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Structural and Functional Differences in the Brains of Individuals with Post-Acute Sequelae of COVID-19: A Systematic Review of Neuroimaging Findings

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Systematic Review

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Abstract

Post-acute sequelae of SARS-CoV-2 infection (PASC) is a heterogeneous condition characterized by a panoply of symptoms presenting after a SARS-CoV-2 infection and persisting for months or years, with no alternative explanation. Many symptoms of PASC, such as fatigue or cognitive complaints, are neurological in nature, and various changes in the brain associated with COVID-19 have been proposed as plausible mechanisms. This systematic review summarizes structural and functional brain magnetic resonance imaging (MRI) and positron emission tomography (PET) findings in adults with PASC. Three databases (PubMed, Scopus, and Europe PMC) were searched, and 34 studies met eligibility criteria and were included in the review. Most PASC patients were female and had a history of mild to moderate acute COVID-19 on average three to thirty months prior to image acquisition, with common symptoms including fatigue, cognitive impairment, and olfactory dysfunction. Included studies varied widely in imaging modality, control group characterization, sample size, and time since infection, but were largely cross-sectional in design. Significant differences in PASC compared with controls were reported for grey and white matter volume, cortical thickness, white matter microstructure, functional connectivity, cerebral perfusion, blood-brain barrier permeability and cerebral gliosis, and glucose metabolism, among other measures, and many of these outcomes correlated with symptom burden and clinical measures. The most consistent findings were cerebral hypometabolism (especially frontotemporal) and hypoperfusion, blood-brain barrier disruption, alterations in white matter microstructure, and changes in multiple metrics in the cerebellum. Findings for volume and cortical thickness in most regions and connectivity alterations were bidirectional and inconsistent. Because most data are cross-sectional, longitudinal, multimodal studies are needed to establish whether these brain changes contribute causally to PASC symptoms.

Introduction

The World Health Organization (WHO) defines Post COVID-19 Condition (here referred to as PASC: post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection (SARS-CoV-2), but also known as “Long COVID,” “Post-COVID Syndrome,” etc.) as a set of symptoms that “occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis” (Soriano et al., 2022). Prevalence estimates of the condition are heterogeneous, due to differing definitions of PASC between different public health organizations and authors (e.g., requiring symptoms to be present for four weeks versus three months). Excess incidence of PASC has been estimated to affect between 5 and 10% of individuals with prior acute COVID-19 infection (Hastie et al., 2023; Mandel et al., 2025; Woodrow et al., 2023). Female sex increases risk of PASC, in contrast to acute COVID-19, where male sex is a risk factor for severity (Gebhard et al., 2024; Jensen et al., 2022). Older age is also a risk factor for PASC, though PASC has been noted in people of all ages including children and adolescents (Gross et al., 2024). Similarly, acute COVID-19 infection severity is a risk factor, though it is possible to acquire PASC with a mild or asymptomatic acute COVID-19 infection (Taquet et al., 2021). Symptoms are heterogeneous but commonly include fatigue, cognitive dysfunction (e.g., “brain fog,” memory deficits), sleep disruptions, olfactory and gustatory dysfunction, anxiety and depression, chest pain, dyspnea, and autonomic dysfunction. Most patients present with multiple symptoms (Hoshijima et al., 2023; Munipalli et al., 2022; Parums, 2024; Thaweethai et al., 2023). Often, these are mild, but in some cases, PASC may be more severe (Carlile et al., 2024), especially after severe acute COVID-19; further, some patients develop comorbid symptoms consistent with other conditions such as Major Depressive Disorder, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Postural Orthostatic Tachycardia Syndrome, and other disorders following an acute infection (Cantrell et al., 2024; Seighali et al., 2024; Vernon et al., 2025). While the acute COVID-19 pandemic has subsided, many patients continue to suffer from post-COVID symptoms (Mandel et al., 2025), and given the current relative lack of effective interventions, a better mechanistic understanding is needed to develop effective treatments. Because many symptoms of PASC are neurological in nature, research on the possible changes in the brain associated with PASC is essential to elucidate mechanisms related to these neurological symptoms.

Studies have reported macro- and microstructural brain alterations, metabolic disturbances, cerebrovascular dysfunction, and neuroinflammation (Douaud et al., 2022; Meyer et al., 2022; Mohammadi & Ghaderi, 2024). Magnetic resonance imaging (MRI) and positron emission tomography (PET) allow for in vivo assessment of changes in parameters related to these hypotheses, and as such, many techniques have emerged in the literature for identification of PASC-related brain changes: Voxel-Based morphometry (VBM) for voxel-wise analysis of grey matter, white matter, and cerebrospinal fluid (CSF) volume, diffusion tensor imaging (DTI) or neurite orientation dispersion and density imaging (NODDI) to assess microstructural integrity, fluid-attenuated inversion recovery (FLAIR) to assess white matter hyperintensities (WMH), blood oxygen level-dependent functional MRI (BOLD fMRI) for identification of functional connectivity, [18F]fluorodeoxyglucose (18F-FDG) PET for identification of global and regional glucose metabolism, and arterial spin labeling (ASL) to assess cerebral perfusion, among others (Pettemeridou et al., 2025). However, findings across these techniques have been variable, highlighting the need for a region-by-region synthesis across a range of MRI and PET techniques in PASC patients compared with healthy controls.

The purpose of this systematic review is to summarize the available evidence examining structural, functional, and metabolic alterations in the brains of individuals with PASC. We searched and summarized the relevant literature and organize findings by imaging modality and brain region. Finally, we highlight the gaps in the current literature related to the neurological underpinnings of PASC and suggest potential directions for future research.

Methods

Eligibility Criteria

Studies were eligible for inclusion if they met all of the following criteria: (1) original, peer reviewed journal article published in English; (2) participants were primarily adults aged 18 years and older and met the definition of Post-COVID-19 condition as defined by the World Health Organization (individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis (Soriano et al., 2022)); (3) brain structure or function was measured using a form of magnetic resonance imaging or positron emission tomography; (4) a matched, healthy control (HC) group or healthy database control was included. Because of the ubiquity of COVID-19 and the difficulty of obtaining controls who had verifiably never been infected, we allowed for studies wherein HC participants could have a prior history of COVID-19 infection, provided they had fully recovered from the acute disease and had no symptoms of PASC at the time of the study. Studies were excluded if they were case reports, pre-prints, examined exclusively or primarily pediatric populations, or exclusively studied patients with severe acute disease (to obtain a sample more representative of a typical PASC population).

Search Strategy

A systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Neither the review nor the protocol was registered. The search was conducted in three databases (PubMed, Scopus, and Europe PMC) in February, 2025 with the guidance of a health sciences librarian.

The PubMed search strategy was as follows: LitCLongCOVID[Filter] AND ("brain" OR "cerebral" OR "cortical" OR "cortex" OR "cerebellum" OR "cerebrum" OR "brainstem" OR "Brain"[Mesh]) AND ("neuroimaging" OR "magnetic resonance imaging" OR "MRI" OR "positron emission tomography" OR "PET" OR "positron-emission tomography" OR "Neuroimaging"[Mesh] OR "Magnetic Resonance Imaging"[Mesh] OR "Positron-Emission Tomography"[Mesh]).

The Scopus strategy was as follows: TITLE-ABS-KEY ("long COVID" OR "long-COVID" OR "long haul* COVID*" OR "long-hauler*" OR "post-COVID*" OR "post COVID*" OR "post-acute COVID*" OR "post-acute sequelae of SARS-CoV-2" OR "PASC" OR "post COVID-19 condition" OR "chronic COVID*" OR "COVID-19 survivor*" OR "SARS-CoV-2 survivor*" OR "persistent COVID*") AND TITLE-ABS-KEY (brain OR cerebral OR cortical OR cortex OR cerebellum OR cerebrum OR brainstem) AND TITLE-ABS-KEY (neuroimaging OR "magnetic resonance imaging" OR mri OR "positron emission tomography" OR pet).

The EuropePMC search strategy was as follows: (TITLE:("long COVID" OR "long-COVID" OR "post-COVID" OR "post COVID" OR "post-acute COVID" OR "post-acute sequelae of SARS-CoV-2" OR "PASC" OR "post COVID-19 condition" OR "chronic COVID" OR "COVID-19 survivors" OR "persistent COVID") OR ABSTRACT:("long COVID" OR "long-COVID" OR "post-COVID" OR "post COVID" OR "post-acute COVID" OR "post-acute sequelae of SARS-CoV-2" OR "PASC" OR "post COVID-19 condition" OR "chronic COVID" OR "COVID-19 survivors" OR "persistent COVID")) AND (TITLE:(brain OR cerebral OR cortical OR cortex OR cerebellum OR cerebrum OR brainstem) OR ABSTRACT:(brain OR cerebral OR cortical OR cortex OR cerebellum OR cerebrum OR brainstem)) AND (TITLE:(neuroimaging OR "magnetic resonance imaging" OR MRI OR "positron emission tomography" OR PET) OR ABSTRACT:(neuroimaging OR "magnetic resonance imaging" OR MRI OR "positron emission tomography" OR PET)) NOT (SRC:PPR).

Study Selection

Search results from databases were imported into Rayyan software for title and abstract screening and removal of duplicates (Ouzzani et al., 2016). Two researchers (CWR and KBM) independently screened titles and abstracts for inclusion eligibility. Conflicts were resolved through verbal discussion before full texts were retrieved. Researchers then independently screened full texts and documented reasons for exclusion. Conflicts were resolved through verbal discussion.

Data Extraction

Data extraction was completed using a Microsoft Excel workbook. Data were first extracted by one researcher (CWR) then verified by another researcher (KBM). Any discrepancies were checked against the original manuscript and resolved through discussion with the study team. Because of heterogeneity in modality, outcome metric and cohort definition, a narrative synthesis was performed, grouped by imaging modality and brain region, rather than a meta-analysis.

Results

Search Results and Study Selection

The database search identified 1,280 total records, 304 from PubMed, 605 from Scopus, and 371 from EuropePMC. After 426 duplicates were removed, 854 titles and abstracts were screened and 776 were excluded. The remaining 78 full text reports were assessed for eligibility and 44 were excluded. The most common reasons for exclusion were absence of a healthy control group (n = 14) or that the population did not meet the WHO definition of the post-COVID-19 condition (n = 13). A total of 34 studies met all eligibility criteria and were included in the review. The study selection process is summarized in **Fig. 1.**

Figure 1. Flow of records through the study selection process, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Records were identified from three databases (PubMed, Scopus, and Europe PMC). After removal of duplicates, records were screened by title and abstract, and the remaining full-text reports were assessed against the eligibility criteria. Reasons for exclusion at the full-text stage are shown with the corresponding number of reports. Abbreviations: MRI, magnetic resonance imaging; PET, positron emission tomography; WHO, World Health Organization.

Characteristics of Included Studies

Table 1 briefly characterizes the 34 studies included in the review. These studies were conducted in 12 countries, most frequently Germany (n = 8) and the United States (n = 5). Together they comprised approximately 1,500 adults with post-COVID-19 condition and approximately 1,200 comparison participants. Among studies that reported it, mean or median participant time since infection ranged from 3.0 to 29.9 months, with a median across studies of 8.4 months. Twenty-three studies used a healthy control group; nine studies used a historical control group, either an existing normative dataset or previously collected cohort (n = 7) or a cohort recruited before the pandemic (n = 2); and five studies compared participants with post-COVID-19 condition against individuals who had been infected and recovered. Finally, two studies by the same research group additionally included an ME/CFS comparator group.

MRI was used in twenty-six studies, and PET was used in eight. Among the MRI studies, most were performed at 3T, with the exception of a few using 7T (n = 3). MRI studies used a variety of sequences; however not all of them were related to the primary outcome measures, and many combined one or more modality in the same participants (n = 13). T1-weighted sequences were the most common (n = 18), followed by BOLD MRI (n = 10), diffusion weighted sequences (n = 9) arterial spin labeling (n = 3), dynamic contrast enhanced (DCE) MRI (n = 2), magnetic resonance spectroscopy (n = 1) and T2 relaxation under spin tagging (TRUST) MRI (n = 1). PET studies primarily used 18F-FDG to assess cerebral glucose metabolism (n = 7), with the exception of one that used 18F-FEPPA to index glial activation.

Table 1
Characteristics of Included Studies.

ID	Authors and Year	Title	Country of Study	Population Summary	Time Since Infection Onset (months)	Imaging Modality	Primary Neuroimaging Outcome(s)
1	Ajčević et al. (2023)	Cerebral hypoperfusion in post-COVID-19 cognitively impaired subjects revealed by arterial spin labeling MRI	Italy	24 Post-COVID-19 with subjective cognitive impairment; 22 healthy controls	5.9*	ASL MRI at 3T	Cerebral Perfusion
2	Barnden et al. (2023)	Altered brain connectivity in Long Covid during cognitive exertion: a pilot study	Australia	10 long-COVID; 13 healthy controls	Not explicitly stated	BOLD fMRI at 7T	Functional Connectivity
3	Besteher et al. (2022)	Larger gray matter volumes in neuropsychiatric long-COVID syndrome	Germany	30 long-COVID with neuropsychiatric symptoms; 20 healthy controls	8.7	T1-weighted MRI at 3T	Grey Matter Volume
4	Besteher et al. (2024)	Cortical thickness alterations and systemic inflammation define long-COVID patients with cognitive impairment	Germany	26 long-COVID with cognitive impairment; 35 long-COVID without cognitive impairment; 30 healthy controls with no prior history of COVID-19; 29 healthy COVID-19 survivors	10.3 with cognitive impairment, 9.7 without	T1-weighted MRI at 3T	Cortical Thickness
5	Bungenberg et al. (2024)	Characteristic functional connectome related to Post-COVID-19 syndrome	Germany	66 PASC; 57 healthy controls	7.0	BOLD fMRI at 3T	Functional Connectivity
6	Cataldo et al. (2024)	Cognitive impact and brain structural changes in long COVID patients: a cross-sectional MRI study two years post infection in a cohort from Argentina	Argentina	109 long-COVID; 28 healthy controls	29.9	T1-weighted MRI at 3T	Brain Volume, Cortical Thickness
7	Chaganti et al. (2024)	Blood brain barrier disruption and glutamatergic excitotoxicity in post-acute sequelae of SARS COV-2 infection cognitive impairment: potential biomarkers and a window into pathogenesis	Australia	14 PASC with cognitive impairment; 10 healthy controls	3.0, 12.0 follow up	DCE MRI, DTI MRI, MR Spectroscopy at 3T	Blood Brain Barrier Integrity, White Matter Integrity,
8	Chang et al. (2023)	Changes in brain activation patterns during working memory tasks in people with post-COVID condition and persistent neuropsychiatric symptoms	USA	29 PCC; 21 healthy controls	8.0	BOLD fMRI at 3T	Task Activation
9	Chien et al. (2024)	Altered brain perfusion and oxygen levels relate to sleepiness and attention in post-COVID syndrome	Germany	47 PCS; 47 healthy controls	8.4	T1-weighted MRI, BOLD fMRI at 3T	BOLD Cerebral Perfusion, Cerebral Oxygen Level Estimates
10	Clouston et al. (2025)	Glial activation among individuals with neurological post-acute sequelae of coronavirus disease 2019: A positron emission tomography study of brain fog using [(18)F]-FEPPA	USA	10 PASC with neurological symptoms (data available for 8); 14 pre-pandemic healthy controls	22.2	18F-FEPPA Dynamic PET at 3T hybrid PET/MRI	Glial Activation
11	Díez-Cirarda et al. (I) (2023)	Multimodal neuroimaging in post-COVID syndrome and correlation with cognition	Spain	86 PCS with cognitive complaints; 36 healthy controls	11.1	T1-weighted MRI, BOLD fMRI, DWI MRI, FLAIR MRI at 3T	Brain Volume, Functional Connectivity, White Matter Lesions, White Matter Integrity

ID	Authors and Year	Title	Country of Study	Population Summary	Time Since Infection Onset (months)	Imaging Modality	Primary Neuroimaging Outcome(s)
12	Díez-Cirarda et al. (II) (2023)	Hippocampal subfield abnormalities and biomarkers of pathologic brain changes: from SARS-CoV-2 acute infection to post-COVID syndrome	Spain	84 PCS with cognitive complaints; 33 healthy controls	11.1	T1-weighted MRI, BOLD fMRI, ASL MRI, DWI MRI, NODDI MRI at 3T	Hippocampal Volume, Microstructure, Connectivity, and Perfusion
13	Díez-Cirarda et al. (2025)	Choroid plexus volume is enlarged in long COVID and associated with cognitive and brain changes	Spain	129 PCC; 36 healthy controls	14.8	T1-weighted MRI, BOLD fMRI, DWI MRI at 3T	Choroid Plexus Volume, Microstructure, and Connectivity, Grey Matter Volume
14	Dressing et al. (2022)	Neuropsychologic profiles and cerebral glucose metabolism in neurocognitive long COVID syndrome	Germany	14 PCS with neurological symptoms; 45 controls (database)	6.6	18F-FDG PET	Cerebral Glucose Metabolism
15	Goehringer et al. (2023)	Brain (18)F-FDG PET imaging in outpatients with post-COVID-19 conditions: findings and associations with clinical characteristics	France	28 PCC; 28 healthy controls (database)	16.4	18F-FDG PET	Cerebral Glucose Metabolism
16	Greene et al. (2024)	Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment	Ireland	11 long-COVID with brain fog; 11 long-COVID without brain fog; 10 COVID-19 recovered controls; 60 age and sex matched healthy controls for volumetric analysis (database)	6.9* with brain fog, 5.8* without brain fog	DCE perfusion MRI, T1-weighted MRI at 3T	Blood Brain Barrier Integrity, Brain Volume, Cortical Thickness
17	Guedj et al. (2021)	(18)F-FDG brain PET hypometabolism in patients with long COVID	France	35 long-COVID; 44 healthy controls (database)	3.2*	18F-FDG PET	Cerebral Glucose Metabolism
18	Heine et al. (2023)	Structural brain changes in patients with post-COVID fatigue: a prospective observational study	Germany	47 PCC; 47 multiple sclerosis patients; 47 healthy controls	7.5*	T1-weighted MRI, DTI MRI at 3T	Subcortical Structure Volume, White Matter Integrity
19	Horowitz et al. (2024)	Persistent brain metabolic impairment in long COVID patients with persistent clinical symptoms: a nine-month follow-up [(18)F]FDG-PET study	France	56 long-COVID; 51 pre-pandemic healthy controls	7.0, 16.0 follow-up	18F-FDG PET	Cerebral Glucose Metabolism
20	Hosp et al. (2024)	Cerebral microstructural alterations in Post-COVID-condition are related to cognitive impairment, olfactory dysfunction and fatigue	Germany	89 PCC; 38 COVID-19 recovered controls; 46 healthy controls	8.4*	T1-weighted MRI, DMI MRI at 3T	Diffusion Microstructure, Brain Volume, Cortical Thickness
21	Joshi et al. (2024)	Structural MRI correlates of cognitive and neuropsychiatric symptoms in Long COVID: a pilot study	USA	15 long-COVID; 8 healthy controls	9.3	T1-weighted MRI, T2-weighted MRI at 3T	Cortical Thickness, Grey Matter Volume
22	Liu et al. (2024)	Elevated cerebral oxygen extraction in patients with post-COVID conditions	USA	25 PCC with neurological symptoms; 59 healthy controls	7.0 to 8.0	TRUST MRI, T1-weighted MRI, FLAIR at 3T	Oxygen Extraction Fraction, White Matter Hyperintensities
23	Martini et al. (2022)	Time-dependent recovery of brain hypometabolism in neuro-COVID-19 patients	Italy	12 subacute COVID-19; 7 PCC with neurological symptoms; 125 healthy controls (database)	5.0 and 7.0 to 9.0	18F-FDG PET	Cerebral Glucose Metabolism

ID	Authors and Year	Title	Country of Study	Population Summary	Time Since Infection Onset (months)	Imaging Modality	Primary Neuroimaging Outcome(s)
24	Muccioli et al. (2023)	Cognitive and functional connectivity impairment in post-COVID-19 olfactory dysfunction	Italy	23 with persistent COVID-19 related olfactory dysfunction; 26 healthy controls	11.0	T1-weighted MRI, BOLD fMRI at 3T	Brain Volume, Cortical Thickness, Functional Connectivity
25	Nelson et al. (2024)	Differences in brain structure and cognitive performance between patients with long-COVID and those with normal recovery	Canada	56 long-COVID; 35 COVID-19 recovered controls	6.0	T1-weighted MRI, DTI MRI at 3T	White Matter Integrity, White Matter Lesions
26	O'Connor et al. (2024)	Macro- and microstructural white matter differences in neurologic postacute sequelae of SARS-COV-2 infection	USA	31 PASC with neurological symptoms; 41 never-infected controls	10.6	T1-weighted MRI, T2-weighted MRI, DWI MRI at 3T	Brain Volume, White Matter Microstructure, White Matter Lesions
27	Pacheco-Jaime et al. (2025)	Structural brain changes in post-COVID condition and its relationship with cognitive impairment	Spain	128 PCC (71 “cognitively altered”, 57 “non-altered”); 37 healthy controls	18.0*	T1-weighted MRI, DWI MRI at 3T	Cortical Thickness, White Matter Integrity
28	Rozenblum et al. (2025)	Cognitive impairment and brain metabolic changes in post-acute sequelae of COVID-19: insights from an [18F] FDG PET/CT cohort study	France	87 PASC with neurocognitive symptoms; 55 healthy controls (database)	13.7*	18F-FDG PET	Cerebral Glucose Metabolism
29	Sakamoto et al. (2024)	Changes in cerebral glucose metabolism among mild long COVID patients: an [18F]FDG PET/CT study	Brazil	22 PCC with cognitive complaints; 20 healthy controls (database)	Not explicitly stated	18F-FDG PET	Cerebral Glucose Metabolism
30	Tanashyan et al. (2024)	Neuroimaging correlates of post-COVID-19 symptoms: A functional MRI approach	Russia	30 post-COVID with fatigue; 20 healthy controls	Not explicitly stated	BOLD fMRI at 3T	Task Activation
31	Thapaliya et al. (2023)	Brainstem volume changes in myalgic encephalomyelitis/chronic fatigue syndrome and long COVID patients	Australia	8 long-COVID; 10 Myalgic encephalomyelitis/chronic fatigue syndrome; 10 healthy controls	Not explicitly stated	T1-weighted MRI at 7T	Brainstem Volume
32	Thapaliya et al. (2025)	Hippocampal subfield volume alterations and associations with severity measures in long COVID and ME/CFS: A 7T MRI study	Australia	15 long-COVID; 29 Myalgic encephalomyelitis/chronic fatigue syndrome; 15 healthy controls	7.2	T1-weighted MRI at 7T	Hippocampal Volume
33	Troll et al. (2025)	Altered corticostriatal connectivity in long-COVID patients is associated with cognitive impairment	Germany	60 long-COVID; 52 healthy controls (26 COVID-19 survivors without long COVID, 26 never infected)	Not explicitly stated	BOLD fMRI at 3T	Functional Connectivity
34	Wang et al. (2025)	Cerebral blood flow alterations and host genetic association in individuals with long COVID: A transcriptomic-neuroimaging study	China	22 long-COVID part of a group of 50 pooled acute and long COVID; 30 healthy controls	3.0*	ASL MRI at 3T	Cerebral Perfusion

Table 1. Characteristics of the 34 studies included in the review listed alphabetically by first author. Population summaries use the terminology described by each study. Control groups described as database were from an existing normative imaging dataset or a retrospective cohort. Time since infection onset is the mean (or median*) interval between infection, symptom onset, or clinical diagnosis and neuroimaging converted to months. Primary neuroimaging outcome(s) are listed, though studies may have had other outcome measures. Abbreviations: ASL, arterial spin labeling; BOLD, blood oxygen level dependent; DCE, dynamic contrast enhanced; DMI, diffusion microstructure imaging; DTI, diffusion tensor imaging; DWI, diffusion weighted imaging; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion recovery; fMRI, functional magnetic

resonance imaging; ME/CFS, myalgic encephalomyelitis and chronic fatigue syndrome; MRI, magnetic resonance imaging; NODDI, neurite orientation dispersion and density imaging; PASC, post-acute sequelae of SARS-CoV-2 infection; PCC, post-COVID-19 condition; PCS, post-COVID syndrome; PET, positron emission tomography; T, tesla; TRUST, T2 relaxation under spin tagging.

Summary of Outcome Measures

Table 2 describes the primary outcomes and region-specific findings compared with controls. Many studies assessed more than one outcome or examined more than one brain region within a given modality. The primary outcomes measured were grey matter volume or cortical thickness (n = 15), white matter microstructure (n = 9), cerebral glucose metabolism (n = 7), functional connectivity (n = 7), cerebral perfusion (n = 4), white matter lesions (n = 3), task-based activation (n = 2), blood-brain barrier permeability (n = 2), glial cell activation (n = 1), and oxygen extraction fraction (n = 1).

Regional measurement varied by study, with the frontal and temporal cortex being the most frequently measured (n = 17), followed by global or whole brain measures (n = 12), limbic and medial temporal structures (n = 9), parietal or occipital cortex (n = 8), insula and cingulate cortex, cerebellum, and white matter tracts (n = 7 each), brainstem (n = 5), basal ganglia and thalamus (n = 3), and olfactory cortex and choroid plexus or ventricular system (n = 2 each). Functional connectivity findings are reported by network or connection rather than by anatomical region.

Table 2
Brain structure and function outcomes in post-COVID-19 condition compared with controls.

Imaging Modality	Brain Region	Direction of Change	Finding	Reference
T1-Weighted MRI (Volumes and Cortical Thickness)	Frontal and Temporal Cortex	Increased thickness	Greater cortical thickness in prefrontal and temporal gyri. Thickness increased stepwise from never infected, to healthy post-COVID, to cognitively unimpaired PASC, to PASC with cognitive impairment.	Besteher et al. (2024)
		Increased thickness	Greater cortical thickness in the right superior frontal and right rostral middle frontal gyri, negatively correlated with working memory performance (in PASC only). Cognitively altered PASC had greater cortical thickness in the right medial orbitofrontal and left rostral middle frontal gyri compared with non-cognitively altered PASC.	Pacheco-Jaime et al. (2025)
		Decreased thickness	Lower cortical thickness in frontal and temporal lobes when comparing all post-COVID to controls and lower frontal pole thickness in all post-COVID groups. Lower superior temporal gyrus thickness in PASC with brain fog only. Lower superior frontal gyrus thickness in PASC with and without brain fog.	Greene et al. (2024)
		Decreased thickness	Lower left superior temporal sulcus thickness. Trend for lower thickness in the right superior temporal gyrus though not significant after correcting for multiple comparisons.	Cataldo et al. (2024)
		No change in thickness	Trend for greater right rostral middle frontal gyrus cortical thickness though not significant after correcting for multiple comparisons.	Joshi et al. (2024)
		Increased volume	Larger grey matter volume in frontotemporal areas. No associations with clinical symptoms.	Besteher et al. (2022)
		Increased volume	Larger frontal lobe white matter volume and grey matter volume in the orbitofrontal cortex.	O'Connor et al. (2024)
		Decreased volume	Smaller frontal and temporal lobe volume in all post-COVID compared with controls.	Greene et al. (2024)
		Decreased volume	Smaller volume in the frontal gyrus and superior temporal lobes (at uncorrected $p < 0.001$). Changes were more pronounced in previously hospitalized patients compared with non-hospitalized. Associated with poorer attention and processing speed.	Díez-Cirarda et al. (I) (2023)
		Decreased volume	Lower mean grey matter volume within a choroid plexus (ChP)-correlated mask including the orbitofrontal cortex, inferior frontal gyrus, and Rolandic operculum (not region specific).	Díez-Cirarda et al. (2025)
		No change in volume	Trend towards smaller volume in the left lateral orbital cortex, though it was not significant after correcting for multiple comparisons.	Muccioli et al. (2023)
		No change in volume	Trend for smaller right inferior temporal volume though not significant after correcting for multiple comparisons.	Cataldo et al. (2024)
	Parietal and Occipital Cortex	Increased thickness	Greater cortical thickness in parietal areas. Cortical thickness was highest in PASC patients with cognitive impairment.	Besteher et al. (2024)
		Decreased thickness	Lower cortical thickness in left lingual gyrus, left postcentral gyrus, and left supramarginal gyrus. Trend for lower cortical thickness in the left superior parietal gyrus, right postcentral gyrus, left and right precuneus, though not significant after correcting for multiple comparisons.	Cataldo et al. (2024)
		Increased volume	Larger occipital lobe volume in all post-COVID compared with controls.	Greene et al. (2024)
		Mixed results	Larger grey matter volume in the left lateral occipital lobe, superior parietal gyrus, angular gyrus and left pre- and post-central gyri. Few clusters of smaller grey matter volume in bilateral lingual gyri, right lateral occipital lobe, and cuneus.	Besteher et al. (2022)

Imaging Modality	Brain Region	Direction of Change	Finding	Reference
		Decreased volume	Smaller volume in the occipital lobe (at uncorrected p < 0.001).	Díez-Cirarda et al. (I) (2023)
		No change in volume	Trend for smaller left inferior parietal and left lingual gyrus volume, though not significant after correcting for multiple comparisons.	Cataldo et al. (2024)
	Insula and Cingulate Cortex	Increased thickness	Greater cortical thickness in the insula and posterior cingulate. Cortical thickness was highest in PASC patients with cognitive impairment.	Besteher et al. (2024)
		No change in thickness	Trend for greater cortical thickness in the caudal anterior cingulate, right posterior and right isthmus cingulate, though not significant after correcting for multiple comparisons.	Joshi et al. (2024)
		Increased volume	Larger grey matter volume in the insula bilaterally.	Besteher et al. (2022)
		Increased volume	Larger grey matter volume in the anterior cingulate.	O'Connor et al. (2024)
		Decreased volume	Lower mean grey matter volume within a choroid plexus-correlated mask including the insula and cingulum.	Díez-Cirarda et al. (2025)
	Limbic and Medial Temporal Structures	Increased thickness	Greater cortical thickness in the parahippocampal gyrus. Cortical thickness was highest in PASC patients with cognitive impairment.	Besteher et al. (2024)
		Increased volume	Larger grey matter volume in the hippocampus and amygdala.	Besteher et al. (2022)
		Increased volume	Larger left hippocampal volume in certain subfields in both PASC and ME/CFS patients compared with controls.	Thapaliya et al. (2025)
		Decreased volume	Smaller volume in the left parahippocampal gyrus (at uncorrected p < 0.001).	Díez-Cirarda et al. (I) (2023)
		Decreased volume	Smaller volume across the whole hippocampus and all but two subfields. Generally accentuated in previously hospitalized patients. Volumes in some subfields correlated with cognition.	Díez-Cirarda et al. (II) (2023)
		Decreased volume	Lower mean grey matter volume within a choroid plexus-correlated mask including the hippocampus.	Díez-Cirarda et al. (2025)
		No change in volume	Trend of smaller volume in amygdala and hippocampus though results did not reach the threshold for significance.	Muccioli et al. (2023)
	Basal Ganglia and Thalamus	Increased volume	Larger grey matter volume in the basal ganglia and thalamus bilaterally.	Besteher et al. (2022)
		Decreased volume	Smaller volume in the left putamen. Deformations observed in the left thalamus, bilateral putamen and pallidum, but not the nucleus accumbens or caudate.	Heine et al. (2023)
		Decreased volume	Lower mean grey matter volume within a choroid plexus-correlated mask including the caudate, putamen, pallidum, and thalamus.	Díez-Cirarda et al. (2025)
	Brainstem	Increased volume	Larger volumes in the pons, superior cerebellar peduncle, and whole brainstem. Trends, but no significant differences in the medulla and midbrain.	Thapaliya et al. (2023)
	Cerebellum	Decreased volume	Smaller volume in the anterior cerebellum (at uncorrected p < 0.001). Changes were more pronounced in previously hospitalized patients compared with non-hospitalized.	Díez-Cirarda et al. (I) (2023)
		Decreased volume	Smaller right cerebellum cortex volume. Trend for smaller left cerebellum cortex though not significant after correcting for multiple comparisons.	Cataldo et al. (2024)

Imaging Modality	Brain Region	Direction of Change	Finding	Reference
		Decreased volume	Smaller cerebellar white matter volume in all post-COVID groups compared to controls.	Greene et al. (2024)
		Decreased volume	Smaller grey matter volume in a cluster of the cerebellum and bilateral lingual gyri.	Besteher et al. (2022)
	Choroid Plexus and Ventricular System	Increased volume	Larger CSF volume in PASC patients with brain fog and in recovered post-COVID individuals, but not in PASC without brain fog. Larger lateral ventricle volume in all post-COVID individuals compared with controls.	Greene et al. (2024)
		Increased volume	Greater choroid plexus volume. Correlated with poorer cognition, lower grey matter volume, altered white matter microstructure, but not with clinical symptoms.	Díez-Cirarda et al. (2025)
	Global/Whole-brain	No change in thickness	Whole brain cortical thickness did not differ between groups.	Pacheco-Jaime et al. (2025)
		No change in thickness	Cortical thickness and surface area did not differ between groups.	Hosp et al. (2024)
		No change in thickness	Whole brain cortical thickness did not differ between groups.	Muccioli et al. (2023)
		Increased volume	Larger total cerebral white matter volume. Nonsignificant trend for lower CSF volume. Grey matter volume did not differ.	O'Connor et al. (2024)
		Decreased volume	Smaller cerebral white matter volume in patients with brain fog and recovered post-COVID individuals, but not in PASC without brain fog. Smaller global brain volume in PASC patients with brain fog.	Greene et al. (2024)
		Decreased volume	Smaller grey matter volume within the choroid plexus-correlated composite mask.	Díez-Cirarda et al. (2025)
		No change in volume	Grey matter and subcortical volumetric measures did not differ between groups.	Pacheco-Jaime et al. (2025)
		No change in volume	Grey matter volume did not differ between groups.	Hosp et al. (2024)
		No change in volume	Whole brain or cerebrum-specific grey matter volume did not differ between groups after correction for multiple comparisons.	Greene et al. (2024)
		No change in volume	Age-adjusted grey matter, white matter, or total brain volume did not differ between groups.	Cataldo et al. (2024)
DTI / dMRI / DKI/ DMI / NODDI (White Matter Microstructure)	White Matter Tracts	Altered white matter microstructure	Lower whole-brain values of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD). Lower MD and AD in specific tracts (corpus callosum, forceps minor, middle longitudinal fasciculus, uncinate tract, and fronto-occipital fasciculus).	Díez-Cirarda et al. (I) (2023)
		Altered grey matter microstructure	Increased intracellular volume fraction (FICVF) and orientation dispersion index (ODI) in the hippocampus, associated with some metrics of poorer cognition.	Díez-Cirarda et al. (II) (2023)
		Mixed white matter microstructure results	Lower FA in the right superior longitudinal fasciculus, splenium and genu of the corpus callosum, right uncinate fasciculus, and forceps major. Associated with subjective memory failure in PASC only. Differences in whole brain FA, MD, AD, and RD did not reach the threshold for significance.	Pacheco-Jaime et al. (2025)
		Mixed white matter microstructure results	Higher FA and lower MD in multiple regions including frontal white matter, corpus callosum, cerebral peduncles, and sagittal striatal white matter. In the superior longitudinal fasciculus, FA increased and MD decreased from baseline to 12-month follow-up.	Chaganti et al. (2024)
		Mixed white matter microstructure results	No differences in FA, AD, or RD; however, lower MD in multiple regions compared with post-COVID individuals with normal recovery.	Nelson et al. (2024)

Imaging Modality	Brain Region	Direction of Change	Finding	Reference
		Mixed white matter microstructure results	Lower FA, correlated with increased ChP volume in the bilateral fornix, bilateral anterior thalamic radiation, and callosal body. FA was positively associated with cognition. Higher AD in PASC within these regions; ChP volume not associated with MD or RD.	Díez-Cirarda et al. (2025)
		Mixed white matter microstructure results	FA increased in the left thalamus, decreased in the right pallidum; did not differ in other subcortical structures tested. RD, MD, and AD did not differ in any subcortical structures tested. No whole brain white matter differences.	Heine et al. (2023)
	Widespread	Increased kurtosis	Widespread increased white matter mean kurtosis.	O'Connor et al. (2024)
		Increased free water	Volume shift from membrane-enclosed to microstructural free-water compartment in grey matter. Increased V-extra in the corpus callosum, internal capsule, brainstem, and cerebellum, more pronounced in post-COVID individuals without PASC.	Hosp et al. (2024)
3D-FLAIR (White Matter Lesions)	Widespread	Decreased lesions	After adjusting for age, lower white matter hyperintensity total lesion volume and number of lesions in PASC.	Díez-Cirarda et al. (I) (2023)
		No change in lesions	White matter hyperintensities greater than expected for age were more prevalent in PASC compared with individuals with normal recovery, though the difference did not reach the threshold for significance.	Nelson et al. (2024)
		No change in lesions	There was no significant group difference in Fazekas score of white matter hyperintensities.	O'Connor et al. (2024)
BOLD fMRI (Task-Based Activation)	Multiple Regions	Increased task-based activation	Greater activation on 2-back memory task in the right superior frontal gyrus and less deactivation of the posterior cingulate gyrus. Hospitalized patients had lesser activation than non-hospitalized patients in some frontal regions. BOLD signals in certain regions correlated with psychological and clinical outcomes.	Chang et al. (2023)
		Increased task-based activation	Greater activation in the supramarginal gyri, posterior cingulate cortex, opercular parts of precentral gyri and cerebellum posterior lobe.	Tanashyan et al. (2024)
BOLD fMRI/rsfMRI (Functional Connectivity/FC)	Brainstem Network	Increased connectivity	Among twenty select ROIs, there was increased connectivity between the medulla and midbrain, and between the medulla and a default mode network node during a cognitive task. Several brainstem correlations were associated with autonomic scores.	Barnden et al. (2023)
		Decreased connectivity	Reduced functional connectivity in the midbrain.	Bungenberg et al. (2024)
	Cerebellar Network	Increased connectivity	Increased functional connectivity involving the cerebellum.	Bungenberg et al. (2024)
	Cingulate Network	Mixed results	Altered connectivity in the cingulate cortex (decreased anterior cingulate connectivity, increased posterior cingulate connectivity).	Bungenberg et al. (2024)
	Corticostriatal Network	Increased connectivity	Increased connectivity between right posterior caudate and bilateral precentral gyri (left precentral connectivity associated with lower MoCA score), and between right anterior globus pallidus and posterior cingulate cortex/temporal pole.	Troll et al. (2025)
	Hippocampal and Parahippocampal Network	Decreased connectivity	Reduced connectivity between the left and right parahippocampal gyri.	Díez-Cirarda et al. (I) (2023)
		Decreased connectivity	Reduced connectivity between the right hippocampal head and each of a parietal area and the left anterior parahippocampal division.	Díez-Cirarda et al. (II) (2023)
	Olfactory Network	Decreased connectivity	Decreased connectivity involving the olfactory and orbitofrontal cortex.	Bungenberg et al. (2024)

Imaging Modality	Brain Region	Direction of Change	Finding	Reference
		Mixed results	Within the olfactory network, reduced global modularity, and increased connectivity centered on the right thalamus.	Muccioli et al. (2023)
	Thalamic Network	Increased connectivity	Increased thalamic (intralaminar nuclei) connectivity.	Bungenberg et al. (2024)
	Widespread	Decreased connectivity	Reduced connectivity between left cerebellar lobule III (vermis) and each of the left and right frontal superior orbital cortices.	Díez-Cirarda et al. (I) (2023)
		Mixed results	Widespread additional connectivity differences identified across ROI-voxel pairs during a cognitive task, mostly weaker in PASC.	Barnden et al. (2023)
		Mixed results	Functional connectivity did not differ between PASC and healthy controls (HC), though FC values between some nodes were associated with ChP volume.	Díez-Cirarda et al. (2025)
Arterial Spin Labeling (Perfusion/Blood Flow)	Frontal and Temporal Cortex	Decreased perfusion	Lower cerebral perfusion in frontal and temporal lobes, more extensive in the right hemisphere.	Ajčević et al. (2023)
		Decreased perfusion	Lower cerebral perfusion in left inferior frontal gyrus, superior temporal gyrus, and middle frontal gyrus in the PASC group compared with HC. Recovered COVID-19 group also had lower cerebral perfusion in the bilateral medial frontal gyrus, superior frontal gyrus and supplementary motor area. In the PASC group, lower CBF associated with greater fatigue and poorer memory.	Wang et al. (2025)
	Parietal and Occipital Cortex	Decreased perfusion	Lower perfusion in the right parietal lobe.	Ajčević et al. (2023)
	Limbic and Medial Temporal Structures	Decreased perfusion	Lower hippocampal perfusion, associated with some measures of memory performance. More severe in previously hospitalized patients.	Díez-Cirarda et al. (II) (2023)
	Global/Whole-brain	Decreased perfusion	Lower global perfusion.	Ajčević et al. (2023)
Resting-State BOLD MRI (Cerebral Perfusion and Oxygenation)	Multiple Regions	Mixed results	Lower whole brain white matter and cortical grey matter oxygen levels. Putamen, thalamic, deep grey matter, and hippocampal oxygen levels were lower, though not significant after multiple comparisons. Perfusion did not differ. Mixed associations with clinical measures.	Chien et al. (2024)
Dynamic Contrast-Enhanced MRI (Blood-Brain Barrier Integrity)	Frontal and Temporal Cortex	Increased permeability	Greater blood brain barrier leakage in the bilateral temporal lobes and frontal cortices in PASC with brain fog.	Greene et al. (2024)
		Increased permeability	Greater blood brain barrier permeability in the frontal white matter.	Chaganti et al. (2024)
	Brainstem	Increased permeability	Greater blood brain barrier permeability in the brainstem.	Chaganti et al. (2024)
	Global/Whole-brain	Increased permeability	Greater blood brain barrier leakage in PASC with brain fog.	Greene et al. (2024)
TRUST MRI (Oxygen Extraction Fraction)	Global/Whole-brain	Mixed results	Previously hospitalized patients had higher oxygen extraction fraction than both controls and non-hospitalized patients. Oxygen extraction fraction did not differ between non-hospitalized patients and controls.	Liu et al. (2024)
18F-FDG PET (Glucose Metabolism)	Frontal and Temporal Cortex	Decreased metabolism	Lower glucose metabolism in three frontotemporal clusters, especially right-sided, associated with poorer symptom/clinical measures.	Goehringer et al. (2023)
		Decreased metabolism	Lower glucose metabolism in the frontotemporal cortex at baseline (7 months) and follow-up (16 months). No significant differences between time points. Lower metabolism correlated with increased symptoms.	Horowitz et al. (2024)
		Decreased metabolism	Lower glucose metabolism in the orbitofrontal cortex and frontal gyri, lessening with time since onset and	Martini et al. (2022)

Imaging Modality	Brain Region	Direction of Change	Finding	Reference
			absent at 7 to 9 months. Correlated with clinical measures.	
		Decreased metabolism	Lower glucose metabolism in the left fusiform gyrus. No significant difference in the frontal gyri.	Rozenblum et al. (2025)
	Parietal and Occipital Cortex	Decreased metabolism	Lower glucose metabolism in the angular gyrus (absent from 3 months onward).	Martini et al. (2022)
		Increased metabolism	Higher glucose metabolism in the right angular gyrus.	Rozenblum et al. (2025)
	Insula and Cingulate Cortex	Decreased metabolism	Lower glucose metabolism in the insula, lessening with time since onset and absent at 7 to 9 months. Correlated with clinical measures.	Martini et al. (2022)
		Decreased metabolism	Lower glucose metabolism in the insula (at baseline and follow-up).	Horowitz et al. (2024)
	Limbic and Medial Temporal Structures	Increased metabolism	Higher glucose metabolism in the bilateral amygdala and hippocampi, associated with CRP levels.	Martini et al. (2022)
		Decreased metabolism	Lower glucose metabolism in the amygdala and parahippocampal area.	Rozenblum et al. (2025)
		Decreased metabolism	Lower glucose metabolism in the medial temporal cortex (at baseline and follow-up).	Horowitz et al. (2024)
	Brainstem	Increased metabolism	Higher glucose metabolism in the brainstem, associated with CRP levels.	Martini et al. (2022)
		Decreased metabolism	Lower glucose metabolism in the pons (at baseline and follow-up).	Horowitz et al. (2024)
		Decreased metabolism	Lower glucose metabolism in the pons.	Rozenblum et al. (2025)
		No change in metabolism	No change in brainstem metabolism.	Goehringer et al. (2023)
	Cerebellum	Increased metabolism	Higher glucose metabolism in the cerebellum. Associated with CRP levels.	Martini et al. (2022)
		Decreased metabolism	Lower glucose metabolism in the cerebellum (at baseline and follow-up).	Horowitz et al. (2024)
		Decreased metabolism	Lower glucose metabolism in the vermis, associated with memory impairment.	Rozenblum et al. (2025)
		No change in metabolism	No change in cerebellar metabolism.	Goehringer et al. (2023)
	Olfactory Cortex	Decreased metabolism	Lower glucose metabolism in the olfactory cortex (at baseline and follow-up).	Horowitz et al. (2024)
		No change in metabolism	No significant whole-group difference in olfactory regions.	Rozenblum et al. (2025)
	Global/Whole-brain	No change in metabolism	Glucose metabolism did not differ between groups, and was not correlated with clinical measures.	Dressing et al. (2022)
		No change in metabolism	Glucose metabolism did not differ between groups.	Martini et al. (2022)
		No change in metabolism	Twenty-six regions were nominally hypermetabolic or hypometabolic, though none reached the threshold for significance.	Sakamoto et al. (2024)
	Multiple Regions	Decreased metabolism	Lower glucose metabolism in two clusters: one spanning the bilateral rectal/orbital gyrus (including the olfactory gyrus) and the right temporal lobe, amygdala, hippocampus, and thalamus, and one spanning the bilateral pons, medulla, and cerebellum. Hypometabolism was associated with worsened symptoms and clinical outcomes.	Guedj et al. (2021)

Imaging Modality	Brain Region	Direction of Change	Finding	Reference
[18F]-FEPPA PET (Cerebral Gliosis)	Widespread	Increased glial activation	Elevated measures of cerebral gliosis in the medial prefrontal cortex, orbital prefrontal cortex, anterior cingulate, hippocampus, ventral striatum, cerebellum, and across grey and white matter broadly.	Clouston et al. (2025)

Table 2. Brain structure and function outcomes in PASC compared with controls. Direction of change reflects the comparison between the post-COVID-19 condition group and controls unless otherwise noted in the finding column. For functional connectivity, findings are organized by network or connection rather than by anatomical region. Studies may have reported additional outcomes not shown. Note that for Díez-Cirarda et al. (2025), grey matter volume and white matter diffusion was compared within masks of regions that correlated with choroid plexus volume in PASC; therefore, differences are not region specific. Abbreviations: AD, axial diffusivity; BOLD, blood oxygen level dependent; CSF, cerebrospinal fluid; DKI, diffusion kurtosis imaging; DMI, diffusion microstructure imaging; dMRI, diffusion magnetic resonance imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; FC, functional connectivity; FDG, fluorodeoxyglucose; FLAIR, fluid-attenuated inversion recovery; FICVF, intracellular volume fraction; fMRI, functional magnetic resonance imaging; HC, healthy controls; MD, mean diffusivity; ME/CFS, myalgic encephalomyelitis and chronic fatigue syndrome; MoCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NODDI, neurite orientation dispersion and density imaging; ODI, orientation dispersion index; PASC, post-acute sequelae of SARS-CoV-2 infection (post-COVID-19 condition); PET, positron emission tomography; RD, radial diffusivity; ROI, region of interest; TRUST, T2 relaxation under spin tagging; V-extra, extraneurite volume fraction.

Discussion

Brain volume and cortical thickness

Fifteen studies used T1-weighted MRI to investigate grey matter volume (GMV) and cortical thickness (CT) in PASC compared with controls. Findings were directionally heterogeneous, though 12 studies reported at least one significant regional difference, and 8 reported multiple changes.

In frontal and temporal regions, Besteher et al. (2024) reported greater CT in prefrontal and temporal gyri, with thickness increasing stepwise from never infected controls, to COVID recovered controls, to cognitively unimpaired PASC, to PASC patients with cognitive impairment (Montreal Cognitive Assessment (MoCA) score < 26). Similarly, Pacheco-Jaime et al. (2025) found greater CT in the right superior frontal and right rostral middle frontal gyri across the full PASC sample relative to controls. A separate, within-group comparison found that cognitively impaired PASC patients also had greater CT than unimpaired PASC patients in the right medial orbitofrontal and left rostral middle frontal gyri, specifically. Besteher et al. (2022) also reported larger GMV in frontotemporal clusters. Joshi et al. (2024) found a similar trend toward greater CT in the right rostral middle frontal gyrus, although it did not survive correction for multiple comparisons, possibly reflecting the study's small sample (n = 15 PASC). In the orbitofrontal cortex, O'Connor et al. (2024) found greater GMV and greater frontal lobe white matter volume in PASC overall, broadly convergent with Pacheco-Jaime et al. (2025) where CT was increased in the right medial orbitofrontal region among cognitively impaired PASC patients. In the parietal cortex, Besteher et al. (2024) found greater CT, highest among patients with cognitive impairment, and Greene et al. (2024) found greater occipital lobe GMV across the PASC group.

In contrast, Muccioli et al. (2023) found a nonsignificant trend toward smaller lateral orbital cortex volume, and Greene et al. (2024) found reduced CT in the frontal pole and superior frontal gyrus, as well as reduced GMV spanning the frontal and temporal lobes. Cataldo et al. (2024) found reduced CT in the left postcentral gyrus, left supramarginal gyrus, left superior temporal sulcus, and left lingual gyrus, with additional nonsignificant trends toward reduced thickness in the right superior temporal gyrus, left superior parietal gyrus, right postcentral gyrus, and the precuneus bilaterally. The lingual gyrus finding is consistent with Besteher et al. (2022), who reported smaller GMV in bilateral lingual gyri, as well as in the right lateral occipital lobe and cuneus. Further, Díez-Cirarda et al. (I) (2023) found smaller GMV in the frontal gyrus and superior temporal lobes, more pronounced in previously hospitalized patients. However, this finding reached significance only at an uncorrected threshold of $p < 0.001$. The same study also found smaller occipital lobe volume at that uncorrected threshold.

Within the insula and cingulate cortex, Besteher et al. (2022) and Besteher et al. (2024) reported increased GMV and CT, respectively, in the insula. O'Connor et al. (2024) found increased anterior cingulate GMV, and Besteher et al. (2024) found increased CT in adjacent but distinct posterior cingulate subregions. Joshi et al. (2024) found increased CT in the caudal anterior cingulate bilaterally, and in the right-sided posterior and isthmus cingulate, along with increased GMV bilaterally in the posterior cingulate and in the right isthmus cingulate. However, none of these differences survived correction for multiple comparisons. Díez-Cirarda et al. (2025) found the opposite pattern: reduced GMV in the insula and cingulum, which was also correlated with larger choroid plexus volume in PASC.

In limbic and medial temporal structures, Besteher et al. (2024) found increased parahippocampal CT, while Díez-Cirarda et al. (I) (2023) found reduced parahippocampal GMV, again at the uncorrected threshold of < 0.001. Hippocampal findings were similarly mixed: Besteher et al. (2022) and Thapaliya et al. (2025) both found increased hippocampal volume (bilaterally for the former; left-sided and across several subfields, including

the whole hippocampal head, for the latter), while Díez-Cirarda et al. (II) (2023) found reduced volumes across the whole hippocampus and all but two subfields, and Muccioli et al. (2023) found a nonsignificant trend toward smaller hippocampal and amygdala volume in PASC. In both the Díez-Cirarda and Thapaliya cohorts, hippocampal and subfield volumes were associated with some clinical severity measures. Additionally, Besteher et al. (2022) found increased GMV of the amygdala, also in contrast with Muccioli et al.'s (2023) trend in the same structure.

Regarding other subcortical regions, Besteher et al. (2022) found increased GMV in the basal ganglia and thalamus bilaterally. In contrast, Díez-Cirarda et al. (2025) found reduced GMV in the caudate and putamen, in conjunction with reduced cortical GMV in the orbitofrontal cortex and frontal inferior gyrus. Both findings correlated with the study's central finding of enlarged choroid plexus volume, as did altered diffusion metrics (reduced fractional anisotropy (FA) and increased axial diffusivity (AD), measures of white matter organization and integrity) in white matter tracts connecting to frontal regions. The authors suggest this may reflect some neuroinflammatory mechanisms involving the blood-CSF barrier, potentially related to the pathogenesis of brain fog in this population. Finally, Heine et al. (2023) found decreased left putamen volume in PASC compared with controls. The same study also found inward surface deformations of the left thalamus and bilateral putamen and pallidum, but not the caudate or nucleus accumbens. In exploratory analyses, smaller thalamic and right putamen volumes were associated with poorer short-term memory.

In the brainstem, Thapaliya et al. (2023) found significantly larger pons, superior cerebellar peduncle (SCP), and whole brainstem volume in PASC compared with controls, despite a small sample (n = 8 PASC); medulla and midbrain volume demonstrated the same trend but did not survive correction for multiple comparisons. Interestingly, when PASC patients were compared with a group of participants with ME/CFS (which shares many symptoms with PASC, but has variable etiologies), they did not differ on any of these measures. Likewise, Thapaliya et al. (2025) found that while the left hippocampal head and several of its subfield volumes were higher in PASC than in HC, there was no difference in volumes between PASC and ME/CFS. Additionally, white and grey matter volumes were consistently reduced across four studies in the cerebellum: Greene et al. (2024) and Besteher et al. (2022), Díez-Cirarda et al. (I) (2023) in the anterior cerebellum (only at an uncorrected threshold), and Cataldo et al. (2024) in the right cerebellar cortex, with a nonsignificant trend on the left.

Greene et al. (2024) also reported increased lateral ventricle volume across all post-COVID individuals, and increased CSF volume confined to patients with "brain fog" and to recovered individuals, but not to PASC without brain fog. They also found decreased cerebral white matter volume in the same subgroups and decreased total brain volume in PASC patients with brain fog only. Hosp et al. (2024) reported a related finding, an increased free water (V-CSF) fraction in grey matter in PASC, which was partly associated with initial disease severity. Díez-Cirarda et al. (2025) reported higher choroid plexus volume in PASC, which was associated with a decrease in grey matter volume in multiple regions. However, the authors did not assess correlations with total CSF volume, although choroid plexus volume positively correlated with lateral ventricle volume. In conjunction with the Greene et al. findings, this may reflect some potentially pathological remodeling of the blood-CSF barrier, although longitudinal data are notably absent. O'Connor et al. (2024) reported higher total cerebral white matter volume alongside a nonsignificant trend for lower CSF volume. Both authors interpreted their results as consistent with neuroinflammation, despite reporting different phenotypes. O'Connor et al. (2024) also noted that these changes may be consistent with extracellular fluid shifts, in line with Hosp et al. (2024).

Several studies found no significant differences in global structural measures. Hosp et al. (2024) found no group difference in CT, surface area, or GMV; similarly, Muccioli et al. (2023) and Pacheco-Jaime et al. (2025) found no difference in whole brain CT; Pacheco-Jaime et al. (2025) found no difference in GMV by VBM or in subcortical volumes; and Cataldo et al. (2024) found no age-adjusted difference in whole brain grey matter, white matter, or total brain volume. Given the directional inconsistency of the aforementioned structural findings, the nature of these parameters in relation to PASC remains unclear.

Cortical thickness and grey matter volume findings were the least directionally consistent outcome among the modalities reviewed, but most studies reported significant regional differences, and these differences were frequently associated with cognitive or clinical parameters, such as measures of memory, fatigue, and cognitive function (e.g. MoCA score). Notably, the direction of change was generally consistent within a given research group despite divergence across groups. For example, Besteher and colleagues (2022, 2024) predominantly reported grey matter increases; in the 2022 study, GMV in several of the affected clusters (frontal, insular, temporal, and parahippocampal regions) was inversely related to time since infection, with higher volumes in patients scanned sooner after onset. In contrast, Díez-Cirarda et al. (I) (2023), Díez-Cirarda et al. (II) (2023), and Díez-Cirarda et al. (2025), consistently reported grey matter decreases, with the notable exception of the enlarged choroid plexus. Both groups' PASC samples were defined using broadly similar diagnostic criteria and imaged with similar T1-weighted protocols, so this within-group consistency may reflect differences in patient population, such as SARS-CoV-2 variant and differences in initial COVID-19 severity, or differences in scanner hardware, processing pipeline, or analytic approach.

To summarize and synthesize the brain volume and cortical thickness results, there was broad heterogeneity in terms of volumetric and cortical thickness findings in frontotemporal areas, occipital and parietal areas, the basal ganglia, and limbic structures. Cerebellar volumes were consistently decreased in four studies, though Thapaliya et al. (2023) reported higher volume in the SCP in PASC. In the insula and cingulate cortex, PASC usually demonstrated greater volume and thickness, though Díez-Cirarda et al. (2025) reported significantly lower GMV in PASC compared with controls within a grey matter mask that included these areas. Thapaliya et al. (2023) demonstrated increased brainstem volume.

Choroid plexus volume and lateral ventricular and CSF volumes were increased in Díez-Cirarda et al. (2025) and Greene et al. (2024), respectively. Whole-brain cortical thickness and volume largely did not differ between PASC and HC.

Because of the heterogeneity of the populations, time since infection and SARS-CoV-2 variant, and study methodologies, it is difficult to discern the biological significance of the heterogeneous findings in many regions. Fluid shifts, atrophic changes, and neuroimmune and inflammatory responses, among other mechanisms, have been proposed to explain these findings, and it is possible that they differ not only regionally, but also between subpopulations of PASC. In some regions, a clearer signal is found, such as in the cerebellum, where both reductions in volume and hypometabolism were noted in PASC. However, how reduced cerebellar volume fits into the pathophysiology of PASC is not yet known. In most regions, the direction of change, if any, remains unclear, and total brain volume and cortical thickness are likely not substantially different. However, in many studies, CT and volumes were found to correlate with cognitive and clinical measures. For example, some studies that found decreased volumes in PASC also reported correlations between smaller volumes and poorer cognitive outcomes. Díez-Cirarda et al. (I) (2023) reported that lower grey matter volume in the parahippocampal gyrus, superior temporal gyrus, and anterior cerebellum was associated with poorer attention and processing speed, and Díez-Cirarda et al. (II) (2023) noted that lower hippocampal volume was associated with poorer attention, processing speed, and working memory. Studies that found increased CT in PASC also linked it to poorer cognitive outcomes. For example, Besteher et al. (2024) reported that frontal cortical thickness was highest in PASC patients with cognitive impairment, and Pacheco-Jaime et al. (2025) found that greater frontal cortical thickness was associated with poorer working memory. Thus, while the exact mechanisms have yet to be elucidated, it seems plausible that macrostructural brain changes (especially in consistently altered regions such as the cerebellum, and regions such as the frontal cortex and hippocampus, where differences were frequently associated with clinical and cognitive measures) may contribute to the symptoms of PASC.

White matter microstructure

Nine studies assessed white matter (or in one case, hippocampal grey matter) microstructure using diffusion-based MRI, though specific metrics varied. Six studies reported standard DTI metrics. Mean diffusivity (MD), a measure of the overall magnitude of water diffusion in the tissue, was generally decreased; Díez-Cirarda et al. (I) (2023), Chaganti et al. (2024), and Nelson et al. (2024) each found decreased MD in various regions, though Nelson et al. (2024)'s comparator was a COVID recovered group rather than healthy controls. Pacheco-Jaime et al. (2025) and Heine et al. (2023) found no difference, though the latter tested only certain subcortical structures. Findings for FA, a measure of the directionality of diffusion (higher FA typically indicating a higher degree of white matter organization), varied by tract and study, being decreased in Díez-Cirarda et al. (I) (2023) and Pacheco-Jaime et al. (2025), increased in Chaganti et al. (2024), and either increased or decreased depending on region in Heine et al. (2023). Some altered diffusion parameters were associated with clinical outcomes such as fatigue. Díez-Cirarda et al. (2025) also found reduced FA and increased AD in multiple tracts, which correlated with the same study's enlarged choroid plexus volume finding. MD and radial diffusivity (RD) showed no such correlation. RD, a measure of diffusion perpendicular to the white matter fiber direction, did not differ between PASC and HC in specific tracts; neither were there consistent findings for AD (a measure of diffusion along the direction of the fiber). O'Connor et al. (2024), interestingly, found widespread increased white matter mean kurtosis, a diffusion kurtosis imaging metric of microstructural complexity, in PASC with neurological symptoms, which the authors suggest may be consistent with neuroinflammatory changes. Hosp et al. (2024) demonstrated regionally varied compartmental volume shifts in terms of the relative contributions of the free water (CSF) volume fraction, the intraneurite volume fraction, and the extraneurite compartment, composed of cell bodies and extracellular matrix (denoted as increased “V-extra”). The authors noted a broad pattern of reduced neocortical grey matter and thalamic V-extra, while in certain regions such as the corpus callosum, internal capsule, cerebellum, and brainstem, V-extra was increased in post-COVID individuals (with and without PASC) compared with controls, though more so in those without PASC symptoms. Certain of these changes correlated with clinical outcomes; for example, reduced V-extra in the thalamus and mesiotemporal regions was correlated with poorer cognitive performance. When using NODDI to assess hippocampal microstructure, Díez-Cirarda et al. (II) (2023) found higher intracellular volume fraction (FICVF) and orientation dispersion index (ODI) (measures of neurite density and dispersion of neurite orientation, respectively) in the PASC hippocampi. Both findings were inversely correlated with attention and memory measures (i.e., higher values correlated with poorer scores) and were further elevated in previously hospitalized patients. Taken together, these findings suggest that altered microstructure may be present in PASC, most notably decreased MD, changes in microstructural complexity, and shifts between tissue compartments. In addition, these changes may relate to clinical symptoms.

White matter lesions

Three studies assessed white matter hyperintensities (WMH), and none found a greater burden in PASC. Díez-Cirarda et al. (I) (2023) found no unadjusted difference in WMH volume or lesion count, with controls in fact showing greater volume and count after adjusting for age. Nelson et al. (2024) found a numerically higher proportion of PASC patients with WMH greater than expected for age (16% versus 8.6% in a normal recovery group), but this difference was not significant. O'Connor et al. (2024) found no group difference in Fazekas score (a measure of WMH severity). Together, these findings suggest PASC is not associated with increased WMH burden, in contrast with the more consistent microstructural findings above. This discrepancy may reflect subtler diffusion level changes below the resolution of conventional FLAIR imaging.

Functional connectivity and task-based activation

Two studies used BOLD fMRI to examine task-related brain activation in PASC compared with HC. Chang et al. (2023) found increased activation in several right superior frontal gyrus (SFG) and posterior cingulate gyrus areas, but only during a 2-back working memory task, not the easier 1-back

or 0-back tasks, indicating alterations may only appear during periods of higher cognitive load. The posterior cingulate finding reflected reduced deactivation of this default mode region rather than increased activation (as seen in the SFG). Interestingly, activation in several frontal areas was lower in post-COVID patients who had been hospitalized for severe acute COVID-19 than in those who had had milder acute disease. Greater brain activation during the 2-back task in some regions also correlated with poorer mental health measures across all participants; lower BOLD signal in the left postcentral gyrus was also correlated with reduced 2-minute walk test performance. Tanashyan et al. (2024) also found increased brain activation using BOLD, in the supramarginal gyri, posterior cingulate cortex, opercular parts of the precentral gyri, and the posterior lobe of the cerebellum.

Seven studies investigated functional connectivity in PASC compared with controls. Differences were found across multiple networks, but differed in directionality depending on the study and network affected. In the brainstem network, Barnden et al. (2023) found increased connectivity between two region of interest (ROI) pairs: a medulla and a midbrain ROI, and a medulla and a default mode network hub ROI, during a cognitive (Stroop) task; a broader ROI-to-voxel analysis showed multiple other nodes of differing (predominantly lower) connectivity. Interestingly, connectivity involving the medulla and the periaqueductal grey, as well as salience network hubs (the anterior cingulate cortex and bilateral rostral prefrontal cortex), was significantly correlated with disability score, heart rate variability, and respiratory rate variability in PASC patients, associations that were absent in controls. This is notable given the presence of autonomic symptoms in a subset of PASC patients; however, this patient population exhibited primarily fatigue, myalgia, dyssomnias, and cognitive complaints rather than autonomic dysfunction. Bungenberg et al. (2024) found connectivity alterations throughout a broad network including the olfactory and cingulate cortices, thalamus, orbitofrontal cortex, and cerebellum; in this study, network alterations commonly correlated with clinical metrics including fatigue, cognitive dysfunction, and sleep disruption. In the cingulate network, they reported decreased anterior cingulate and increased posterior cingulate connectivity, with posterior cingulate hyperconnectivity correlating with poorer attention (Trail Making Test Part A). This resting-state finding may related to Chang et al. (2023) where authors reported reduced task-related deactivation in the right posterior cingulate.

In the corticostriatal network, Troll et al. (2025) found a hyperconnective pattern: between the right posterior caudate and bilateral precentral gyri, and between the right anterior globus pallidus and each of the posterior cingulate cortex and temporal pole, with right posterior caudate to left precentral gyrus hyperconnectivity associated with poorer cognition (lower MoCA score, longer Trail Making Test B time). In the hippocampal and parahippocampal network, Díez-Cirarda et al. (I) (2023) found reduced connectivity between the left and right parahippocampal gyri, and Díez-Cirarda et al. (II) (2023) found reduced connectivity between the right hippocampal head and each of a parietal area and the left anterior parahippocampal division. In the olfactory network, Bungenberg et al. (2024) found decreased connectivity, while Muccioli et al. (2023) found a mixed pattern within the network involving reduced global modularity (lesser network segregation into modules), associated with greater hyposmia severity, and hyperconnective involvement of the right thalamus, which was associated with reduced short term verbal memory scores. Bungenberg et al. (2024) also found increased connectivity of the intralaminar nuclei, correlating with fatigue severity. This may be of interest, given the significance of these nuclei in arousal and alertness. Díez-Cirarda et al. (I) (2023) also demonstrated reduced connectivity between the left cerebellar lobule III (vermis) and each of the left and right frontal superior orbital cortices in PASC, associated with poorer learning and recall performance. Finally, Díez-Cirarda et al. (2025) showed that larger choroid plexus volume correlated with connectivity between several regions.

Overall, widespread network connectivity alterations appear to be present in PASC, including in the brainstem, cerebellum, thalamus, posterior cingulate, and other regions. Despite the widespread distribution of these findings, there is a common pattern of correlation between altered connectivity or BOLD signal and clinical, cognitive, and symptom-specific outcomes. Some of these correlations may also reflect potential mechanisms, such as the association between altered connectivity in the intralaminar nuclei and fatigue. However, given the variability among studies and the cross-sectional nature of the research, it is difficult to draw causal conclusions. This makes functional connectivity a potentially compelling target for further investigation.

Glucose metabolism

Seven studies investigated glucose metabolism in the brains of people with PASC via Positron Emission Tomography (PET). Three studies (Goehringer et al., 2023; Guedj et al., 2021; Horowitz et al., 2024) demonstrated significant hypometabolism with no regions of hypermetabolism; two studies (Martini et al., 2022; Rozenblum et al., 2025) demonstrated a mixed pattern, with hypometabolism in some regions and hypermetabolism in others; and two studies found no significant group-level difference (Dressing et al., 2022; Sakamoto et al., 2024) although Sakamoto et al. (2024) used a different, individual-patient-level analysis (see below).

Regarding hypometabolic findings, regions throughout most of the brain were implicated in at least one study population, and several were consistent across the majority of studies. Most notably, hypometabolism in frontotemporal areas (most commonly the orbitofrontal cortex), was reported by Goehringer et al. (2023), Horowitz et al. (2024), Guedj et al. (2021), and Martini et al. (2022) (though Martini et al. (2022) reported that the finding was present only in shorter-duration patients and had resolved by 7 to 9 months). Rozenblum et al. (2025) found hypometabolism in the left fusiform gyrus, with no significant difference in the frontal gyri specifically. The cerebellum was also implicated in multiple studies (Guedj et al., 2021; Rozenblum et al., 2025; Horowitz et al. 2024). Other hypometabolic areas included the insula (Goehringer et al., 2023; Martini et al., 2022; Horowitz et al., 2024), the brainstem, especially the pons (Guedj et al., 2021; Horowitz et al., 2024; Rozenblum et al., 2025), and multiple limbic structures; the amygdala (Guedj et al., 2021; Rozenblum et al., 2025), hippocampus (Guedj et al., 2021; a nonsignificant trend in Rozenblum et al., 2025), and thalamus (Guedj et al., 2021; Goehringer et al., 2023). Many of these hypometabolic regions had clinical correlates; for example, lower

metabolism was associated with pain, insomnia and symptom burden (Guedj et al., 2021), concentration and memory impairment (Rozenblum et al., 2025), and with worse cognitive performance (Goehringer et al., 2023; Martini et al., 2022). In the Rozenblum et al. (2025) study, hypometabolism was also generally more marked in patients at shorter intervals post-infection.

Rozenblum et al. (2025) also demonstrated a smaller hypermetabolic pattern, significant in the right angular gyrus. Martini et al. (2022) was the main study to demonstrate hypermetabolism in PASC patients compared with controls, primarily in the brainstem, cerebellum, amygdala, and hippocampus. Hypermetabolism in these regions correlated with C-reactive protein levels, suggesting an inflammatory process. Given the above evidence for hypometabolism in these and other structures, this discrepancy may reflect either a methodological difference, a difference in PASC subtype in the Martini et al. (2022) population, or a difference due to small sample size (n = 11 subjects at > 3 months post-infection, the subgroup driving the C-reactive protein correlation specifically). The authors reported no change in global glucose uptake.

Sakamoto et al. (2024) took a different analytic approach from the other six studies, additionally quantifying the percentage of individual patients with significant regional hypo-or hypermetabolism (Z-score less than − 2 or greater than + 2, respectively, relative to a normative database). Using this method, both hypometabolism and hypermetabolism were observed in small percentages of patients across several regions, including prefrontal, temporal, parietal, occipital, and pontine areas, with the right mesial temporal region showing the highest rate of hypometabolism (13.64% of patients), consistent with other studies (Guedj et al., 2021; Horowitz et al., 2024; Rozenblum et al., 2025). These findings may also be consistent with the common complaints of memory loss and “brain fog” in this population. However, no significant group-level differences were found in any of the 26 tested regions.

Taken together, these PET studies point to widespread, though not universal, glucose hypometabolism in PASC, especially in frontotemporal, brainstem, cerebellar, and limbic regions, alongside a smaller but notable pattern of regional hypermetabolism in a subset of studies. Coupled with the findings of cerebral hypoperfusion and blood-brain barrier (BBB) dysfunction, this may point to vascular or neurovascular involvement in PASC, although global oxygen extraction was elevated only in previously hospitalized patients (Liu et al., 2024), and reduced neuronal activity or neuroinflammation are plausible alternatives. Multimodal longitudinal studies in the same patients will be needed to clarify whether these abnormalities share a common mechanism.

Cerebral blood flow and perfusion

Three studies demonstrated a widespread reduction in cerebral blood flow and perfusion in PASC measured using ASL. Díez-Cirarda et al. (II) (2023) found a reduction in hippocampal perfusion, which was related to memory performance and was accentuated in previously hospitalized patients. Ajčević et al. (2023) showed a widespread, bilateral (though more pronounced in the right hemisphere) reduction in global and regional cerebral blood flow (CBF) in the frontal (bilateral), temporal (bilateral), and parietal (right) lobes in patients with subjective cognitive impairment. This may be of interest in the context of the hypometabolic findings in frontotemporal areas noted above, although none of these studies examined such an association. Additionally, Wang et al. (2025) found lower CBF in a region spanning the left inferior frontal, superior temporal, and middle frontal gyri in PASC patients compared with controls, which correlated with fatigue and poorer immediate memory performance in individuals with PASC only. However, the study’s pooled COVID-19 sample, including individuals with and without persistent symptoms, demonstrated a similar pattern of reduced CBF. This suggests the effect of acute COVID-19 may be distinct from the effect of PASC, given that an additive effect (greater in PASC with hospitalization history) was observed in the Díez-Cirarda et al. (II) (2023) study. Together, these data suggest a disruption in cerebral perfusion after infection with SARS-CoV-2, which may be partially independent of persistent symptoms, though it appears to be associated with them. Finally, Chien et al. (2024) used BOLD resting state fMRI to estimate changes in blood oxygenation and perfusion, demonstrating significantly increased oxygen level estimates (OLE, indicative of reduced oxygenation) in the whole brain white matter and cortical grey matter. They also reported trends for regional reductions in the putamen, hippocampus, thalamus, and whole deep grey matter (including the brainstem), though these were not significant after adjustment for multiple comparisons. However, perfusion (as estimated by BOLD delay) did not differ significantly between PASC and controls. Associations with clinical metrics were mixed in directionality: higher OLE in the putamen and globus pallidus was associated with reduced daytime sleepiness scores (measured on Epworth Sleepiness Scale), but deep grey matter OLE was associated with increased daytime sleepiness. The authors suggest that the OLE changes could reflect increased oxygen metabolism in those areas. In summary, there seems to be a general reduction in cerebral blood flow, perfusion, and potentially oxygenation in PASC, which is possibly related to clinical symptoms. This finding may be consistent with the generally hypometabolic pattern seen in PASC, though this association has not yet been tested.

Blood-brain barrier integrity

Two studies demonstrated BBB disruption in PASC patients. In a study by Greene et al. (2024), DCE-MRI revealed a significant increase in the percentage of BBB-disrupted voxels in PASC patients who experienced brain fog compared with both patients with PASC but without brain fog, and recovered post-COVID patients (notably, there was no never-infected healthy control group comparison available for the BBB integrity portion of the Greene et al. study). Regionally, significantly affected areas included the bilateral temporal lobes and frontal gyri (with increased permeability in the former being associated with anosmia duration). A small longitudinal study by Chaganti et al. (2024) supported these findings by investigating changes in K-trans (a measure of BBB permeability). PASC patients demonstrated significantly higher K-trans values than controls at baseline (3 months post-infection) in the frontal white matter and in the brainstem. K-trans values within patients were unchanged between baseline and

follow-up (12 months). Taken together, these findings may indicate a persistent reduction of BBB integrity in PASC, which is potentially a source and a consequence of persistent neuroinflammation, a commonly hypothesized etiology for many of the above findings. In addition, BBB disruption may also provide a potential route for viral component entry into the brain, another hypothesized mechanism underlying certain post-COVID sequelae (Chen et al., 2023; Proal et al., 2023).

Oxygen extraction fraction

Liu et al. (2024) used TRUST MRI to investigate oxygen extraction fraction (OEF). Previously hospitalized PASC patients demonstrated higher OEF than both controls and non-hospitalized PASC patients, which the authors speculate may be due to insufficient oxygen delivery, potentially reflecting cerebral hypoperfusion at a microvascular level. However, OEF did not differ between non-hospitalized PASC patients and controls. Higher OEF was associated with slower gait speed in PASC. These results suggest that impaired cerebral oxygen delivery may contribute to motor dysfunction in PASC, but impairment may be dependent on acute COVID-19 severity. This would be in accordance with the Díez-Cirarda et al. (II) (2023) cerebral perfusion findings, wherein post-hospitalized patients exhibited a more marked hypoperfusion. Replication in larger cohorts is needed to support this association.

Glial cell activation

Clouston et al. (2025) used 18F-FEPPA-PET to investigate glial activation in patients with PASC. Patients with PASC demonstrated widespread increased glial activation, especially in the hippocampus, grey matter, and cerebellum, which was associated with fatigue severity and cognitive dysfunction. The authors suggest that this may indicate a persistent neuroimmune response. This is consistent with a prior study demonstrating subcortical glial activation in PASC patients with depressive symptoms (Braga et al., 2023).

Impression

There is a growing body of evidence on structural and functional brain correlates of PASC. While some metrics, such as cortical thickness and regional brain volumes, fail to demonstrate a unifying signal, others point towards plausible mechanistic explanations for certain aspects of the condition. For example, a relatively consistent picture of cerebral hypoperfusion is observed alongside hypometabolism (especially in frontotemporal areas), in conjunction with findings of glial activation and decreased blood-brain barrier integrity, potentially indicating neuroinflammatory or immune-mediated neurovascular disruption. Changes in functional connectivity and network architecture are also seen across numerous regions, and certain regions, such as the cerebellum, are repeatedly implicated across multiple modalities. These differences are often associated with clinical measures in many studies and may offer insight into the pathogenesis of persistent post-COVID symptoms. However, because most studies are cross-sectional, the exact etiology of the condition remains unclear and may differ between subtypes and individuals with PASC.

Limitations and Future Directions of Research

This review has several strengths including a thorough screening and text extraction protocol and a region-by-region synthesis spanning multiple MRI and PET modalities. However, the research was limited to peer-reviewed, English-language articles in three databases (PubMed, Scopus, and Europe PMC); therefore, relevant studies may have been missed. No formal risk of bias assessment was performed. Furthermore, there was no meta-analysis performed due to heterogeneity in modalities, outcomes and comparison groups. In addition, the search yielded multiple studies from the same research groups; thus, conclusions may be drawn from overlapping samples. Nonetheless, this review provides a framework to synthesize findings across modalities and brain regions, and to guide future multimodal longitudinal studies of PASC.

The literature involving neuroimaging in PASC patients faces several limitations. First, due to practical constraints, it is primarily composed of cross-sectional studies, from which it is impossible to determine whether the abnormalities observed in the brains of individuals with PASC are indeed sequelae of COVID-19, or preexisting differences that might predispose these individuals to experience post-COVID symptoms. While prospective studies are difficult to perform in this context, a comprehensive comparison of brain structure and symptoms between PASC patients and individuals without PASC who exhibit similar symptoms (such as those with ME/CFS) could help to determine which symptoms and differences are unique to the PASC milieu. Another problem is the heterogeneity of the PASC population. The condition remains poorly defined more than five years after its identification, and most definitions of PASC do not specify the type or necessary duration of symptoms. While most of the participants in this review suffer from primarily or exclusively neurocognitive symptoms such as fatigue and cognitive complaints, PASC has been associated with symptoms across multiple body systems, and presentations can vary widely between individuals (Blankestijn et al., 2024; Kenny et al., 2023). Furthermore, differences in the variant of SARS-CoV-2 by which patients were infected, the duration of time since that infection, and individual and genetic differences between populations make comparisons difficult. It is possible, and indeed likely, that different presentations of PASC involve different pathophysiology, and thus it may be incorrect to draw conclusions based on pooled samples of individuals with heterogeneous presentations. This review encompassed studies primarily of individuals with neurocognitive symptoms due to PASC, all months to years after infection. Future research should better define the condition and its phenotypic and etiologic subtypes. Long-term follow-up studies of these individuals are also needed, given the evidence of various pathological differences in this population. Finally, studies with pre-COVID neuroimaging data available for patients who later develop PASC would be helpful to better understand causality.

Conclusion

Myriad neuroimaging techniques have demonstrated objective structural and functional differences in the brains of individuals with PASC, including differences in task-based activation and functional connectivity, cortical thickness, grey and white matter volume, white matter microstructure, glucose metabolism, glial activation, blood-brain barrier permeability, cerebral perfusion and blood flow, and oxygen extraction. Findings are widely distributed throughout the brain, and limbic, subcortical, frontotemporal, and other structures are all commonly involved. Some metrics, such as blood-brain barrier permeability and cerebral hypometabolism, demonstrate generally consistent patterns, while other metrics, such as functional connectivity and grey/white matter volume, demonstrate bidirectional changes that often vary substantially by region and study population. Notably, differences in these metrics in the brains of individuals with PASC often correlate with patient symptoms and clinical data, suggesting a potential role for these changes in patient symptomatology. Further research is needed to fully elucidate the significance and causality of these findings. In addition, evaluating the potential risks that PASC-associated brain changes may pose for long-term neurocognitive health may help inform better treatment options for patients who suffer long-term effects from COVID-19.

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Figures

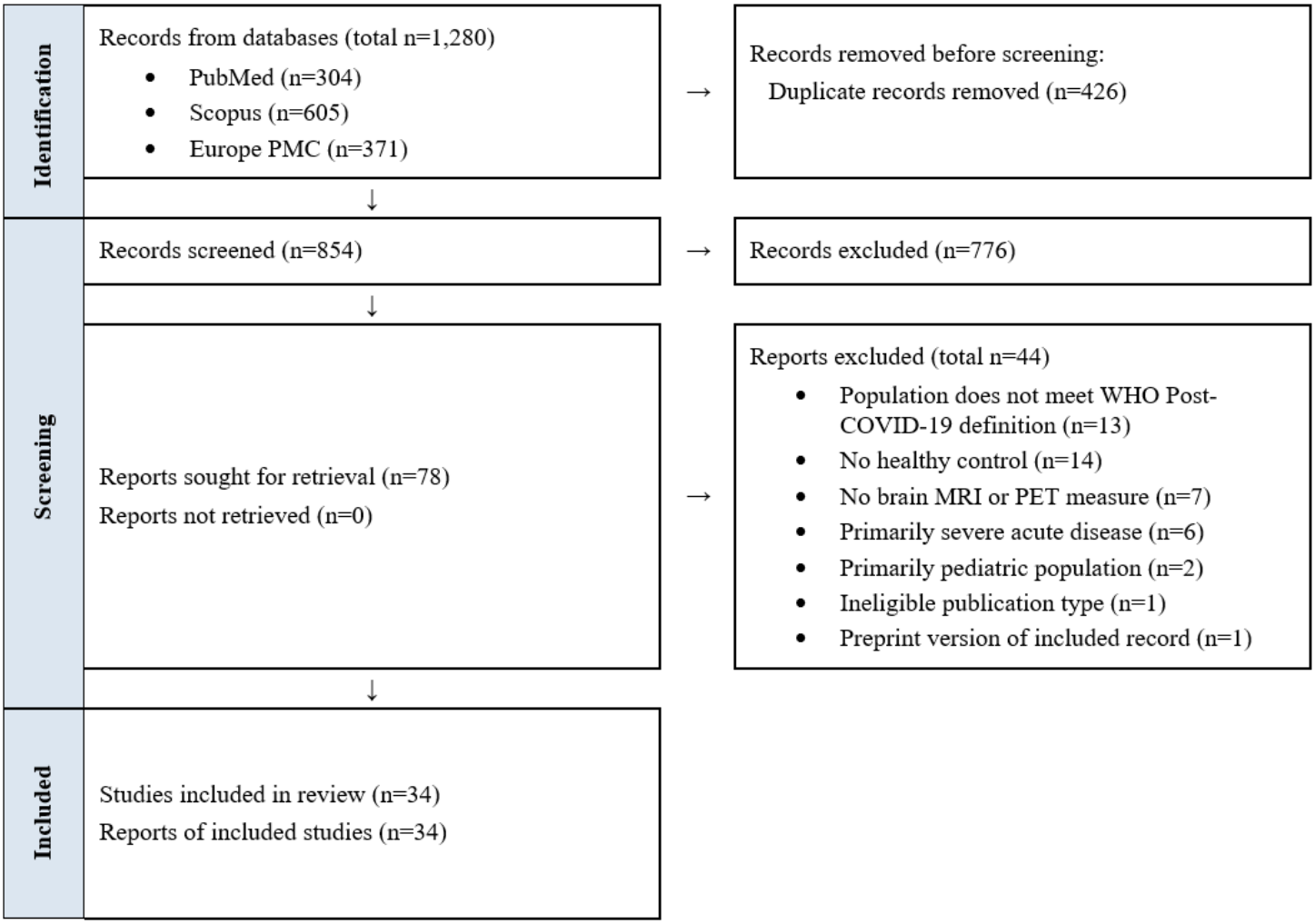


Figure 1

PRISMA-based study selection flowchart