

EDITORIAL

Does Microglial Activation Lead to Cognitive Changes After COVID-19 Infection?

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One of the many issues we have yet to understand in relation to the COVID-19 pandemic is the mechanism by which the infection can cause long-lasting neuropsychiatric symptoms, particularly cognitive symptoms and depression as part of the post-



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acute period, referred to as post-COVID-19 condition (also known as long COVID). Since as many as 20% of individuals might experience cognitive impairment 12 or more weeks following COVID-19 diagnosis,¹ it is paramount to understand the underlying pathophysiology in order to develop potential therapeutic avenues. Microglial activation as part of the neuroinflammatory response of the brain can occur as an answer to a direct insult to the brain (this includes viral infection) but can also occur following respiratory inflammation and might play an important role in the development of cognitive problems after COVID-19 infection.²

Braga et al³ present elegant work on this matter. They have examined the in vivo neuroinflammatory changes in patients with persistent depressive and cognitive symptoms after COVID-19 infection using positron emission tomography (PET) and the ligand [¹⁸F]FEPPA for the translocator protein 18 kDa (TSPO), which is expressed by activated microglia as part of the neuroinflammatory response of the brain.

They found an increased expression of TSPO in patients with persistent neurocognitive symptoms after COVID-19 infection compared to healthy control individuals, especially in the ventral striatum and dorsal putamen. TSPO binding in the dorsal putamen of individuals with post-COVID-19 conditions negatively correlated with speed in motor tasks.

These findings indicate that microglial activation was associated with the development of neurocognitive symptoms after COVID-19 infection and the imaging technique the authors used has the advantage that it allows the imaging of this part of the neuroinflammatory process in vivo. The authors conclude that increased microglial activation in the ventral striatal and dorsal putamen reflects a possible mechanism to explain persistent depressive cognitive symptoms after COVID-19 infection.

The work by Braga et al³ has important pilot character, as it elucidates a possible mechanism behind neurocognitive symptoms after COVID-19 infection. One could speculate that suppression of microglial activation might lead to improvement of these symptoms. While this is an important piece in the jigsaw puzzle of neuroinflammation in chronic neurological disease, it is important to keep in mind that we still lack understanding of the complex picture for several reasons.

1. Although the PET technique Braga and colleagues³ applied has been used with their own and other TSPO tracers for more than 25 years, particularly in the investigation of neurodegenerative disorders and their association with neuroinflammatory changes, it has a number of limitations—mainly the fact that the PET signal is particularly noisy and is not restricted to microglial cells.^{4,5}
2. TSPO expression is only one part of the complex neuroinflammatory response of the brain (however, it is the only one we can currently relatively reliably image in vivo in patients). Our PET techniques do not currently allow us to distinguish between different states of microglial activation.
3. To target neuroinflammatory changes therapeutically, we will need a much more detailed understanding of microglial activation at different time points of neurological disorders. Not surprisingly, relatively simplistic attempts to suppress microglial activation have so far not resulted in clinical meaningful results.⁶

Future work aiming to understand the potential neuroinflammatory basis of cognitive symptoms and mood changes after COVID-19 infection will therefore need to concentrate on additional targets other than TSPO. Furthermore, longitudinal imaging (PET) studies should be carried out, allowing us to establish the correlation between the time course of central inflammatory changes and clinical parameters and, in turn, with peripheral inflammatory changes. Combining these lines of investigation might ultimately allow us to modulate neuroinflammatory changes after COVID-19 and other neuropsychiatric disorders in a way that is beneficial to patients.

ARTICLE INFORMATION

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