Heliyon 10 (2024) e34941

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Impact of COVID-19 on brain connectivity and rehabilitation outcome after stroke

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Stroke
Magnetic resonance imaging
Diffusion tensor imaging
Recovery of function

ABSTRACT

Background: Coronavirus disease (COVID-19) may induce neurological issues, impacting brain structure and stroke recovery. Limited studies have explored its effects on post-stroke rehabilitation. Our study compares brain structure and connectivity, assessing rehabilitation outcomes based on pre-stroke COVID-19 infection.

Methods: A retrospective analysis of 299 post-stroke rehabilitation cases from May 2021 to January 2023 included two groups: those diagnosed with COVID-19 at least two weeks before stroke onset (COVID group) and those without (control group). Criteria involved first unilateral supratentorial stroke, <3 months post-onset, initial MR imaging, and pre- and post-rehabilitation clinical assessments. Propensity score matching ensured age, sex, and initial clinical assessment similarities. Using lesion mapping, tract-based statistical analysis, and group-independent component analysis MRI scans were assessed for structural and functional differences.

Results: After propensity score matching, 12 patients were included in each group. Patient demographics showed no significant differences. Analyses of MR imaging revealed no significant differences between COVID and control groups. Post-rehabilitation clinical assessments improved notably in both groups, however the intergroup analysis showed no significant difference.

Conclusions: Previous COVID-19 infection did not affect brain structure or connectivity nor outcomes after rehabilitation.

1. Introduction

Coronavirus disease (COVID-19) induces various neurological dysfunctions, impacting brain structure and function. Neurologic manifestations may be caused directly by CNS invasion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or by systemic immune responses to infection [1–3]. Direct brain invasion by SARS-CoV-2 may cause microstructural damage that affects stroke recovery. Previous studies have shown that the coexistence of COVID-19 and stroke is associated with worse patient outcomes,

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https://doi.org/10.1016/j.heliyon.2024.e34941
Received 7 March 2024; Received in revised form 5 July 2024; Accepted 18 July 2024
Available online 19 July 2024

Abbreviations

DTI	diffusion tensor imaging
rfMRI	resting state functional MRI
FMA	Fugl-Meyer motor assessment
MMSE	Korean version of the Mini-Mental Status Examination
FAC	functional ambulation category
MBI	Korean version of the modified Barthel index

including longer ICU stays and increased mortality [4–6]. However, studies on the effects of SARS-CoV-2 infection on recovery during post-stroke rehabilitation are lacking. Structural and functional changes in the brain caused by SARS-CoV-2 have also been studied by comparing brain structure, connectivity, and EEG waveforms in healthy and infected individuals [1,7–11], but no studies have examined changes in brain imaging caused by SARS-CoV-2 in stroke patients. Therefore, we aimed to compare brain structure and connectivity using T1-weighted, diffusion tensor imaging (DTI), functional connectivity using resting-state functional MRI (rfMRI), and changes in clinical assessments (motor, cognition, locomotion, and activities of daily living) after rehabilitation in stroke patients with or without a history of COVID-19 infection.

2. Methods

2.1. Study design and patients

The Institutional Review Board of Severance Hospital approved the study and the requirement for informed consent was waived because of the retrospective nature of the study. Data can be obtained upon reasonable request to the corresponding author. We conducted a retrospective review of medical records for 299 patients who received inpatient rehabilitation following an acute ischemic stroke between May 2021 and January 2023. The inclusion criteria were (a) first-ever unilateral supratentorial stroke, as confirmed by magnetic resonance imaging (MRI); (b) < 3 months after stroke onset; (c) underwent T1-weighted, DTI, and rfMRI at the beginning of inpatient rehabilitation; (d) underwent clinical assessments at the beginning and after 6 weeks of inpatient rehabilitation; and (e) To exclude the effect of reduced rehabilitation due to quarantine, we recruited people who were diagnosed with COVID-19 at least 2 weeks before stroke onset (COVID group) or non-COVID-19 patients (control group). The diagnosis of COVID-19 was based on PCR results, according to World Health Organization guidelines. The exclusion criteria were (a) coexisting orthopedic, neurologic, or psychiatric conditions that may affect recovery after stroke; (b) severe neurologic symptoms that could be associated with COVID-19; or (c) COVID-19 confirmed during inpatient rehabilitation. Clinical assessments, including Fugl-Meyer motor assessment (FMA) for motor impairment, Korean version of the Mini-Mental Status Examination (MMSE) for cognition, functional ambulation category (FAC) for locomotion, and the Korean version of the modified Barthel index (MBI) for activities of daily living, were performed at the beginning and end of rehabilitation.

Twelve and sixty-four patients met the criteria for the COVID or control groups, respectively. We matched the COVID and control groups using the logit of the propensity score with a caliper width equal to 0.1 of the standardized differences [12]. The propensity scores for age, sex, FMA, MMSE, FAC, and MBI were similar between the COVID and control groups after matching.

2.2. MRI acquisition and pre-processing

All MRI scans were acquired using a 3-T MR scanner (Ingenia CX; Philips Healthcare, Best, The Netherlands). The T1-weighted images parameters were: matrix $= 192 \times 192$, field of view (FOV) $= 240 \times 240$ mm^2, slice thickness $= 1$ mm, repetition time $=$ 6.891 ms, and flip angle $= 9^\circ$. The diffusion tensor imaging (DTI) parameters were: 75 axial slices, matrix $= 112 \times 112$, FOV $= 224 \times$ 224 mm^2, slice thickness $= 2$ mm, repetition time $= 4532$ ms, flip angle $= 90^\circ$, 32 directions, and b $= 1000$ s/mm^2. The resting state functional MRI (rfMRI) were collected while the participants were directed to close their eyes and maintain stillness, using whole-brain echo planar imaging: 165 whole brain images, 80 axial slices, matrix $= 80 \times 80$, FOV $= 220 \times 209$ mm^2, slice thickness $= 3$ mm, repetition time $= 2000$ ms, and flip angle $= 90^\circ$.

Before pre-processing, all MRI scans were visually inspected by one neuroradiologist and one neurorehabilitationist (J.K. and D.H. K., respectively) with >10 years of clinical experience for the apparent artifacts because of patient's motion. No scan was excluded for excessive head motion during MRI acquisition. The DTI, rfMRI data and T1-weighted images were pre-processed using the FMRIB Software Library (FSL 5.0.10; http://www.fmrib.ox.ac.uk/fsl). The MRI images of Lt. hemispheric lesions were reversed to find the corresponding lesion area in the Rt. hemisphere for further analysis. The DTI images were corrected for geometric distortions based on the two acquisitions with opposing polarities of the phase-encode maps and for eddy current distortions via affine transformation, followed by brain extraction, to construct a fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) image in native space. The first 10 echo planar imaging time points were discarded to ensure magnetization equilibrium in the rfMRI images. The rfMRI sequences underwent correction for geometric distortions, motion correction through realignment to the middle volume of each run, spatial normalization and smoothing with a Gaussian kernel of 8 mm full-width at half maximum, 0.01 Hz high-pass temporal filtering, and grand mean intensity normalization.

3. MRI analysis

3.1. Voxel-based lesion mapping

For measurement of lesion volume and voxel-based lesion differences, one neuro-rehabilitationist (D.H.K) marked each patient's lesion on native diffusion weighted imaging using 3D Slicer software (version 5.2.1.; https://www.slicer.org) and calculated the lesion volume from all lesions [13]. Native-space lesion segmentation images were co-registered to T1-weighted images and transformed to the standard MNI space using the transformation matrix. Voxel-based lesion mapping was performed on the normalized lesion segmentation maps by using a custom MATLAB script (Mathworks, Inc, Natick, MA), with the age, sex, and lesion volume as the covariates. For the analyses, only voxels with damage present in at least 20 % of all patients were included to avoid lowering the statistical power by including infrequently damaged voxels, while increasing the number of computed comparisons [14].

3.2. Tract-based spatial statistics for DTI

Tract-based statistical analyses of FA, MD, AD and RD maps were performed in the FMRIB Software Library (FSL 5.0.10; http://www.fmrib.ox.ac.uk/fsl). All patients' maps were transformed to generate an averaged and thinned symmetric maps in the Montreal Neurological Institute space. The warped maps for each patient were then projected onto the mean skeleton maps, representing the centers of the common fiber bundles. The resulting maps were fed into voxel-wise statistical analyses to compare the COVID and control groups. Statistics were performed with the threshold-free cluster enhancement nonparametric permutation test, using 5000 Monte Carlo simulations [15]. The statistical threshold was set at a corrected p value of less than 0.05.

3.2.1. Group independent component analysis for rfMRI

Multi-stage temporal concatenation group independent component analysis was performed across the entire brain region [16]. In

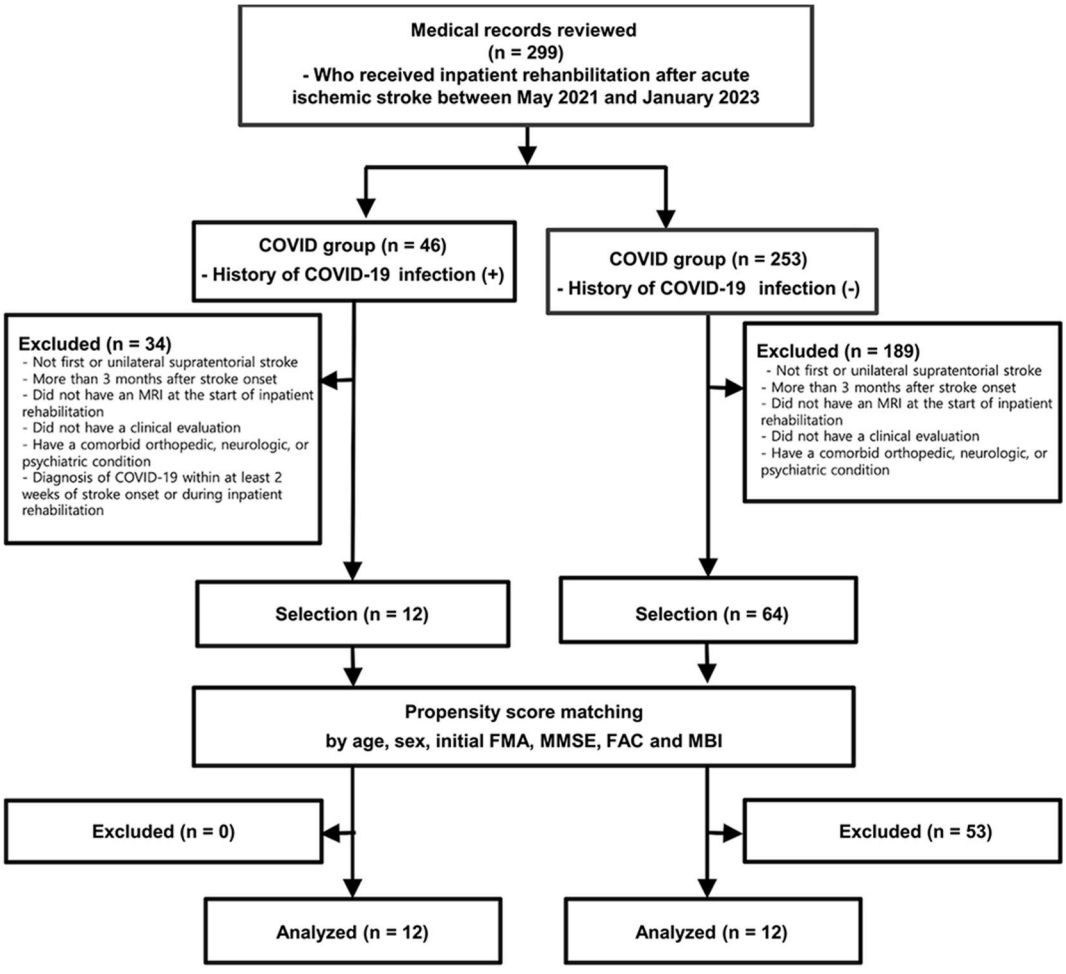

Fig. 1. Flow chart.

the first stage, the 155 rfMRI preprocessed data from each patient were reduced to 30 principal components, which explained over 99 % of the variance. Next, a total of 720 components (30 components/patient × 24 patients) were temporally concatenated, reduced to 20 principal components, and fed into the ICA infomax algorithm [17]. In the last stage, spatial maps and the corresponding time courses for each patient were back-reconstructed using the dual regression approach [16,18]. The 20 spatial ICA maps were labeled upon visual inspection: In COVID group, (1, 4, 5, 11, 14, 20) noise components; (7, 8, 10, 13, 16) not defined; (2) posterior cingulate cortex–default mode network (DMN); (3) bilateral primary motor area (M1); (6) left dorsolateral prefrontal cortex (DLPFC); (9) lesion; (12) pons; (15) midbrain; (17) bilateral upper cerebellum; (18) bilateral occipital network; and (19) bilateral orbitofrontal area. In control group, (1, 2, 3, 7, 8, 9, 10) noise components; (5, 11, 12, 16, 17) not defined; (4) pons; (6) bilateral cerebellum; (13) DLPFC; (14) medulla (15) lesion; (18) bilateral M1; (19) bilateral orbitofrontal area; and (20) DMN. Connectivity differences between groups used independent sample t-tests. The significant changes in intra-network functional connectivity were identified for each network at a cluster-level corrected p value of less than 0.05, with a cluster-defining threshold set to p value of less than 0.001. The significant changes in inter-network functional connectivity were identified applying the Benjamini-Hochberg procedure at a false discovery rate-corrected threshold of p value of less than 0.05 [19].

3.3. Statistical analyses

To initially assess differences between groups, independent sample t-tests were performed for continuous variables, and chi-square tests were used for categorical variables. Paired t-tests were used for intragroup comparisons before and after treatment. Two-way repeated-measures analysis of variance was employed to assess alterations in the average scores of clinical assessments between the groups, both at the beginning and end of rehabilitation. All analyses were conducted using SPSS (ver. 25.0; SPSS Inc, Chicago, IL, USA), and significance was determined at a p-value threshold of <0.05.

4. Results

4.1. Demographics

Following propensity score matching, there were 12 patients in both groups (Fig. 1). The mean (SD) age between in the COVID and control groups was 69.9 (14.2) and 70.4 (15.1), respectively. Patient demographics including age, sex, stroke characteristics, initial clinical assessments, hours of rehabilitation therapy for physical, occupational, speech, cognitive, and neuromuscular electrical stimulation, and discharge destination were not significantly different between the COVID and control groups (Tables 1 and 2).

4.1.1. Clinical improvement

Clinical assessments, including FMA, FAC, and MBI, showed significant improvement post-rehabilitation compared with the initial assessment in intragroup analyses, but the difference was not significant between groups (Fig. 2, Table 3).

4.1.2. MRI analyses

Voxel-based lesion mapping analysis showed no significant lesion differences between the groups (Fig. 3). Tract-based statistical analyses showed increased FA for the frontal lobe and inferior cerebellar peduncle in lesioned hemisphere (uncorrected $p < 0.001$) but no significant differences in FA after the threshold-free cluster enhancement nonparametric permutation test (Fig. 4, corrected $p < 0.05$). There were no significant differences in intra- and inter-network functional connectivity between COVID and control group in subacute and chronic stroke phases (Fig. 5).

5. Discussion

To our knowledge, this is the first study comparing multimodal MRI and stroke outcomes in COVID-19 recovery patients versus those without a history of COVID-19. This study found no differences in brain microstructure and connectivity, and clinical improvements between the two groups.

Table 1
Patient demographics in unmatched and propensity score-matched groups.

Match Variables (Mean (SD))	Non-Matched			Propensity Score-Matched		
	COVID group (n = 12)	Control group (n = 64)	SMD	COVID group (n = 12)	Control group (n = 12)	SMD
Sex (Male: Female)	5 : 7	40 : 24	0.083	5 : 7	5 : 7	<0.001
Age	69.92 (14.24)	66.48 (15.45)	0.232	69.92 (14.24)	70.41 (15.17)	0.033
FMA	30.00 (18.46)	43.28 (31.48)	0.515	30.00 (18.46)	33.25 (26.86)	0.141
MMSE	16.67 (12.91)	16.70 (11.03)	0.003	16.67 (12.91)	15.75 (11.08)	0.076
FAC	0.67 (1.44)	1.12 (1.59)	0.303	0.67 (1.44)	0.92 (1.51)	0.170
MBI	25.83 (25.63)	28.70 (25.46)	0.112	25.83 (25.63)	30.08 (29.83)	0.153

FAC, Functional Ambulatory Category; FMA, Fugl-Meyer assessment; MBI, Modified Barthel Index Score; MMSE, Mini-Mental State Examination; SD, Standard Deviation; SMD, Standardized mean difference.

Table 2
Demographic and baseline clinical characteristics of propensity score-matched groups.

	COVID group (n = 12)	Control group (n = 12)	*P*-value
Demographic			
Age (years, mean (SD))	69.9 (14.2)	70.4 (15.1)	0.936
Sec (male: female)	5:7	5:7	1.000
Stroke lesion and severity			
Lesion side (Righ: Left)	5:7	10:2	0.035*
Lesion volume (cm^3, mean (SD))	25.0 (32.2)	25.2 (34.9)	1.000
Initial NIHSS (mean (SD))	7.86 (5.0)	7.8 (6.3)	1.000
MEP no response (%)	83.30	50.00	0.083
Stroke cause (TOAST), n			0.699
Atherothrombotic	5	6	
Cardioembolic	1	1	
Lacunar	4	5	
Unusual	1	0	
Undetermined	1	0	
Clinical assessments (mean (SD))			
FMA	30.0 (18.4)	33.2 (26.8)	0.719
MMSE	16.6 (12.9)	15.7 (11.0)	0.608
FAC	0.6 (1.4)	0.9 (1.5)	0.681
MBI	25.8 (25.6)	30.0 (29.8)	0.961
Hospital course (mean (SD))			
Hospital days (days)	51.5 (15.2)	53.5 (11.9)	0.734
Total rehabilitation time(hours)	84.5 (28.6)	82.8 (28.6)	0.882
Physical therapy time(hours)	20.5 (7.6)	18.7 (6.9)	0.563
Occupational therapy time(hours)	14.0 (4.1)	13.6 (2.9)	0.801
Neuromuscular Electrical Stimulation time(hours)	15.5 (6.2)	9.58 (9.1)	0.074
language therapy time(hours)	1.6 (2.1)	3.4 (3.7)	0.161
Cognitive therapy time(hours)	1.2 (1.6)	1.2 (1.3)	1.000
Discharge destination, n			0.307
Rehabilitation hospital	1	3	
Nursing home	6	7	
Home	5	2	

FAC, Functional Ambulatory Category; FMA, Fugl-Meyer assessment; MBI, Modified Barthel Index Score; MEP, Motor evoked potential; MMSE, Mini-Mental State Examination; NIHSS, National Institutes of Health Stroke Scale; SD, Standard Deviation; SMD, Standardized mean difference; TOAST, Trial of Org 10,172 in acute stroke treatment.

The mechanisms by which SARS-CoV-2 potentially invades and affects the brain are not yet fully understood. Viral entry into the brain has two routes. The olfactory bulb, partially unprotected by the dura, presents a plausible route for SARS-CoV-2 direct transmission to the brain and may link to olfactory symptoms. The olfactory cortex, receiving direct axonal projections from the olfactory bulb and secondary olfactory areas, is also considered susceptible to SARS-CoV-2 [20,21]. One longitudinal MR study found damaged brain tissue functionally connected to the olfactory cortex, which is caused by anterograde degeneration starting from olfactory neurons [1]. An absence of functional MRI findings in the secondary olfactory area was also observed in a patient with persistent cacosmia after COVID-19 [20]. However, MR abnormalities in the olfactory bulb and secondary olfactory area disappeared on follow-up MRI in another patient with recovering olfactory symptoms [22,23]. In our study, orbitofrontal functional connectivity and microstructure were not significantly different between the groups and did not influence rehabilitation recovery.

An indirect damage route of SARS-CoV-2 is the attachment of SARS-CoV-2 spike proteins to angiotensin-converting enzyme 2 receptors on the endothelium of blood-brain barrier [2]. Infected endothelial cells produce chemokines that trigger a cytokine storm and damage the blood-brain barrier, leading to neuroinflammation and damage to nerve tissue. It has been suggested that cytokines from the indirect pathway cause systemic coagulopathy, and macrophages release tissue factor to activate the extrinsic coagulation pathway, leading to microthrombi and microangiopathy, which may lead to ischemic stroke due to COVID-19 [24–26]. Previous studies have not supported the hypothesis that SARS-CoV-2 is highly neurovirulent and causes severe neuronal damage [2].

The hypothesis of a poorer prognosis in ischemic stroke patients with COVID-19 may complicate stroke cases and patient rehabilitation [27]. Previous studies have shown that prolonged immobilization of stroke patients can lead to significant functional decline [28]. During a COVID-19 quarantine of at least one week, patients may receive reduced rehabilitation, hindering optimal recovery due to limited care and mobility [29]. Therefore, in this study, we recruited people diagnosed with COVID-19 at least two weeks prior to stroke onset to exclude the effects of reduced rehabilitation. Consistent with our results, recent studies have demonstrated no differences in stroke recovery among pre- and post-pandemic stroke patients [30] or those with/without COVID-19 infection [27]. Thus, it can be inferred that SARS-CoV-2 infection does not cause lasting effects on the blood-brain barrier.

However, in previous studies comparing brain imaging between healthy groups and COVID-19 patients regardless of their relationship with stroke, significant differences in brain images were observed in COVID-19 patients. Global brain size reduction, signal changes in white matter, and overall decrease in brain metabolism on FDG-PET were observed across various periods from 3 months to 1 year post-infection [1,8,31]. In contrast, our study focusing on stroke patients found no significant differences in structural or functional connectivity of brain MRI and DTI images. This may be attributed to the fact that imaging studies were conducted within an

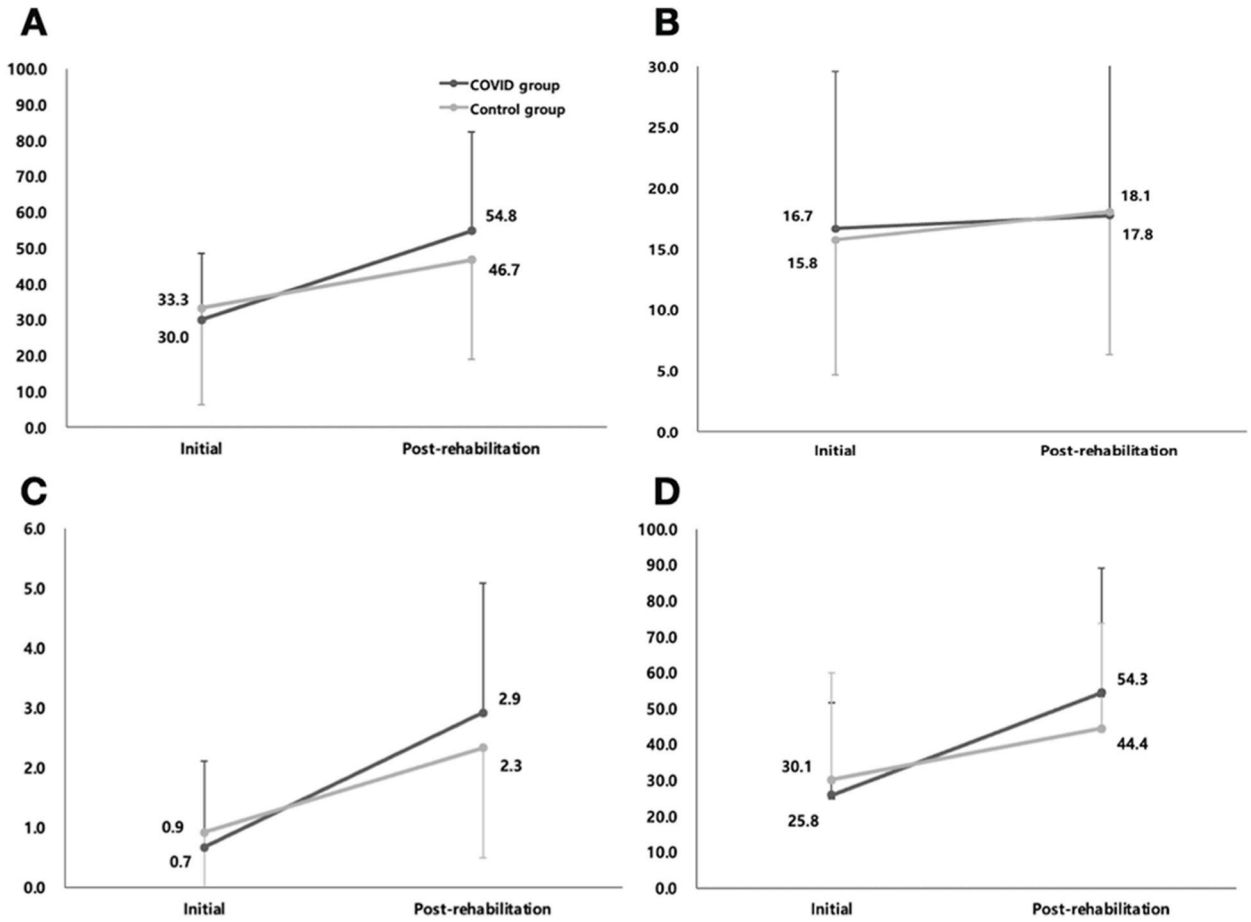

Fig. 2. Changes of clinical assessments. (A) FMA. (B) MMSE. (C) FAC. (D) MBI.

Table 3
Comparison of rehabilitation parameters within groups and between groups.

Variables	COVID group (n = 12)	Control group (n = 12)
FMA		
Pre	30.00 (18.46)	33.25 (26.86)
Post	54.83 (27.53)[a]	46.67 (27.69)*
MMSE		
Pre	16.67 (12.92)	15.75 (11.08)
Post	17.75 (12.61)	18.08 (11.73)
FAC		
Pre	0.67 (1.44)	0.92 (1.51)
Post	2.92 (2.16)[a]	2.33 (1.83)*
MBI		
Pre	25.83 (25.63)	30.08 (29.83)
Post	54.33 (34.70)[a]	44.42 (29.29)

FAC, Functional Ambulatory Category; FMA, Fugl-Meyer assessment; MBI, Modified Barthel Index Score; MMSE, Mini-Mental State Examination; Post, post-rehabilitation; Pre, pre-rehabilitation.
[a] $p < 0.05$ compared at pre-rehabilitation.

average of 72 days post-diagnosis of COVID-19 in patients participating in our study, whereas previous studies had imaging follow-ups of at least 3 months. This short duration in our study might have been insufficient to observe brain imaging changes due to COVID-19, and the limited number of patients could also contribute to its lack of representativeness.

This study has several limitations. Although the baselines were similar after propensity score matching, the small sample size prevented complete matching. Considering that in previous brain studies, the sample sizes for mean diffusivity parameter were 4, for fractional anisotropy parameter were 23, and for brain volume were 145 [32,33], the sample size of our study is indeed relatively

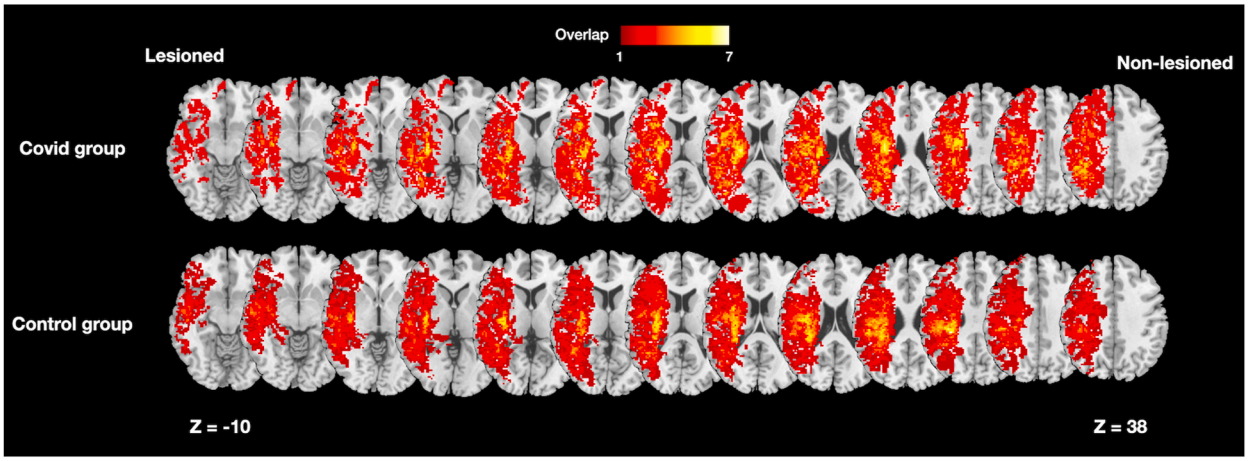

Fig. 3. Lesion overlapping maps of the COVID and control groups. The color scale indicates the number of overlapping lesions across the patients. Z: z-axis in the Montreal Neurological Institute space.

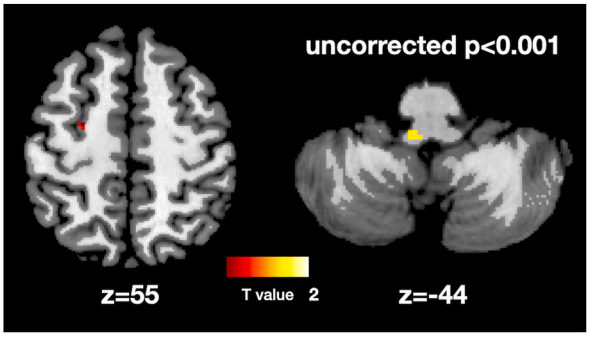

Fig. 4. Differences of FA between two groups. Red areas indicate increased FA values in control group compared with the COVID group.

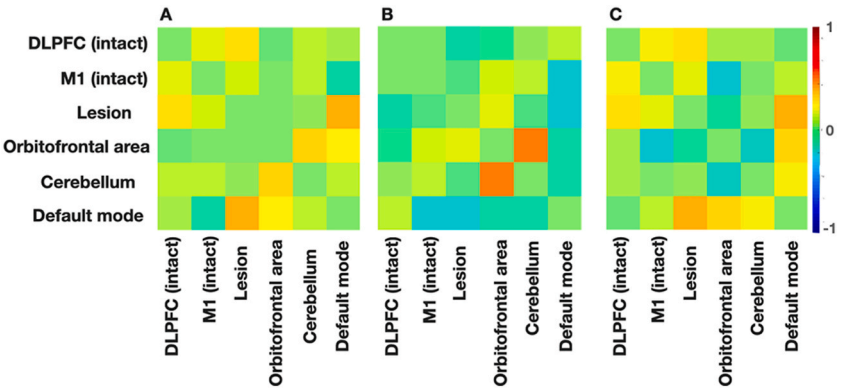

Fig. 5. Internetwork functional connectivity is depicted in matrices, illustrating average values in COVID (A) and control (B) groups and t values obtained from the independent t-tests between the two groups (C).

small. Nonetheless, there was no significant difference in the initial clinical assessment between the two groups. Moreover, the incidence of direct brain invasion is relatively low, and not all patients in the COVID group may have experienced direct invasion of the brain by the virus. Third, for patients with a history of COVID-19, the study did not take into account the severity of COVID-19 or the presence of residual symptoms from the infection. As previous studies [8,34] have shown that changes in brain imaging vary depending on the severity of the initial infection and the presence or absence of residual symptoms at long-term follow-up, further sub-analyses that take these factors into account are warranted. Finally, we did not consider the differences between SARS-CoV-2

variants. All but one of the COVID group were diagnosed after the omicron variant period, and existing research suggests that disease severity of COVID-19 during the omicron period was lower than that during previous periods of high transmission [35,36].

Nevertheless, this study is the first to confirm whether a history of COVID-19 infection affects rehabilitation during stroke recovery. This study's strengths lie in its comprehensive comparison of recovery across various domains, encompassing motor function, cognition, locomotion, and activities of daily living. Additionally, it incorporated microstructure and functional connectivity into the analysis. The findings will help provide clinicians with insights into image analysis and recovery of patients with a history of stroke after the COVID-19 pandemic. Our findings suggest that because a history of COVID-19 does not make a difference in neuroimaging in stroke patients, stroke patients who recover from COVID-19 are unlikely to require additional neuroimaging follow-up to see the effects of COVID-19 beyond standard stroke care. Furthermore, rehabilitation protocols for post-stroke patients with a history of COVID-19 infection do not appear to need to be modified differently as recovery is similar to patients without such a history. However, long-term monitoring of COVID-19 patients, especially those with severe initial infection or prolonged symptoms, is still essential as previous studies have shown differences in neurologic symptoms and neuroimaging.

6. Conclusion

This study identified no significant differences in brain microstructure, connectivity, or clinical improvement outcomes between the stroke patients with and without a history of COVID-19 infection. However, we still don't know the mechanisms by which COVID-19 causes reversible and in some cases permanent complications, so further research is needed in this area.

Ethics declarations

This study was reviewed and approved by the Institutional Review Board of Severance Hospital, with the approval number: 4-2022-1565.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [Dae Hyun Kim], upon reasonable request.

Funding

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2023-00262005).

CRediT authorship contribution statement

Jong Mi Park: Writing – original draft, Formal analysis, Data curation. **Jinna Kim:** Methodology, Data curation. **Yong Wook Kim:** Methodology. **Deog Young Kim:** Formal analysis. **Seo Yeon Yoon:** Methodology, Data curation. **Dae Hyun Kim:** Writing – review & editing, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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