Pre-COVID brain network topology prospectively predicts social anxiety alterations during the COVID-19 pandemic

Qingyuan Li [a,b,c,d], Xun Zhang [b,c,d], Xun Yang [e], Nanfang Pan [b,c,d], Xiao Li [a], Graham J. Kemp [f], Song Wang [b,c,d,*], Qiyong Gong [b,c,g,**]

[a] Department of Interventional Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100021, China
[b] Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, Chengdu, 610041, China
[c] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, Chengdu, 610041, China
[d] Functional & Molecular Imaging Key Laboratory of Sichuan Province, West China Hospital of Sichuan University, Chengdu, 610041, China
[e] School of Public Affairs, Chongqing University, Chongqing, 400044, China
[f] Liverpool Magnetic Resonance Imaging Centre (LiMRIC) and Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, L69 3BX, UK
[g] Department of Radiology, West China Xiamen Hospital of Sichuan University, Xiamen, 361000, China

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ABSTRACT

Background: Social anxiety (SA) is a negative emotional response that can lead to mental health issues, which some have experienced during the coronavirus disease 2019 (COVID-19) pandemic. Little attention has been given to the neurobiological mechanisms underlying inter-individual differences in SA alterations related to COVID-19. This study aims to identify neurofunctional markers of COVID-specific SA development.
Methods: 110 healthy participants underwent resting-state magnetic resonance imaging and behavioral tests before the pandemic (T1, October 2019 to January 2020) and completed follow-up behavioral measurements during the pandemic (T2, February to May 2020). We constructed individual functional networks and used graph theoretical analysis to estimate their global and nodal topological properties, then used Pearson correlation and partial least squares correlations examine their associations with COVID-specific SA alterations.
Results: In terms of global network parameters, SA alterations (T2-T1) were negatively related to pre-pandemic brain small-worldness and normalized clustering coefficient. In terms of nodal network parameters, SA alterations were positively linked to a pronounced degree centrality pattern, encompassing both the high-level cognitive networks (dorsal attention network, cingulo-opercular task control network, default mode network, memory retrieval network, fronto-parietal task control network, and subcortical network) and low-level perceptual networks (sensory/somatomotor network, auditory network, and visual network). These findings were robust after controlling for pre-pandemic general anxiety, other stressful life events, and family socioeconomic status, as well as by treating SA alterations as categorical variables.
Conclusions: The individual functional network associated with SA alterations showed a disrupted topological organization with a more random state, which may shed light on the neurobiological basis of COVID-related SA changes at the network level.

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has posed a serious threat to the global economy, social fabric, and public mental health (Coelho et al., 2020; Li et al., 2020). In some individuals the perceived threat of COVID-19 infection, coupled with the consequences of social isolation and movement restrictions, has led to negative psychological reactions such as fear, anxiety, depression, and posttraumatic stress (Coelho et al., 2020; Schweda et al., 2021). Among these psychological effects, social anxiety (SA) has been notable (Kindred and

Bates, 2023). Characterized by fear of or anxiety about potential scrutiny by others in social situations, SA covers a spectrum from subclinical symptoms to clinical social anxiety disorder (SAD) (Miskovic and Schmidt, 2012), which can lead to significant adverse effects on social, emotional, and behavioral functioning (Stein et al., 2017). Although the impact of the COVID-19 pandemic on SA is well established (Hawes et al., 2022; Zheng et al., 2020; Zhu et al., 2021), less attention has been paid to individual variability in susceptibility to SA. Study of the underlying neuropsychological mechanisms, as well as illuminating the pathophysiology, may help in identifying practical markers of vulnerability.

Studies using magnetic resonance imaging (MRI), especially functional MRI (fMRI), have yielded insights into the neural mechanisms underlying SA/SAD (Brühl et al., 2014; Mizzi et al., 2022; Zhang et al., 2023b). Most fMRI studies have focused on SAD patients: the most consistent reported abnormalities are in activity in the frontolimbic circuitry, including the superior frontal gyrus (SFG), middle frontal gyrus (MFG), anterior cingulate cortex (ACC), hippocampus (HG)/parahippocampal gyrus (PHG), and amygdala (Brühl et al., 2014; Etkin and Wager, 2007; Gentili et al., 2016; Mizzi et al., 2022), and in resting-state functional connectivity (RSFC) in various networks including the default mode network (DMN), fronto-parietal task control network (FPN), cingulo-opercular task control network (CON), dorsal attention network (DAN), subcortical network (SCN), auditory network (AN), visual network (VN), and sensory/somatomotor network (SMN) (Kim et al., 2023; Liao et al., 2010; Liu et al., 2015; Zhang et al., 2022b). fMRI studies of SA in nonclinical populations have focused on similar brain regions: abnormalities are reported in activity in the ACC, SFG, MFG, amygdala, HG/PHG, superior temporal gyrus (STG), and insula (Bas-Hoogendam et al., 2016, 2019, 2020; Boehme et al., 2015; Kim et al., 2022; Shany et al., 2022; Tei et al., 2020; Terasawa et al., 2013), and of RSFC particularly in the DMN, FPN, DAN, SCN, AN, VN, and salience network (Avery and Blackford, 2016; Bas-Hoogendam et al., 2021; Evans et al., 2020; He et al., 2021; Kajimura et al., 2015; Luo et al., 2018; Mao et al., 2020; Schultz et al., 2019; Zhao et al., 2022). These findings suggest that SA and SAD may rely on overlapping stable dysfunction in mechanisms involved in cognitive, emotional, and sensory processing (Bas-Hoogendam and Westenberg, 2020).

Previous studies have primarily focused on exploring local neural activity or brain organization by quantifying the strength of the connectivity; this however overlooks the higher level of complex organization which is accessible via graph analysis, a powerful framework to characterize the topological patterns of functional connectivity (FC), which has been successfully applied in several psychiatric disorders (Kambeitz et al., 2016; Li et al., 2017; Sporns, 2018). A network approach to the topological organization of functional networks promises rich insights into the neurobiological basis of SA/SAD. However, few such studies have been done. Earlier functional network studies in SAD have highlighted disrupted brain networks, reflected in changes to both global and nodal network property parameters: decreased global normalized shortest path length (λ) (Yang et al., 2019), increased global shortest path length (L_p) (Zhu et al., 2017), decreased global clustering coefficient (C_p) (Zhu et al., 2017), and nodal degree centrality alterations in the PHG, posterior cingulate cortex (PCC), MFG, and insula (Yang et al., 2019). The only study of SA in a nonclinical population reported a relationship between nodal centrality in the parietal regions and fear of negative evaluation, which is a core symptom in SAD (Kajimura et al., 2015). This approach has not previously been applied to SA in the context of the COVID-19 pandemic. Our aim was to explore prospective graph theory-based global and nodal neurofunctional markers for susceptibility to COVID-related SA changes.

To this end, we explored pre-pandemic brain topological characteristics to retrospectively predict SA alterations between the pre-pandemic and pandemic periods in a group of normal adults. We used a dimensional approach, which focused on SA symptom levels, to yield more reliable neurobiological biomarkers of specific clinical presentations (Li

et al., 2023; Liu et al., 2023). First, to characterize resting-state topological properties of functional network at global and nodal scales, we conducted graph theory analysis, a well-validated tool to quantify properties of structural and functional networks (Bullmore and Bassett, 2011). Next, we performed partial correlation and multivariate analysis [partial least squares correlation (PLSC) (Krishnan et al., 2011; Lai et al., 2023)] to evaluate the underlying patterns of the functional brain network linked to SA alterations. Given the previous evidence of disrupted functional brain network in SAD (Yang et al., 2019), we hypothesized that highly socially anxious individuals would manifest some common and distinct alterations. Finally, we examined the specificity and robustness of our findings by additionally controlling for the possible confounding effects of general anxiety symptoms, other stressful life events and family socioeconomic status, and also by performing categorical comparisons.

2. Methods

2.1. Participants

Fig. 1A gives an overview of the data collection and experimental procedures. A total of 151 general university students (77 females, mean age: 21.2 ± 2.1 years) with no history of mental or neurological diseases were recruited for brain MRI scans and self-reported behavioral measures from October 2019 to January 2020 (T1, prior to the declaration of emergency and nationwide lockdown in China). During the first COVID-19 outbreak from February to April 2020 (T2, when China was most severely impacted by the pandemic), all 151 individuals were recontacted and invited to participate for online behavioral assessments to evaluate pandemic-specific SA changes (Zhang et al., 2023a). Of these participants, a subsample of 115 (66 females, mean age: 22.4 ± 2.1 years) responded and completed behavioral measures at T2. After excluding 1 participant with excessive head motion and 4 participants exhibiting non-typical features of small-world organization (see sections on 'MRI data acquisition and preprocessing' and 'Functional brain network construction'), 110 participants (61 females, mean age: 22.4 ± 2.1 years) were included for the final analyses. The standard polymerase chain reaction test was used to ensure no participants or their household members had been diagnosed with COVID-19.

2.2. Behavioral assessments

To investigate the changes in SA during the pandemic, we used the self-administered Liebowitz Social Anxiety Scale (LSAS) (Heimberg et al., 1999; Liebowitz, 1987; Mennin et al., 2002) in all individuals at both T1 and T2. The LSAS is commonly used in Chinese populations for its good psychometric properties (Zhang et al., 2020, 2022a), including test-retest reliability, internal consistency, convergent validity, and discriminant validity (Baker et al., 2002; Czorniej et al., 2022; Pan et al., 2006). The LSAS consists of 24 items that represent common daily scenarios pertaining to social interaction or performance conditions. Individuals are required to rate the level of fear evoked by each specific situation and the subjective probability of avoiding it on a four-point (0–3) Likert scale, corresponding to the fear factor (LSASF) and social avoidance factor (LSASA), respectively; their sum is the total score of the LSAS (LSAST), with higher scores indicating greater severity of SA symptoms (Baroni et al., 2022); Cronbach's α were 0.94 at T1 and 0.96 at T2 in our dataset, indicating satisfactory internal reliability.

To assess potential confounders of the relationship between brain network topologies and SA changes (such as general anxiety symptoms, other stressful life events, and socioeconomic status), we used several other tests at T1: the Trait Anxiety Inventory (TAI), which determines the participants' general tendency to feel anxious (Spielberger, 1983); the Self-Rating Life Events Checklist (SRLEC), which evaluates the frequency and intensity of stressful life events during the past 12 months (Liu et al., 1997); and the Socioeconomic Status Scale (SSS), which
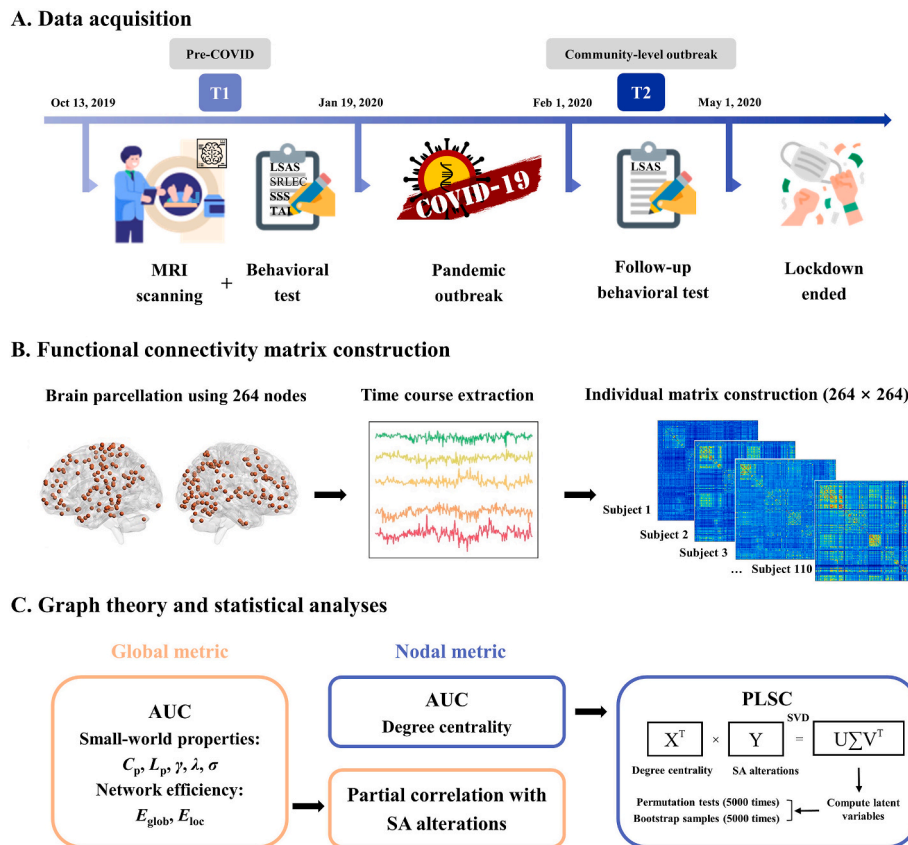
A. Data acquisition

B. Functional connectivity matrix construction

C. Graph theory and statistical analyses

Fig. 1. Workflow of the study. (A) Timeline of data acquisition. Before the COVID-19 pandemic (T1: October 2019 to January 2020), participants underwent brain MRI scanning and completed baseline behavioral measures. During the most severe pandemic period (T2: February 2020 to April 2020), participants were re-contacted for follow-up behavioral testing. 110 subjects were identified as eligible for the study. (B) Construction of 264×264 functional connectivity matrix for each subject. (C) Topological graph theory and statistical analyses. We computed both global and nodal metrics for each individual to describe the characteristics of each weighted network, and for each network metric we used the AUC over a range of network sparsity thresholds (0.02: 0.01: 0.33) in subsequent statistical analyses. We used partial correlation to investigate the association between each global metric and SA alterations (T2-T1), and PLSC to determine the degree centrality pattern of nodes linked to SA alterations. Abbreviations: AUC, area under the curve; COVID-19, coronavirus disease 2019; LSAS, Liebowitz Social Anxiety Scale; MRI, magnetic resonance imaging; PLSC, partial least squares correlation; SA, social anxiety; SRLEC, Self-Rating Life Events Checklist; SSS, Socioeconomic Status Scale; SVD, singular value decomposition; TAI, Trait Anxiety Inventory; C_p, clustering coefficient; E_{glob}, global efficiency; E_{loc}, local efficiency; L_p, shortest path length; γ, normalized clustering coefficient; λ, normalized shortest path length; σ, small-worldness.

assesses participants' family sociological and economic status (Adler et al., 2000). In our sample internal reliability for TAI, SRLEC, and SSS at T1 was adequate (Cronbach's α being 0.89, 0.90, and 0.83 respectively).

2.3. MRI data acquisition and preprocessing

MRI data were acquired using a 3.0 T whole-body scanner (Siemens Trio, Erlangen, Germany), equipped with a 12-channel array coil. For details of Resting-state fMRI (RS-fMRI) data acquisition and pre-processing (see the Supplementary Methods).

2.4. Functional brain network construction

As shown in Fig. 1B, the construction of individual interregional functional brain networks was performed with GRETNA (http://www.nitrc.org/projects/gretna) (Wang et al., 2015). We defined the network nodes using the Power 264-node functional parcellation, which comprises 264 putative functional regions-of-interest (ROI) associated to 14 large-scale functional networks (Power et al., 2011). For each functional ROI, we also reported the corresponding anatomical descriptions in the Automated Anatomical Labeling (AAL) Atlas 3 (Rolls et al., 2020). The Pearson's correlation coefficients (r) between mean time courses of all pairs of nodes were considered as the network edges, and transformed using Fisher's r-to-z transformation to improve

normality. Finally, a symmetric 264×264 functional network matrix with 34,716 ($264 \times 263/2$) unique connectivity edges was created per participant.

Each individual network matrix was converted into a binarized matrix according to predefined sparsity thresholds, providing each network matrix with the same number of edges. Specifically, we thresholded each network matrix over a wide range from 0.02 to 0.33 with a step size of 0.01. The minimum limit, 0.02, was calculated using the widely-used GRETNA function "Gretna_get_rmax", which estimates the minimum sparsity threshold to ensure small-world estimation (Sun et al., 2022; Wang et al., 2020); the maximum limit, 0.33, was chosen to ensure small-world characteristics for all included participants (Yun et al., 2020). Data from 4 participants were excluded due to poor small-world characteristics (the small-worldness σ of the thresholded networks was < 1) and 110 participants were included for final analyses.

2.5. Graph-theoretical analysis

As shown in Fig. 1C, to describe both global and nodal characteristics of the functional network at each sparsity threshold, we computed 7 commonly used global metrics and 1 nodal metric. There are 5 global small-world parameters: C_p (average clustering coefficient over all nodes), a measure of functional segregation; L_p (averaged shortest path length between all node pairs), which indicates how well its elements

are integrated; normalized shortest path length (*λ*) and normalized clustering coefficient (*γ*), which are the normalized measures calculated by comparing each original network with its corresponding random networks; and small-worldness (*σ*), which reflects the network balance between functional integration and segregation. There are 2 global network efficiency parameters: global efficiency (E_{glob}, average inverse shortest path length), a measure of integration, and local efficiency (E_{loc}, average efficiency of the local subgraphs), a measure of segregation (Latora and Marchiori, 2001; Rubinov and Sporns, 2010). The nodal-level topological property was degree centrality, which indicates the functional importance of nodes within the whole brain (Zuo and Xing, 2014). For each network metric we calculated the area under the curve (AUC) for the sparsity range from 0.02 to 0.33 with an interval of 0.01, which provides a robust measure of integrated topological characteristics across the sparsity range (Reijmer et al., 2010; Zhang et al., 2011). The individual AUC for each network metric (global and nodal) was used for subsequent statistical analyses.

2.6. Statistical analysis

2.6.1. Behavioral data analyses

For each participant, SA alterations were computed by subtracting LSAST scores at T1 from LSAST scores at T2. Bivariate associations between study measures were assessed by Pearson's correlation coefficient. The paired-sample *t*-test was used to assess changes of LSAST at T2 relative to T1 among participants. All tests used IBM SPSS Statistics 22.0.

2.6.2. Partial correlation between global-level brain metrics and SA alterations

We examined the relationship between each global metric and SA alterations with partial correlation analyses in IBM SPSS Statistics 22.0. Correlations were computed controlling for sex, age, and mean framewise displacement (FD) to eliminate potential confounding effects. Bonferroni correction for multiple comparisons (7 tests) $p < 0.007$ was deemed significant.

2.6.3. PLSC for nodal-level topological property link to SA alterations

To evaluate multivariate patterns of correlation between the nodal-level topological property (degree centrality) and SA alterations across subjects, we used PLSC via the publicly available PLS toolbox (https://www.rotman-baycrest.on.ca/index.php?section=84) in MATLAB R2018b (MathWorks, Natick, USA). PLSC is a powerful method often used to jointly analyze neuroimaging and behavioral variables (Krishnan et al., 2011; McIntosh et al., 1996; Siffredi et al., 2022). Its significant advantage lies in taking into consideration the multivariate nature of brain data; importantly, no further multiple testing correction is needed in PLSC. Besides, it obviates the need for a feature selection step to reduce feature dimension, which is particularly advantageous when dealing with highly collinear and dimensional variables (Sui et al.,

2020) (detailed introduction of PLSC and procedures in the Supplementary Methods). Brain networks were visualized with the BrainNet Viewer (Xia et al., 2013).

3. Results

3.1. Behavioral and sample characteristics

The descriptive statistics and bivariate correlations of study measures are shown in Table 1. No significant correlations were found between SA alterations (T2-T1 LSAS scores) and age (r = −0.120, p = 0.212), sex (r = −0.014, p = 0.887), or head motion (r = 0.080, p = 0.406) at T1. The paired-sample *t*-test revealed that the LSAS scores at T2 were significantly higher than those at T1 [t (109) = 2.810, *p* = 0.006].

3.2. Associations between global metrics and SA alterations

We investigated the relationships between global functional network metrics and SA alterations. In the 0.02–0.33 range of sparsity threshold, all subjects had small-world properties, with $\lambda \approx 1$, $\gamma > 1$, and $\sigma > 1$ (Bullmore and Bassett, 2011). In partial correlations adjusted for age, sex, and mean FD, SA alterations were negatively associated with AUC of the parameters σ (r = −0.288, p = 0.003) and γ (r = −0.273, p = 0.004) (Fig. 2). In contrast, there were no significant relations between SA alterations and AUC of the parameters L_p (r = −0.097, p = 0.320), λ (r = 0.107, p = 0.272), C_p (r = 0.174, p = 0.073), E_{glob} (r = 0.133, p = 0.172), and E_{loc} (r = 0.174, p = 0.074).

3.3. Degree centrality pattern linked to SA alterations

After controlling for age, sex, and mean FD, PLSC analyses revealed a generalizable degree centrality pattern that contributed to stable individual differences in SA alterations. As shown in Fig. 3A, the degree centrality pattern was positively correlated with SA alterations [r = 0.410, $p_{(permutated)}$ = 0.030]; i.e. if this degree centrality pattern was more evident in an individual's functional network, the individual had a larger increase in SA at T2 relative to T1. The bootstrap approach indicated substantial contributions of 40 nodes to this identified mixed pattern, where a large positive/negative weighting indicates a larger contribution of the specific brain feature in shaping this pattern (Fig. 3B and Supplementary Table S1). In pursuit of a deeper understanding of the complex interactions, we grouped these nodes into networks based on the Power's brain atlas (Power et al., 2011): 27 nodes with positive weightings came from DAN [right superior occipital gyrus (SOG), right SFG, and right middle temporal gyrus (MTG)], CON [left STG and right supramarginal gyrus (SMG)], DMN [left PHG and left inferior temporal gyrus (ITG)], FPN [left posterior orbital gyrus], SMN [right postcentral gyrus (PoCG), right precuneus (PCUN), and right precentral gyrus

Table 1
Summary and correlations of demographics and behavioral measures.

Variable	Mean ± SD	Range	1	2	3	4	5	6	7	8	9	10
1. Sex[a] (T1)	–	–	–									
2. Age (years) (T1)	22.4 ± 2.1	19.4–27.7	−0.086	–								
3. FD (T1)	0.18 ± 0.07	0.06–0.43	−0.081	−0.115	–							
4. SA (T1)	41.4 ± 19.3	4–99	−0.084	0.117	−0.042	–						
5. TAI (T1)	42.0 ± 8.0	24–61	0.251**	−0.024	−0.094	0.362***	–					
6. SRLEC-Number (T1)	12.1 ± 5.6	1–27	−0.063	−0.077	−0.140	0.119	0.229*	–				
7. SRLEC-Impact (T1)	27.7 ± 16.2	2–77	0.016	−0.020	−0.117	0.143	0.262**	0.922***	–			
8. SSS (T1)	4.9 ± 1.5	1.5–9	−0.013	0.056	−0.013	−0.066	−0.312***	−0.246**	−0.234*	–		
9. SA (T2)	46.4 ± 24.5	3–106	−0.077	0.001	0.027	0.663***	0.328***	0.070	0.083	−0.103	–	
10. SA-alterations (T2 - T1)	5.0 ± 18.6	−31–72	−0.014	−0.120	0.080	−0.166	0.056	−0.032	−0.040	−0.067	0.628***	–

Note: There were 110 subjects (61 females). Abbreviations: FD, framewise displacement during scanning; SA, social anxiety; SD, standard deviation; SRLEC, Self-Rating Life Events Checklist; SSS, Socioeconomic Status Scale; TAI, Trait Anxiety Inventory; T1, sampling point October 2019 to January 2020; T2, sampling point February to April 2020. ***p < 0.001; **p < 0.01; *p < 0.05. [a] Analysed as Male = 0; Female = 1.
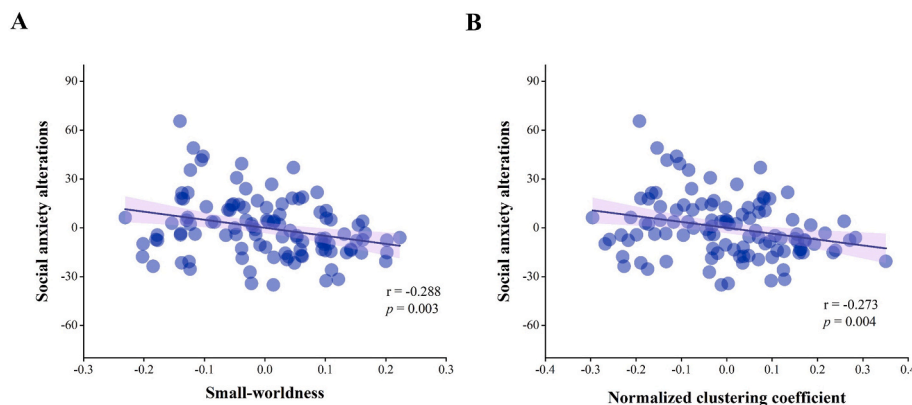
Fig. 2. Relationships between social anxiety alterations and two global metrics of the brain functional network. The y-axis represents the alterations in social anxiety from T1 to T2; the x-axis represents the residuals of the global metrics' AUCs after controlling for age, sex, and mean framewise displacement during scanning. (A) Higher AUC of the small-worldness parameter (σ) is associated with smaller SA alterations. (B) Higher AUC of the normalized clustering coefficient (γ) is associated with smaller SA alterations. Abbreviations: AUC, area under the curve; SA, social anxiety.
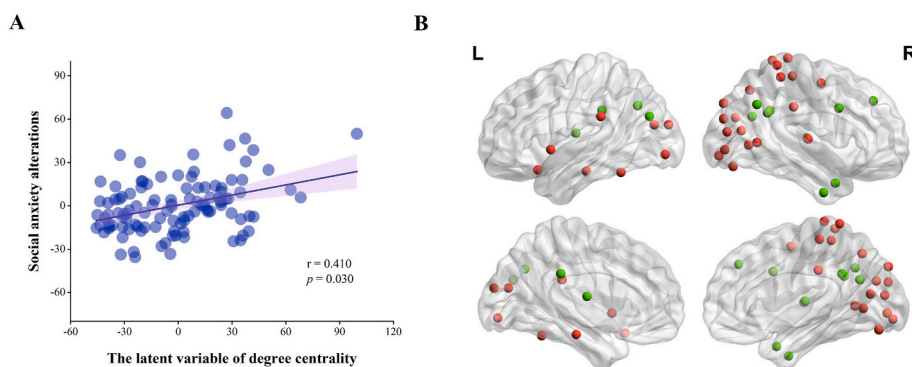

Fig. 3. Partial Least Squares Correlation analysis of the relationship between social anxiety alterations and degree centrality of nodes of the brain functional network. (A) SA alterations are positively linked to a latent variable that comprised a degree centrality pattern of the functional network. (B) 40 regions had absolute values of standardized weighting >2, so made a substantial contribution to the identified degree centrality pattern: for 27 of these regions the contribution was positive (red), and for 13 it was negative (green). Abbreviations: SA, social anxiety; L, left; R, right. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

(PreCG)], AN (right STG and left SMG), and VN [right cuneus, right fusiform gyrus (FG), right lingual gyrus (LING), bilateral middle occipital gyrus (MOG), and right SOG]; 13 nodes with negative weightings came from DMN [bilateral angular gyrus (AG), right ITG, right middle cingulate and paracingulate gyri (MCC), left MOG, right PCUN, right SFG, and right MTG], memory retrieval network (MRN, left PCC), FPN [right inferior frontal gyrus (IFG)], and SCN (bilateral thalamus). For the details of the brain regions in the functional networks, see Supplementary Table S1.

To test whether there were sex differences in the association between SA alterations and brain features, condition-by-covariate interaction analyses (Pan et al., 2023; Wang et al., 2021a) were performed with sex as a condition, SA alterations as covariates of interest, and age and mean FD as covariates of no interest. No sex differences were observed in the association between SA alterations and both global and nodal metrics after Bonferroni correction.

3.4. Specificity and robustness of the findings

Given the impact of general anxiety symptoms (Kuo et al., 2011), other stressful life events (Chou, 2009), and family socioeconomic status (Itani et al., 2021) on SA, we performed all the above analyses additionally controlling for scores of TAI, SRLEC, and SSS as confounding variables. Second, having investigated SA alterations as continuous variables (as described above), we categorized subjects into two groups

of higher SA (HSA) and lower SA (LSA). Two main results were consistent with the main analysis, and can therefore be deemed specific and robust (see the Supplementary Results).

4. Discussion

In this prospective study of healthy young adults, we applied graph theory analysis to RS-fMRI data in order to define a widespread brain functional network topology underlying COVID-related alterations in SA. There were two key findings: (1) lower pre-pandemic small-worldness and lower normalized clustering coefficient of the functional brain network were related to SA exacerbation; (2) a latent variable consisting of a generalizable degree centrality pattern positively contributed to inter-individual variability in SA alterations. Nodes showing substantial contributions to this pattern came from a highly integrated set of brain connections involving multiple internal networks, including both high-level cognitive networks (DAN, CON, DMN, MRN, FPN, and SCN) and low-level perceptual networks (SMN, AN, and VN). Our main findings survived additional adjustment for pre-pandemic general anxiety, other stressful life events, and family socioeconomic status, and they were consistent with the results of the categorical analyses, suggesting substantial specificity and robustness. Our study provides insight into the neurobiological basis underlying COVID-related changes in SA and suggests potential functional network neural markers for the prediction of individual susceptibility to SA.

4.1. Global topology associated with SA alterations

Although the brain functional network of all subjects had, as expected, stable small-world characteristics, lower pre-pandemic small-worldness and lower normalized clustering coefficient were related to SA exacerbation during the outbreak. Consistent with this, lower global clustering coefficient of functional network has been reported in individuals with SAD (Kim et al., 2023; Zhu et al., 2017), along with lower clustering coefficient, normalized clustering coefficient, and small-worldness in gray matter networks (Chen et al., 2022; Zhao et al., 2020), suggesting a possible common network-topology pathophysiological profile in SAD. Segregation (reflected by high clustering and local efficiency) and integration (reflected by short path length and high global efficiency) are two major brain network organizational principles (Bullmore and Sporns, 2012; Fan et al., 2022). Our finding of lower normalized clustering coefficient in high-SA individuals implies impaired local processing capacity (a less segregated network organization) associated with SA changes. 'Small-worldness' describes networks that are simultaneously highly segregated and integrated (Rubinov and Sporns, 2010), and our finding of lower small-worldness in high-SA individuals reflects an imbalance between local specialization and global integration which may underpin less efficient information transfer, contributing to cognitive, emotional, and behavioral impairments in SA/SAD. We did not find a significantly higher normalized shortest path length, so the lower small-worldness is predominantly due to the lower normalized clustering coefficient. Collectively, our findings of reduced local segregation and maintained global integration demonstrate a trend toward more random topology in high-SA individuals (Fan et al., 2022). In comparison to small-world architecture, a more random network exhibits lower fault tolerance (Latora and Marchiori, 2001), signal-propagation speed, computational power, and synchronizability (Watts and Strogatz, 1998). This shift toward randomization may be a key way in which suboptimal brain network topology contributed to excessive SA syndromes during the pandemic.

4.2. Networks positively contributing to the multivariate pattern associated with SA alterations

In addition to the global topologies, high-SA individuals displayed a generalizable degree centrality pattern that was characterized by a positive correlation with alterations in SA.

We found one such correlation for higher nodal degree centrality in the DAN (right SOG, right SFG, and right MTG). This is broadly in accordance with RS-fMRI studies providing evidence for abnormal intrinsic FC within DAN in families genetically enriched for SAD (Bas-Hoogendam et al., 2021), patients with confirmed SAD (Liao et al., 2010), and participants with high levels of social inhibition (a basic human behavior and core feature of SA) (Blackford et al., 2014). Furthermore, task-based fMRI studies in SA/SAD have linked brain activation within DAN to negative attention bias (Kreifelts et al., 2014), social threats (harsh faces) (Goldin et al., 2009), and cognitive control during the perception of negative emotional stimuli (Brühl et al., 2013). There is evidence that the DAN plays a role in top-down spatial and feature-based attention (i.e. orienting to specific regions across the visual field), regulating attention in favor of task-relevant goals, as well as emotion regulation (Liao et al., 2010; Sripada et al., 2014). Our finding of increased nodal centrality in DAN may reflect maladaptive emotional regulation, a high level of self-awareness, and hypervigilance toward social stressors (e.g. the COVID-19 pandemic), all typical of those who become excessively social anxious.

We found another such correlation for higher nodal degree centrality in the CON (left STG and right SMG). This is consistent with previous reports of altered connectivity of the CON in SAD (Liao et al., 2010) and in participants experiencing perceived social isolation (a potential risk factor for SAD) (Layden et al., 2017). The CON is broadly associated with executive functions, including maintenance of tonic alertness, stable maintenance of task contexts (i.e. instructed rules) (Dosenbach et al., 2007), salience encoding, and detecting errors to signal the need for increased cognitive control (Botvinick et al., 2001; Sylvester et al., 2012). Therefore, it is possible that higher centrality levels of CON reflect these neural mechanisms, including a heightened tonic alertness (e.g. increased gaze fixations on negative social scenes), greater personal salience and maintenance of mental task sets involved in negative social information processing (Layden et al., 2017), and a hyperactive 'false-positive'-prone error monitoring mechanism (Becker et al., 2023), which may predispose to developing pandemic-related SA.

We found such correlations for higher nodal degree centrality in the FPN (left posterior orbital gyrus) and in the DMN (left PHG and left ITG). These regions have consistently been implicated in SA symptoms in meta-analyses of neuroimaging studies in SAD (Brühl et al., 2014; Mizzi et al., 2022). The orbital gyrus has a crucial role in recognition and perception of emotional response and fear modulation via the amygdala, including evaluating the negative emotion state and mediating the response toward negative stimuli (Geiger et al., 2016; Klumpp et al., 2014). Higher nodal centrality in the orbital gyrus may align with high-SA individuals' enhanced response to stressors or fear stimuli (Hahn et al., 2011), resulting in severe impairments in social behavior. In addition, the PHG is typically involved in fear conditioning and assigning accurate saliency to a stimulus (Hattingh et al., 2013). Thus these findings may reflect a neural substrate of emotional and cognitive dysfunction that contributed to pandemic-specific SA (Yang et al., 2013).

Further, we found higher degree centrality in several low-level perceptual networks, including the SMN (right PoCG, right PCUN, and right PreCG), AN (right STG and left SMG), and VN (right cuneus, right FG, right LING, bilateral MOG, and right SOG). In line with this, previous neuroimaging studies in SAD have reported abnormal activity and connectivity of SMN, AN, and VN during socially related tasks (i.e. social threat stimuli and negative self-beliefs) (Dixon et al., 2020; Goldin et al., 2009) and at resting state (Geiger et al., 2016; Liao et al., 2010; Liu et al., 2015; Zhang et al., 2022b). A pilot structural MRI study revealed that SAD patients had significant bilateral cortical thinning in the visual and sensory regions relative to healthy controls (Syal et al., 2012). The SMN is involved in multi-sensory processing of body perception and motion preparation, e.g. increased bodily awareness and various somatic symptoms (Northoff, 2020); this aligns well with the fact that in SA/SAD, enhanced awareness of bodily sensation (such as blushing, heart rate, and muscle tension) and preparation for coping with a physical threat are core symptoms (Wood et al., 2022). Additionally, beyond the traditional view that sensory cortices have merely perceptual functions, AN is responsible for emotion processing of socially important auditory information (Koelsch et al., 2018). Our results may reflect aberrant auditory information perception and affective processes in SA/SAD, resulting in difficulties in identifying social signals from voice expressions (Kreifelts et al., 2010). Moreover, VN is involved in emotional facial processing, which is crucial for social and communicative functioning (Nickl-Jockschat et al., 2015). A meta-analysis in SAD identified significant clusters in visual cortex in which faces evoked a higher neural response (Gentili et al., 2016). As the constant alertness to social-evaluative threats in the environment serves as a maintenance factor of SAD (Wong and Rapee, 2016), increased degree centrality in VN may be related to constant hypervigilance to social threats (e.g. angry faces) (Mizzi et al., 2022). In summary, the increased nodal centrality of the low-level perceptual networks in our study may reflect perceptual and emotional impairments responding to social intercourse during the pandemic.

4.3. Networks negatively contributing to the multivariate pattern associated with SA alterations

We found lower nodal degree centrality in DMN (bilateral AG, right

ITG, right MCC, left MOG, right PCUN, right SFG and right MTG) and in the MRN (left PCC) high-SA individuals. This align with fMRI studies in SAD reporting lower deactivation in the PCC/PCUN during task conditions (Gentili et al., 2009) and decreased perfusion of the right PCUN in the resting state (Warwick et al., 2008); these networks have also been previously identified as displaying aberrant intrinsic FC patterns in SAD (Arnold Anteraper et al., 2014; Liao et al., 2010; Liu et al., 2015). The DMN comprises several interconnected brain regions and is activated during rest or internally-oriented mental processes (Schmaal et al., 2013). The DMN is hypothesized to perform multiple cognitive-social processes, including autobiographical/episodic memory retrieval, self-referential processing, scene construction, emotion regulation as well as social cognition (Sambuco et al., 2022; Sreenivas et al., 2012; Xu et al., 2016; Yeshurun et al., 2021). Thus, our results support the notion of aberrant processing in the DMN leading to disturbed self-evaluative and self-referential processing, heightened public self-consciousness, post-event rumination, and disruptions in emotion regulation (Cremers and Roelofs, 2016; Pan et al., 2022; Yoon et al., 2019), all of which underlie the psychopathology of SA/SAD. In addition, in the parcellation by Power et al. (2011), the MRN consists of PCC, posterior medial and lateral parietal cortex, regions frequently included in the DMN in other parcellations (Allen et al., 2011; Yeo et al., 2011). Considering the key role of MRN in autobiographical, episodic, and semantic memory retrieval, the altered nodal degree centrality of the MRN may contribute to the bias of retrieving negative life events (e.g. the COVID-19 pandemic) in SA/SAD (Fan et al., 2019). Our results therefore offer further evidence for general SA psychopathology associated with cognitive, emotional and self-social deficits.

We also revealed lower nodal degree centrality in the FPN (right IFG) and SCN (bilateral thalamus). Emerging literature links SA/SAD to structural/functional abnormalities and network connectivity involving the IFG (Dixon et al., 2020; Liao et al., 2010; Qiu et al., 2015) and thalamus (Duval et al., 2013; Heitmann et al., 2016; Mizzi et al., 2022; Terasawa et al., 2013; Wang et al., 2018; Zhang et al., 2022a). The IFG is implicated in top-down modulation of the fear response (Wang et al., 2021b), emotional stimuli processing (e.g. emotional content of speech and emotional face identification), and emotional empathy (Camacho et al., 2019; Dixon et al., 2020). Furthermore, the thalamus is an integral part of the emotional salience, emotion modulation, and cognitive/executive networks (Yamamura et al., 2016). Moreover, significant habituation effects were found in the thalamus of SAD patients (Sladky et al., 2012). Together with the literature, our results suggest that the IFG and thalamus are important network hubs for dysfunction in emotional processing and impaired cognitive control over emotion (e.g. worse inhibitory control over the emotional responses) in the socially-anxious brain during the pandemic (Wang et al., 2021b).

4.4. Limitations and future directions

This study has several limitations. First, while the Power 264 atlas is commonly used to define the network nodes (Power et al., 2011), the reasons for variations in graph-based theoretical parameters caused by different predefined template parcellations are still unclear (Wang et al., 2009) and thus need to be investigated. Second, the measure of SA relied on a classic self-report scale. Despite the appropriate reliability and validity of this standard scale, self-report measurements are inherently subject to response bias (Van de Mortel, 2008). In future work, structured interview assessment and task performance will enhance the robustness of the findings (Brach et al., 2002; Ganellen, 2007). Third, given that graph theory faces challenges regarding interpretation and sensitivity to arbitrary parameters (Stam and Reijneveld, 2007), our findings need to be compared and tested by employing other RS-fMRI methodologies (e.g. connectome-based predictive model, seed-based correlation analysis, and independent component analysis) (Geiger et al., 2016; Lin et al., 2023; Wang et al., 2023). Besides, no connections were observed between SA and other anticipated regions of interest (e.g.

amygdala), therefore future studies using different analytic approaches may aid our developing understanding of the neurofunctional markers of SA alterations during stressful events. Fourth, since our study relied on a relatively small and homogeneous sample of general college students, the results should be interpreted with caution. To enhance the generalizability of our findings, future research should be conducted using larger, independent samples, encompassing populations with more diverse backgrounds (e.g. age, occupation, and mental illness). Finally, the applicability of the current findings in clinical settings is constrained due to the fundamental nature of our research as an exploratory study. Subsequent investigations are essential to validate and build upon our findings.

5. Conclusion

In conclusion, using graph theory analyses based on RS-fMRI data, this study provided evidence for pre-pandemic brain functional network topology associated with SA alterations during the COVID-19 pandemic. We found the individual functional networks of high SA individuals tended toward a more randomly organized network, and a pronounced degree centrality pattern positively associated with SA alterations, including both the high-level cognitive networks (DAN, CON, DMN, MRN, FPN, and SCN) and low-level perceptual networks (SMN, AN, and VN). Our findings throw new light on the neurobiology underlying the development of SA at the network level, and may help to identify robust neurofunctional biomarkers which can be used to prescribe and monitor interventions such as psychosocial strategies (Mayo-Wilson et al., 2014) and noninvasive brain stimulation techniques (Rosson et al., 2022), for individuals who be more susceptible to SA symptoms in response to stress- and trauma-related events such as a global pandemic, all in line with the goals of psychoradiology (Gong, 2020; Li et al., 2021; Lui et al., 2016; Sun et al., 2015).

Ethics approval statement

The study was approved by the Research Ethics Committee of West China Hospital of Sichuan University, and signed ethical consents were obtained for all participants in line with the Declaration of Helsinki.

Data and code availability statement

Data will be made available on request.

CRediT authorship contribution statement

Qingyuan Li: Formal analysis, Visualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Xun Zhang:** Formal analysis, Visualization, Writing – original draft. **Xun Yang:** Data curation. **Nanfang Pan:** Data curation. **Xiao Li:** Writing – review & editing. **Graham J. Kemp:** Writing – review & editing. **Song Wang:** Supervision, Writing – review & editing. **Qiyong Gong:** Supervision.

Declaration of competing interest

The authors declare no competing interests.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.ynstr.2023.100578.

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