

ABSTRACT

The COVID-19 pandemic has had a profound impact worldwide, not only due to its acute effects but also because of its long-term health consequences, particularly neurological and cognitive impairments. Many individuals who have recovered from COVID-19 continue to experience symptoms such as cognitive dysfunction, memory deficits, attention deficits, fatigue, insomnia, and brain fog, collectively termed as post-COVID syndrome (PCS). Despite increasing recognition of these persistent symptoms, the neurobiological mechanisms underlying PCS are still poorly understood. This thesis systematically investigates the long-term impact of COVID-19 on brain structure, white matter microstructure, functional connectivity, and cerebral blood flow using an exploratory multi-sequence Magnetic Resonance Imaging (MRI) approach. A controlled cross-sectional study was conducted, involving a cohort of COVID-19 recovered patients (CRPs) and a matched group of healthy controls (HCs). Participants underwent a comprehensive MRI scan session, including T1-weighted MRI, diffusion-weighted imaging (DWI), resting-state functional MRI (rs-fMRI), and Arterial Spin Labeling (ASL) imaging. These images were analysed to investigate the morphology, microstructure, function, and perfusion in the brain, respectively.

T1-weighted imaging was employed to assess morphological changes in cortical and subcortical regions. Macro-scale analyses highlighted volumetric changes in subcortical components of the basal ganglia and the limbic system. Morphometric analyses, including voxel-based morphometry (VBM) and surface-based morphometry (SBM), revealed significant gray matter volume reduction and cortical thickness alterations in several brain regions, including the orbitofrontal cortex, medial prefrontal cortex, and the superior temporal gyrus. Further, analyses of white matter microstructure using DWI revealed significant alterations in the CRPs. Tract-Based Spatial Statistics (TBSS) and Automated Fiber Quantification (AFQ) revealed significant white matter disruptions in CRPs, particularly in the uncinate fasciculus, cingulum bundle, inferior longitudinal fasciculus, and the inferior fronto-occipital fasciculus. Fixel-Based Analysis (FBA) was employed to study and quantify white matter microstructure at the sub-voxel level using fiber density and cross-sectional measures, highlighting changes in the tracts of the limbic system. These findings show that COVID-19 has a significant impact on the integrity of major white matter tracts that could be linked with cognitive processing, memory, and emotion in the brain.

Functional connectivity alterations were examined using resting-state fMRI, focusing on large-scale brain networks. Independent Component Analysis (ICA) and thalamocortical functional connectivity analyses revealed significant disruptions in the default mode network (DMN), salience network, and thalamocortical connectivity of mediodorsal thalamic nuclei in CRPs. Reduced functional connectivity within the DMN, particularly between the posterior cingulate cortex, medial prefrontal cortex, and the caudate nucleus, was observed, which could be associated with difficulties in sustained attention, multi-tasking, and lack of sleep. Additionally, altered thalamocortical interactions suggest disruptions in key circuits involved in memory recollection.

Notably, it was observed that while functional dysfunction was prominent only in hospitalized CRPs, abnormalities in morphology and white matter integrity were consistent across survivors of mild and severe COVID-19 infections. Cerebral perfusion was assessed using ASL-MRI to evaluate alterations in blood flow, which could contribute to the neurological symptoms observed in PCS. Results of our study did not highlight a significant impact of COVID-19 on blood flow.

This research provides compelling evidence of morphological, microstructural, and functional changes in individuals recovering from COVID-19, supporting the hypothesis that the virus has long-term neurological effects. The integration of multi-sequence MRI techniques allows for a comprehensive understanding of brain health. Using the findings of this thesis, we proposed a series of hypotheses to facilitate future investigations on underlying neurological mechanisms behind the characteristic symptoms of PCS, brain fog, fatigue, insomnia, and memory problems. The findings of this study have significant implications for public health, clinical management, and rehabilitation strategies aimed at mitigating the long-term neurological consequences of COVID-19. Future work should focus on longitudinal studies to determine whether these changes are progressive or reversible over time. Additionally, further investigations into the relationship between specific post-COVID symptoms and neuroimaging biomarkers will be essential to develop targeted interventions. This thesis lays the foundation for future research exploring specific neural correlates of PCS and therapeutic strategies to support COVID-19 survivors experiencing persistent cognitive and neurological challenges.