Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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When even the ground was burning: Neuroinflammation in the wake of COVID-19

Andrew Schrepf

Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA

We are only beginning to grasp the scale of psychological, behavioral, and physical changes that have occurred over the last two and a half years of the COVID-19 pandemic, but a brief survey of the literature tells us that our world has rarely been upended to this degree. Symptoms of depression have tripled while deaths from drug overdoses continue to climb, and these troublesome trends appear to be linked at least in part to physical isolation.(Cartus et al., 2022; Ettman et al., 2020; Joseph et al., 2022) *Brain, Behavior, and Immunity* recently published, "The Pandemic Brain: neuroinflammation in non-infected individuals during the COVID-19 pandemic," a novel multimodal analysis of neuroinflammation in healthy individuals prior to and during the COVID-19 pandemic.(Brusaferri et al., 2022) Brusaferri and colleagues hold up a neurobiological mirror to the profound suffering engendered by COVID-19 and its disruptive reorganization of society.

Translocator protein (TSPO) levels in the brain can be assessed *in vivo* via positron emission tomography (PET) with the PBR-28 radioligand. Seminal work in chronic pain patients has demonstrated that brain levels of TSPO serve as a marker of glial activation, and by implication, neuroinflammatory processes.(Loggia et al., 2015) Brusaferri et al. show that not only is TSPO higher in individuals scanned during the pandemic, but a putative marker of neuroinflammation derived from H^1-MRS, myoinositol, was also elevated in the thalamus. Analysis of brain transcriptomics in parallel with TSPO levels showed that genes expressed by astrocytes and microglia were overexpressed in regions of TSPO elevations. Although each of these metrics of neuroinflammatory activity has drawbacks, it is reassuring to see them pointing in the same direction. Because the participants in this study were unlikely to have been infected with the SARS-CoV-2 virus, as evidenced by negative serological antibody testing at time of scanning, these findings point to profound neuroinflammatory consequences of the psychosocial and environmental stress that accompanied the pandemic.

Of course, the burden of this pandemic has not been equally distributed: Brusaferri et al. find that individuals with higher levels of physical fatigue and mental fatigue/mood, showed increases in TSPO levels in the intraparietal sulcus/precuneus and hippocampus, respectively. One of the most exciting things about the TSPO protocol is that it allows us to quantify activity in *glial* cells, which may hold promise for refining the CNS signal associated with distinct patterns of symptoms, and thereby increasing the likelihood of advancing tailored approaches to treatment. Peripheral markers of inflammation were also assayed in blood plasma, with trending indications that interleukin-6 and monocyte-chemotactic protein 1 are elevated in tandem with brain levels of TSPO. While these findings did not reach statistical significance after correction for multiple-testing, the pursuit of peripheral markers of neuroinflammation is absolutely essential for future clinical and translational impact. Because TSPO is also expressed by peripheral immune cells, it is possible that some of the central TSPO signal is derived from infiltrating circulating immune cells to the CNS. This in turn would suggest that cross-talk between the central and peripheral immune systems plays an important faciliatory role in persistent neuroinflammation.

One limitation of the current study is that it relied on almost completely different samples of patients for pre- and post-pandemic evaluations of TSPO (only one patient was scanned pre/post and demonstrated large increases in TSPO levels during the pandemic). Brusaferri and colleagues conducted a number of sensitivity analyses to show that the observed effects were not dependent on age, sex, genotype, or scanner. While reassuring, this approach does not allow for inference about the timescale of pandemic-related neuroinflammatory changes. Did these changes begin with knowledge of a novel, deadly, and contagious disease? With public health measures like physical distancing, stay-at-home orders, and the suspension of many social activities? While these individuals appear to have been spared the infection, were their loved ones? What is the toll on our brains of a surfeit of grief?

Similarly, the *behavioral* pathways to increased neuroinflammation during the pandemic could not be explored in the current study. Diet, exercise, substance/alcohol use, and sleep are a short list of behaviors linked to inflammation that have changed substantially during the pandemic, but identifying their relative contributions to the phenomenon of enhanced neuroinflammation will require larger, longitudinal studies. The burden of social isolation and loneliness has been known from experimental and observational contexts for decades, yet rarely have so many of us gotten so lonely at the same time, disrupting our

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ability to reinforce one another. By their very ability to participate in research, this sample may also have been less affected by the pandemic than others who lost transportation, childcare, or assistance with disabilities.

Long-COVID remains a major concern for the infected with significant minorities of survivors experiencing fatigue, pain, depressive symptoms, and cognitive fog.(Ziauddeen et al., 2022) Putative causes of long-COVID include persistent inflammatory activity and/or autoimmune responses. The current study strongly suggests that the "pandemic brain" is far from undisturbed in the absence of COVID infection and may be primed to struggle in response to new insults. Interestingly, the best-established risk factors for long-COVID – older age, higher BMI, and female sex – have been associated with an increased neuroinflammatory burden.(Eidson et al., 2019) The implication is that the events of the pandemic lowered the resilience of the central nervous system at a *population level,* the consequences of which we are only beginning to grasp.

COVID-19 is unlikely to be the last pandemic of the twenty-first century, and it may not be the last pandemic of this decade. If or when broad and restrictive public health measures are again required, we must be prepared for the psychological, behavioral, and physiological consequences that follow. What Brusaferri and colleagues have shown us is that we were all touched by the virus, whether we were infected or not.

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