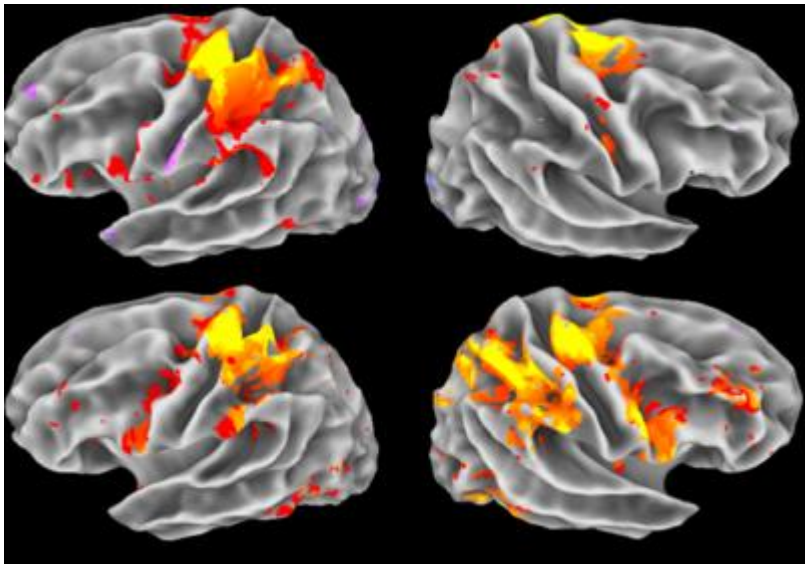
More than two years after the global COVID-19 pandemic, it is clear that infection with severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) can lead to a new disease called post-acute COVID-19 syndrome (PASC) or long COVID. In the post-acute phase of COVID-19, there is an increased risk of neurologic sequelae, affecting the central nervous system (CNS) or the peripheral nervous system (PNS). In this study, researchers from the United States used blood-oxygenation-dependent functional MRI (BOLD-fMRI) to investigate whether patients with post-COVID neuropsychiatric symptoms had abnormal brain activation during a working memory task. They also examined the possible relationships between abnormal brain activation and performance on three NIH-Toolbox (NIHTB) batteries for cognitive, emotional, and motor functions.

Prior studies have comprehensively mapped the spectrum of neurologic sequelae in post-COVID patients, but there has been no significant progress in understanding the underlying mechanisms. It seems that SARS-CoV-2 uses various neuroinvasive strategies and pathways to invade the CNS, such as infection of the nasal olfactory epithelium and axonal transport along the olfactory nerve, retrograde axonal transport, invasion by compromising the blood-brain barrier (BBB), and the use of infected hematopoietic cells as “Trojan horses” (hematogenous route). It is assumed that the olfactory bulb serves as the main gateway for viruses to enter the brain.

It is worth noting that a brain lesion, as a stroke, induces changes in unaffected brain regions due to mechanisms such as deafferentation, removal of inhibition, activity-dependent synaptic changes, changes in membrane excitability, growth of new connections, and unmasking of preexisting connections. After an injury to the primary motor cortex, the recovery process involves functional changes characterized by increased activity in the motor cortex of the unaffected contralateral hemisphere. It was speculated that persistent activation in the contralesional hemisphere correlates with poor recovery and represents maladaptive plasticity, but other authors suggest that increased activity in the contralesional hemisphere contributes to functional improvement, particularly in less-well-recovered patients. This process represents a kind of adaptation using available resources.



About the study

The authors used BOLD-fMRI to examine brain activation during a working memory task in participants diagnosed with post-COVID neuropsychiatric symptoms and healthy controls. Patients who developed post-COVID had documented COVID-19 at least six weeks before enrollment. Healthy controls had no history of COVID-19 and tested negative for SARS-CoV-2.

Of the 50 usable fMRI datasets, nine participants (six post-COVID, three controls) had minor abnormalities on their structural MRIs that were not exclusionary. Five individuals (three post-COVID participants, two controls) had slightly more than age-related white matter lesions, two (one in each group) had lacunar infarcts, one control had microhemorrhages, and one control had small old infarcts and a microhemorrhage.

Participants were assessed with three NIHTB batteries for cognition (NIHTB-CB), emotion (NIHTB-EB), and motor function (NIHTB-MB), and selected Patient-Reported Outcomes Measurement Information System (PROMIS) tests.

Results

The study included 50 participants, 29 developed post-COVID neuropsychiatric symptoms after the acute infection with SARS-CoV-2, and 21 healthy controls who tested negative for SARS-CoV-2.

Individuals with post-COVID reported a high prevalence of cognitive disorders, such as

concentration problems (93%), memory problems (79%), and confusion (64%). They also reported neurological symptoms, such as headaches (57%), visual disturbances (50%), gait disturbances (50%), paresthesias (43%), and coordination problems (39%). This group also had a high prevalence of other symptoms, including fatigue (86%), depression/anxiety (68%), sleep disturbances (64%), myalgia (61%), light-headedness (46%), and urinary problems (28%). The NIHTB-EB results demonstrated significantly worse psychological well-being in post-COVID participants compared to healthy controls.

BOLD-fMRI findings

The brain activation during the 0-back and 1-back tasks did not differ between participants with post-COVID and healthy controls. However, BOLD-fMRI findings showed that the brain activity in the post-COVID participants differed from that of healthy controls in the more difficult 2-back task, with lower activation in several brain regions.

The two large clusters with lower activation included regions localized in the left hemisphere, such as the postcentral gyrus, insula, precentral gyrus, and inferior parietal lobule. However, all brain regions with higher activation in the 2-back task were localized in the right hemisphere. Interestingly, the post-COVID group had lesser deactivation in the right posterior cingulate cortex and greater activation in the right superior frontal gyrus. It is worth noting that these findings are consistent with the results of a recent resting-state fMRI study that investigated characteristics and changes of the complex network known as brain functional connectome in patients with primarily neurological symptoms of post-COVID syndrome. This study demonstrated a decreased connectivity of the anterior cingulate cortex and increased connectivity of the posterior cingulate gyrus, a central node in the default mode network, in patients with post-COVID syndrome. The authors of this study speculated that a strong correlation between a test of attention and the hyperconnectivity of the posterior cingulate gyrus could contribute to the executive functioning deficit in patients with post-COVID syndrome.
https://discovermednews.com/changes-in-brain-functional-connectome-in-post-covid-syndrome/

Despite these group differences in brain activation, the two groups had similar accuracy and reaction times for each task. Importantly, on the NIHTB battery for motor function, the participants with post-COVID neuropsychiatric symptoms performed worse than healthy controls in the domains of endurance, locomotion, and the manual dexterity of the dominant hand (controlled by the motor area of the dominant hemisphere).

According to the authors, these findings indicate suboptimal functioning in the normal

network and increased brain activation in the contralateral hemisphere during working memory tasks in individuals who developed post-COVID neuropsychiatric symptoms.

Conclusion

This is the first task-activated BOLD-fMRI study conducted in individuals diagnosed with post-COVID neuropsychiatric symptoms. The results discovered a reorganized working memory network and different brain activity in post-COVID participants compared to healthy controls with no history of COVID-19. In addition, the participants with post-COVID performed worse than the control group in endurance, locomotion, and dexterity of the dominant hand (motor function of the dominant left hemisphere).

Several brain regions that showed lower activation were in the left hemisphere. At the same time, there was a greater or compensatory use of the brain regions in the right hemisphere to maintain normal performance.

The authors concluded that BOLD-fMRI was sensitive enough to detect a process of brain reorganization in individuals diagnosed with post-COVID neuropsychiatric symptoms.

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