**Supplementary Materials**

Behavioral data acquisition

***SA measurement:*** SA was measured at T1 and T2 by the self-administered LSAS;[1] this has been widely used and has demonstrated good reliability and validity in Chinese populations.[2-6] For each of 24 items, participants indicate (on a 4-point Likert scale ranging from 0 to 3) how frequently they fear the situation and how much they avoid it. Adding these gives a score for a fear factor (LSASF) and a social avoidance factor (LSASA) respectively, whose sum is the total score (LSAST), with higher scores indicating worse SA. In our sample, internal reliability for LSAS was excellent (Cronbach's alpha = 0.94 and 0.96 at T1 and T2, respectively).

***COVID-specific OCS measurement****:* Pandemic-specific obsession-compulsive symptoms (OCS) levels were measured at T2 using the unidimensional Obsession with COVID-19 Scale (OCS-19).[7] This contains 4 items in which participants rate (on a 5-point Likert scale from 1 = not at all to 5 = nearly every day) the frequency of enduring and maladaptive thoughts about COVID-19 in the past month; the ratings of all items are summed as the overall OCS-19 score, with higher scores indicating worse OCS. The Chinese version of OCS-19 has satisfactory reliability and validity for assessing pandemic-specific OCS.[8] In our sample, the internal reliability for OCS-19 was adequate (Cronbach's alpha was 0.80).

***Other controlling measurements***: To exclude possible confounding effects on the relationships between SA, OCS, and brain structures, several other tests were administered at T1: the Trait Anxiety Inventory (TAI), which assesses general anxiety symptoms;[9] the Self-Rating Life Events Checklist (SRLEC), which assesses the frequency and impact of stressful life events experienced in the previous year;[10,11] and the Socioeconomic Status Scale (SSS), which assesses family Socioeconomic Status (SES) levels.[12] In our sample, the internal reliability for TAI, SRLEC, and SSS were adequate (Cronbach's alpha was 0.89, 0.90, and 0.73 respectively).

Image acquisition and pre-processing

***Image acquisition:*** Whole-brain structural MRI was performed on 3.0 Tesla MR scanner (Siemens Trio, Erlangen, Germany) with 12-channel head coil. During the scan, the subjects were instructed to lie still and keep their eyes closed. Earplugs were used to reduce scanner noise, and foam pads were used to restrict head motion. High-resolution three-dimensional T1-weighted images (3D-T1WI) were acquired using whole-head magnetization-prepared rapid gradient echo sequence with these parameters: repetition time/echo time/inversion time 1900/2.26/900 ms, flip angle 9°, slice thickness 1 mm, data matrix size 256×256, 176 slices with 1 mm isotropic resolution.

***Image pre-processing:*** Pre-processing of 3D-T1WI was conducted using Statistical Parametric Mapping software (SPM12; Welcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/) in the following steps:[13] all images were checked for structural anomalies or artefacts, then manually reoriented to the anterior commissure for better registration; the high-resolution T1WI images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid with the new segmentation tool in SPM12; the GM data were aligned, resampled to 1.5 × 1.5 × 1.5 mm3, transformed to Montreal Neurological Institute (MNI) space, modulated for the preservation of GM volume (GMV) (using the inverse Jacobian of the local transformations), and smoothed with an 8-mm full-width at half-maximum Gaussian kernel using DARTEL in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/);[14] lastly, to remove edge effects around the GM/WM borders, the smoothed images were masked with an absolute threshold masking of 0.2.

***Quality control:*** During scanning, each participant was asked to keep still and relaxed, close eyes and not think of anything deliberately. Foam pads and earplugs were employed to reduce head motion and scanning noise. Before data pre-processing, each scanned file was inspected by an experienced neuroradiologist to rule out visible movement artefacts and gross structural abnormalities. During data pre-processing, two researchers independently checked the quality of segmentation and normalization. According to these quality control procedures, no participants had to be excluded.

Statistical analyses

***Psychological measures and sample characteristics:*** Group differences were assessed by the *Chi*-square test for the categorical variable (gender), the independent-sample *t*-test for normally distributed continuous variables (age, LSAS, TAI, SRLEC, and SSS scores), and Mann‐Whitney U test for non-normal distribution data (OCS-19). The paired *t*-test was used to assess the changes of LSAS at T2 relative to T1. All tests used IBM SPSS Statistics 22.0 (IBM Corp, Released 2013. IBM SPSS Statistics for Windows, Armonk, New York, USA).

***Voxel-based morphometry group comparison:*** Whole-brain voxel-wise comparisons between the HSA and LSA groups for pre-pandemic GM volume (GMV) were performed using independent-sample *t*-test with age, sex, and total GMV as covariates in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/). The false discovery rate (FDR) correction approach was used for multiple comparisons with a significance threshold of voxel-wise *P* < 0.001 and FDR‐corrected *P* < 0.05 at cluster level.[15]

***GMV-SA correlation:*** To explore the correlations between the GM structural variations and SA dimensional alterations, the average GMVs in the significant clusters with between-group differences were extracted, and then a partial correlation analysis was performed between LSAS scores and GMV in the identified clusters with sex, age, and total GMV as covariates using IBM SPSS Statistics 22.0 (IBM Corp, Released 2013. IBM SPSS Statistics for Windows, Armonk, New York, USA).

***Mediation analyses:*** To investigate the potential roles of pandemic-specific OCS levels in the relationship between the identified pre-pandemic GM structural variations and SA alterations, a mediating analysis was conducted with the SPSS (IBM Corp, Released 2013. IBM SPSS Statistics for Windows, Armonk, New York, USA) macro PROCESS by bootstrapping approach.[16,17] GMV of each brain region with group differences was the independent variable (X); OCS-19 scores were the mediator variable (M); categorized or dimensional alterations in SA were the dependent variable (Y), and age, gender and total GMV were covariates. The indirect effect (i.e. mediation effect) was estimated as the product of path a (the correlation of X and M) and path b (correlation of M and Y after controlling for X). If the bootstrapped 95% confidence intervals (CIs) with 5000 surrogate datasets did not include zero, the estimated indirect effect was considered significant.

Results

## Correlations between pre-pandemic GMV and SA changes in the pandemic

After adjusting the confounders of age, gender, total GMV, and pre-pandemic TAI, SRLEC, and SSS scores, the pre-pandemic GMV of right SMG was significantly and positively correlated with the SA dimensional alterations (*r* = 0.252, *P* = 0.008).

## OCS links pre-pandemic GMV to SA changes in the pandemic

After adjusting for the confounders of age, gender, total GMV, and pre-pandemic TAI, SRLEC, and SSS scores, mediating effect analysis demonstrated that there was a mediating role for pandemic-specific OCS between GMV of SMG and categorical SA alterations (indirect effect = 4.010; 95% CI: [0.014, 13.230]; *P <* 0.05), and dimensional SA alterations (indirect effect = 24.766; 95% CI: [0.398, 57.666]; *P <* 0.05).

## Supplementary Table 1: The differences in psychological and demographic characteristics between HSA and LSA groups.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **HSA (*n* = 63)** | **LSA (*n*= 52)** | ***χ2/t/U*** | ***P* values** |
| Male | 27 (42.9) | 22 (42.3) | 0.004\* | 0.953 |
| Age (years, T1) | 22.3±2.0 | 22.5±2.1 | -0.549† | 0.584 |
| **LSAS (T1)** | | | |  |
| LSAST | 40.4±18.6 | 42.4±20.0 | -0.561† | 0.576 |
| LSASF | 22.3±10.3 | 22.3±10.9 | -0.017† | 0.986 |
| LSASA | 18.1±10.0 | 20.1±10.3 | -1.050† | 0.296 |
| TAI (T1) | 42.4±8.3 | 41.2±7.9 | 0.771† | 0.442 |
| **SRLEC (T1)** |  |  |  |  |
| SRLEC\_F | 12.3±5.8 | 12.2±5.8 | 0.121† | 0.904 |
| SRLEC\_I | 28.6±16.5 | 27.5±17.0 | 0.335† | 0.739 |
| SSS (T1) | 5.0±1.6 | 4.9±1.3 | 0.537† | 0.592 |
| **LSAS (T2)** | | | |  |
| LSAST | 57.8±22.8 | 32.1±17.5 | 6.655† | < 0.001 |
| LSASF | 30.8±12.7 | 18.8±11.0 | 5.330† | < 0.001 |
| LSASA | 27.0±12.1 | 13.2±8.0 | 7.022† | < 0.001 |
| OCS-19 (T2) | 6.0 (5.0, 8.0) | 5.0 (4.0, 6.0) | -3.081‡ | 0.002 |

Continuous variables with normal distribution are presented as mean±standard deviation; the non-normally distributed continuous variables are presented as median (Q1, Q3); the categorical variables are presented as *n* (%). \****χ2*** values. †*t* values; ‡*U* values. HAS: Higher social anxiety group; LSA: Lower social anxiety group; LSAS: Liebowitz social anxiety scale; LSASA: Avoidance factor scores of the Liebowitz social anxiety scale; LSASF: Fear factor scores of the Liebowitz social anxiety scale; LSAST: Total score of the Liebowitz social anxiety scale; OCS-19: Obsession with COVID-19 scale; SRLEC: Self-rating life events checklist; SRLEC\_F: Frequency subscale of self-rating life events checklist; SRLEC\_I: Impact subscale of self-rating life events checklist; SSS: Socioeconomic status scale; TAI: Trait anxiety inventory.

## Supplementary Table 2: Brain regions with significant GMV differences between HSA and LSA groups.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Significant clusters** | **BA** | **Peak MNI coordinate of significant clusters** | | | **Cluster size (voxels)** | **Peak T value** |
| **X** | **Y** | **Z** |
| **Controlling for age, gender, and total GMV** | | | | | | |
| Right SMG | 40 | 48 | -31.5 | 13.5 | 560 | 5.239 |
| **Controlling for age, gender, total GMV, TAI, SRLEC, and SSS** | | | | | | |
| Right SMG | 40 | 49.5 | -31.5 | 13.5 | 488 | 5.087 |

BA: Brodmann’s area; GMV: Gray matter volume; HAS: Higher social anxiety group; LSA: Lower social anxiety group; MNI: Montreal neurological institute; SMG: Supramarginal gyrus; SRLEC: Self-rating life events checklist; SSS: Socioeconomic status scale; TAI: Trait anxiety inventory.

**C:\Users\Administrator\Desktop\1.tif**

**Supplementary Figure 1:** Schematic flow of the study. A total of 115 subjects were identified as eligible for the present study, of whom 63 participants who scored higher total scores of Liebowitz Social Anxiety Scale at T2 compared to T1 were designated as the HSA group, and 52 participants who scored lower total scores at T2 were assigned to the LSA group. Whole-brain VBM and mediating effects analyses were performed to explore the neuropsychological relationships between the pre-pandemic brain structure and the discrepant alterations of SA during the COVID-19 pandemic, and the mediating effects of obsession with COVID-19 on the linking of brain structure and SA alterations. COVID-19: Coronavirus disease 2019; HAS: Higher social anxiety group; LSA: Lower social anxiety group; LSAS: Liebowitz social anxiety scale; MR: Magnetic resonance; OCS-19: Obsession with COVID-19 scale; SA: Social anxiety; SRLEC: Self-rating life events checklist; SSS: Socioeconomic status scale; TAI: Trait anxiety inventory; VBM: Voxel-based morphometry.

References

1. Mennin DS, Fresco DM, Heimberg RG, Schneier FR, Davies SO, Liebowitz MR. Screening for social anxiety disorder in the clinical setting: using the Liebowitz Social Anxiety Scale. J Anxiety Disord 2002;16:661-673. doi: 10.1016/s0887-6185(02)00134-2.

2. Bas-Hoogendam JM, van Steenbergen H, Tissier R, Houwing-Duistermaat JJ, Westenberg PM, van der Wee N. Subcortical brain volumes, cortical thickness and cortical surface area in families genetically enriched for social anxiety disorder - A multiplex multigenerational neuroimaging study. EBioMedicine 2018;36:410-428. doi: 10.1016/j.ebiom.2018.08.048.

3. Frick A, Engman J, Alaie I, Björkstrand J, Faria V, Gingnell M, et al. Enlargement of visual processing regions in social anxiety disorder is related to symptom severity. Neurosci Lett 2014;583:114-119. doi: 10.1016/j.neulet.2014.09.033.

4. Zhang X, Luo Q, Wang S, Qiu L, Pan N, Kuang W, et al. Dissociations in cortical thickness and surface area in non-comorbid never-treated patients with social anxiety disorder. EBioMedicine 2020;58:102910. doi: 10.1016/j.ebiom.2020.102910.

5. He YL, Zhang MY. Study on reliability and validity of the Liebowitz Social Anxiety Scale. J Diagn Concepts Pract 2004;3:89–93.

6. Zhang X, Suo X, Yang X, Lai H, Pan N, He M, et al. Structural and functional deficits and couplings in the cortico-striato-thalamo-cerebellar circuitry in social anxiety disorder. Transl Psychiatry 2022;12:26. doi: 10.1038/s41398-022-01791-7.

7. Lee SA. How much "Thinking" about COVID-19 is clinically dysfunctional? Brain Behav Immun 2020;87:97-98.

8. Chen JH, Tong KK, Su X, Yu EW, Wu A. Measuring COVID-19 related anxiety and obsession: Validation of the Coronavirus Anxiety Scale and the Obsession with COVID-19 Scale in a probability Chinese sample. J Affect Disord 2021;295:1131-1137. doi: 10.1016/j.jad.2021.08.104.

9. Spielberger CD. Manual for the State-trait Anxiety Inventory STAI (Form Y). Palo Alto, CA: Consulting Psychologists Press, 1983.

10. Liu X, Liu LQ, Yang J, Zhao GF. Reliability and validity of the Adolescents Self-rating Life Events Checklist. Chin J Clin Psychol 1997;5:34-36.

11. Liu X, Tein JY. Life events, psychopathology, and suicidal behavior in Chinese adolescents. J Affect Disord 2005;86:195-203. doi: 10.1016/j.jad.2005.01.016.

12. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol 2000;19:586-592. doi: 10.1037//0278-6133.19.6.586.

13. Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005;26:839-851. doi: 10.1016/j.neuroimage.2005.02.018.

14. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95-113. doi: 10.1016/j.neuroimage.2007.07.007.

15. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. Ann Stat 2001;29:1165-1188.

16. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. New York, NY: The Guilford Press, 2013.

17. Gaynor SM, Schwartz J, Lin X. Mediation analysis for common binary outcomes. Stat Med 2019;38:512-529. doi: 10.1002/sim.7945.