Review Article

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Identifying cerebral microstructural changes in patients with COVID-19 using MRI: A systematic review

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Abstract:

Coronavirus disease 2019 (COVID-19) is an epidemic viral disease caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Despite the excessive number of neurological articles that have investigated the effect of COVID-19 on the brain from the neurological point of view, very few studies have investigated the impact of COVID-19 on the cerebral microstructure and function of the brain. The aim of this study was to summarize the results of the existing studies on cerebral microstructural changes in COVID-19 patients, specifically the use of quantitative volumetric analysis, blood oxygen level dependent (BOLD), and diffusion tensor imaging (DTI). We searched PubMed/MEDLINE, ScienceDirect, Semantic Scholar, and Google Scholar from December 2020 to April 2022. A well-constructed search strategy was used to identify the articles for review. Seven research articles have met this study's inclusion and exclusion criteria, which have applied neuroimaging tools such as quantitative volumetric analysis, BOLD, and DTI to investigate cerebral microstructure changes in COVID-19 patients. A significant effect of COVID-19 was found in the brain such as hypoperfusion of cerebral blood flow, increased gray matter (GM) volume, and reduced cortical thickness. The insula and thalamic radiation were the most frequent GM region and white matter tract, respectively, that are involved in SARS-CoV-2. COVID-19 was found to be associated with changes in cerebral microstructures. These abnormalities in brain areas might lead to be associated with behaviors, mental and neurological alterations that need to be considered carefully in future studies.

Keywords:

Cerebral, coronavirus disease 2019, microstructure, magnetic resonance imaging, severe acute respiratory syndrome coronavirus 2

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Introduction

Coronavirus disease 2019 (COVID-19) is an epidemic viral disease caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was identified in early December 2019 in China and has spread worldwide. To date, 109,594,835 confirmed cases globally and 2,424,060 deaths have been reported to the World Health Organization. The main infection source is pneumonia patients infected with SARS-CoV-2, and the transmission route is suggested to be human to human.[1] The symptoms of COVID-19 range from no symptoms (asymptomatic) to severe pneumonia and death.[1] The virus can affect the respiratory,[2] digestive,[2] urinary,[2] hematological,[2] and neurological systems.[3] The common clinical manifestation of SARS-CoV-2 is fever,

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cough, dyspnea, muscle soreness or fatigue, and chest distress.[4] SARS-CoV-2 can be detected using serological, molecular, and radiological techniques.[2]

Neurological complications affecting the central nervous system (CNS) have been reported in patients who are infected by respiratory viruses such as influenza virus,[5-7] respiratory syncytial virus,[8-10] parainfluenza virus,[11] metapneumovirus,[12,13] rhinovirus,[11,14] coronaviruses,[3,15-18] adenoviruses,[19] and bocaviruses.[20,21] Even though the predominant clinical manifestations of SARS-CoV-2 were found in the respiratory system, neurological manifestations such as headache, anosmia, seizure, stroke, encephalitis, and meningitis are now significantly recognized.[3,4,16-18,22-30] SARS-CoV-1 and SARS-CoV-2 assign the same receptor, angiotensin-converted enzyme 2, which can be found in the CNS and mediate the disease process.[31] The invasion of severe SARS-CoV-2 can directly or indirectly affect the CNS.[15] A smell dysfunction and headaches are found to be very common in mild COVID-19 cases, especially in younger and female patients; muscle pain is found to be common in both mild and severe COVID-19 cases, and ischemic strokes are reported to be a possible complication of the hypercoagulability that is associated with severe SARS-CoV-2 infections.[32] Seizures are found to be associated with the coronavirus as some coronavirus patients demonstrate signs of epilepsy.[33] Other neurological consequences of COVID-19 were reported, including anosmia, nausea, dysgeusia, damage to respiratory centers, and cerebral infarction.[34]

Neural plasticity is defined as the capability of the CNS to alter as a reaction to intrinsic and extrinsic stimuli by reorganizing its structure, functions, and connectivity.[35] Despite the fact that the imaging abnormalities of bacterial and fungal meningitis are specific to certain agents that can activate the immune system, many viral infections of the CNS produce imaging abnormalities unnoticed by any other infectious agents.[36] Viral infections can cause brain dysfunctions by damaging the primary molecular mechanism, for example, Borna disease virus can enter the brain and affect the limbic system.[37] Patients with severe COVID-19 and without ischemic infarcts show a wide range of neurologic manifestations: diffusion hyperintensities in the mesial temporal lobe and splenium of the corpus callosum, multifocal white matter (WM) hyperintense lesions, hemorrhagic lesions, WM microhemorrhagic lesions, and acute necrotizing encephalopathy that can indicate restricted molecular diffusion owing to lack of WM net movement.[38] Possible dissemination pathways for coronavirus to gain access to the CNS have been proposed based on the mouse model: transneuronal route (olfactory nerve to the olfactory cortex of temporal lobe to the hippocampus to the amygdala), neurotransmitter pathway (via serotoninergic dorsal raphe system), hematogenous route (via hematogenous route and Virchow–Robin spaces), and the lymphatic system.[39]

Investigating the cerebral microstructure and function of the brain could provide valuable insights into the neurological consequences of COVID-19, and build the relationship between some clinical assessment outcomes and some neurological manifestations of the virus in order to understand the neurological pathophysiology of SARS-CoV-2. Despite the excessive number of neurological studies that have studied the effect of COVID-19 from the neurological point of view on the brain, limited studies have investigated the impact of COVID-19 on the cerebral microstructure level and function of the brain using advanced magnetic resonance imaging (MRI) analysis tools. The current study aims to give an overview of studies examining the differences of cerebral microstructure and function in patients with COVID-19, highlight the possible changes in the cerebral microstructure level of the brain, and discuss the correlation between these changes and the clinical assessment outcomes.

Methods

Literature search and inclusion criteria

A widespread database search was performed (from December 2019 up to April 2022) to identify original research articles in PubMed/MEDLINE and other databases such as ScienceDirect, Semantic Scholar, and Google Scholar. The following keywords were used: MRI, COVID-19, and brain (MRI and [COVID-19 or SARS-CoV-2] and brain). MRI was chosen as the only brain imaging technique in this literature search due to it is a safe, noninvasive method to examine human brain and is power enough to detect changes in brain. All studies' titles and abstracts were screened to identify those that might be related to structural and functional brain changes in COVID-19 patients. Inclusion criteria were set as the following: human studies, comparison between healthy controls and COVID-19 patients, available in English, and using at least one neuroimaging analysis tool.

A well-constructed search strategy was used to identify the articles for review [Figure 1]. The initial search found 552 results; however, 322 articles were excluded because they are duplicated records marked as ineligible by automation tools. Of 230 articles, 180 were excluded because they did not directly assess COVID-19-related structural or functional changes using MRI. Fifty articles were obtained in preparation for full-text screening, and 32 articles were not retrieved because they are not

available. Eighteen papers were assessed for eligibility, and 11 articles were excluded because of using positron emission tomography/computed tomography modality, recruiting only patients' groups, and case report studies because they are not met the inclusion criteria of this study. Seven articles met the inclusion and exclusion criteria in this review study. Table 1 exhibits a list of articles that met this study's criteria.

Data extraction and literature quality assessment

The eligibility criteria of selected research articles were assessed by two independent clinical consultant scientist reviewers (WMA and FHA) for inclusion in the systematic review. Furthermore, the risk of bias was assessed using the JBI Critical Appraisal Checklist for Cross-sectional Studies.[39] All research articles recognized from the search were introduced into Mendeley software to remove duplicate articles. Data extraction was carried out from the selected studies to synthesize the following: publication information (first author and year), subject characteristics, MR acquisition, and analysis methods, and neuroimaging findings.

Strategy for data synthesis

All extracted data were presented in a formal narrative synthesis approach by coding study information, outlining subject characteristics, summarizing MR acquisition and analysis methods, and synthesizing neuroimaging findings. Tabulation of extracted data from included studies was performed to assess the number of studies contributing to this particular topic.

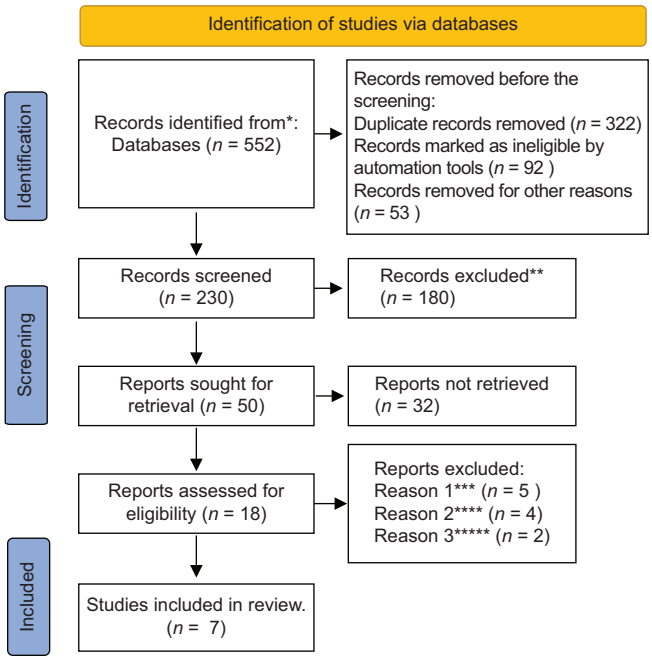

Figure 1: Search strategy used to identify the articles for review following PRISMA guidelines. *Records identified from PubMed/MEDLINE and other databases: ScienceDirect, Semantic Scholar, and Google Scholar. **Records excluded due to they did not directly assess COVID-19-related structural or functional changes using MRI. ***Reason 1: Recruiting only patients' groups, and case report studies. **** Reason 2: Not available in English. *****Reason 3: Using PET/CT modality. MRI: Magnetic resonance imaging, PET/CT: Positron emission tomography/computed tomography

Ethics statement

As no humans were recruited for this review study, and the analysis is based on the data published in the literature from other studies, the ethical approval of this study was waived.

Results of literature methods

The literature search identified a total of 18 neuroimaging studies investigating the cerebral microstructural changes in COVID-19 patients. 11 of these studies have been excluded because they are either case studies (6 studies) or cohort studies (5 studies). Consequently, a total of 7 studies assessing the cerebral microstructural changes in COVID-19 patients were included in the final review of this study. The quality assessment of the included studies was performed according to the JBI Critical Appraisal Checklist for Cross-Sectional Studies.[39] The percentage scored points ranged from 62.5% to 100%, and the mean percentage scored points was 83.9%.

List of studies investigating cerebral microstructure changes in coronavirus disease 2019 patients is displayed in [Table 2]. A total of 1,457 participants were identified in the total included studies in this review. The total number of healthy controls (non-COVID-19 volunteers) was 778 subjects, while the total number of COVID-19 patients was 679. All included studies utilized a 3T MR scanner to acquire MR images. T1-weighted images were acquired in all included studies for anatomical reference.[40-46] Five studies have gained diffusion tensor imaging (DTI),[40,41,43,44,46] one study has acquired 3D-pulsed continuous arterial spin labeling (pcASL),[43] and one study has acquired resting state echo planar imaging.[44] In terms of MR image analysis,

Table 1: Summarized quality assessment of the included studies according to the Joanna Bridge Institute (JBI) Critical Appraisal Checklist for Cross-sectional Studies

Included studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Quality assessment
Lu *et al.* (2020)[40]	Y	Y	Y	Y	Y	Y	Y	Y	100%
Newcombe *et al.* (2020)[41]	Y	N	Y	Y	U	U	Y	Y	62.5%
Crunfli *et al.* (2021)[42]	Y	N	Y	Y	U	U	Y	Y	62.5%
Qin *et al.* (2021)[43]	Y	Y	Y	Y	Y	Y	Y	Y	100%
Silva *et al.* (2021)[44]	Y	N	Y	Y	U	U	Y	Y	62.5%
Douaud *et al.* (2021)[45]	Y	Y	Y	Y	Y	Y	Y	Y	100%
Yang *et al* (2021)[46]	Y	Y	Y	Y	Y	Y	Y	Y	100%

Y: Yes, N: No, U: Unclear

Table 2: Studies investigating cerebral microstructure changes in COVID-19 patients

Study	Subject characteristics		MR Image acquisition	MR Image analysis
	Controls	COVID-19 patients		
Lu *et al.* (2020)[40]	N=39 (22 M)	N=60 (34 M)	3T,	Quantitative VBM
	45.88±13.90 Yrs	44.10±16.00 Yrs	3D-T1WI, DTI	Quantitative DTI
Newcombe *et al.* (2020)[41]	N=15 (10 M)	N=6 (5M)	3T,	Quantitative VBM
	(45 – 77 Yrs)	67.5±9.89 Yrs	3D-T1WI, DTI	Quantitative DTI
Crunfli *et al.* (2021)[42]	N=145 (42 M)	N=81 (21 M)	3T,	Quantitative VBM
	38 Yrs	37 Yrs	3D-T1WI	
Qin *et al.* (2021)[43]	N=31 (18 M)	MG N=19 (7 M)	3T,	Quantitative VBM
	60.58±6.42 Yrs	59.37±5.87 Yrs	3D-T1WI, DTI,	Quantitative DTI
		SG N=32 (17 M)	3D-PCAST	Quantitative CBF
		63.19±5.37 Yrs		
Silva *et al.* (2021)[44]	N=133	N=87 (23 M)	3T,	
		36 Yrs	3D-T1WI, DTI, RS-EPI	Quantitative DTI - BOLD
Douaud *et al.* (2021)[45]	N=388 (166 M)	N=394 (170 M)	3T,	Quantitative VBM
	60.4±7.5 Yrs	59.1±7.0 Yrs	3D-T1WI	Quantitative SBM
Yang *et al.* (2021)[46]	N=27 (13 M)	N=28 (12 M)	3T,	Quantitative DTI
	37.7±9.0 Yrs	40.0±7.9 Yrs	3D-T1WI, DTI	

N: Number, M: Male, MG: Mild group, SG: Server group, Yrs: Years, T: Tesla, D: Dimension, T1WI: T1 weighted image, DTI: Diffusion tensor imaging, PCAST: Pseudo-continuous arterial spin labeling, RS: Resting state, EPI: Echo planer imaging, VBM: Voxel-based morphometry, SBM: Surface-based morphometry, BOLD: Blood oxygenation level dependent

the quantitative voxel-based morphometry (VBM) approach was applied in 5 studies,[40-43,45] quantitative DTI was applied in 5 studies,[40,41,43,44,46] quantitative cerebral blood flow (CBF) was applied in 1 study,[43] blood oxygen level dependent (BOLD) was applied in 1 study,[44] and quantitative surface-based morphometry was applied in 1 study.[45]

Results

Findings in the gray matter among COVID-19 patients

The total number of gray matter (GM) regions that show involvement in COVID-19 is 27 GM regions [Table 3]. A significant effect of COVID-19 was found in the brain with a greater GM volume, reduced cortical thickness, and hypoperfusion of CBF in the insula compared to healthy controls.[40,43,45] Furthermore, a significant enlargement of GM volume and reduced cortical thickness of the hippocampus was found in COVID-19 patients compared to healthy controls.[40,43] The superior temporal gyrus (STG) significantly reduces cortical thickness and correlates significantly with logical memory scores in COVID-19 patients[42,43] [Table 4].

COVID-19 patients show a significantly higher GM volume in bilateral olfactory cortices, left Rolandic operculum, Heschl's gyrus, and right cingulate gyrus.[40] The subcortical GM volume was significantly reduced in the bilateral thalamus, left putamen, and caudate.[43] The CBF of subcortical nuclei was reduced significantly in the bilateral caudate, putamen, right globus pallidus, amygdala, and accumbens[43] [Table 4].

Table 3: The findings in gray matter regions among coronavirus disease 2019 patients

GM regions	Contingency tables			
	Frequency			Total
	1	2	3	
Accumbens	1	0	0	1
Amygdala	1	0	0	1
Calcarine sulcus	1	0	0	1
Caudate	1	0	0	1
Central sulcus	1	0	0	1
Cingulate gyrus	1	0	0	1
Cuneus	1	0	0	1
Global pallidus	1	0	0	1
Heschl's gyrus	1	0	0	1
Hippocampi	0	1	0	2
Inferior frontal gyrus	1	0	0	1
Insula	0	0	1	3
Lingual gyrus	1	0	0	1
Olfactory cortices	1	0	0	1
Orbitofrontal cortex	1	0	0	1
Parahippocampal gyri	1	0	0	1
Parieto-occipital sulcus	1	0	0	1
Perirhinal cortex	1	0	0	1
Postcentral gyrus	1	0	0	1
Putamen	1	0	0	1
Rectus gyrus	1	0	0	1
Rolandic operculum	1	0	0	1
Superior occipital gyrus	1	0	0	1
Superior medial frontal gyrus	1	0	0	1
Superior temporal gyrus	0	0	1	3
Thalamus	1	0	0	1
Precentral gyrus	1	0	0	1
Total	24	1	2	27

GM: Gray matter, COVID-19: Coronavirus disease 2019

A significant reduction of cortical thickness was found in the left lingual gyrus, calcarine sulcus, cuneus,

parieto-occipital sulcus, olfactory sulcus and rectus gyrus,[42] parahippocampal gyrus, orbitofrontal cortex, and perirhinal cortex.[45] On the other hand, a significant increase in cortical thickness was found in the right central sulcus, precentral and postcentral gyri, superior occipital gyrus, and cuneus[42] [Table 4].

Findings in the white matter among COVID-19 patients

The total number of WM tracts showing involvement in the COVID-19 pandemic is 27 [Table 5]. A significant effect of COVID-19 was found in the structural connectivity of the brain that was mainly found in the thalamic radiation,[41,43,46] corpus callosum,[44,46] corona radiate,[40,46] inferior longitudinal fasciculus,[43,44] superior longitudinal fasciculus,[43,46] external capsule,[40,46] and corticospinal tract[43,44] [Table 6].

A single incident was found in the superior fronto-occipital fasciculus (SFOF),[40] association and striate fibers,[41] cingulum bundle dorsal (CBD), anterior commissure, forceps minor, fronix, acoustic radiation, optic radiation, inferior fronto-occipital fasciculus, arcuate fasciculus, middle longitudinal fascicle, frontal aslant tract,[43] doral cinguli, parahippocampal cinguli, uncinate fasciculi,[44] cingulum, superior fronto-occipital fasciculus (SFOF), and internal capsule (IC)[46] [Table 6]. The consistent results are displayed in [Figure 2].

Discussion

This review results show the involvement of different brain GM regions and WM tracts in the pathophysiology of COVID-19 infection. The results show that most reported cerebral microstructural changes are allocated in the insula, STG, hippocampus, and thalamic radiation tract. The neuroimaging results of COVID-19 reported in the literature and other neuroimaging results of other viral findings will be discussed to provide valuable insights for imaging biomarkers in the clinical settings of COVID-19 infections. This review is consistent with other reports with mild difference, in that it is focused on the neuroimaging findings as depicted on MRI, while the other reports used various imaging modalities.

Cortical and subcortical abnormalities are associated with neuronal migration abnormalities that are

Table 4: The studies' findings of the GM regions that show the involvement in COVID-19

	Included studies						
	Lu et al. (2020)[40]	Newcombe et al. (2020)[41]	Crunfli et al. (2021)[42]	Qin et al. (2021)[43]	Silva et al. (2021)[44]	Douaud et al. (2021)[45]	Yang et al. (2021)[46]
Olfactory Cortices	✓						
Hippocampi	✓			✓			
Insulas	✓			✓		✓	
Rolandic operculum	✓						
Heschl's gyrus	✓						
Cingulate gyrus	✓						
Putamen				✓			
Thalamus				✓			
Caudate				✓			
Global pallidus				✓			
Amygdala				✓			
Accumbens				✓			
Superior medial frontal gyrus				✓			
Rectus gyrus			✓				
Perirhinal cortex						✓	
Superior temporal gyrus			✓	✓		✓	
Central sulcus			✓				
precentral gyrus			✓				
Postcentral gyrus			✓				
Superior Occipital gyrus			✓				
Cuneus			✓				
Lingual gyrus			✓				
Calcarine sulcus			✓				
Parieto-occipital sulcus			✓				
Inferior frontal gyrus			✓				
Orbitofrontal cortex						✓	
Parahippocampal gyri						✓	

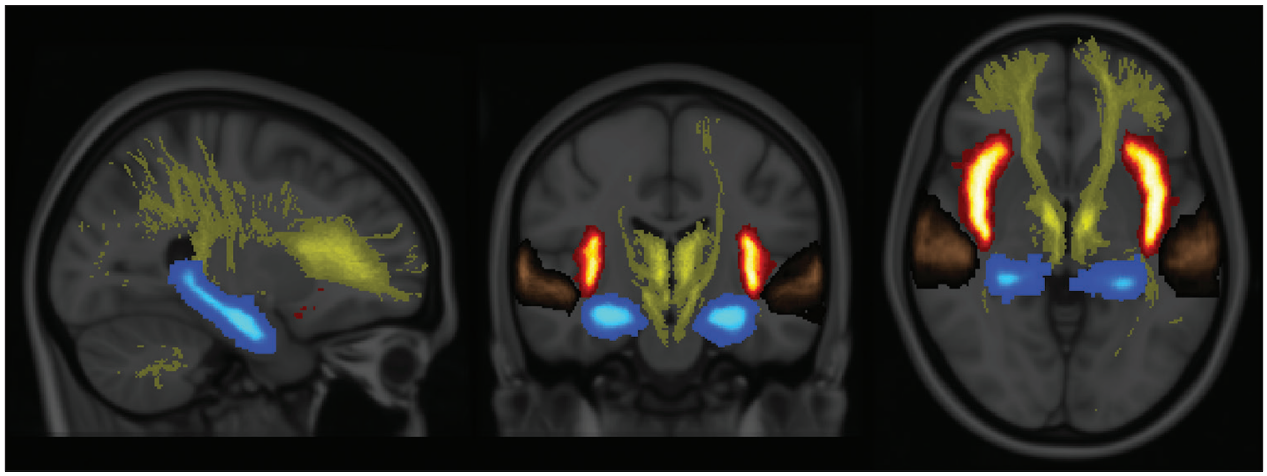

Figure 2: Consistent results are displayed in the orthogonal projection. Insula GM regions are displayed in red color. The STG region is displayed in copper color. The hippocampus region is displayed in blue color. Thalamic radiation tracts are shown in yellow color. FSL software was used to display the areas of consistence results and overlay them on a standard template MNI152 T1 0.5 mm brain. GM: Gray matter, STG: Superior temporal gyrus

Table 5: The findings in white matter tracts among coronavirus disease 2019 patients

Contingency tables				
WM tracts	Frequency			Total
	1	2	3	
AR	1	0	0	1
AC	1	0	0	1
AF	1	0	0	1
Association	1	0	0	1
Brain stem	1	0	0	1
Cingulum	1	0	0	1
CBD	1	0	0	1
CR	0	1	0	2
CC	0	1	0	2
CST	0	1	0	2
Doral cinguli	1	0	0	1
EC	0	1	0	2
FMI	1	0	0	1
FX	1	0	0	1
FAT	1	0	0	1
IFO	1	0	0	1
ILF	0	1	0	2
IC	1	0	0	1
MDLF	1	0	0	1
OR	1	0	0	1
Parahippocampal cinguli	1	0	0	1
Striatal	1	0	0	1
SFOF	1	0	0	1
SFF	1	0	0	1
SLF	0	1	0	2
Thalamic radiation	0	0	1	1
UF	1	0	0	1
Total	20	6	1	27

WM: White matter, AR: Acoustic radiation, AC: Anterior commissure, AF: Arcuate fasciculus, CBD: Cingulum bundle dorsal, CR: Corona radiate, CC: Corpus callosum, CST: Corticospinal tract, EC: External capsule, FMI: Forceps minor, FX: Fronix, FAT: Frontal aslant tract, IFO: Inferior fronto-occipital fasciculus, ILF: Inferior longitudinal fasciculus, IC: Internal capsule, MDLF: Middle longitudinal fasciculus, OR: Optic radiation, SFOF: Superior fronto-occipital fasciculus, SFF: Superior fronto-occipital fasciculus, SLF: Superior longitudinal fasciculus, UF: Uncinate fasciculi

common landmarks of the abnormal organization of the layers within the brain.[47] COVID-19 autopsy studies showed that a hypoxic brain injury could induce neuronal damage in hypoxia's most vulnerable brain regions, including the neocortex, the hippocampus, and the cerebellum.[48-51] The hippocampus is a brain structure located within the temporal lobe and lying on the level of the inferior horn of the lateral ventricle.[52] It plays an important role in representing spatial contextual information and its central role is in spatial mapping.[48] The hippocampus mainly contains cornu ammonis fields (CA1, CA2, CA3, and CA4) and dentate gyrus (DG).[49] Recently, the hippocampus has been considered one of the most frequently used model systems to investigate the structure and functional connectivity of mammalian cortical circuits.[50] It has connections with various parts of brain: entorhinal cortex, perforant path, recurrent collaterals, and DG.[51] In addition, it has a connection with the prefrontal cortex and amygdala as it is critically involved in aspects of cognition related to executive function and emotional regulation.[53] The intrinsic functional connectivity of the hippocampus formation was found in a large distribution of direct or indirect hippocampal projections, including the following brain regions: amygdala, entorhinal cortex, temporal pole, frontal lobe, anterior cingulate gyrus, orbitofrontal cortex, posterior cingulate gyrus, insula, and thalamic nucleus.[54] Hippocampus atrophy was found in COVID-19 patients as the hippocampus volume was significantly higher in COVID-19 patients compared to the non-COVID-19 controls.[40] The hippocampus appears to be particularly exposed to coronavirus infections, thus increasing the chance of postinfection memory impairment and the quickening of neurodegenerative disorders.[39,50-59] It was reported that the hypoxemia brought on by COVID-19 and the

Table 6: The studies' findings of the WM tracts that show the involvement in COVID-19

	Included studies						
	Lu *et al*. (2020)[40]	Newcombe *et al*. (2020)[41]	Crunfli *et al*. (2021)[42]	Qin *et al*. (2021)[43]	Silva *et al*. (2021)[44]	Douaud *et al*. (2021)[45]	Yang *et al*. (2021)[46]
Association		✓					
Striatal		✓					
Cingulum							✓
Cingulum Bundle Dorsal (CBD)				✓			
Doral Cinguli					✓		
Parahipocampal cinguli					✓		
Corpus Callosum (CC)					✓		✓
Anterior Commissure (AC)				✓			
Forceps Minor (FMI)				✓			
Phoenix (FX)				✓			
Thalamic Radiation		✓		✓			✓
Acoustic Radiation (AR)				✓			
Corona Radiate (CR)	✓						✓
Optic Radiation (OR)				✓			
Inferior Fronto-Occipital Fasciculus (IFO)				✓			
Inferior Longitudinal Fasciculus (ILF)				✓	✓		
Superior Fronto-Occipital Fasciculus (SFOF)							✓
Superior Longitudinal Fasciculus (SLF)				✓			✓
Arcuate Fasciculus (AF)				✓			
Superior Fronto-occipital Fasciculus (SFF)	✓						
Middle Longitudinal Fascicle (MDLF)				✓			
Uncinate fasciculi (UF)					✓		
Internal capsule (IC)							✓
External capsule (EC)	✓						✓
Frontal Aslant Tract (FAT)				✓			
Corticospinal Tract (CST)				✓	✓		
Brain stem		✓					

malfunction of the vascular endothelium may possibly be a factor in the neurological alterations.[44]

The insula is another cortical abnormality that showed involvement in COVID-19, as the GM volume of the insula was found to be significantly higher in COVID-19 patients compared to non-COVID-19 controls.[40] Breathlessness or shortness of breath (dyspnea) is one of the most common hallmark symptoms of COVID-19, and it has been reported in several studies.[4,60-67] The insula is a cortical brain region that is hidden in the depths of the lateral sulcus, and is located on the frontal, parietal, and temporal lobes.[68] It is divided into three parts; the rostroventral agranular insula is related to olfactory and autonomic functions, the intermediate dysgranular insula is associated with gustatory functions, and the caudal dorsal granular insula is associated with somatosensory, auditory, and visual functions.[69] It plays an important role in the neural circuitry of addiction as it is structurally connected with the main brain areas of the brain that are involved in addiction, including the amygdala, the basil ganglia, the thalamus, the orbitofrontal cortex, and the prefrontal cortex.[70] The dysfunctional of insula activity was reported in patients with anxiety and depression.[71] Furthermore, the insula is recognized as a node of the distributed cortical network that is involved in pain pathophysiology process.[72]

Newcombe *et al*. (2021) reported a significant fractional anisotropy (FA) reduction in thalamic radiation in COVID-19 patients compared to non-COVID-19 controls.[41] This significant anisotropy reduction may indicate disrupted fiber tracts and demyelination that are more sensitive in the early detection of changes in WM microstructure.[73] Compared to healthy controls, COVID-19 patients showed a significant reduction of FA and increased radial diffusivity and mean diffusivity in the WM tract of the corpus callosum.[44,46] Thalamic radiation fibers are WM bundles that connect the subcortical regions of thalamus with the cerebral cortex. They are sending sensory information as well as besides olfaction to the cerebral cortex; they are involved in the controls of the cortical arousal and consciousness, and play a role in movement disorders such as Parkinson's disease.[74] Microstructure differences were reported in the thalamus and thalamic radiations in the congenitally deaf.[75] Thalamus calcifications, which include toxic,

are caused by infectious diseases such as tuberculosis, HIV, and cytomegalovirus.[76] The involvement of the corpus callosum in COVID-19 is believed to be related to the potential effect of the cytokine storm[77] that is a life-threatening systemic inflammatory syndrome involving elevated levels of circulating cytokines and immune-cell hyperactivation.[78]

Newcombe *et al*. (2020) reported a significant FA reduction in corona radiata fibers in COVID-19 patients compared to non-COVID-19 controls.[41] A WM integrity abnormality of the corona radiata was found in HIV patients.[79] This finding may indicate that the pathophysiology of SARS-CoV-2 causes axonal damage and the demyelination of corona radiata fibers that extend from thalamus to cortex and cortex to thalamus, brainstem, and spinal cord.[80] Corona radiata fibers are WM tracts located at the lateral ventricle level, which are sending neuronal information between the brainstem and the cerebral cortex. They are composed of both afferent and efferent fibers in order to connect the motor and sensation nerve pathways between these CNS structures.

Based on the variety of imaging study methodologies, MRI is the top imaging technique that provides guidance for assessing the cerebral microstructural alterations in COVID-19. Most studies investigating the effect of COVID-19 focused on neurological manifestations rather than the cerebral microstructural changes in COVID-19 patients. Therefore, the number of included studies was limited due to the exclusion criteria. After summarizing the results of the existing studies on cerebral microstructural changes in COVID-19 patients, specifically the use of quantitative volumetric analysis, BOLD, and DTI, it can be clearly stated that COVID-19 could be associated with changes in cerebral microstructures. These abnormalities in brain areas might lead to be associated with behaviors and mental alterations that need to be considered carefully in future studies.

Conclusion

The observed changes in the cerebral microstructure of the brain in COVID-19 patients were mainly reported in the Insula, STG, hippocampus, and thalamic radiation tract. The critical question is whether these cerebral microstructural changes are caused by the decrease in oxygen to the brain or whether the SARS-CoV-2 is attaching itself to the brain which suggests a potential pathological mechanism to induce neurological signs in the brain. Abnormalities in these brain areas might associate with some behaviors and mental and neurological alterations that need to be considered in future studies.

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Conflicts of interest

There are no conflicts of interest.

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