Changes in Brain Activation Pattern During Working Memory Tasks in People With Post-COVID Condition and Persistent Neuropsychiatric Symptoms

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Cite as: Neurology® 2023;100:e2409-e2423. doi:10.1212/WNL.00000000000207309

Study Question
Do patients with postcoronavirus disease (COVID) condition (PCC) have abnormal brain activation on blood oxygenation level-dependent functional MRI (BOLD-fMRI) during working memory (WM) tasks?

What Is Known and What This Paper Adds
PCC is common and may include multiple neuropsychiatric symptoms such as fatigue, inability to concentrate or “brain fog,” headaches, hyposmia or dysgeusia, sleep disorders, anxiety, and depression. The exact pathophysiology or mechanisms underlying PCC remain unknown. Several neuroimaging studies have evaluated patients with postacute COVID. PET studies reported decreased brain glucose metabolism that correlated with poorer cognitive function during the early months of recovery but normal metabolism at 6 months after infection despite persistent memory and attention complaints. Longitudinal structural MRI showed greater than normal age-related decreased cortical thickness in brain regions related to olfaction. Diffusion imaging also found abnormalities that indicated disrupted microstructural integrity. However, no studies used task-activated BOLD-fMRI to evaluate brain function in patients with PCC, especially those with persistent neuropsychiatric symptoms. This study’s results showed that patients with PCC had greater brain activation and reorganized networks relative to controls during WM tasks on BOLD-fMRI, which indicated their usage of compensatory neural networks to maintain normal WM. Altered brain activation also correlated with neuropsychiatric symptoms. BOLD-fMRI provides a sensitive and objective measure to evaluate post-COVID brain abnormalities, capable of detecting subtle brain changes that might precede clinically observable cognitive deficits.

Methods
This cross-sectional cohort study was conducted between February 2021 and February 2022 using data from 50 patients (of 169 screened) who fulfilled the study criteria and had complete, useable data sets. All provided written informed consent. The protocol was approved by the University of Maryland, Baltimore Institutional Review Board. PCC participants had documented COVID-19 ≥ 6 weeks before enrollment and had at least 1 persistent neuropsychiatric symptom. Controls had no history of COVID-19 and were negative on the PCR test (<7 days) or the antigen test (on study day). Each completed a standardized detailed neuropsychiatric evaluation. PCC participants also completed a survey regarding their acute symptoms, treatments, premorbid conditions, and long-COVID symptom severities. All participants completed the NIH-Toolbox (NIHTB) Cognition Battery (NIHTB-CB), Emotion Battery (NIHTB-EB), and Motor Battery (NIHTB-MB) and the Patient-Reported Outcomes Measurement Information System (PROMIS). Each participant performed WM tasks with increasing attentional/WM load (0-back, 1-back, 2-back), with block design fMRI. Group differences in BOLD activation were evaluated in SPM12, using 2-sample t tests, thresholded at ≥100 voxel clusters, and T ≥1.7. A false discovery rate–corrected p ≤ 0.05 at the cluster level was considered significant.

Results and Study Limitations
The PCC participants and controls had similar ages (42 ± 12 vs 41 ± 12 years), gender proportion (65% vs 57% women), racial/ethnic distribution, comorbidities, substance use, handedness, education, and socioeconomic status. The PCC participants were diagnosed with COVID 242 ± 156 days earlier; 9 were hospitalized; and they had a high prevalence of memory (79%) and concentration (93%) complaints, fatigue (86%), and depression/anxiety (68%). Despite the cognitive complaints, the PCC group had normal scores on all 7 NIHTB-CB domains. On the NIHTB-EB and PROMIS, the PCC group endorsed markedly poorer psychological well-being than controls (all p ≤ 0.001).

On BOLD-fMRI during WM tasks, PCC and controls had similar brain activation during the 0-back and 1-back tasks. However, several group differences were shown on the 2-back task: (1) PCC participants had greater brain activation than controls in the right superior frontal gyrus (SFG, Cohen d = 0.81, 95% CI 0.15–1.46, p = 0.009) but lesser deactivation in the posterior cingulate gyrus (PCG), the default mode regions (d = 1.3, 95% CI 0.61–1.99, p = 0.001) (Figure, A and B). (2) An anticorrelation between deactivation in the PCG and activation in the SFG was observed only for controls (Figure, C). (3) The PCC group had a reorganized neural network, with suboptimal activation in the normal network but greater activation in contralateral brain regions to maintain normal WM (Figure, D). (4) Greater activation in the WM network predicted a lesser positive affect (right SFG: r = −0.49, β = −6, 95% CI −10 to −2, p < 0.001) and more

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perceived stress for all participants (right parietal: $r = 0.50, \beta = 14, 95\% CI 6–23, p < 0.001$). However, only the PCC participants showed correlations between brain activation and anger (right extranuclear, $r = 0.69, \beta = 15, 95\% CI 6–25, p < 0.001$), sadness (right superior temporal gyrus, $r = 0.68, \beta = 15, 95\% CI 8–23, p < 0.001$), and poorer psychological well-being (left frontal white matter, $r = -0.68, \beta = -24, 95\% CI -35 to -14, p < 0.001$). (5) Finally, lesser brain activation within the left postcentral sensorimotor gyrus predicted poorer dominant hand dexterity in the PCC participants ($r = 0.58, \beta = 11, 95\% CI 5–18, p = 0.003$) and lower endurance with the 2-minute walk in all participants ($r = 0.51, \beta = 16, 95\% CI 8–24, p < 0.001$). A limitation of this study is its cross-sectional design, which precludes the casual inference of the altered brain activation to PCC.

**Study Funding and Competing Interests**

This study was funded by the National Institute of Neurological Disorders and Stroke (R21-NS121615). Some authors report competing interests. Go to Neurology.org/N for full disclosures.
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Neurology 2023;100;e2409-e2423 Published Online before print April 26, 2023
DOI 10.1212/WNL.0000000000207309

This information is current as of April 26, 2023

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