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Long COVID syndrome encompasses a wide range of organ dysfunction, but the most frequent, persistent, and disabling symptoms are neurological. In this study, the Brazilian authors used neuropsychological assessment, magnetic resonance imaging (MRI), the 18Fluorine-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT), and biomarker analysis to investigate individuals who had COVID-19 at least four months before testing.

Multiple brain regions are involved in visuospatial abilities, such as the occipito-parietal regions, the dorsal and ventral streams, and connections with the cingulate, temporal, and frontal cortices. Visuospatial abilities involve mostly the regions of the right hemisphere, but, some tasks require bilateral brain activity. The inability of the patient to assemble or organize parts into a whole, and to copy accurately two-dimensional or three-dimensional constructions, is referred to as constructional apraxia. Constructional apraxia can be found in brain lesions or neurodegenerative diseases that affect the parietal or frontal lobes, and corpus callosum, the largest interhemispheric commissure connecting the cortical zones of the left and right hemispheres. Lesions of the right parietal region are frequently associated with visuospatial deficits.

Of note, a recent functional MRI study has revealed altered cortical lateralization and brain reorganization in individuals diagnosed with long COVID syndrome and neuropsychiatric symptoms. During working memory tasks, these participants displayed increased subdominant hemisphere activation and lower activation in the dominant left hemisphere, including frontal and parietal regions. Interestingly, they also performed worse in dominant hand dexterity on the motor function test battery.

<https://discovermednews.com/patients-with-post-covid-syndrome-and-neuropsychiatric-symptoms-have-different-brain-activation-during-the-working-memory-task/>

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About the study

This prospective observational cohort study included individuals who had COVID-19, confirmed by positive reverse transcription polymerase chain reaction of nasopharyngeal swabs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most participants had mild acute COVID-19, and only 6% were hospitalized. About 8% of the participants had a history of mental disorders, mostly depression and anxiety.

The participants underwent a neuropsychological assessment, neurological examination, brain MRI, and 18F-FDG-PET/CT brain imaging. Neuropsychological assessment included the following tests: language (verbal fluency), visuoconstructive (Rey-Osterrieth Complex Figure Test), memory (Logical Memory and ROCF recall), attention (Trail Making Test), executive functions (Verbal Fluency Switching and Five Point Test) and working memory (Digit Span). Rey-Osterrieth Complex Figure Test is a drawing task test used to measure visuospatial abilities, executive functions, and memory.

The sera samples were collected and analyzed for biomarkers, such as chemokines, inflammatory and regulatory cytokines, and growth factors.

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Results

The study included 192 individuals who had COVID-19, 71% were women. The average time interval between confirmation of infection and study enrollment was 4.35 (± 2.45) months.

The most frequently reported long-lasting symptoms were headache (77%), myalgia (68%), and anosmia (64%), followed by subjective daily problems with thinking/or memory (51%), problems with judgment (39%), and remembering appointments (34%). The neurological examination showed different pathological signs, such as optokinetic nystagmus, absence of ankle reflex, ankle clonus, global tendon hyperreflexia, indifferent plantar response, and postural or intention tremor.

The SRQ-20 screening showed non-psychotic psychiatric symptoms in 48% of participants. Self-reported DSM-5 demonstrated depression in 49% of participants, anxiety in 53%, anger in 47%, and sleep disorders in 50%. The Rey-Osterrieth Complex Figure Test showed impaired visuospatial abilities in 26% of 191 participants.

Serum biomarker levels

The authors first stratified sera samples from 100 participants according to visuospatial impairment. The results showed that individuals with visuospatial impairment and poorer performance on the Rey-Osterrieth Complex Figure Test had higher serum levels of eleven biomarkers, including LIF interleukin 6 family cytokine, C-X-C motif chemokine ligand 10



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(CXCL10), C-C-motif chemokine ligand 2 (CCL2), CCL11, C-type lectin domain family 11, member A (CLEC11A), interleukin 1 receptor antagonist (IL1RA), IL10, IL31, granulocyte-macrophage colony-stimulating factor (CSF), hepatocyte growth factor (HGF), and nerve growth factor (NGF) than participants without this deficit. Four biomarkers are components of the canonical “neuroinflammation signaling pathway” and the other four are components of the “IL-17 signaling pathway”. Some upregulated biomarkers, such as HGF and NGF facilitate neuronal growth and promote survival in the brain, whereas LIF, CXCL10, and CCL11 promote neuroinflammation.

Interestingly, 10 of the 11 plasma biomarkers elevated in participants with visuospatial impairment form a functional interaction network where they either upregulate or downregulate each other. Since six upregulated biomarkers are associated with hepatic necrosis, and five with cardiac necrosis, the authors emphasized the possibility of a certain degree of cardiac and/or hepatic damage in individuals with visuoconstructive impairment, given that post-COVID syndrome is regarded as a multisystemic disease.

Neuroimaging results

A total of 135 participants underwent MRI and 18F-FDG-PET/CT neuroimaging. The results of the 18F-FDG PET uptake demonstrated that nine clusters of voxels correlated with the performance on the Rey-Osterrieth Complex Figure Test. The test performance correlated positively with two clusters in the left temporal and left occipital regions, and negatively with six clusters in the frontal and occipital regions.

The most important MRI finding on the MRI scan performed in 135 patients was a negative correlation between the Rey-Osterrieth Complex Figure Test results and increased white matter volume in the left and right genu of the corpus callosum, extending to the cingulum in both hemispheres. The additional clusters involved white matter in the inferior frontal gyrus and fronto-occipital fasciculus bilaterally, the right fusiform gyrus, and the bilateral lingual gyri.

There were no structural changes on the brain MRI scans, such as thromboembolism, atrophy, acute encephalitis, or leptomeningeal enhancement.



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Conclusion

This study has shown a specific visuospatial deficit associated with the brain neuroimaging findings and upregulation of certain biomarkers in approximately one-quarter of individuals who had COVID-19 at least four months before testing. The authors emphasized that visuospatial abilities are important for daily living activities, such as driving, drawing, and spatial orientation, and, therefore, their impairment can affect numerous people diagnosed with neuro-long-COVID syndrome.

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Journal Reference

de Paula JJ , Paiva RERP, Souza-Silva NG et al. Selective visuoconstructional impairment following mild COVID-19 with inflammatory and neuroimaging correlation findings. *Molecular Psychiatry* (2023) 28:553-563. <https://doi.org/10.1038/s41380-022-01632-5>