Post-acute COVID or long COVID syndrome involves a wide range of organ dysfunction and clinical symptoms, but the most frequent, persistent, and disabling symptoms are neurological. Despite advances in understanding how infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affects the brain and extensive mapping of the spectrum of neurological sequelae, no significant progress has been made in comprehending the underlying pathological mechanisms. In this study, the authors from Germany used resting-state functional magnetic resonance imaging (fMRI) to investigate the characteristics and changes in the complex network known as the brain functional connectome in individuals diagnosed with neurological manifestations of post-acute COVID syndrome (neuro-PASC).

Recent in-depth metabolic, microstructural, and functional brain imaging studies have begun to uncover changes in the central nervous system (CNS) related to SARS-CoV-2 infection, which appear macrostructurally unnoticed in conventional brain imaging. These alterations have been found in numerous brain regions across distinct brain networks, such as the olfactory cortex, thalamus, basal ganglia, limbic system, brainstem, and cerebellum. For example, a more advanced magnetic resonance imaging (MRI) technique, quantitative susceptibility mapping (QSM), 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.
https://discovermednews.com/abnormalities-in-the-brain-stem-of-covid-19-survivors/

In regard to the brain functional connectivity, the study of Diéz-Circada et al. found substantial network disruptions, manifested as reduced connectivity between the left and right parahippocampal regions and the orbitofrontal and cerebellar areas in 86 individuals, eleven months after COVID-19. The changes in the brain functional network were accompanied by decreased grey matter volume in the cortical, limbic, and cerebellar regions and were associated with cognitive dysfunction.
https://doi.org/10.1093/brain/awac384 Additionally, a recent task-activated fMRI study discovered a reorganized working memory network in individuals diagnosed with post-COVID neuropsychiatric symptoms. Several brain regions in the left hemisphere showed lower activation, with a greater or compensatory use of the brain regions in the right hemisphere to maintain normal performance. These results suggest suboptimal functioning in the normal network, but increased brain activation in the contralateral hemisphere during working memory tasks.
https://discovermednews.com/patients-with-post-covid-syndrome-and-neuropsychiatric-symptoms-have-different-brain-activation-during-the-working-memory-task/



About the study

The authors analyzed the resting-state fMRI data in patients with primarily neurological manifestations of post-acute COVID syndrome (neuro-PASC). In non-vaccinated individuals, SARS-CoV-2 infection was confirmed by reverse transcription polymerase chain reaction of nasopharyngeal swabs for SARS-CoV-2 or antibodies against SARS-CoV-2.

To uncover differences in network topology between patients with neuro-PASC and healthy controls, researchers calculated a set of measures characterizing distinct network features, distinguished by whether they characterize a feature of the entire graph (*global* measure) or a feature of individual nodes in the graph (*local* measure).

All patients with post-COVID symptoms underwent a neurological examination. Cognitive deficits, affective symptoms, and sleep disturbances were evaluated by using the Fatigue Scale for Motor and Cognitive Functions, the Hospital Anxiety and Depression Scale, the Epworth Sleepiness Scale, the Pittsburgh Sleep Quality Index, the Montreal Cognitive Assessment, and the Trail-Making Test (TMT), parts A and B. The TMT-A is a primarily visual attention skill test, whereas part B is a more complex task and is considered to measure other components of executive functioning.

Results

The study included 123 participants: 66 patients with primarily neurological symptoms of neuro-PASC syndrome after a mild SARS-CoV-2 infection, and 57 healthy controls. The neuro-PASC group had a greater proportion of women than healthy controls, 57 *versus* 38. There was no difference in average age between the two groups, 42.3 years *versus* 42.1 years. The mean time from the onset of COVID-19 was seven months.

The resting-state fMRI data analysis

On a whole-brain level, there were no significant differences for all measures. However, in the neuro-PASC group, regional differences were found in the olfactory gyrus, cingulate cortex, red nucleus, thalamus, and crus II of the cerebellum.

The functional connectivity was decreased in the olfactory cortex and the medial orbital gyrus, which forms the olfactory sulcus and is adjacent to the olfactory tract. The connectivity changes also affected the cingulate cortex, with decreased connectivity of the anterior cingulate cortex and increased connectivity of the left posterior cingulate gyrus, which is considered a central node in the default mode network.

The findings showed the abundance of the angiotensin-converting enzyme 2 receptors, which are important for SARS-CoV-2 viral entry, in the excitatory neurons of the posterior cingulate cortex, interneurons, and cerebellum, potentially rendering these regions vulnerable to acute and long-term damage induced by the SARS-CoV-2 infection.

The TMT-A test, which measures cognitive processing speed, was correlated with connectivity changes in 19 brain regions, including the cingulate cortex, the insula, and the paracentral lobule. In particular, this test was strongly correlated with the hyperconnectivity of the posterior cingulate gyrus. According to the authors, those findings could explain executive function disorders in individuals diagnosed with neuro-PASC. The TMT-B test, which evaluates task-switching capabilities, was correlated with the connectivity changes in four brain regions.

The red nucleus, a key component of the motor pathway connecting the cerebral cortex to the spinal cord, displayed a significantly decreased connectivity across most regional graphs.

Fatigue, as measured by the total score of the Fatigue Scale, was correlated with the connectivity changes in numerous brain regions, with some emphasis on the cerebellum, temporal and occipital lobes, and thalamus. Fatigue was strongly correlated with increased connectivity in the thalamic intralaminar nuclei, which receive input from various brain regions, including the cortex, basal ganglia, and brainstem, and modulate wakefulness, attention, and the sleep-wake cycle.

The Montreal Cognitive Assessment score was correlated with connectivity changes in 12 brain regions, particularly in the cerebellum and bilateral hippocampus. This test was strongly correlated with increased connectivity of the right cerebellar crus II, a structure associated with various cognitive functions in working memory and spatial processes.

Conclusion

This study showed the characteristics and changes of the complex network known as the brain functional connectome in individuals diagnosed with the neuro-PASC syndrome. Compared to age- and sex-matched healthy controls, individuals with the neuro-PASC showed widespread changes in the network architecture of the brainstem, olfactory cortex,

cingulate cortex, thalamus, orbitofrontal cortex, and cerebellum.

The observed changes in the brain's functional connectome were associated with clinical manifestations, such as fatigue and cognitive dysfunction. The authors suggested that further longitudinal clinical studies should closely monitor the evolution of clinical and imaging findings in participants with long COVID syndrome.

This study was published in the Scientific Reports.

Journal Reference

Bungenberg, J., Hohenfeld, C., Costa, A.S. *et al.* Characteristic functional connectome related to Post-COVID-19 syndrome. *Sci Rep* 14, 4997 (2024). https://doi.org/10.1038/s41598-024-54554-3