NeuroImage: Clinical 37 (2023) 103338

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Brain diffusion alterations in patients with COVID-19 pathology and neurological manifestations

Anna Caroli [a], Serena Capelli [a], Angela Napolitano [b], Giulia Cabrini [c], Alberto Arrigoni [a], Giulio Pezzetti [b], Mattia Previtali [a], Luca Giovanni Longhi [d], Rosalia Zangari [e], Ferdinando Luca Lorini [f], Maria Sessa [g], Andrea Remuzzi [c], Simonetta Gerevini [b,*]

[a] Bioengineering Department, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 24020 Ranica, BG, Italy
[b] Department of Neuroradiology, ASST Papa Giovanni XXIII, 24127 Bergamo, Italy
[c] Department of Management, Information and Production Engineering, University of Bergamo, 24044 Dalmine, BG, Italy
[d] Neurosurgical Intensive Care Unit, Department of Anesthesia and Critical Care Medicine, ASST Papa Giovanni XXIII, Bergamo, Italy
[e] FROM Research Foundation, ASST Papa Giovanni XXIII, 24127 Bergamo, Italy
[f] Department of Emergency and Critical Care Area, ASST Papa Giovanni XXIII, Bergamo, Italy
[g] Department of Neurology, ASST Papa Giovanni XXIII, 24127 Bergamo, Italy

ARTICLE INFO

Keywords:
COVID-19
Diffusion weighted imaging
ADC
Neuroinflammation

ABSTRACT

Background and objective: COVID-19 neurological manifestations have been progressively recognized. Among available MRI techniques, diffusion weighted imaging (DWI) shows promise to study microstructure, inflammation, and edema. Previous DWI studies reported alterations in brain diffusivity in COVID-19 patients, as assessed by morphologic evaluation of brain DWI scans only. The aim of this study was to assess and quantify brain diffusion alterations in COVID-19 patients with neurological manifestations.

Methods: 215 COVID-19 patients with neurological manifestations (olfactory and/or other neurological disorders) and 36 normal controls were compared and studied with DWI and T1-weighted MRI scans. MRI scans were processed by a semi-automatic processing procedure specifically developed for the purpose of this study, and the Apparent Diffusion Coefficient (ADC) was quantified in different brain tissues and individual white matter (WM) and gray matter (GM) regions. Differences in ADC values were assessed between COVID-19 patients and normal controls, as well as in the COVID-19 patient population grouped by hospitalization and neurological symptoms.

Results: Among COVID-19 patients (median [IQR] = 52 [42 – 60] years of age, 58 % females), 91 were hospitalized and 26 needed intensive care. 84 patients had hyposmia/ageusia only, while 131 ones showed other neurological disorders. COVID-19 patients showed significantly increased ADC values in the WM and in several GM regions ($p < 0.001$). ADC values were significantly correlated with MRI time from disease onset ($p < 0.05$). Hospitalized patients showed significantly higher ADC alteration than non-hospitalized patients in all brain tissues; similarly, COVID-19 patients with neurological disorders showed significantly higher ADC values than those with olfactory loss only. ADC alteration was highest in patients with cognitive or memory disorder and in those with encephalitis or meningitis. ADC values were neither associated with the duration of hospitalization nor with the need for intensive care.

Conclusion: Current findings suggest DWI potential as a non-invasive marker of neuroinflammation in COVID-19, and the transient nature of the same. Future longitudinal studies are needed to confirm our findings.

Abbreviations: ADC, Apparent Diffusion Coefficient; ACE2, Angiotensin Converting Enzyme 2; BAL, BronchoAlveolar Lavage; CM, Cognitive and Memory disorders; COVID-19, Coronavirus Disease 2019; CTRL, Controls; DTI, Diffusion Tensor Imaging; DWI, Diffusion Weighted Imaging; EM, Encephalitis and Meningitis; FLAIR, FLuid-Attenuated Inversion Recovery; GM, Gray Matter; OD, Olfactory Disorders; NM, Neuromuscular Disorders; RT-PCR, Real-Time Reverse-Transcriptase Polymerase-Chain-Reaction; SARS-CoV-2, Severe Acute Respiratory Syndrome CoronaVirus 2; WM, White Matter.

* Corresponding author at: Department of Neuroradiology, ASST Papa Giovanni XXIII, Piazza OMS 1, 24127 Bergamo, Italy.
E-mail address: sgerevini@asst-pg23.it (S. Gerevini).

https://doi.org/10.1016/j.nicl.2023.103338
Received 15 September 2022; Received in revised form 18 January 2023; Accepted 23 January 2023
Available online 28 January 2023

1. Introduction

Coronavirus disease 2019 (COVID-19) pandemic, caused by the rapid and huge spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has rocked the whole world. In addition to the well-known pulmonary manifestations, neurological manifestations have been increasingly recognized, with a rising number of studies detecting central nervous system abnormalities in patients affected by COVID-19 (Ellul et al., 2020; Sarubbo et al., 2022). Smell and taste disorders, cranial nerve deficits, polyneuropathies, cerebrovascular disorders, encephalopathies and inflammatory central nervous system (CNS) syndromes, headache, and seizures are just some of the neurological complications observed in COVID-19 patients.

It is fully acknowledged that, by binding to the angiotensin converting enzyme 2 (ACE2), SARS-CoV-2 can enter and damage endothelial cells in the lungs, the heart, and the kidneys by activating inflammatory and thrombotic pathways (Verdecchia et al., 2020). The major factor responsible for acute respiratory distress syndrome is the so-called "cytokine storm", an host immune system response inducing an exaggerated release of proinflammatory cytokines/chemokines (Castelli et al., 2020). Similarly, these processes may explain cerebral damages observed in COVID-19 patients (Pacheco-Herrero et al., 2021).

Based on potential pathophysiological mechanisms involved in neurological manifestations of SARS-Cov-2, Fotuhi et al., 2020 recently proposed a conceptual framework of "NeuroCovid Staging": i) stage I, where SARS-Cov-2 binding to ACE2 receptors is limited to the nasal and gustatory epithelial cells, the cytokine storm activated by the virus remains low and controlled, and patients only have smell or taste impairments; ii) stage II, where SARS-Cov-2 activates a robust immune response with high levels of cytokines, and patients may experience strokes and vasculitis damaging cranial and peripheral nerves, and/or muscles; and iii) stage III, where the cytokine storm damages the blood brain barrier and results in infiltration of inflammatory factors causing edema and brain injury leading to delirium, encephalopathy and/or seizures.

A wide range of neuroradiological findings has been reported in patients with COVID-19 (Choi and Lee, 2020; Moonis et al., 2021; Ladopoulos et al., 2021), and increasing evidence supports the key role of brain MRI in assessing cerebral structural and functional alterations in COVID-19 patients with neurological manifestations (Parsons et al., 2021; Katal et al., 2021; Chen et al., 2020).

Among available MRI techniques, diffusion weighted imaging (DWI), allowing to investigate diffusion of the water molecules in the tissue, shows promise to study brain microstructure, inflammation, and edema, and has been included in the MRI protocol recently recommended by a European group of experts to investigate patients with COVID-19 and neurological manifestations (Kremer et al., 2022). However, so far, brain diffusion MRI studies have been mainly limited to small investigational studies, case series, and case reports, with some exceptions (Chougar et al., 2020; Kremer et al., 2020; Kremer et al., 2020; Kandemirli et al., 2020; Alonazi et al., 2021; Douaud et al., 2022). Given the well-known potential of DWI in assessing neuroinflammation, and the fact that COVID-19 can initiate an inflammatory response in the CNS (Lou et al., 2021), we hypothesized to find significant brain diffusion alterations in a cohort of patients with neurological complications following COVID-19 infection, possibly limited to specific white matter or grey matter regions.

Previous DWI studies reported alterations in brain diffusivity in COVID-19 patients (Parsons et al., 2021; Chougar et al., 2020; Kremer et al., 2020; Kandemirli et al., 2020; Douaud et al., 2022; Rhally et al., 2021; Zhang et al., 2011; Huang et al., 2021), as assessed by morphologic evaluation of brain DWI scans only. The diffusion tensor imaging (DTI) studies published so far confirmed significant alterations in mean diffusivity in COVID-19 survivors (Newcombe et al., 2021; Lu et al., 2020; Benedetti et al., 2021; Díez-Cirarda et al., 2022). Changes in diffusion metrics were mostly found in limbic structures (Douaud et al., 2022).

The aim of this study was to assess and quantify brain diffusion alterations on DWI scans from 215 patients with COVID-19 pathology and neurological manifestations. The population under study, that to the best of our knowledge is the largest such populations ever reported in the literature, was heterogeneous in terms of COVID-19 disease severity and neurological complications and well characterized, allowing to assess differences in brain diffusion based on possible hospitalization and type of neurological manifestations.

2. Materials and methods

2.1. Patient population

Consecutive patients with confirmed COVID-19 who were admitted to the ASST Papa Giovanni XXIII hospital in Bergamo, Italy, due to hyposmia/ageusia, neurological disorders, or both (neuroCOVID stage I to III (Fotuhi et al., 2020)) and underwent brain MRI from March 2020 to October 2021 were eligible for inclusion. COVID-19 diagnosis was confirmed: 1) by real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) on nasopharyngeal specimens; or 2) by RT-PCR on bronchoalveolar lavage (BAL) in case of high clinical suspicion of SARS-CoV-2 infection besides negative test results on at least two nasopharyngeal swabs performed at least 24 h apart; or 3) in the presence of characteristic radiological interstitial pneumonia associated with typical symptoms (fever, dry cough, dyspnea), even with negative RT-PCR. Patients with neurological disorders prior to COVID-19 (e.g., multiple sclerosis, previous history of vascular lesions, psychiatric diseases) and/or pre-existing brain parenchymal lesions (e.g., chronic stroke, tumors) were excluded from the study. Patients showing cerebrovascular disorders with parenchymal lesions (e.g., stroke, cerebral venous thrombosis) due to COVID-19 were further excluded.

Patients who underwent brain MRI for reasons other than COVID-19 complications with no remarkable MRI findings were included in the study as control patients.

The local ethics committee approved the collection and scientific use of the patients' data as part of a larger observational study protocol (Reg. 118/22). Informed consent was obtained from individual patients or provided by their next of kin (in case of ICU patients).

2.2. Clinical data

Clinical data were extracted from the patients' electronic medical records contained in the Hospital Information System and included sociodemographic information (both COVID-19 and control patients), COVID-19 date of onset, possible hospitalization and need for intensive care, initial presenting symptoms and neurological manifestations (COVID-19 patients only).

2.3. MRI acquisition

All brain MRI scans were acquired at the ASST Papa Giovanni XXIII hospital in Bergamo, Italy, using a General Electric 3 Tesla MRI scanner (Discovery MR 750w GEM).

Brain MRI acquisition protocol was based on both morphological and advanced sequences, including pre-contrast coronal T2-weighted, pre-contrast axial T1-weighted and post-contrast 3D T1-weighted, pre- and post-contrast sagittal FLAIR, diffusion weighted and tensor imaging, susceptibility weighted imaging (SWI) and perfusion imaging.

In this study, only DWI and pre-contrast T1-weighted scans were considered for evaluation. DWI scans were acquired axially using a single-shot echo planar imaging sequence, with the following parameters: matrix = 128x128, field of view = 240x240, thickness = 3 mm (no gap), TE/TR = 73/4000 ms, b-values: 0 and 1000 s/mm^2, three averaged diffusion encoded direction, NEX = 3, ASSET = 2, and fat suppression. T1-weighted scans were acquired by an axial Multi Echo Multi

Planar (MEMP) sequence with the following parameters: matrix = 288x244, field of view = 250x250 mm, thickness/gap = 3.0/0.4 mm, TE/TR = 9/600 ms.

2.4. MRI processing

DWI and T1-weighted MRI scans were processed by a semi-automatic processing procedure specifically developed for the purpose of this study (Fig. 1), making use of different image analysis software tools: Statistical Parametric Mapping (SPM12) (Penny et al., 2007), ImageJ version 1.52 t (https://imagej.nih.gov/ij), and an in-house code written in Matlab, version R2018b (Natick, MA, USA).

First, T1-weighted and $b = 0$ DWI scans were converted to NIfTI format, and the T1-weighted image sequence was coregistered to the $b = 0$ DWI sequence by SPM, using a rigid-body deformation (step 1). The coregistered T1-weighted image sequence was then segmented by SPM, generating probability maps of the gray matter (GM), white matter (WM), CSF, bone tissue and soft tissue (step 2). GM, WM, and CSF probability maps were binarized using SPM, setting the threshold at 0.6, empirically chosen to have each voxel assigned to a tissue class while minimizing overlap between different tissue classes. In addition, the whole brain mask was obtained by summing up GM, WM, and CSF binary masks, and then checked and edited by ImageJ software to fill possible holes and remove external regions accidentally taken as brain (e.g., eye socket) (step 3). DWI scans were then processed in-house Matlab code: $b = 1000$ DWI scans were registered to $b = 0$ DWI scans to account for possible motion; the apparent diffusion coefficient (ADC) was fitted voxel-wise using the following mono-exponential equation

$$S(b) = S_0 \cdot e^{-b \cdot ADC} \quad (1)$$

where S is the signal as a function of the b-value, and S_0 is the signal at $b = 0$; the resulting ADC parametric maps were masked using the brain mask computed before, thus obtaining the ADC whole brain maps (step 4). The latter were restricted to GM, WM and CSF by using pertinent binary masks. The ADC whole brain maps were then normalized to the standard MNI space through SPM along with whole brain and individual tissue masks, and then also restricted to individual brain regions by using available brain atlases (AAL3 GM atlas (Rolls et al., 2020), where brain regions were grouped according to Lu et al., 2020, JHU WM atlas (Oishi et al., 2009), and IIT human brain WM bundle atlas v5.0 (Qi and Arfanakis, 2021)), preliminarily registered to the MNI space, and further masked by the respective GM or WM binary masks (step 5). Descriptive statistics (mean, standard deviation, median and quartiles) were finally extracted for ADC in the whole brain as well as in the different brain tissues and regions (step 6).

2.5. Statistical analysis

Comparisons between COVID-19 and control patients were performed by non-parametric Wilcoxon rank sum test or Fisher test (continuous and binary variables, respectively) due to unequal sample sizes. Comparisons between COVID-19 patient subgroups (hospitalized vs non-hospitalized patients, patients in need vs no need for ICU, patients with olfactory vs other neurological disorders) were performed by two-tailed independent *t*-test or Chi-squared test (continuous and binary variables, respectively). The distribution of ADC value in COVID-19 patients, grouped by main neurological complication, was displayed by boxplots. Pairwise comparisons were performed by Wilcoxon test or *t*-test, based on normality of the data distribution. The overall comparison was performed by Kruskal-Wallis test. Bonferroni correction was performed to account for multiple comparisons. Normality of the data distribution was assessed by Shapiro-Wilk test. Linear regression analyses were performed to disentangle the effect of hospitalization (or olfactory vs other neurological complications) from the effect of possible covariates (age, gender and MRI time) on ADC. Separate multiple linear regression models were built with median ADC as dependent variable and hospitalization (or olfactory vs other neurological complications), age, gender, and MRI time as independent variables. The strength of associations between ADC and age, and between ADC and time from disease onset to MRI acquisition was assessed by Spearman correlation. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using R software (https://www.r-project.org/), version 4.0.2.

2.6. Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

3. Results

A total of 215 COVID-19 patients with neurological manifestations and 36 control patients were included in the study. Sociodemographic features are summarised in Table 1. Out of the 215 COVID-19 patients, 91 (57 [50 – 66] years, 44% females) were hospitalized for a median of 19 ([10 – 38]) days, 26 of whom (56 [50 – 63] years, 42% females) needed intensive care (21 underwent mechanical ventilation, while the other 5 were treated with Continuous Positive Airway Pressure (CPAP)). 131/215 COVID-19 patients underwent brain MRI due to neurological disorders, including cognitive and memory disorders (n = 68), cerebrovascular disorders (e.g., transient ischemic attack, vasculopathies; n = 6), psychiatric disorders (n = 9), neuromuscular disorders (e.g., myalgia, hypoesthesia, Guillain-Barré syndrome; n = 37), encephalitis and meningitis (n = 8), neuropathies (n = 2) and other neurological symptoms (e.g., headache, vertigo, seizures; n = 58) (Table 2), while the remaining 84 complained about hyposmia and/or ageusia only (Table 3). Supplementary Fig. 1 is a flowchart that describes the study participants.

3.1. ADC alteration in COVID-19 vs control patients

No difference in age and sex was found between COVID-19 patients with neurological manifestations and control patients. COVID-19 patients showed significantly higher ADC values in the GM and in the WM (Table 1).

In the COVID-19 patient group, a widespread significant increase in ADC was found in the WM (Fig. 2, Supplementary Table 1, and Supplementary Table 2). A statistically significant increase in ADC was also found in several GM regions, most significant (uncorrected $p < 0.001$) in the left precentral gyrus, in the right rolandic operculum, in the lingual gyrus, as well as in the right precuneus, pallidum, and thalamus (Supplementary Table 3). Right precuneus and pallidum survived correction for multiple comparisons (corrected $p < 0.05$).

In the whole group of patients (including both COVID-19 and control patients), age was positively correlated with ADC values in the whole brain (Spearman $\rho = 0.61$, $p < 0.001$), as well as in the GM ($\rho = 0.49$, $p < 0.001$) and in the WM ($\rho = 0.25$, $p < 0.001$) separately. The statistically significant positive correlation was maintained in the COVID-19 group both in the whole brain and individual tissues ($p < 0.001$ in all cases).

In the COVID-19 patient group, median ADC values were significantly correlated with the MRI time, defined as number of days between disease onset and MRI acquisition (204 [89 – 325] days) in the whole brain ($\rho = -0.31$, $p < 0.001$), as well as in individual brain tissues (GM: $\rho = -0.21$, $p = 0.003$; WM: $\rho = -0.17$, $p = 0.017$) (Supplementary Fig. 2).

3.2. ADC alteration in COVID-19 patient subgroups

Patients hospitalized from COVID-19 were significantly older than COVID-19 patients who have not been hospitalized (57 [50 – 66] vs 50

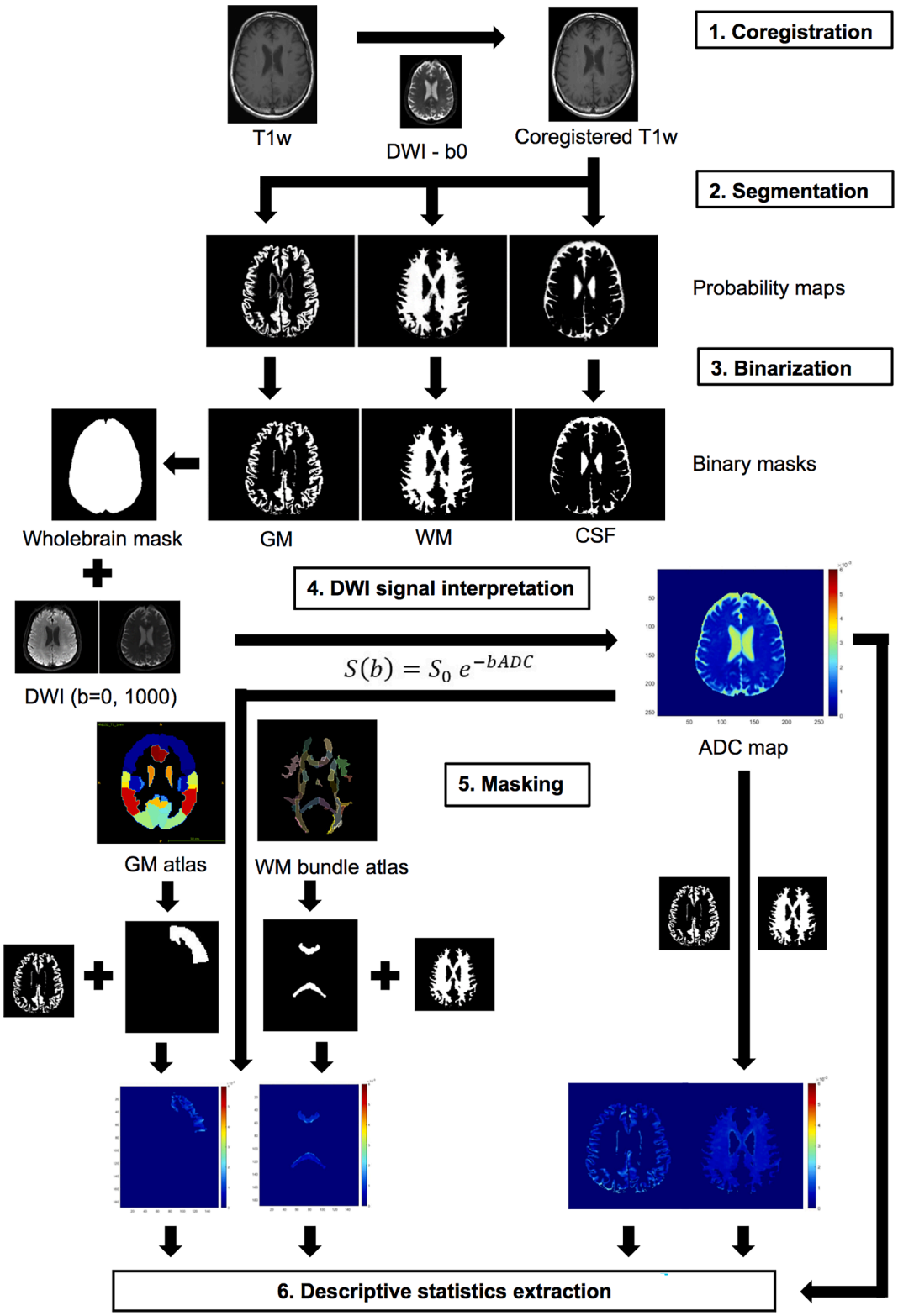

Fig. 1. Diagram summarising the brain diffusion weighted imaging (DWI) processing procedure developed and used in the study. First, T1-weighted brain MRI scans are coregistered to the DWI ($b = 0$) sequence (step 1). The resulting images are segmented, obtaining probability maps of the different brain tissues (step 2). Gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) probability maps are binarized and then added up to create the whole brain mask (step 3). DWI signal acquired at different b-values is interpreted by a mono-exponential model, and the apparent diffusion coefficient (ADC) whole brain map is generated by fitting the model in each voxel of the brain mask (step 4). The ADC brain map is restricted to the GM and WM. The ADC map is also restricted to individual brain regions by using available brain atlases, and further masked by the patient-specific GM or WM binary masks (step 5). ADC summary values are finally computed in the whole brain as well as in the different brain tissues and regions (step 6).

Table 1
Sociodemographic features and diffusion-weighted magnetic resonance imaging (DWI) findings in the 215 COVID-19 and 36 control patients included in the study.

	COVID-19	Control	p
n	215	36	
Age, years	52 [42 – 60]	52 [42 – 65]	0.624
Gender, F	125 (58 %)	18 (50 %)	0.370
Hospitalization	91 (42 %)	—	—
ICU	26 (12 %)	—	—
Days from disease onset to MRI	204 [89 – 325]	—	—
Brain ADC	0.856 [0.834 – 0.896]	0.851 [0.823 – 0.889]	0.233
GM ADC	0.856 [0.837 – 0.878]	0.845 [0.821 – 0.865]	**0.015**
WM ADC	0.768 [0.752 – 0.787]	0.753 [0.743 – 0.766]	**0.001**

Data are shown as median [IQR] or number (%).
p-values were computed by Wilcoxon rank sum test - independent samples test (continuous variables) or Fisher's test (binary variables). p-values are highlighted in bold in case of statistical significance of the differences.
Abbreviations: ADC: apparent diffusion coefficient; GM: gray matter; WM: white matter; MRI = magnetic resonance imaging.

Table 2
Prevalence of neurological symptoms in 131 COVID-19 patients with neurological complications other than olfactory dysfunction.

Symptom	Prevalence
Cognitive and memory disorders	68
Neuromuscolar disorders	37
Psychiatric disorders	9
Encephalitis, meningitis	8
Cerebrovascular disorders	6
Cranial nerve neuropathies	2
Others	58

[38 – 56] years, $p < 0.001$), were mainly men (56%), and showed significantly higher ADC alterations in whole brain, GM and WM (Table 3), as well as in most WM and few GM individual regions (Supplementary Table 4, Supplementary Table 5, Supplementary Table 6). Hospitalized patients underwent brain MRI acquisition significantly closer to disease onset than non-hospitalized patients (77 vs 252 median number of days, $p < 0.001$) (Table 3). Brain ADC values were not associated with the number of hospitalization days ($\rho = -0.010$, $p = 0.93$). Moreover, no significant differences in ADC values were found between hospitalized patients requiring and not requiring intensive care.

Despite the significant interaction between age and hospitalization, linear regression analysis showed a statistically significant effect of hospitalization on ADC increase in the WM, while ADC increase in the GM was mainly due to age differences (Supplementary Table 7).

COVID-19 patients showing neurological disorders were significantly older than those complaining about hyposmia and/or ageusia only (54 [49 – 62] vs 49 [35 – 57] years, $p < 0.001$), and showed significantly higher ADC alteration in whole brain, GM and WM (Table 3) and most WM and GM regions (uncorrected $p < 0.05$; Supplementary Table 4, Supplementary Table 5, Supplementary Table 6), although they underwent brain MRI significantly closer to disease onset (146 vs 237 median number of days, $p = 0.018$) (Table 3).

Despite the significant effect of age, linear regression analysis showed a statistically significant effect of neurological disorders other than olfactory loss on ADC increase in the WM (Supplementary Table 8). On the contrary, ADC increase in the GM was mainly due to age and gender differences.

61/215 COVID-19 patients reported a cognitive or memory disorder (e.g., confusion, insomnia, attention deficit) as the main neurological manifestation. These patients showed significantly higher ADC values as compared with the control group, in the whole brain (0.872 [0.848 – 0.913] vs 0.851 [0.823 – 0.889], $p = 0.012$), in WM (0.770 [0.756 – 0.802] vs 0.753 [0.743 – 0.766], $p < 0.001$) and in GM (0.873 [0.848 – 0.899] vs 0.845 [0.821 – 0.865], $p < 0.001$) (Fig. 3). The increase in ADC was found to be highly significant (uncorrected $p < 0.001$) in many GM and WM regions. Only WM regions survived correction for multiple comparisons (Supplementary Fig. 3).

COVID-19 patients with encephalitis or meningitis as predominant neurological manifestation (n = 7) showed a statistically significant increase in ADC values in the WM (0.776 [0.764 – 0.861], $p = 0.035$) (Fig. 3).

Contrarily, no statistically significant increase in ADC was found in the 30 patients showing neuromuscular disorders (such as neuropathies, myalgia or Guillain-Barré syndrome) as the main neurological manifestation following COVID-19, compared with normal controls (Fig. 3).

4. Discussion

In this study we found a significant increase in brain diffusivity in COVID-19 patients, as compared with normal controls, mainly in the WM. Hospitalized patients showed significantly higher ADC alteration than non-hospitalized patients. Similarly, COVID-19 patients with neurological disorders showed significantly higher ADC values than those complaining of olfactory system disorders only.

Most of the previous studies assessing brain DWI alterations in COVID-19 patients were limited to case reports or case series (Parsons et al., 2021) or focused on specific neurological complications such as encephalopathy, where white matter abnormalities were associated with high peripheral inflammatory markers (Rhally et al., 2021).

The widespread increase in WM diffusivity reported in the current paper is in line with a recent paper by Benedetti et al (Benedetti et al., 2021) finding a diffuse axonal damage in COVID-19 patients (assessed by DTI and confirmed in independent studies up to 3 months (Lu et al.,

Table 3
Sociodemographic features and diffusion-weighted magnetic resonance imaging (DWI) findings in the 215 COVID-19 patients included in the study, grouped by hospitalization and brain symptoms (anosmia only vs neurological disorders).

	Hospitalization	No hospitalization	p	Anosmia/ageusia only	Neurological disorders	p
n	91	124		84	131	
Age, years	57 [50 – 66]	50 [38 – 56]	**< 0.001**	49 [35 – 57]	54 [49 – 62]	**< 0.001**
Gender, F	40 (44 %)	85 (69 %)	**0.001**	50 (60 %)	75 (57 %)	0.625
Days from disease onset/hospitalization to MRI	77 [22 – 180]	252 [191 – 364]	**< 0.001**	237 [180 – 323]	146 [43 – 328]	**0.018**
Brain ADC	0.884 [0.851 – 0.937]	0.846 [0.831 – 0.870]	**< 0.001**	0.846 [0.828 – 0.875]	0.867 [0.842 – 0.903]	**< 0.001**
GM ADC	0.870 [0.849 – 0.908]	0.849 [0.832 – 0.869]	**< 0.001**	0.849 [0.831 – 0.868]	0.864 [0.840 – 0.895]	**< 0.001**
WM ADC	0.773 [0.758 – 0.802]	0.766 [0.750 – 0.782]	**0.004**	0.765 [0.745 – 0.782]	0.772 [0.755 – 0.793]	**0.017**

Data are shown as median [IQR] or number (%).
p values were computed by independent *t*-test (continuous variables) or Chi-squared test (binary variables), without controlling for possible covariates. p-values are highlighted in bold in case of statistical significance of the differences. Please refer to Supplementary Tables 7 and 8 for the results controlled for covariates. Abbreviations: ADC: apparent diffusion coefficient; GM: gray matter; WM: white matter; MRI = magnetic resonance imaging.

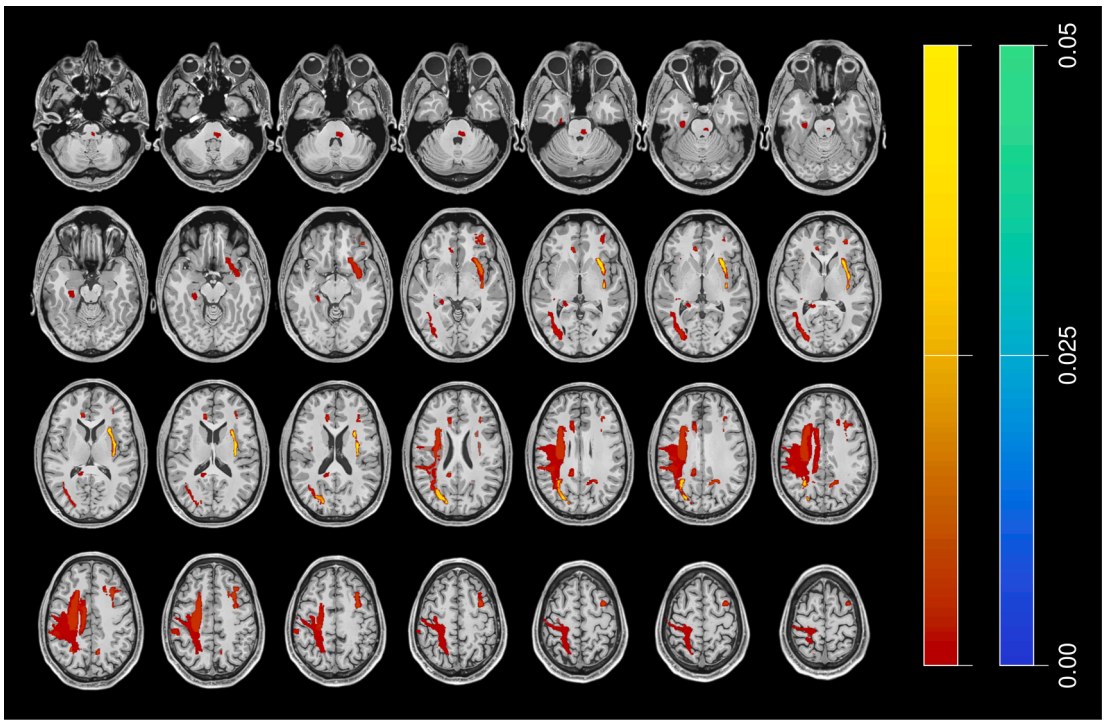

Fig. 2. White matter regions with significant diffusion differences in the 215 COVID-19 patients included in the study. WM regions of the JHU WM atlas (Oishi et al., 2009) were colour-coded based on the statistical significance (Bonferroni corrected p-value < 0.05) of the increase (red-yellow) or decrease (blue-green) in ADC in COVID-19 patients as compared with the normal controls. P-values were computed by non-parametric Wilcoxon rank sum test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

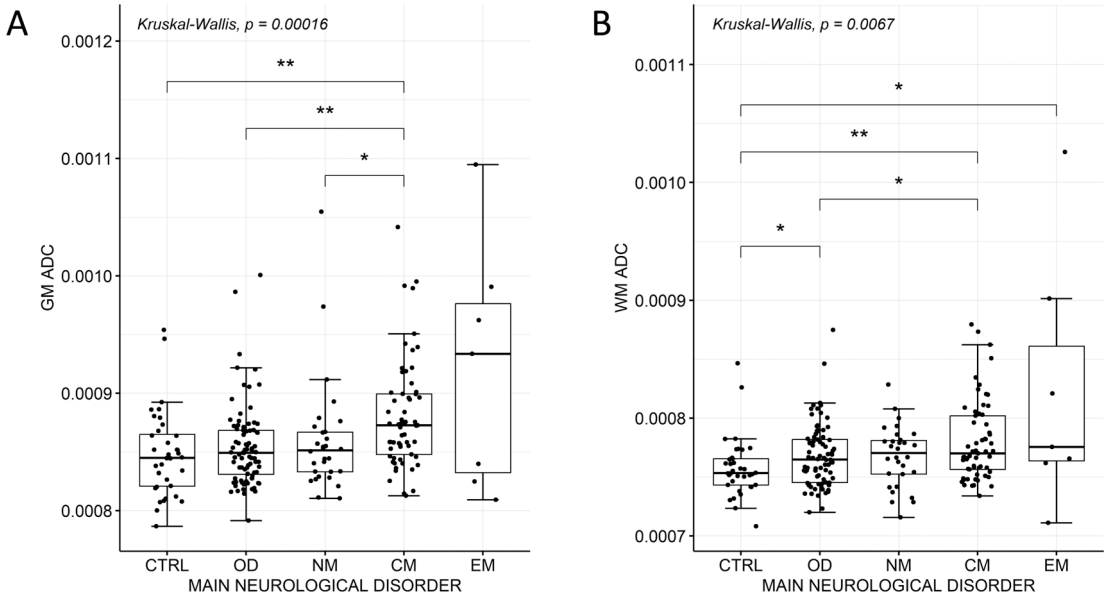

Fig. 3. ADC distribution in COVID-19 patients, subgrouped by neurological complication. The distribution of WM (A) and GM (B) ADC values in COVID-19 patients with olfactory disorders only (OD, n = 84), neuromuscular disorders (NM, n = 30), cognitive and memory disorders (CM, n = 61), or encephalitis and meningitis as main neurological complication (EM, n = 7) is compared with the distribution of corresponding values in in the control group (CTRL, n = 36). Pairwise p-values were assessed by Wilcoxon test or *t*-test, based on normal distribution of the data, while overall p-values were assessed by Kruskal-Wallis test. * indicates the level of significance (** $p < 0.001$, * $p < 0.05$). Abbreviations: WM = white matter, GM = gray matter, ADC = apparent diffusion coefficient, OD = olfactory disorders, NM = neuromuscular disorders, CM = cognitive and memory disorders, EM = encephalitis and meningitis, CTRL = controls.

2020) and 1 year after recovery (Huang et al., 2021)), associated with the systemic immune-inflammation index assessed at admission to the emergency department, and suggesting a massive microglia activation following SARS-Cov-2 infection, prompting neuroinflammation and ultimately causing cerebral damage.

Our findings are also in line with previous studies showing the association between the diffusion signal and the inflammatory component in several brain diseases (De Santis and Canals, 2019), and a recent paper showing DWI potential as a sensitive and specific marker of neuroinflammation, with glia activation associated with an increase in

mean diffusivity (Garcia-Hernandez et al., 2021). Consistently with this interpretation, we observed higher diffusivity in hospitalized versus non-hospitalized patients, in line with a recent paper (Díez-Cirarda et al., 2022) finding more pronounced cognitive alterations in hospitalized patients compared to non-hospitalized patients, as well as with another paper identifying COVID-19 as a strong independent risk factor for stroke in hospitalized patients (Katz et al., 2020). Similarly, brain diffusivity was highest in patients with neurological disorders that, besides being older, are likely denoted by higher neuroinflammation than patients with hyposmia or ageusia only.

Besides the widespread increase in WM diffusivity, significant ADC increase was observed in the GM, albeit limited to few regions in the medial temporal lobe and cortex. This is in line with previous DWI studies reporting increased diffusion in the medial temporal lobe (Kremer et al., 2020) and in the cortex (Kandemirli et al., 2020), and independent DTI studies revealing increased mean diffusivity in the cortex and hippocampi (Newcombe et al., 2021). Despite the latter two studies being focused on COVID-19 patients requiring intensive care, our study suggests that this finding may be independent on intensive care. Moreover, most of the GM regions where we found highest significant increase in ADC, and in particular the orbitofrontal and cingulate cortex, as well as the left insula, were also reported in a recent DTI study as areas of increased diffusivity indices (Douaud et al., 2022). In the same study, hospitalized patients were found to have higher increase in GM mean diffusivity than non-hospitalized patients, in line with the current findings.

ADC value increased in specific regions (precuneus, hippocampus, thalamus, insula) in patients with COVID-19 and cognitive impairment, similarly to preclinical Alzheimer's disease (Zhang et al., 2011; den Heijer et al., 2012). Convincing evidence of brain disfunction is also provided by a fluorodeoxyglucose (FDG)-PET study, that revealed neocortical hypometabolism in patients recovering from COVID-19 with cognitive impairment, when conventional MRI were unremarkable (Guedj et al., 2021).

In another paper (Hugon et al., 2022), brainstem hypometabolism has also been described in a small number of COVID-19 patients with "brain fog", with a similar pattern of our ADC maps.

Although this is a cross-sectional study, the negative association observed between brain ADC and MRI time from disease onset suggests the transient nature of the reported neuroinflammation, likely not associated with significant infiltration of adaptive immune cells into the brain, blood–brain barrier breakdown or cell death (DiSabato et al., 2016). Future longitudinal studies are needed to clarify the temporal evolution of the alteration in brain diffusivity, especially in the white matter, and therefore the transient or permanent nature of the neuroinflammation.

One of the major strengths of the study is the noteworthy number of COVID-19 patients with neurological manifestations and brain DWI included in this study, that to the best of our knowledge is the largest ever published. Moreover, the heterogeneity and thorough characterization in terms of COVID-19 disease severity and neurological complications allowed to assess differences in brain diffusion by hospitalization and type of neurological manifestations. Secondly, while previous COVID-19 studies were limited to qualitative evaluation of the DWI scans, the processing procedure specifically developed for the purpose of the study allowed to compute quantitative measures of brain diffusivity in the whole brain, in the different brain tissues and in individual brain regions.

Study limitations include the small number of normal controls. For MRI protocol consistency, it was not possible to include in the control group MRI scans acquired before the study starting. Moreover, we cannot rule out the possibility that some normal controls, despite never having COVID-19-related symptoms, were affected by entirely asymptomatic COVID-19 pathology, and could therefore have partly biased the study results. Secondly, since data acquisition was performed during clinical practice and not as part of a clinical trial, MRI time from disease onset was not standardised and even very variable from patient to patient. Hospitalized patients underwent brain MRI significantly earlier than non-hospitalized patients, and the same is true for patients with neurological disorders as compared with patients with hyposmia or ageusia only. The variability in MRI acquisition time could have biased the results, and particularly the comparison between COVID-19 patients' subgroups. The positive correlation between brain ADC and age was expected and in line with previous studies (Naganawa et al., 2003). The effect of age on ADC increase observed in COVID-19 patients was accounted for by including age as covariate in each comparison. In addition, the fact that some COVID-19 patients are known to have anosognosia (as reported by Daroische et al., 2021, Voruz et al., 2022, and Parsons et al., 2021 for both cognitive and olfactory deficits), may have biased the patients' classification. Last, no quantitative clinical variable was collected to assess the severity of cerebral damage (such as different neurological symptoms other than olfactory dysfunction and specifically cognitive disorders generally defined as brain fog) and therefore it was not possible to investigate the association between increase in diffusivity and severity of cerebral damage.

Future longitudinal studies are needed to investigate changes in diffusivity over time and provide definitive evidence of the transient nature of the COVID-19-related neuroinflammation. A systematic acquisition of serial DWI data and the concomitant evaluation of the nature and severity of cerebral damage will allow to validate brain DWI potential as a non-invasive window to neuroinflammation in COVID-19.

5. Data and code availability statement

The data that support the findings of this study are available from the corresponding author, prior submission of a project outline.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

Acknowledgements

The authors gratefully acknowledge Cristina Casalini, radiology technician, for acquisition of most MRIs in the first part of the pandemic, Carmelo Parisi, MR zone clinical leader for setting of adequate DWI and DTI sequences, nurses, and technicians of Neuroradiology Unit for devotion and support in managing these particular patients especially at the beginning of the pandemic.

Funding

The study was supported in part by a grant from Brembo SpA (Curno, Bergamo, Italy), under the initiative "Progetto TrexUno".

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2023.103338.

References

Alonazi, B., Farghaly, A.M., Mostafa, M.A., Al-Watban, J.A., Zindani, S.A., Altaimi, F., Fagiry, M.A., Mahmoud, M.Z., 2021. Brain MRI in SARS-CoV-2 pneumonia patients with newly developed neurological manifestations suggestive of brain involvement. Sci. Rep. 11 (1) https://doi.org/10.1038/s41598-021-00064-5.

Benedetti, F., Palladini, M., Paolini, M., Melloni, E., Vai, B., De Lorenzo, R., Furlan, R., Rovere-Querini, P., Falini, A., Mazza, M.G., 2021. Brain correlates of depression, post-traumatic distress, and inflammatory biomarkers in COVID-19 survivors: a multimodal magnetic resonance imaging study. Brain Behav Immun Health. 18 https://doi.org/10.1016/j.bbih.2021.100387.

Castelli, V., Cimini, A., Ferri, C., 2020. Cytokine Storm in COVID-19: "When You Come Out of the Storm, You Won't Be the Same Person Who Walked in". Front. Immunol. 11, 2132. https://doi.org/10.3389/fimmu.2020.02132.

Chen, B., Chen, C., Zheng, J., Li, R., Xu, J., 2020. Insights Into Neuroimaging Findings of Patients With Coronavirus Disease 2019 Presenting With Neurological Manifestations. Front. Neurol. 11, 593520 https://doi.org/10.3389/fneur.2020.593520.

Choi, Y., Lee, M.K., 2020. Neuroimaging findings of brain MRI and CT in patients with COVID-19: A systematic review and meta-analysis. Eur. J. Radiol. 133, 109393 https://doi.org/10.1016/j.ejrad.2020.109393.

Chougar, L., Shor, N., Weiss, N., Galanaud, D., Leclercq, D., Mathon, B., Belkacem, S., Ströer, S., Burrel, S., Boutolleau, D., Demoule, A., Rosso, C., Delorme, C., Seilhean, D., Dormont, D., Morawiec, E., Raux, M., Demeret, S., Gerber, S., Trunet, S., Similowski, T., Degos, V., Rufat, P., Corvol, J.-C., Lehéricy, S., Pyatigorskaya, N., 2020. Retrospective Observational Study of Brain MRI Findings in Patients with Acute SARS-CoV-2 Infection and Neurologic Manifestations. Radiology 297 (3), E313–E323.

Daroische, R., Hemminghyth, M.S., Eilertsen, T.H., Breitve, M.H., Chwiszczuk, L.J., 2021. Cognitive impairment after COVID-19-a review on objective test data. Front. Neurol. 12, 699582 https://doi.org/10.3389/fneur.2021.699582.

De Santis, S., Canals, S., 2019. Non-invasive MRI windows to neuroinflammation. Neuroscience 403, 1–3. https://doi.org/10.1016/j.neuroscience.2019.01.051.

den Heijer, T., der Lijn, F.V., Vernooij, M.W., de Groot, M., Koudstaal, P.J., der Lugt, A. V., Krestin, G.P., Hofman, A., Niessen, W.J., Breteler, M.M.B., 2012. Structural and diffusion MRI measures of the hippocampus and memory performance. Neuroimage 63 (4), 1782–1789.

Díez-Cirarda, M., Yus, M., Gómez-Ruiz, N., et al. Multimodal neuroimaging in post-COVID syndrome and correlation with cognition. Brain. Published online October 26, 2022. doi:10.1093/brain/awac384.

DiSabato, D.J., Quan, N., Godbout, J.P., 2016. Neuroinflammation: the devil is in the details. J. Neurochem. 139 (Suppl 2(Suppl 2)), 136–153. https://doi.org/10.1111/jnc.13607.

Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., Lange, F., Andersson, J.L.R., Griffanti, L., Duff, E., Jbabdi, S., Taschler, B., Keating, P., Winkler, A.M., Collins, R., Matthews, P.M., Allen, N., Miller, K.L., Nichols, T.E., Smith, S.M., 2022. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 604 (7907), 697–707.

Ellul, M.A., Benjamin, L., Singh, B., Lant, S., Michael, B.D., Easton, A., Kneen, R., Defres, S., Sejvar, J., Solomon, T., 2020. Neurological associations of COVID-19. Lancet Neurol. 19 (9), 767–783.

Fotuhi, M., Mian, A., Meysami, S., Raji, C.A., 2020. Neurobiology of COVID-19. J. Alzheimers Dis. 76 (1), 3–19. https://doi.org/10.3233/JAD-200581.

Garcia-Hernandez, R., Cerdán Cerdá, A., Carpena, A.T., et al., 2021. Mapping microglia and astrocytes activation in vivo using diffusion MRI. *bioRxiv*. Published online. https://doi.org/10.1101/2020.02.07.938910.

Guedj, E., Campion, J.Y., Dudouet, P., Kaphan, E., Bregeon, F., Tissot-Dupont, H., Guis, S., Barthelemy, F., Habert, P., Ceccaldi, M., Million, M., Raoult, D., Cammilleri, S., Eldin, C., 2021. 18F-FDG brain PET hypometabolism in patients with long COVID. Eur. J. Nucl. Med. Mol. Imaging 48 (9), 2823–2833.

Huang, S., Zhou, Z., Yang, D., et al. Persistent white matter changes in recovered COVID-19 patients at the 1-year follow-up. *Brain*. Published online December 16, 2021. doi: 10.1093/brain/awab435.

Hugon, J., Queneau, M., Sanchez Ortiz, M., Msika, E.F., Farid, K., Paquet, C., 2022. Cognitive decline and brainstem hypometabolism in long COVID: A case series. Brain Behav. 12 (4), e2513.

Kandemirli, S.G., Dogan, L., Sarikaya, Z.T., Kara, S., Akinci, C., Kaya, D., Kaya, Y., Yildirim, D., Tuzuner, F., Yildirim, M.S., Ozluk, E., Gucyetmez, B., Karaarslan, E., Koyluoglu, I., Demirel Kaya, H.S., Mammadov, O., Kisa Ozdemir, I., Afsar, N., Citci Yalcinkaya, B., Rasimoglu, S., Guduk, D.E., Kedir Jima, A., Ilksoz, A., Ersoz, V., Yonca Eren, M., Celtik, N., Arslan, S., Korkmazer, B., Dincer, S.S., Gulek, E., Dikmen, I., Yazici, M., Unsal, S., Ljama, T., Demirel, I., Ayyildiz, A., Kesimci, I., Bolsoy Deveci, S., Tutuncu, M., Kizilkilic, O., Telci, L., Zengin, R., Dincer, A., Akinci, I.O., Kocer, N., 2020. Brain MRI Findings in Patients in the Intensive Care Unit with COVID-19 Infection. Radiology 297 (1), E232–E235.

Katal, S., Balakrishnan, S., Gholamrezanezhad, A., 2021. Neuroimaging and neurologic findings in COVID-19 and other coronavirus infections: A systematic review in 116 patients. J. Neuroradiol. 48 (1), 43–50. https://doi.org/10.1016/j.neurad.2020.06.007.

Katz, J.M., Libman, R.B., Wang, J.J., Sanelli, P., Filippi, C.G., Gribko, M., Pacia, S.V., Kuzniecky, R.I., Najjar, S., Azhar, S., 2020. Cerebrovascular Complications of COVID-19. Stroke 51 (9). https://doi.org/10.1161/STROKEAHA.120.031265.

Kremer, S., Lersy, F., de Sèze, J., Ferré, J.-C., Maamar, A., Carsin-Nicol, B., Collange, O., Bonneville, F., Adam, G., Martin-Blondel, G., Rafiq, M., Geeraerts, T., Delamarre, L., Grand, S., Krainik, A., Kremer, S., Adam, G., Alleg, M., Anheim, M., Anxionnat, R., Ardellier, F.-D., Baloglu, S., Bapst, B., Benzakoun, J., Berge, J., Bolognini, F., Bonneville, F., Bornet, G., Boulay, C., Boulouis, G., Boutet, C., Brisset, J.C., Caillard, S., Carré, S., Carsin-Nicol, B., Collange, O., Comby, P.-O., Constans, J.M., David, J.-S., de Beaurepaire, I., de Sèze, J., Delamarre, L., Desal, H., Edjlali-Goujon, M., Fabre, X., Fafi-Kremer, S., Ferré, J.-C., Feuerstein, P., Henry Feugeas, M.-C., Forestier, G., Gaudemer, A., Geeraerts, T., Grand, S., Hansmann, Y., Heintz, A., Helms, J., Hemmert, C., Hmeydia, G., Jager, L., Kazémi, A., Kerleroux, B., Khalil, A., Krainik, A., Lacalm, A., Lecler, A., Lecocq, C., Lefèbvre, N., Lersy, F., Maamar, A., Martin-Blondel, G., Matthieu, M., Megdiche, I., Mertes, P.-M., Messié, J., Metanbou, S., Meyer, N., Meziani, F., Mutschler, V., Nesser, P., Oesterlé, H., Ohana, M., Oppenheim, C., Pyatigorskaya, N., Rafiq, M., Ricolfi, F., Saleme, S., Schenck, M., Schmitt, E., Schneider, F., Sebag, N., Talla Mba, Y., Thouant, P., Willaume, T., Zhu, F., Zorn, P.-E., Cotton, F., 2020. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology 297 (2), E242–E251.

Kremer, S., Lersy, F., Anheim, M., Merdji, H., Schenck, M., Oesterlé, H., Bolognini, F., Messie, J., Khalil, A., Gaudemer, A., Carré, S., Alleg, M., Lecocq, C., Schmitt, E., Anxionnat, R., Zhu, F., Jager, L., Nesser, P., Mba, Y.T., Hmeydia, G., Benzakoun, J., Oppenheim, C., Ferré, J.-C., Maamar, A., Carsin-Nicol, B., Comby, P.-O., Ricolfi, F., Thouant, P., Boutet, C., Fabre, X., Forestier, G., de Beaurepaire, I., Bornet, G., Desal, H., Boulouis, G., Berge, J., Kazémi, A., Pyatigorskaya, N., Lecler, A., Saleme, S., Edjlali-Goujon, M., Kerleroux, B., Constans, J.-M., Zorn, P.-E., Mathieu, M., Baloglu, S., Ardellier, F.-D., Willaume, T., Brisset, J.-C., Caillard, S., Collange, O., Mertes, P.M., Schneider, F., Fafi-Kremer, S., Ohana, M., Meziani, F., Meyer, N., Helms, J., Cotton, F., 2020. Neurologic and neuroimaging findings in patients with COVID-19: a retrospective multicenter study. Neurology 95 (13), e1868–e1882.

Kremer, S., Gerevini, S., Ramos, A., Lersy, F., Yousry, T., Vernooij, M.W., Anzalone, N., Jäger, H.R., 2022. Neuroimaging in patients with COVID-19: a neuroradiology expert group consensus. Eur. Radiol. 32 (6), 3716–3725.

Ladopoulos, T., Zand, R., Shahjouei, S., Chang, J.J., Motte, J., Charles James, J., Katsanos, A.H., Kerro, A., Farahmand, G., Vaghefi Far, A., Rahimian, N., Ebrahimzadeh, S.A., Abedi, V., Papathanasiou, M., Labedi, A., Schneider, R., Lukas, C., Tsiodras, S., Tsivgoulis, G., Krogias, C., 2021. COVID-19: neuroimaging features of a pandemic. J. Neuroimaging 31 (2), 228–243.

Lou, J.J., Movassaghi, M., Gordy, D., et al., 2021. Neuropathology of COVID-19 (neuro-COVID): clinicopathological update. Free Neuropathol. 2, 2. https://doi.org/10.17879/freeneuropathology-2021-2993.

Lu, Y., Li, X., Geng, D., Mei, N., Wu, P.-Y., Huang, C.-C., Jia, T., Zhao, Y., Wang, D., Xiao, A., Yin, B.o., 2020. Cerebral micro-structural changes in COVID-19 patients - an MRI-based 3-month Follow-up Study. EClinicalMedicine. 25 https://doi.org/10.1016/j.eclinm.2020.100484.

Moonis, G., Filippi, C.G., Kirsch, C.F.E., Mohan, S., Stein, E.G., Hirsch, J.A., Mahajan, A., 2021. The spectrum of neuroimaging findings on CT and MRI in adults with COVID-19. AJR Am. J. Roentgenol. 217 (4), 959–974.

Naganawa, S., Sato, K., Katagiri, T., Mimura, T., Ishigaki, T., 2003. Regional ADC values of the normal brain: differences due to age, gender, and laterality. Eur. Radiol. 13 (1), 6–11. https://doi.org/10.1007/s00330-002-1549-1.

Newcombe, V.F.J., Spindler, L.R.B., Das, T., Winzeck, S., Allinson, K., Stamatakis, E.A., Menon, D.K., Anwar, F., Bullmore, E., Coles, A., Coles, J., Jones, J., Lupson, V., Needham, E., Rowe, J., Sawcer, S., Valerio, F., 2021. Neuroanatomical substrates of generalized brain dysfunction in COVID-19. Intensive Care Med. 47 (1), 116–118.

Oishi, K., Faria, A., Jiang, H., Li, X., Akhter, K., Zhang, J., Hsu, J.T., Miller, M.I., van Zijl, P.C.M., Albert, M., Lyketsos, C.G., Woods, R., Toga, A.W., Pike, G.B., Rosa-Neto, P., Evans, A., Mazziotta, J., Mori, S., 2009. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: Application to normal elderly and Alzheimer's disease participants. Neuroimage 46 (2), 486–499.

Pacheco-Herrero, M., Soto-Rojas, L.O., Harrington, C.R., Flores-Martinez, Y.M., Villegas-Rojas, M.M., León-Aguilar, A.M., Martínez-Gómez, P.A., Campa-Córdoba, B.B., Apátiga-Pérez, R., Corniel-Taveras, C.N., Dominguez-García, J.d.J., Blanco-Alvarez, V.M., Luna-Muñoz, J., 2021. Elucidating the neuropathologic mechanisms of SARS-CoV-2 infection. Front. Neurol. 12, 660087 https://doi.org/10.3389/fneur.2021.660087.

Parsons, N., Outsikas, A., Parish, A., Clohesy, R., D'Aprano, F., Toomey, F., Advani, S., Poudel, G.R., 2021. Modelling the anatomic distribution of neurologic events in patients with COVID-19: a systematic review of MRI findings. AJNR Am. J. Neuroradiol. 42 (7), 1190–1195.

Penny, W., Friston, K., Ashburner, J., Kiebel, S., Nichols, T., Statistical Parametric Mapping: The Analysis of Functional Brain Images.; 2007. doi: 10.1016/B978-0-12-372560-8.X5000-1.

Qi, X., Arfanakis, K., 2021. Regionconnect: Rapidly extracting standardized brain connectivity information in voxel-wise neuroimaging studies. Neuroimage 225, 117462. https://doi.org/10.1016/j.neuroimage.2020.117462.

Rhally, A., Griffa, A., Kremer, S., Uginet, M., Breville, G., Stancu, P., Assal, F., Lalive, P. H., Lövblad, K.-O., Allali, G., 2021. C-reactive protein and white matter microstructural changes in COVID-19 patients with encephalopathy. J. Neural Transm. (Vienna) 128 (12), 1899–1906.

Rolls, E.T., Huang, C.C., Lin, C.P., Feng, J., Joliot, M., 2020. Automated anatomical labelling atlas 3. Neuroimage 206, 116189. https://doi.org/10.1016/j.neuroimage.2019.116189.

Sarubbo, F., El Haji, K., Vidal-Balle, A., Bargay, L.J., 2022. Neurological consequences of COVID-19 and brain related pathogenic mechanisms: A new challenge for neuroscience. Brain Behav Immun Health. 19, 100399 https://doi.org/10.1016/j.bbih.2021.100399.

Verdecchia, P., Cavallini, C., Spanevello, A., Angeli, F., 2020. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur. J. Intern. Med. 76, 14–20. https://doi.org/10.1016/j.ejim.2020.04.037.

Voruz, P., Cionca, A., Jacot de Alcântara, I., Nuber-Champier, A., Allali, G., Benzakour, L., Thomasson, M., Lalive, P.H., Lövblad, K.-O., Braillard, O., Nehme, M., Coen, M., Serratrice, J., Pugin, J., Guessous, I., Landis, B.N., Adler, D., Griffa, A., Van De Ville, D., Assal, F., Péron, J.A., 2022. Functional connectivity underlying cognitive and psychiatric symptoms in post-COVID-19 syndrome: is anosognosia a key determinant? Brain Commun. 4 (2) https://doi.org/10.1093/braincomms/fcac057.

Zhang, B., Zhang, J.-g., Zhao, H., Zhang, X., Li, M., Qian, L., Wang, K., Tian, C.-S., Guo, W.-H., Cao, Q.-Y., Zhou, Z.-Y., Yu, H., Li, C., Xu, J., Cao, W., Zhu, B., Xu, Y., 2011. Evaluation of apparent diffusion coefficient mappings in amnestic mild cognitive impairment using an image analysis software brain search. Acta Radiol. 52 (10), 1147–1154.