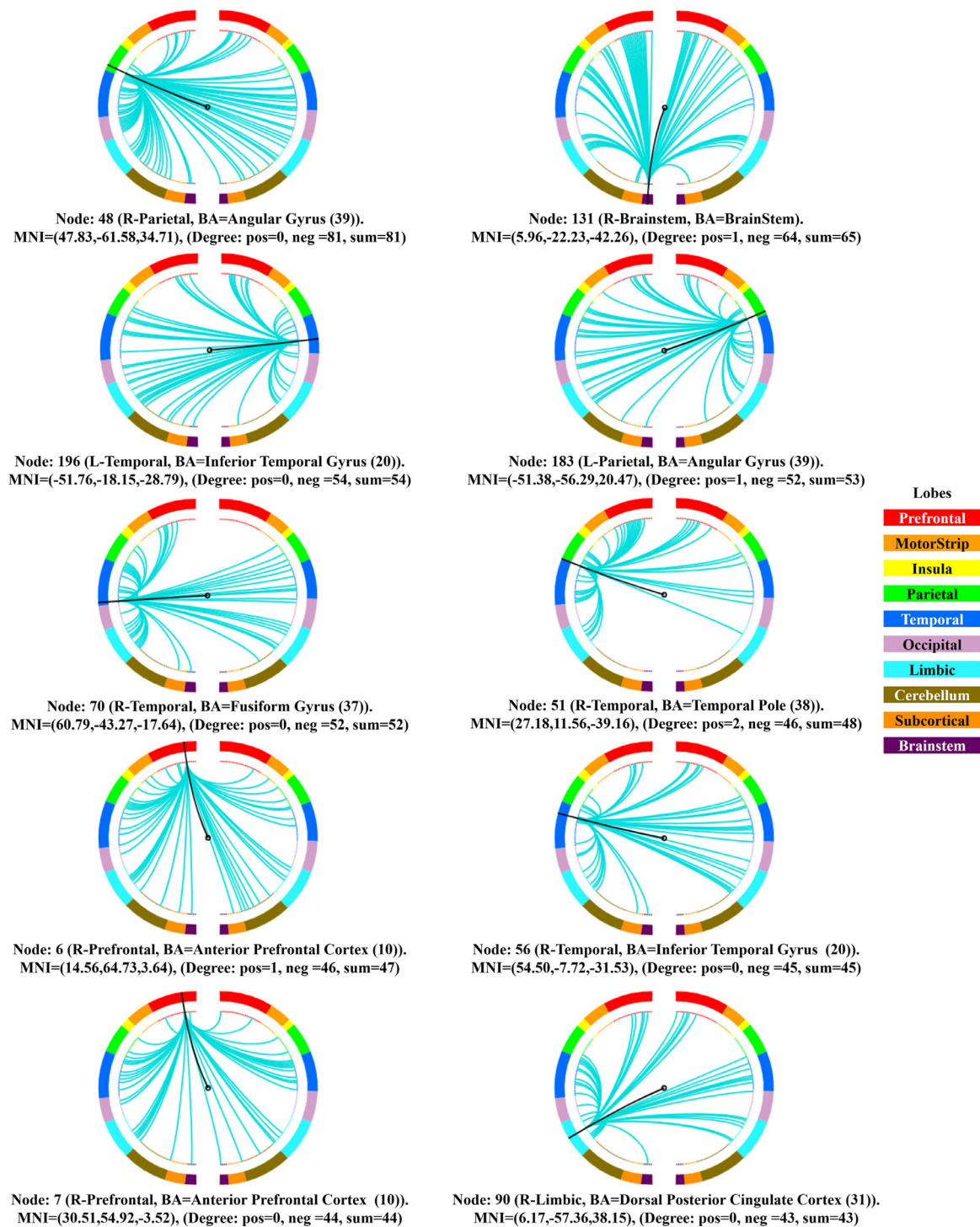


Fig. 4. Connectivity patterns of the top ten nodes with the most connections. The top 10 most highly connected nodes were located in the bilateral angular gyrus and inferior temporal gyrus, right temporal pole, fusiform gyrus, anterior prefrontal cortex, dorsal posterior cingulate cortex and brainstem which played the key roles in the prediction of VTQ scores. Abbreviations: L, left; R, right; BA, Brodmann Area; MNI, Montreal Neurological Institute.

frontal and motor networks. Mediation analyses suggested that vicarious traumatization significantly mediates the link of the functional connectome with general distress in the pandemic, even when controlling for potential confounds like the effects of family SES, other stressful life events and general mental health. Our study provides insight into the neuropsychological pathway underlying vicarious traumatization-related distress, and suggests potential for functional brain markers of vicarious traumatization in the prediction of individual susceptibility to the related distress.

Confirming our first hypothesis, individual variations in vicarious traumatization were primarily in functional connectivity in the DMN, FPN, SN, medial frontal and motor networks. Vicarious traumatization causes lasting alterations to the cognitive systems which have evolved to help individuals make sense of their world (McCann and Pearlman, 1990). There are reasons to regard these are particularly important in the various components of vicarious traumatization. Intrusion and dissociation (a form of trauma re-experiencing) can be distressing in vicarious traumatization (Lugris, 2000), even though less severe than

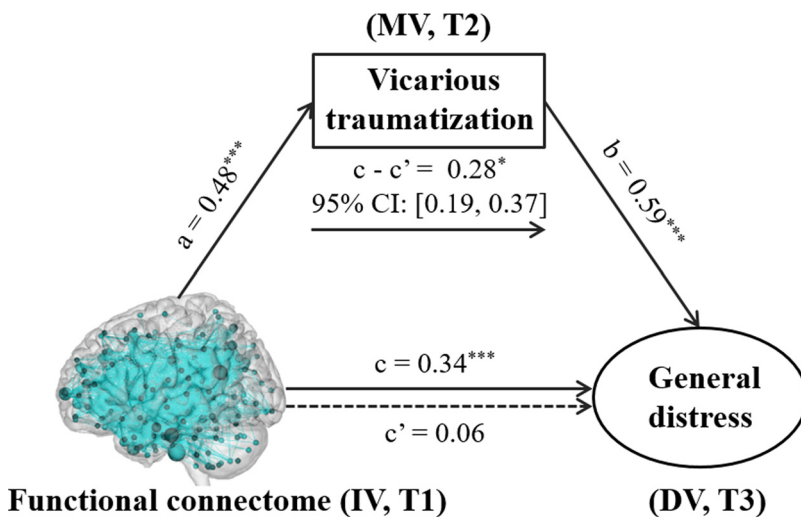


Fig. 5. Vicarious traumatization mediates the influence of the functional connectome on general distress. Standardized regression coefficients are presented next to the path arrows. Sex, age and head motion were regressed out in the models. Abbreviations: IV, independent variable; MV, mediator variable; DV, dependent variable.

in those directly exposed (Lerias and Byrne, 2003). Functional connectivity between the SN and FPN is decreased in individuals with high dissociative-traumatic dimension symptoms (Carbone et al., 2022). The FPN/medial frontal network is critical for cognitive/executive control of behavior and emotions (Pan et al., 2021; Seeley et al., 2007; Yip et al., 2019) and the SN orients attention to salient internal and external information (Menon, 2011); these may form the cognitive foundation for intrusion-dissociation symptoms (Cai et al., 2021). Altered DMN connectivity may underlie or reflect disruption of self-identity. Stressors deplete personal resources and lower self-awareness (Pearlman and Saakvitne, 1995); the DMN is involved in self-referential processing and autobiographical rumination (Buckner et al., 2008), and DMN disruption has been related to impaired self-awareness (Gusnard et al., 2001). The motor network contributes to motor skill learning (Butefisch et al., 2000; Rioult-Pedotti et al., 1998), and its activation might represent the neural correlate of motor preparation for coping with a threat (Bremner et al., 1999). Motor networks are critically integrated into working memory processes (Marvel et al., 2019; Zhu et al., 2021). Individuals during the COVID-19 epidemic have higher negative emotions (Li et al., 2020a; Wang et al., 2021a), which can have an impact on a variety of cognitive domains, including working memory (Cesare et al., 2018). We suggest that disruptions across these functional networks reflect a general posttraumatic psychopathology (Harnett et al., 2021) which in vicarious traumatization is associated with cognitive, emotional and self-social deficits.

Consistent with our second hypothesis, vicarious traumatization served as a mediator in the link between functional connectome and general distress. Behaviorally, the association of vicarious traumatization with general distress is well-known (Gleichgerrcht and Decety, 2013; Greene et al., 2014; Jenkins and Baird, 2002; Nagamine et al., 2018; Zerach and Milevsky, 2022), and was replicated in our sample. Vicarious traumatization still accounted for significant variance in general distress even after excluding the influences of family SES, stressful life events and general mental health as well as sex, age and head motion. Neurofunctionally, a significant component of the variance in general distress could be explained by the functional connectome. Although few studies have investigated the relationship between functional connectome and general distress, there is abundant evidence for a role of functional connectivity in depression, anxiety and stress (Harnett et al., 2021; van Oort et al., 2020), which are increasingly understood as network-based disorders (Bao et al., 2021; Mulders et al., 2015; Xu et al., 2019). For example, functional connectivity within DMN, and between DMN and SN/FPN, are altered in depression (Mulders et al., 2015); anxiety is characterized by hypo-connectivity of multiple brain networks, notably the FPN, DMN, SN and motor network (Xu et al., 2019); stress can be linked to

the balance between FPN and SN (Hermans et al., 2014, 2011). These findings suggest common neuropsychological correlates of depression, anxiety and stress susceptibility, all of which are prevalent and comorbid post-trauma (Chew et al., 2020; Dar et al., 2021; Dubey et al., 2020; Nochaiwong et al., 2021; Srfuengfung et al., 2021). This raises the possibility that general distress is also a network-based pathophysiology, which may have important implications for brain-stimulation-based treatment (Liu et al., 2021a; Scult et al., 2019). Events inducing a prolonged activation of the stress system, such as the COVID-19 pandemic, might cause long-term maladaptive consequences (i.e. general distress) by provoking changes in multiple brain functional networks. Our study indicates that vicarious traumatization may be a potential linking mechanism.

Several limitations must be acknowledged. First, brain imaging data and behavioral measures were only acquired in one session. As CPM approach is based on correlational associations of MRI features and behavioral measures, we cannot conclude that vicarious traumatization was “caused” by network changes. Although there is growing evidence for brain functional connectivity as a reliable and objective imaging marker of individual phenotype (Beaty et al., 2018; Finn et al., 2015), CPM has not yet been widely used in clinical research, possibly because of current concerns about low test–retest reliability in fMRI research (Milham et al., 2021). Also, the extent to which brain functional connectivity reflects transient states vs. stable traits is still unknown. A longitudinal design will be needed to follow the trajectories of brain dysfunction. Second, RS-fMRI data are largely constrained by anatomical pathways (Honey et al., 2009). A combined analysis of multimodal neuroimaging may in the future aid our developing understanding of vicarious traumatization. Third, we found only the negative network model predicted individuals’ vicarious traumatization scores, and the q^2 value was negative in the predictive model, indicating that the current model was performing worse than simply estimating the mean of the vicarious traumatization scores (Scheinost et al., 2019). Increasing evidence has shown that sample characteristics (e.g., sample size and diversity) can influence the stability of the predictive model (Scheinost et al., 2019; Sui et al., 2020). Given that our study just relied on a relatively small and single sample of general college students, caution is needed to interpret the current findings. The generalization of the current findings requires further validation using an independent and larger sample, and studies focused on other general public populations (e.g., children and the elderly) and highly vulnerable groups (e.g., frontline medical workers) are warranted. Fourth, a group-level atlas were used in the individualized prediction, which might miss subtle brain–behavior associations; individualized prediction with the group-level atlas has less predictive power than with the individualized template (Wang et al., 2020). Fifth,

the mediation effects found in our study may be biased or overestimated because the a path in the mediation model was overinflated due to double dipping (Button, 2019; Kriegeskorte et al., 2009), i.e. the a path was computed with the functional connectivity related to VTQ and identified from the CPM analysis. Because there were no CPM results for DASS scores in our dataset, we were unable to perform a conjunction analysis, an unbiased and more appropriate method to reveal the neural link between two behavioral constructs (Kong et al., 2015; Mackey et al., 2015; Wang et al., 2017). Thus, the current mediation findings should be interpreted with caution, and confirmed in future studies. Sixth, our findings are in contrast to studies reporting that global signal regression *strengthens* the associations between resting-state functional connectivity and behavioral measures (Li et al., 2019). The global signal contains neural information (Matsui et al., 2016; Scholvinck et al., 2010; Wen and Liu, 2016), so regressing the global signal might *weaken* these associations, and this is what we found. Whether and when global signals should be regressed out is the subject of ongoing research, and different choices likely yield complementary insights into brain functional organization.

5. Conclusion

Vicarious traumatization is a common negative psychological response during the pandemic, especially for those vulnerable young people who confronted increased media exposure to COVID-19 information (Rousseau and Miconi, 2020). In a sample of young adults, we identified a brain functional connectome principally constituting connectivity of several distributed networks (DMN, FPN, SN, medial frontal and motor networks) that encodes vicarious traumatization related to COVID-19. Furthermore, we revealed a potential neuropsychological pathway to predict distress symptoms in which vicarious traumatization mediates the impact of the pre-pandemic functional connectome on post-pandemic general distress. These findings may advance our understanding of the neurobiological basis of vicarious traumatization, and may have implications for developing psychological therapies (Swartz, 2020) and brain interventions (Sitaram et al., 2017) for individuals who are at risk of psychological dysfunction and distress in the pandemic, all in line with the goals of psychoradiology (Gong, 2020; Li et al., 2021; Lui et al., 2016; Sun et al., 2015).

Data and code availability statement

Matlab scripts to run the CPM analyses can be found at <https://www.nitrc.org/projects/bioimagesuite/>. Tools used for visualization can be accessed at <http://bioimagesuite.com/>. West China Hospital of Sichuan University has an institutional commitment to data-sharing. To get access to the data and comply with the terms of our research ethics committee approval an application to the corresponding author will be required, specifying the geographical extent of sharing.

Declaration of Competing Interest

None.

Credit authorship contribution statement

Xueling Suo: Formal analysis, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Chao Zuo:** Methodology, Visualization. **Huan Lan:** Data curation, Investigation. **Nanfeng Pan:** Data curation, Validation. **Xun Zhang:** Data curation, Investigation. **Graham J. Kemp:** Writing – review & editing. **Song Wang:** Conceptualization, Investigation, Supervision, Writing – review & editing. **Qiyong Gong:** Conceptualization, Funding acquisition, Supervision.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2022.119185.

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