Brain abnormalities in survivors of COVID-19 after 2-year recovery: a functional MRI study

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Summary

Background A variety of symptoms, particularly cognitive, psychiatric and neurological symptoms, may persist for a long time among individuals recovering from COVID-19. However, the underlying mechanism of these brain abnormalities remains unclear. This study aimed to investigate the long-term neuroimaging effects of COVID-19 infection on brain functional activities using resting-state functional magnetic resonance imaging (rs-fMRI).

Methods Fifty-two survivors 27 months after infection (mild-moderate group: 25 participants, severe-critical: 27 participants), from our previous community participants, along with 35 healthy controls, were recruited to undergo fMRI scans and comprehensive cognitive function measurements. Participants were evaluated by subjective assessment of Cognitive Failures Questionnaire-14 (CFQ-14) and Fatigue Scale-14 (FS-14), and objective assessment of Montreal Cognitive Assessment (MoCA), N-back, and Simple Reaction Time (SRT). Each had rs-fMRI at 3T. Measures such as the amplitude of low-frequency fluctuation (ALFF), fractional amplitude of low-frequency fluctuations (fALFF), and regional homogeneity (ReHo) were calculated.

Findings Compared with healthy controls, survivors of mild-moderate acute symptoms group and severe-critical group had a significantly higher score of cognitive complains involving cognitive failure and mental fatigue. However, there was no difference of cognitive complaints between two groups of COVID-19 survivors. The performance of three groups was similar on the score of MoCA, N-back and SRT. The rs-fMRI results showed that COVID-19 survivors exhibited significantly increased ALFF values in the left putamen (PUT.L), right inferior temporal gyrus (ITG.R) and right pallidum (PAL.R), while decreased ALFF values were observed in the right superior parietal gyrus (SPG.R) and left superior temporal gyrus (STG.L). Additionally, decreased ReHo values in

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the right precentral gyrus (PreCG.R), left postcentral gyrus (PoCG.L), left calcarine fissure and surrounding cortex (CAL.L) and left superior temporal gyrus (STG.L). Furthermore, significant negative correlations between the ReHo values in the STG.L, and CFQ-14 and mental fatigue were found.

Interpretation This long-term study suggests that individuals recovering from COVID-19 continue to experience cognitive complaints, psychiatric and neurological symptoms, and brain functional alteration. The rs-fMRI results indicated that the changes in brain function in regions such as the putamen, temporal lobe, and superior parietal gyrus may contribute to cognitive complaints in individuals with long COVID even after 2-year infection.

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Keywords: Brain abnormalities; Cognitive function; fMRI; Long COVID

Research in context

Evidence before this study

We conducted a comprehensive search on PubMed for studies investigating long-term brain function changes among COVID-19 survivors, published up to March 11, 2024, without any language restrictions. The search terms we used were ("COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" OR "novel coronavirus") AND ("recovery" OR "discharge") AND ("cognitive impairment" OR "brain fog"). To our knowledge, most of the studies available only assess cognitive function through a single method, such as symptom questionnaire, cognitive function measurements, or neuroimaging studies. One study that utilized rs-fMRI at a 1-year follow-up discovered altered amplitudes of ALFF in certain brain regions among COVID-19 survivors, including the left precentral gyrus, angular gyrus, thalamus, and others. However, it should be noted that this study had a relatively small sample size and only examined a single index of spontaneous brain activity. In conclusion, due to the limited number of long-term follow-up neuroimaging studies, further exploration is necessary to understand the mechanisms underlying the brain damage associated with COVID-19 infection.

Added value of this study

We conducted exploration of the changes in brain imaging manifestations among COVID-19 survivors 27 months after infection, compared to a healthy control group. The fMRI study identified specific brain functional regions that were susceptible to COVID-19, including the putamen, temporal lobe, and superior parietal gyrus, which are involved in cognitive function and emotional regulation. Moreover, significant correlations were found between the ReHo values in the STG.L and cognitive failure and mental fatigue. These findings contribute neuroimaging information to the understanding of the mechanisms of long COVID, which may offer potential targets for the treatment and intervention of long COVID.

Implications of all the available evidence

Compared with healthy controls, cognitive complaints, psychiatric and neurological symptoms were more common among COVID-19 survivors several months after recovery. Notably, significant differences were reported in ALFF and ReHo values in brain regions associated with cognitive function when comparing survivors to healthy controls. Additionally, we discovered correlations between cognitive function indices and spontaneous brain function, suggesting the presence of persistent brain abnormalities even after 2-year infection. Future research should involve long-term follow-up studies to investigate the cognitive function trajectory, as well as the mechanisms of brain damage and SARS-CoV-2 infection.

Introduction

Long COVID or post-COVID syndrome is common among people who recovered from COVID-19 and often involves a variability of symptoms that may persist for a long time.[1,2] Specifically, COVID-19 is associated with a range of neurological, cognitive and mental health symptoms both acutely and chronically, including brain fog, inability to concentrate, fatigue, anxiety, depression, and sleep disorders.[3–6] However, the underlying pathophysiology or mechanism of neuropsychiatric symptoms related to long COVID remains unclear.

Investigations of the long-term impact of COVID-19 infection on cognitive function reveal that deficits can be seen in the global cognition and certain domains of cognition.[7–11] A multicenter cross-sectional study demonstrated that patients with post-COVID-19 conditions (PCC) have pronounced cognitive slowing.[12] A large

observational study in England found that people with COVID-19 symptoms had greater deficits in global cognition than those never infected, and additionally, larger cognitive deficits were observed in participants infected with the original virus or the α variants and in those who had been hospitalized.[13] Moreover, a study using a series of neuropsychological tests at 7-month after COVID-19 infection revealed prominent deficits in processing speed, executive functioning, phonemic fluency and category fluency, memory encoding, and memory recall.[14] Previous studies revealed that executive functioning and memory were vulnerable to COVDI-19 infection, but the follow-up time of these studies were relatively shorter.[10–13] Therefore, the long-term follow-up investigations for global and specific domains of cognition and with healthy control group are needed.

With respect to neuroimaging studies, most have identified brain abnormalities during both the acute and convalescent phases of COVID-19.[15–18] MRI scans revealed signal intensity abnormalities in 37% of COVID-19 patients during the acute phase,[15] while brain CT scans showed acute lesions in 9 out of 23 cases among severe COVID-19 ICU patients.[16] Moreover, several studies shed light on brain structural changes in recovery from COVID-19 infection. A 3-month follow-up study reported a decrease in cortical thickness and cerebral blood flow, with more severe changes in white matter microstructure, particularly in the frontal and limbic systems, among COVID-19 patients.[19] A prospective study conducted at one and two years after discharge indicated that the decreased gray matter volume (GMV) in the left middle frontal gyrus, inferior frontal gyrus of the operculum, right middle temporal gyrus, and inferior temporal gyrus returned to normal at the second year, but the GMV in the left temporal lobe was aggravated.[20] A resting-state fMRI at 1-year follow-up found that COVID-19 survivors exhibited altered amplitudes of low-frequency fluctuation (ALFF) in certain brain regions, including the left precentral gyrus, angular gyrus, and thalamus.[21] However, this study had a relatively small sample size and only assessed a single index of spontaneous brain activity. The underlying mechanisms contributing to the neuropsychiatric manifestations and cognitive complaints in COVID-19 are likely a combination of multiple factors, including viral neurotropism, widespread systemic inflammation, and psychological burden of the pandemic across the world.[22,23] In summary, due to the lack of long-term follow-up neuroimaging studies, further exploration is needed to understand the mechanisms underlying the brain damage associated with COVID-19 infection.[24]

This study investigated the long-term cognitive, psychiatric, and neurological effects of COVID-19 and explored the brain alteration and imaging mechanisms using resting-state fMRI two years after infection.

Methods

Study design and participants

The epidemiology survey of COVID-19 survivors with laboratory-confirmed or clinician-diagnosed cases was conducted in Wuhan City, Hubei Province, from October 12 to November 19, 2021.[25] The participants' characteristics of this survey are displayed in Table S1. Based on the community cohort, COVID-19 survivors were recruited to participate the fMRI neuroimaging study from February to September of 2022. To minimize potential sources of bias or confounds, the healthy control participants were recruited from the same community to match the age range, sex proportion, and education level.

The inclusion criteria for both groups included 18–65 years of age, having a middle school or higher, who were able to understand and complete the cognitive function tests. COVID-19 survivors were required to provide a confirmed COVID-19 diagnosis from medical records, while healthy controls were required to have no history of COVID-19 symptoms, and no history of a positive PCR test or a positive SARS-CoV-2 antigen test. Exclusion criteria for both groups included (1) any current or history of psychiatric diseases or neurological diseases that may confound study measures (e.g., dementia, Parkinson's disease, traumatic brain injury or stroke); (2) pregnancy or breastfeeding; (3) contraindications for MRI studies including electronic implants, metallic objects, or severe claustrophobia; (4) MRI scans demonstrating space-occupying lesions.

Written informed consent was obtained from all participants. This study received approval from the ethics committee of Peking University Sixth Hospital (Institute of Mental Health).

Measurements

Demographic characteristics included sex, age, and education. Smoking, drinking, physical comorbidities, a history of mental disorders, COVID-19 vaccination status, total duration of hospitalization and time from diagnosis to follow-up were collected. The severity of acute illness classified by the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment was also collected.[26]

Cognitive function was assessed by the abbreviated Cognitive Failures Questionnaire-14 (CFQ-14) and the validated Chinese version of MoCA. The CFQ-14 measures daily life cognitive failures, which has 14 questions with a 5-point Likert scale resulting in a factored score ranging from 0 to 100, with a score of ≥43 indicating cognitive failures.[27,28] The MoCA evaluates global cognitive function with a total score of 0–30, which was interpreted as follows: normal cognitive function (22–30), mild cognitive impairment (19–21) and dementia (0–18).[29]

We designed 3 N-back tasks (0-back, 1-back and 2-back) to assess working memory (1000 ms stimulus

presentation period, 2000 ms response period, and 30 repeats for each task).[30] Briefly, during the 0-back task, participants pressed a button when the target number flashed on the screen, and during the 1-back and 2-back tasks, participants responded to the occurrence of target numbers that matched the previous screen (1-back) or occurred two screens previously (2-back). The accuracy rate and average reaction time were calculated. We designed Simple Reaction Time (SRT) task to assess proceed speed (stimuli repeated in 30 times).[31] In the SRT task, participants were asked to respond to the appearance of a target on the screen by pressing a button, and the average reaction time was calculated.

The Fatigue Scale-14 (FS-14) is a standardized questionnaire reflecting physical and mental fatigue and comprises 14 questions. Each question has two options (yes or no), resulting in a total score ranging from 0 to 14. The physical fatigue dimension is composed of the first eight items and the mental fatigue dimension is composed of the last six items. Higher scores indicate a higher level of chronic fatigue.[32,33]

For all participants, psychiatric symptoms included depression symptoms measured by the Patient Health Questionnaire-9 (PHQ-9),[34] anxiety symptoms measured by the Generalized Anxiety Disorder-7 (GAD-7),[35] insomnia symptoms measured by the Insomnia Severity Index (ISI),[36] and PTSD symptoms measured by the PTSD checklist for DSM-5 (PCL-5).[37] The total scores of these scales were interpreted as follows: PHQ-9, normal (0–4), mild (5–9), moderate to severe (10–27) depression symptoms; GAD-7, normal (0–4), mild (5–9), moderate to severe (10–21) anxiety symptoms; ISI, normal (0–7), subthreshold (8–14), moderate to severe (15–28) insomnia symptoms. We used the following cut-off scores to define the presence of depression (PHQ-9 ≥10), anxiety (GAD-7 ≥10), insomnia (ISI ≥15), or PTSD symptoms (PCL-5 ≥33). The neurological symptoms were assessed by a symptom questionnaire including self-report items related to smell disorder, taste disorder, headache and dizziness.

fMRI image acquisition and preprocessing

All scans were acquired on a 3T MR Scanner (GE SIGNA Architect 3.0T, Germany). The MRI scanning sequences included three-dimensional magnetization-prepared rapid acquisition gradient echo (3D-MPRAGE), and BOLD fMRI. The 3D-MPRAGE scanning parameters were as follows: 192 sagittal slices, repetition time = 2530 ms, echo time = 2.98 ms, flip angle = 7°, voxel size = 1 × 1 × 1 mm, slice thickness = 1 mm, field of view = 256 × 256 mm. The BOLD parameters were: 33 axial slices, repetition time = 2000 ms, echo time = 30 ms, flip angle = 90°, voxel size = 3.5 × 3.5 × 4.2 mm, slice thickness = 4.2 mm, field of view = 224 × 224 mm.

MRI data were preprocessed using Data Processing Assistant for Resting-State fMRI (DPABI, 4.3, Advanced edition) software (http://rfmri.org/dpabi) based on MATLAB 2018a.[38] The specific process was as follows: (1) removal of the initial 10 scanning volumes to allow for steady-state magnetization; (2) slice timing and realignment; (3) registering the resting-state image with the T1-structural image for each participant; (4) nuisance covariates were regressed out, including the 24 Friston parameters for head motion, white matter signals, and cerebrospinal fluid signals; (5) spatially normalized resting-state and T1-structural images were converted to Montreal Neurological Institute (MNI) space; (6) the resampled image was spatially smoothed using a 6-mm full-width half-maximum Gaussian kernel to reduce spatial noise.

Only fMRI data with <3 mm translations, <3° rotations, and mean FD values less than 0.5 during each scan were included in the final analyses. While the amplitude of low-frequency fluctuations (ALFF) and fractional amplitude of low-frequency fluctuations (fALFF) were calculated after preprocessing based on smoothed data, regional homogeneity (ReHo) were calculated based on unsmoothed data.[39]

Statistical analysis

Continuous variables were presented as mean (SD) for normal distribution or median (IQR) for non-normal distribution. Binary and categorical variables were presented as counts and percentages. Demographic characteristics, psychiatric and neurological symptoms, and cognitive function were compared among the mild-moderate, severe-critical and healthy control groups using analysis of variance (ANOVA) for normal distribution, nonparametric Kruskal–Wallis tests for non-normal distribution. Post hoc tests were using Bonferroni correction when there is significant difference for the three groups. The χ^2 tests and Fisher's exact test were used to compare the difference for categorical variables. All tests were two-tailed and p values of less than 0.05 were considered statistically significant. These above analyses used Stata MP version 16.

Differences in ALFF, fALFF and ReHo values of survivors and healthy controls were examined in DAPABI software using 2-sample t tests, threshold at ≥60 voxel clusters, based on the results of cognitive, psychiatric and neurological symptoms. Only corrected p values at the cluster level, with a false discovery rate (FDR) <0.05, were considered significant. The age, gender, education level, and head movement parameters of the two groups were used as covariates.

For normally distributed data, Pearson correlation analysis was applied to explore correlations between the ALFF and ReHo values in several brain regions and the scores for CFQ-14, FS-14, mental fatigue and physical fatigue, with Spearman correlation analysis used for non-normally distributed data. Multiple comparison correction was through FDR correction. Significance levels were set at $p < 0.05$.

Role of the funding source
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Results
Participants characteristics
In the study, a total of 75 COVID-19 survivors and 56 healthy controls were initially contacted by phone. However, only 69 survivors and 40 healthy participants met the study criteria, completed the behavioral studies, and underwent fMRI scans (referred to as total participants). Ultimately, the final analysis included 52 COVID-19 survivors including 25 mild-moderate survivors (mild: 10, moderate: 15) and 27 severe-critical survivors (severe 23, critical: 4) and 35 healthy controls with useable fMRI scans (referred to as fMRI participants) (see Fig. 1).

The two group survivors and healthy controls had similar age, sex proportion, education levels, drinking habits, and histories of physical diseases and mental disorders. Among all participants, the hospitalized survivors were diagnosed [mild-moderate: 828.00 (808.00, 865.00); severe-critical: 837.50 (793.00, 864.00)] (~27 months) days ago and the median length of hospital stay for the survivors was [mild-moderate: 22.50 (16.00, 41.50); severe-critical: 33.00 (23.00, 50.00)] days. The proportion of COVID-19 vaccination was lower among the survivors compared to the controls. More details of the participants characteristics are displayed in Table 1 and Table S2.

Cognitive function, psychiatric and neurological symptoms in COVID-19 survivors and control group
There were significant differences of cognitive function among the mild-moderate, severe-critical, and control groups, including cognitive failure assessed by CFQ-14 [mild-moderate: 32.14 (23.21, 50.00) vs. severe-critical: 30.36 (19.64, 67.86) vs. healthy controls: 19.64 (8.93, 33.93), $p = 0.006$], and fatigue (including physical fatigue and mental fatigue) assessed by FS-14 [10.00 (7.00, 12.00) vs. 10.00 (6.00, 13.00) vs. 5.00 (3.00, 8.00), $p < 0.001$]. In post hoc tests, compared with the healthy controls, both the mild-moderate and severe-critical groups had a higher level of cognitive complaints, including cognitive failure (mil-moderate vs. healthy control: $p = 0.007$, severe-critical vs. healthy control: $p = 0.002$), and fatigue (mil-moderate vs. healthy control: $p < 0.001$, severe-critical vs. healthy control: $p < 0.001$), but no significant differences of cognitive complaints were found between the mild-moderate and severe-critical group (cognitive failure: $p = 0.339$, fatigue: $p = 0.498$). Additionally, three groups' performance was similar on the objective function measurements including MoCA, N-back and SRT. (see Table 2 and Table S2).

Compared with the healthy controls, both mild-moderate group and severe-critical group had a higher rate of the psychiatric symptoms, including depression symptoms (mild-moderate: 80.00% vs. severe-critical: 74.07% vs. healthy controls: 37.14%, $p = 0.001$), insomnia symptoms (68.00% vs. 74.07% vs. 31.43%, $p = 0.001$), anxiety symptoms (60.00% vs. 59.26% vs. 25.71%, $p = 0.008$), PTSD symptoms (24.00% vs. 22.22% vs. 0.00%, $p = 0.009$), and neurological symptoms including smell disorder (60.00% vs. 59.26% vs. 14.29%, $p < 0.001$), and taste disorder (48.00% vs. 40.74% vs. 2.86%, $p < 0.001$). The symptoms of headache (20.00% vs. 37.04% vs. 14.29%, $p = 0.099$) and dizziness (24.00% vs. 18.52% vs. 11.43%, $p = 0.436$) was not different in three

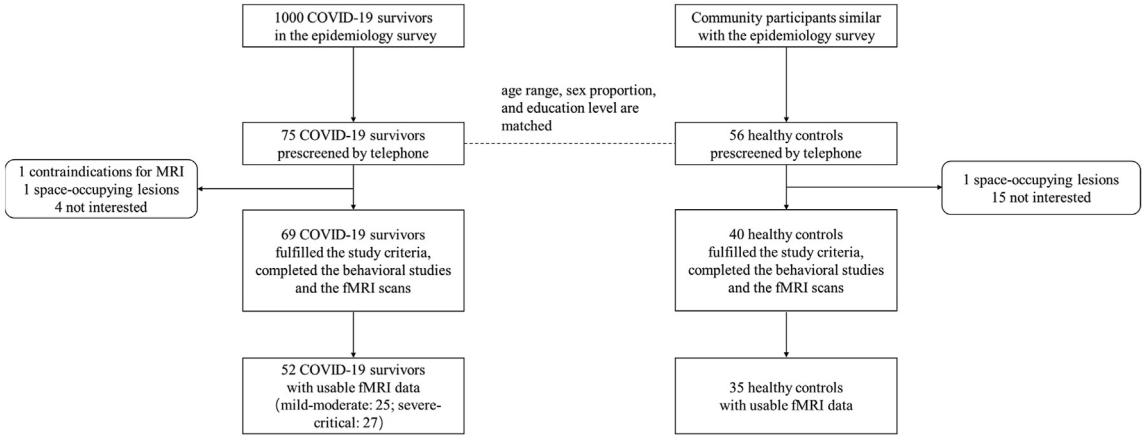

Fig. 1: Participants flow diagram.

Variables	COVID-19 survivors (N = 52)		Healthy controls (N = 35)	p value
	Mild-moderate (N = 25)	Severe-critical (N = 27)		
Age	53.12 (6.73)	53.93 (7.55)	50.83 (7.74)	0.234
Sex				0.374
Men	10 (40.00%)	14 (51.85%)	12 (34.29%)	
Women	15 (60.00%)	13 (48.15%)	23 (65.71%)	
Education				0.225
Middle school	6 (24.00%)	3 (11.11%)	5 (14.29%)	
High school	8 (32.00%)	15 (55.56%)	11 (31.43%)	
College or higher	11 (44.00%)	9 (33.33%)	19 (54.29%)	
Smoking				0.017
Never-smoker	20 (80.00%)[a]	23 (85.19%)[b]	25 (71.43%)	
Former smoker	5 (20.00%)	3 (11.11%)	2 (5.71%)	
Current smoker	0 (0.00%)	1 (3.70%)	8 (22.86%)	
Drinking				0.386
Never-drinker	23 (92.00%)	23 (85.19%)	28 (80.00%)	
Former drinker	1 (4.00%)	3 (11.11%)	2 (5.71%)	
Current drinker	1 (4.00%)	1 (3.70%)	5 (14.29%)	
History of physical diseases	12 (48.00%)	20 (74.07%)	16 (45.71%)	0.058
History of mental disorders	1 (4.00%)	1 (3.70%)	0 (0.00%)	0.501
Vaccination status for SARS-CoV-2				0.063
Yes	21 (84.00%)	24 (88.89%)	35 (100.00%)	
No	4 (16.00%)	3 (11.11%)	0 (0.00%)	
Total duration of hospitalization, days	22.50 (16.00, 41.50)	33.00 (23.00, 50.00)		0.143
Time from diagnosis to follow-up, days	828.00 (808.00, 865.00)	837.50 (793.00, 864.00)		0.706

[a]There was significant difference between the mild-moderate group and the healthy controls. [b]There was significant difference between the severe-critical group and the healthy controls.

Table 1: **The characteristics of the participants included in the fMRI analyses.**

groups. In post hoc tests, the two survivors had higher depression, anxiety, insomnia, PTSD symptoms, smell and taste disorders, compared with the healthy controls. However, there was no difference of psychiatric and neurological symptoms between two survivor groups (see Table 2).

Results of rs-fMRI and correlation analysis

Since there are no significant differences of cognitive function between mild-moderate survivor group and severe-critical survivor group, we integrated two survivor participants into the survivors group, which was compared with healthy controls in the fMRI data analysis. Compared with the healthy controls, the COVID-19 survivors demonstrated significantly increased ALFF values in the left putamen (PUT.L), right inferior temporal gyrus (ITG.R), and right pallidum (PAL.R). On the contrary, the ALFF values in survivors in the right superior parietal gyrus (SPG.R) and left superior temporal gyrus (STG.L) were lower than those in controls. In addition, the survivors had decreased ReHo values in the right precentral gyrus (PreCG.R), left postcentral gyrus (PoCG.L), left calcarine fissure and surrounding cortex (CAL.L) and left superior temporal gyrus (STG.L) compared with the controls. More details are provided in Table 3 and Fig. 2.

Fig. 3 showed the association between ReHo values and cognitive function. After correcting for multiple comparisons, there was negative correlations between the ReHo values in the STG.L and the CFQ-14 ($r = -0.38$, $p = 0.04$) and mental fatigue ($r = -0.40$, $p = 0.04$). See Table S3 and Table S4 for the correlations between ALFF and ReHo values and cognitive function.

Discussion

Based on the fMRI neuroimaging study, we discovered that COVID-19 survivors commonly experienced cognitive complaints, psychiatric, and neurological symptoms. In addition, we conducted a comparative analysis of brain imaging manifestations in COVID-19 survivors more than 2 years after infection, as compared to a healthy control group. The fMRI study identified specific brain functional regions that were particularly susceptible to COVID-19, including the putamen, temporal lobe, and superior parietal gyrus, along with other brain regions. These regions have a comprehensive impact on cognitive function and emotional regulation. Furthermore, we found significant negative correlations between the ReHo values in the STG.L and cognitive failure and mental fatigue. These findings provide valuable neuroimaging insights

Variables	COVID-19 survivors (N = 52)		Healthy controls (N = 35)	p value
	Mild-moderate (N = 25)	Severe-critical (N = 27)		
Scores for CFQ-14	32.14 (23.21, 50.00)[a]	30.36 (19.64, 67.86)[b]	19.64 (8.93, 33.93)	0.006
Cognitive failure by CFQ-14				0.015
Normal	14 (56.00%)[a]	18 (66.67%)[b]	31 (88.57%)	
Cognitive failure	11 (44.00%)	9 (33.33%)	4 (11.43%)	
Fatigue				
Total scores	10.00 (7.00, 12.00)[a]	10.00 (6.00, 13.00)[b]	5.00 (3.00, 8.00)	<0.001
Physical fatigue	7.00 (5.00, 8.00)[a]	6.00 (3.00, 8.00)[b]	4.00 (1.00, 5.00)	<0.001
Mental fatigue	4.00 (2.00, 5.00)[a]	4.00 (3.00, 5.00)[b]	2.00 (1.00, 3.00)	<0.001
Scores for MoCA	25.50 (22.50, 27.00)	26.00 (23.00, 27.00)	26.00 (24.00, 27.00)	0.720
Visuospatial/executive function	4.00 (3.00, 5.00)	4.50 (4.00, 5.00)	5.00 (4.00, 5.00)	0.502
Naming	3.00 (3.00, 3.00)	3.00 (2.00, 3.00)	3.00 (3.00, 3.00)	0.672
Attention	6.00 (5.00, 6.00)	6.00 (6.00, 6.00)	6.00 (6.00, 6.00)	0.744
Language	2.00 (1.00, 2.00)	3.00 (2.00, 3.00)	2.00 (1.00, 3.00)	0.042
Abstraction	1.50 (1.00, 2.00)	1.00 (1.00, 2.00)	2.00 (0.00, 2.00)	0.960
Delayed memory	3.00 (1.47)	3.15 (1.38)	2.80 (1.18)	0.585
Orientation	6.00 (6.00, 6.00)	6.00 (6.00, 6.00)	6.00 (6.00, 6.00)	0.854
Mild cognitive impairment by MoCA				0.537
Normal	19 (79.17%)	23 (88.46%)	31 (88.57%)	
Mild cognitive impairment[c]	5 (20.83%)	3 (11.54%)	4 (11.43%)	
N-back accuracy rate				
0-back	100.00 (100.00, 100.00)	100.00 (96.88, 100.00)	100.00 (96.88, 100.00)	0.465
1-back	96.97 (93.94, 100.00)	93.94 (90.91, 96.97)	96.97 (90.91, 100.00)	0.568
2-back	81.09 (11.82)	76.74 (13.18)	82.92 (12.06)	0.222
N-back reaction time				
0-back	558.92 (120.59)	598.10 (101.00)	617.36 (95.82)	0.130
1-back	695.63 (595.28, 788.30)	766.24 (671.00, 852.35)	723.53 (663.77, 875.93)	0.423
2-back	918.67 (788.25, 971.16)	826.73 (773.19, 1086.78)	847.89 (737.26, 1021.42)	0.754
SRT	268.97 (36.43)	256.23 (43.80)	281.20 (48.36)	0.140
Psychiatric symptoms				
Depression symptoms (PHQ-9)	20 (80.00%)[a]	20 (74.07%)[b]	13 (37.14%)	0.001
Insomnia symptoms (ISI)	17 (68.00%)[a]	20 (74.07%)[b]	11 (31.43%)	0.001
Anxiety symptoms (GAD-7)	15 (60.00%)[a]	16 (59.26%)[b]	9 (25.71%)	0.008
PTSD symptoms (PCL-5)	6 (24.00%)[a]	6 (22.22%)[b]	0 (0.00%)	0.009
Neurological symptoms				
Smell disorder	15 (60.00%)[a]	16 (59.26%)[b]	5 (14.29%)	<0.001
Taste disorder	12 (48.00%)[a]	11 (40.74%)[b]	1 (2.86%)	<0.001
Headache	5 (20.00%)	10 (37.04%)	5 (14.29%)	0.099
Dizziness	6 (24.00%)	5 (18.52%)	4 (11.43%)	0.436

[a]There was significant difference between the mild-moderate group and the healthy controls. [b]There was significant difference between the severe-critical group and the healthy controls. [c]There was one participant who were classified as dementia by MoCA in severe-critical group.

Table 2: **Differences of cognitive function, psychiatric and neurological symptoms between COVID-19 survivors and healthy controls.**

into the cognitive complaints of long COVID, thereby offering potential targets for treatment and intervention in individuals with brain fog of long COVID.

Consistent with our findings, several studies have reported that fatigue, cognitive dysfunction (brain fog, memory issues, attention disorder) and sleep disturbances appeared to be key features of post-COVID-19 syndrome, and psychiatric manifestations (anxiety, depression, and insomnia) were common and increased significantly in prevalence over time.[23,40–42] Although cognitive complaints including cognitive failure and mental fatigue were common in the survivors, they had relatively normal performance on the cognitive function assessments. While subjective cognitive impairment like cognitive failure and mental fatigue is the first instance of an objective cognitive deficit, it may not necessarily indicate a clinically significant impairment in cognition. Our findings concurred with a long COVID study, which reported that despite the subjective complaints, the participants with post-COVID conditions had similar performance on the NIHTB-CB as the healthy controls.[43] In contrast, a UK multicenter study

Brain regions	MNI coordinates			Peak intensity	Cluster size
	x	y	z		
ALFF					
SPG.R	3	−72	60	−5.84	139
PUT.L	−27	−9	−3	5.27	124
ITG.R	54	−33	−18	5.02	97
PAL.R	24	−3	−6	5.37	62
STG.L	−42	−36	18	−6.34	61
ReHo					
PreCG.R	42	−21	60	−5.57	693
PoCG.L	−15	−51	66	−5.73	538
CAL.L	0	−87	9	−4.98	193
STG.L	−36	−30	15	−6.77	116

SPG.R: the right superior parietal gyrus; PUT.L: the left putamen; ITG.R: the right inferior temporal gyrus; PAL.R: the right pallidum; STG.L: the left superior temporal gyrus; PreCG.R: the right precentral gyrus; PoCG.L: the left postcentral gyrus; CAL.L: the left calcarine fissure.

Table 3: **Significant ALFF and ReHo differences between COVID-19 survivors and healthy controls.**

identified pronounced cognitive slowing assessed by objective assessments.[13] Another study indicated that impairments in executive functioning and memory were predominant among patients 7 months after diagnosis of COVID-19.[14] This discrepancy may be explained by the fact that cognitive function measurements we employed were not extensive to assess attention, executive functioning and other cognitive function, or we had longer follow-up times. The recent study indicated that blood–brain barrier disruption and sustained systemic inflammation may be related to long COVID-associated cognitive impairment.[44]

ALFF values in the PUT.L and PAL.R were greater in the COVID-19 survivors than in the healthy controls, paralleled with a 1-year follow-up fMRI study, which found that ALFF values in the left putamen were greater than those in the healthy controls.[21] The putamen, as part of the basal ganglia, plays a critical role in motor execution and learning.[45] Recent data also suggests its involvement in learning and memory processes not

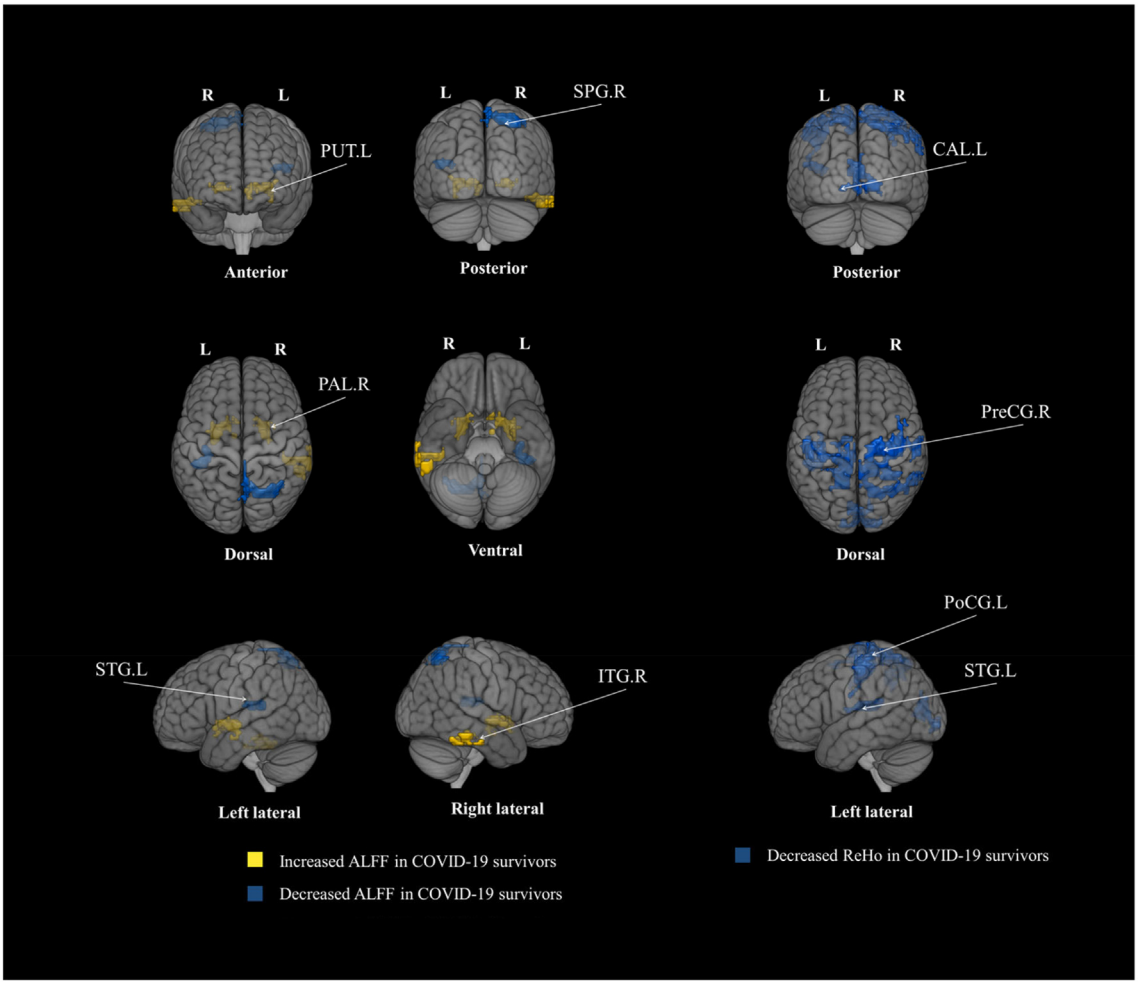

Fig. 2: Significant ALFF and ReHo differences between COVID-19 survivors and healthy controls.

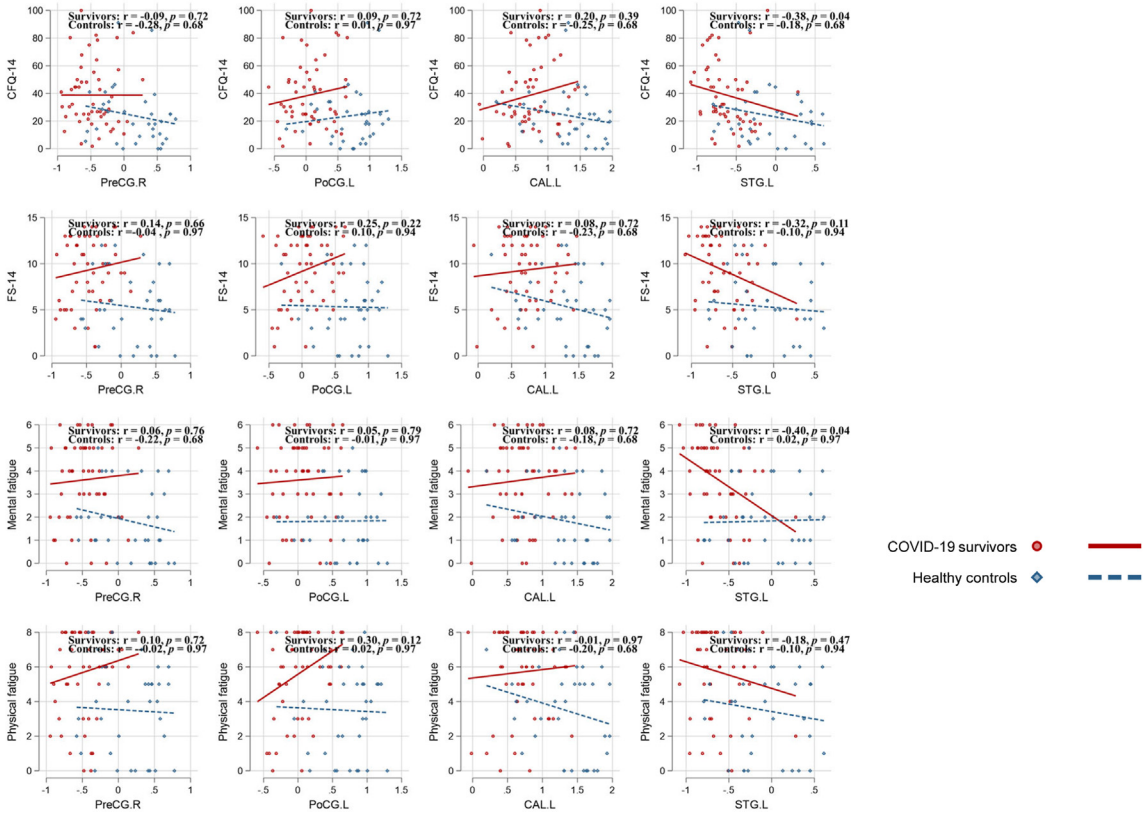

Fig. 3: Correlations between ReHo values and cognitive function.

directly related to motor functioning.[45] Consistent with our findings, a task-fMRI study indicated that both right insula and right putamen-based network connectivity patterns reflected cognitive failure across all tasks and could underpin subjective experience of cognitive failure.[46] Supporting this abnormal function in the putamen, decreased thickness in the left putamen in a 3-month follow up of the COVID-19 survivors was reported, which may suggest damages in the putamen.[19] We speculated that the cause of our findings may be related to the compensatory repair of brain tissue, but the specific underlying mechanism behind the impaired putamen remains unclear.

Our study revealed various degrees of damage to multiple regions of the temporal lobe involving STG.L and ITG.R in COVID-19 survivors, which is involved in emotional regulation, sensory processing, memory storage and retrieval, and language comprehension.[47] Previous evidences suggested that damages in STG may resulted to various cognitive impairment disease like subjective cognitive impairment, mild cognitive impairment and dementia.[48,49] Moreover, we also found that the ReHo values in the STG.L were negatively correlated with the CFQ-14 and mental fatigue, which indicated cognitive complaints including cognitive failure and mental fatigue may result from the functional alteration in the STG.L among COVID-19 survivors. Our findings of abnormal functional activity in the STG align with these previous studies, and a structural MRI study in COVID-19 survivors also reported decreased cortical thickness in the STG compared to healthy controls at 3 months after recovery.[19] Regarding ITG, our data showed increased ALFF values in this region, which is consistent with findings from a one-year follow-up resting-state fMRI study of COVID-19 survivors.[21]

Our study also indicated a significant association between COVID-19 and decreased spontaneous brain activity in SPG.R. Superior parietal cortex plays an important role in visuospatial and attentional processing, and working memory.[50,51] Additionally, a review on COVID-19 cognitive impairment reported that the survivors appeared to experience cognitive impairment in memory, attention and executive function, which may indicate more brain damage.[52] Our findings align with a recent Mendelian randomization study that suggested a nominal association between the severe COVID-19 phenotype and reduced cortical surface area in the superior parietal gyrus, pericalcarine and parahippocampal gyrus.[53] Taken together, these evidences

indicated that the superior parietal gyrus may be vulnerable to COVID-19 infection, but the precise mechanism is unclear.

The strengths of our study lie in its comprehensive investigation of cognitive function, psychiatric and neurological symptoms, and brain function among COVID-19 survivors based on a fMRI study after 27-month infection. However, our study does have several limitations. Firstly, due to the lack of psychiatric and neurological symptoms, cognitive function measurements and fMRI data which were collected before the COVID-19 infection and baseline survey, we cannot draw a clear conclusion as to whether the changes in cognitive function and spontaneous brain activity were attributed to the infection of SARS-CoV-2. Secondly, we cannot completely rule out that there may be asymptomatic subjects in the control group who have been infected, but we have conducted strict screening and tried our best to exclude these patients. Last but not least, due to the lack of extensive cognitive function measurements, we only found the association between cognitive complaints and STG dysfunction, but whether cognitive impairment assessed by objective cognitive function measurements can be resulted from COVID-19 infection need to be further explored.

In conclusion, our study revealed that COVID-19 survivors commonly experienced psychiatric symptoms, neurological symptoms and cognitive complaints even 2 years after recovery. We observed significant differences in ALFF and ReHo values in brain regions associated with cognitive function when comparing survivors to healthy controls. Additionally, we found correlations between cognitive function indices and spontaneous brain function, indicating the persistence of brain impairment even after 2 years of infection. Long-term follow up studies are needed to further explore the trajectory of psychiatric symptoms, neurological symptoms and cognitive function, and understand the mechanisms of brain damage and SARS-CoV-2 infection.

Contributors

LL, and YB proposed the topic and main idea; YZ, QL, HM, NZ, SS, PL, XL, and YB designed the questionnaire, YZ, QL, ZJ, HM, SW, YG, PL, XL, YT, YH, YLPW, JS, XL, YB, and LL contributed to recruiting participants and the data collection. YZ, NZ, YG, PL, XL analyzed the data and wrote the initial draft of the manuscript; YZ, QL, NZ, PL, XL, WL, YG, PW, GW, KY, LS, WY, XZ, YMW, YXW, JS, YB, and LL commented on and revised the manuscript; LL, YB, XL, and YMW finalized the manuscript. All authors have read and agreed to the published version of the manuscript.

Data sharing statement

Unidentified data can be made available upon request.

Declaration of interests

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101086.

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