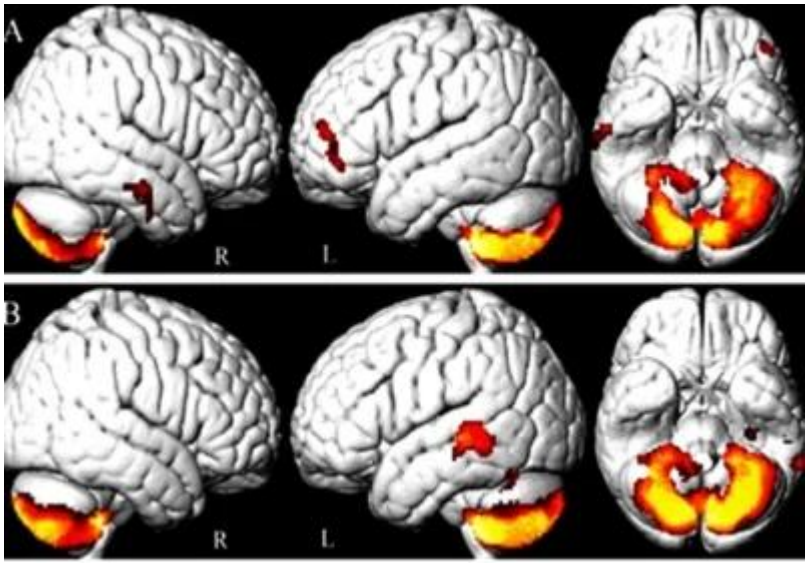
More than two years after the global COVID-19 pandemic, it is clear that infection with severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) can lead to a new syndrome called Long-COVID or post-acute COVID-19 syndrome (PACS). PASC is an umbrella term used to describe a heterogeneous group of patients. This disease is more common in hospitalized survivors, but even those who have experienced mild acute COVID-19 have a wide range of organ dysfunction. The neurologic sequelae affect the central nervous system (CNS) and peripheral nervous system (PNS) and include cognitive and memory disorders, headaches, stroke, extrapyramidal and movement disorders, mental disorders, encephalitis or encephalopathy, insomnia, peripheral neuropathy, acute inflammatory polyradiculoneuropathy, orthostatic intolerance, and syncope. In this study, the authors from the United States used integrated [11C]PBR28 PET/MR brain imaging and analysis of peripheral blood samples to investigate the association between neuroinflammation and parameters of vascular health in individuals diagnosed with PASC.



[11C]PBR28 PET/MR brain signaling, as an indicator of neuroinflammation,

About the study

This cross-sectional study enrolled 12 individuals diagnosed with PASC and 43 control individuals not exposed to SARS-CoV-2. Two participants with PASC were hospitalized during the acute COVID-19, and one of them was vaccinated before the acute COVID-19. Participants with PASC completed questionnaires related to their symptoms and history. All participants completed the Brief Pain Inventory (BPI) and the Beck Depression Inventory

(BDI). None of the PASC participants reported a history of depression before COVID-19.

Neuroinflammation was studied using integrated [11C]PBR28 PET/MR neuroimaging at least ten months after COVID-19 diagnosis (mean 20.5 months). The parameters of vascular health, inflammation, and angiogenesis were analyzed in peripheral blood samples taken immediately before the PET/MRI scan. Most control individuals (34/43) were scanned before the pandemic.

The parameters of vascular health, inflammation, and angiogenesis analyzed in peripheral blood samples taken immediately before the [11C]PBR28 PET/MR brain imaging included α2-macroglobulin, orosomucoid, C-reactive protein, fetuin A, fibrinogen, haptoglobin, sL-selectin (soluble leukocyte selectin, or sCD62L), platelet factor 4 (PF4), and pentraxin-2.

Researchers also analyzed cytokine levels: interleukin (IL)-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12(p40), IL-12(p70), IL-13, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, monocyte chemotactic protein 1 (MCP-1), and tumor necrosis factor (TNF)-α, as well as indicators of angiogenesis: angiopoietin-2, bone morphogenic factor (BMP)-9, epidermal growth factor (EGF), endoglin, endothelin- 1, fibroblast growth factor (FGF)-1 and -2, follistatin, granulocyte colony-stimulating factor (G-CSF), heparin-binding EGF-like growth factor (HB-EGF), hepatocyte growth factor (HGF), IL-8, leptin, placental growth factor (PLGF), and vascular endothelial growth factor (VEGF)-A, -C, and-D.

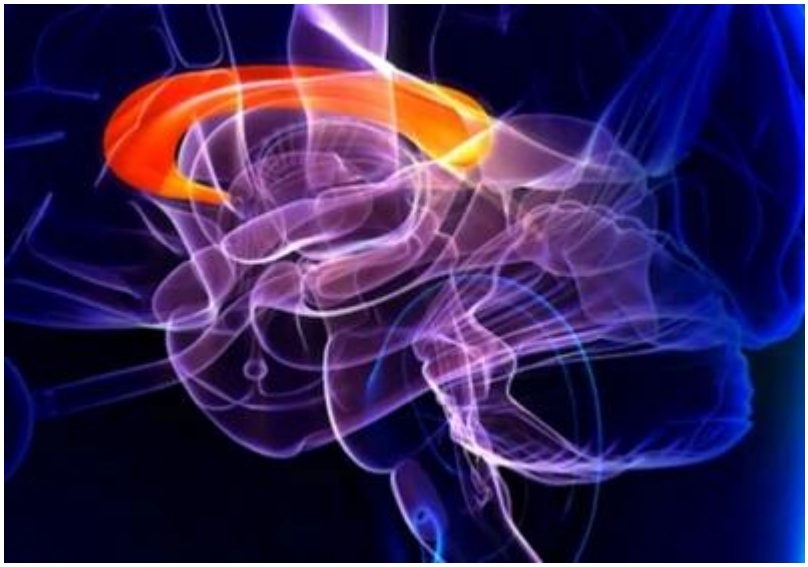
Results

Only two of the 12 individuals diagnosed with PASC met the threshold for moderate depression, and the average depression score was mild. Depression was either denied as a problem (50%), reported as a new (~42%), or seriously new (~8%) problem after COVID-19.

[11C]PBR28 PET/MR scan showed elevations in binding, as an indicator of neuroinflammation, in a wide range of brain regions, including the midcingulate cortex, corpus callosum, thalamus, basal ganglia/striatum, subfornical organ, anterior cingulate cortex, medial frontal gyrus, and precentral gyrus, in individuals with PASC compared to controls.

The intensity of the whole-brain PET signal, as an indicator of neuroinflammation, correlated positively with most parameters of vascular health, including fibrinogen, α2-macroglobulin, orosomucoid, fetuin A, sL-selectin, pentraxin-2, and haptoglobin.

Interestingly, the PET signal did not correlate with concentrations of cytokines and indicators of angiogenesis.



Corpus callosum

Conclusion

These results provide indirect evidence that differences in [11C]PBR28 PET/MR brain binding across a wide range of brain regions, as an indicator of neuroinflammation, could partially reflect variations in vascular anatomy and perivascular immune infiltration. Since the integrity of the blood-brain barrier can be compromised in neuroinflammation, vascular factors may penetrate the brain parenchyma.

These results do not establish a causal relationship between neuroinflammation and vascular health. However, they indicate that the interaction between neuroinflammation and vascular health could contribute to symptoms of PASC.

This study has been published in Brain, Behavior and Immunity.

Journal Reference

VanElzakker MB, Bues HF, Brusaferri L, et al. Neuroinflammation in post-acute sequelae of COVID-19 1 (PASC) as assessed by [11C]PBR28 PET correlates with vascular disease measures. Brain, Behavior and Immunity 2024; 119: 713-23.
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