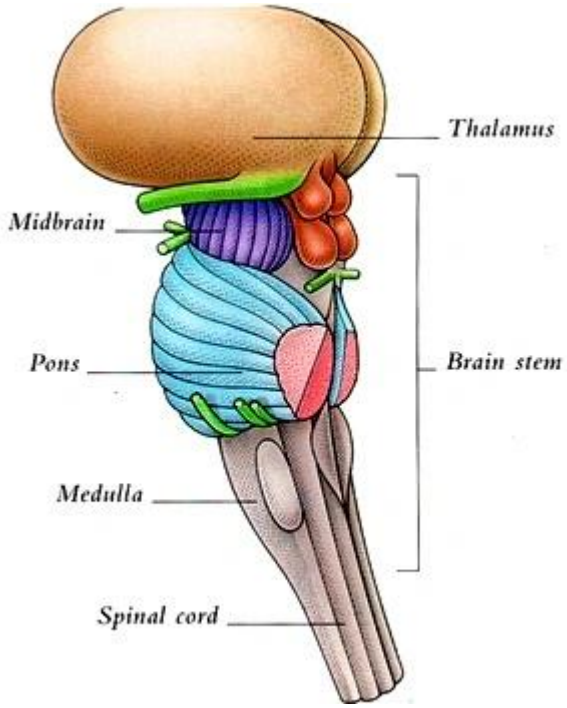
The most common neuroradiological changes found in hospitalized patients severely affected by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) are cerebral microhemorrhages, encephalopathy, and white matter hyperintensities. As previous autopsy studies reported brainstem involvement in COVID-19 patients, with tissue inflammation and neurodegeneration, the authors from the United Kingdom used a more advanced magnetic resonance imaging (MRI) technique, quantitative susceptibility mapping (QSM), to investigate the microstructural brainstem abnormalities in COVID survivors several months after hospitalization. Also, they utilized a voxel-by-voxel approach to localize the brainstem clusters of atrophy and determine whether brainstem abnormalities found on QSM correlate with clinical measures, laboratory results, and recovery.

QSM is a technique that effectively detects increased iron deposition in the basal ganglia and midbrain, chronic inflammation in multiple sclerosis, and cerebral microbleeds. High-resolution, ultra-high field (≥7 T) QSM detects microstructural alterations with greater sensitivity and identifies more subtle abnormalities and neuroanatomical changes. In their preliminary analysis, the same group of researchers showed abnormal brainstem QSM findings in post-hospitalized COVID survivors.

Previous studies suggested that brainstem abnormalities are involved in the pathophysiology of long COVID or post-acute COVID syndrome (PACS). A recent resting-

state functional magnetic resonance imaging (fMRI) study demonstrated changes in the functional connectome of the brainstem, limbic system, olfactory system, thalamus, and cerebellum in participants with long COVID syndrome seven months after acute infection. https://discovermednews.com/changes-in-brain-functional-connectome-in-post-covid-syndrome/ A PET study, using a novel radiopharmaceutical agent [18F]F-AraG, demonstrated higher [18F]F-AraG uptake in the brainstem (pons), thoracic spinal cord, cauda equina, lumbar and iliac crest, bone marrow, and many other anatomical regions in vaccinated COVID convalescents, including those with and without long COVID symptoms. https://discovermednews.com/elevated-t-cell-activation-vaccinated-covid-convalescents-2-years-after-infection/



Brainstem

About the study

The researchers used 7 T QSM to investigate abnormalities in the brainstem subregions, including midbrain, pons, medulla, and superior cerebellar peduncle, defined *a priori* as regions of interest (ROIs). The study enrolled COVID patients after hospitalization and healthy controls. Inclusion criteria for COVID patients were: evidence of COVID-19 infection

confirmed by polymerase chain reaction (PCR) of respiratory samples for SARS-CoV-2, no pre-COVID history of neurological or psychiatric disorders, and no contradictions for 7 T MRI. The healthy controls were individuals scanned before the COVID-19 pandemic and asymptomatic individuals with no history of positive PCR for SARS-CoV-2, scanned during the pandemic.

Laboratory tests included C-reactive protein (CRP) and D-dimer levels, and the lowest platelet count during hospital stay. At follow-up, functional recovery was assessed using the modified Rankin Scale, and mental health was assessed using the anxiety (the Generalized Anxiety Disorder-7) and depression (the Patient Health Questionnaire-9) questionnaires.

Results

The study included 30 COVID-19 patients after hospitalization and 51 healthy controls. Age did not differ between the two groups (57 ± 12 years in the post-hospitalization COVID group and 53 ± 15 years in the control group). There were more men in the control group than in the COVID group (34 *vs.* 18). The median time from hospital admission to the MRI scan in the post-hospitalization COVID group was 199 days (93–548 days).

The analysis focused on changes in the brainstem subregions: midbrain, pons, medulla, and superior cerebellar peduncle. Voxel-wise analysis demonstrated increased QSM microstructural abnormalities in the medulla, pons, and midbrain regions in the post-hospitalization COVID group compared with healthy controls. Specifically, the clusters in the inferior medullary reticular formation, the raphe obscurus and pallidus, displayed significant abnormalities. Importantly, the locations of these clusters partially overlap with brainstem regions associated with respiratory function and body homeostasis. Neurons in the medullary reticular formation are responsible for the central control of the respiratory cycle, and neurons in the raphe pallidus and obscurus are central chemoreceptors responsible for the full ventilatory response to hypercapnia.

The patients with increased microstructural QSM abnormalities in the inferior medullary reticular formation, the raphe obscurus, and pallidus had more severe acute COVID-19, the highest CRP levels, and worse functional recovery. In contrast, patients with a more favorable functional outcome, shorter hospital stay, or less severe acute COVID-19 had decreased QSM tissue abnormalities in the medullary clusters.

Conclusion

This study used non-invasive ultra-high-field 7 T MRI and demonstrated imaging evidence of pathophysiological changes and microstructural abnormalities in the brainstem of post-hospitalization COVID patients. Several regions of the medulla oblongata, pons, and midbrain showed increased QSM abnormalities at a median of 6.5 months after hospitalization, suggesting that these regions were still affected over months after acute SARS-CoV-2 infection. These changes were more evident in patients with longer hospital stays, higher COVID severity, more prominent inflammatory responses, and worse functional outcomes.

Because ultra-high-field 7 T QSM identified pathological changes in the brainstem that are not detected at standard clinical field strengths, the researchers suggested that this more sensitive approach may be a valuable tool for investigating the long-term effects of COVID-19 on the human brain.

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Rua C, Raman B, Rodgers CT *et al*. Quantitative susceptibility mapping at 7 T in COVID-19: brainstem effects and outcome associations, *Brain*, 2024: 00; 1–10. https://doi.org/10.1093/brain/awae215