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Previews

COVID fog demystified

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Acute mild respiratory SARS-CoV-2 infection can lead to a more chronic cognitive syndrome known as "COVID fog." New findings from Fernández-Castañeda et al. reveal how glial dysregulation and consequent neural circuit dysfunction may contribute to cognitive impairments in long COVID.

More than 2 years since the first detected cases of COVID-19, the virus continues to evolve new variants, infect hundreds of millions of people, and pose both acute and chronic threats to global health. In most infections, a patient's symptoms resolve within 2 weeks. However, recovery from initial infection is not always straightforward. In a significant fraction of patients, symptoms can persist for several months. This syndrome, which has become known as "long COVID," may occur even following initially mild cases (that is, those not requiring hospitalization) and can include significant cognitive dysfunction.

Initial awareness of long COVID emerged from anecdotal accounts, shared by patients on social media platforms such as Twitter, Facebook, and Slack (Callard and Perego, 2021). Since then, a large number of studies have used more formal methods to catalog the nature and frequency of long COVID symptoms. Within the cognitive domain, as many as one in four patients experience a range of symptoms that have become known colloquially as "COVID fog," which includes problems in attention, language fluency, processing speed, executive function, and memory (Becker et al., 2021).

Given the sheer scale of infections, there is a pressing need to understand how cognitive dysfunction emerges in long COVID. In this issue of *Cell*, a new paper by Fernández-Castañeda and colleagues (Fernández-Castañeda et al., 2022) begins to address this need. Using mice as a model, they expressed human ACE2, the viral entry receptor required for successful COVID infection. Because ACE2 expression was restricted to the trachea and lungs, these mice developed only a mild form of the disease that was limited to the respiratory system and largely cleared within a week following intranasal inoculation with SARS-CoV-2 virus.

As a starting point, the researchers noted the striking similarities between COVID fog and another cognitive syndrome known as "chemobrain." Chemobrain (or cancer-therapy-related cognitive impairment, CRCI), is a neuroinflammatory condition that patients often experience following radiation or chemotherapy. In CRCI, elevations in neurotoxic cytokines and reactive microglia (brain-resident macrophages) lead to cascades of multicellular events that impact forms of both gray and white matter plasticity that are important for healthy cognition (Gibson and Monje, 2021).

Adopting this framework, the authors quantified changes in cytokines and microglial/macrophage reactivity following SARS-CoV-2 infection. Reminiscent of CRCI, they found that microglial/macrophage reactivity was elevated in subcortical and hippocampal white matter in mice following mild respiratory COVID. Remarkably, this elevation was persistent and still evident even 7 weeks post infection. Outside of the brain, they detected elevated cytokine levels in the cerebrospinal fluid and serum of mice. Although levels of many cytokines were altered, one in particular grabbed their attention. CCL11 remained persistently elevated in mouse cerebrospinal fluid 7 weeks post infection. Notably, elevated CCL11 levels have been causally linked to cognitive impairments observed in normal aging (Villeda et al., 2011).

Similar patterns were found in patients with COVID-19 (Figure 1). Reactive microglia were elevated in subcortical white matter in individuals with COVID-19 (these patients were symptomatic for COVID-19 but died from other causes). Moreover, CCL11 was elevated in plasma from patients with long COVID. Remarkably, elevated CCL11 plasma levels were only detected in those long COVID patients with cognitive symptoms. CCL11 plasma levels were unaltered in long COVID patients who did not have cognitive symptoms. These findings suggest that CCL11 plays a central role in the brain pathology contributing to COVID fog.

There are several ways in which such a neuroinflammatory state might impact cognition. Previous work has shown that persistently reactive microglia in hippocampal white matter suppress hippocampal neurogenesis by blocking neuronal progenitor-cell differentiation into new granule cells (Monje et al., 2003). These newly generated neurons are important for the formation and stability of hippocampus-dependent memories. The authors found the numbers of new neurons were reduced in infected mice, and this reduction correlated with numbers of reactive microglia in the hippocampus. Remarkably, systemic administration of CCL11 recapitulated this same pattern in uninfected mice. Increased numbers of

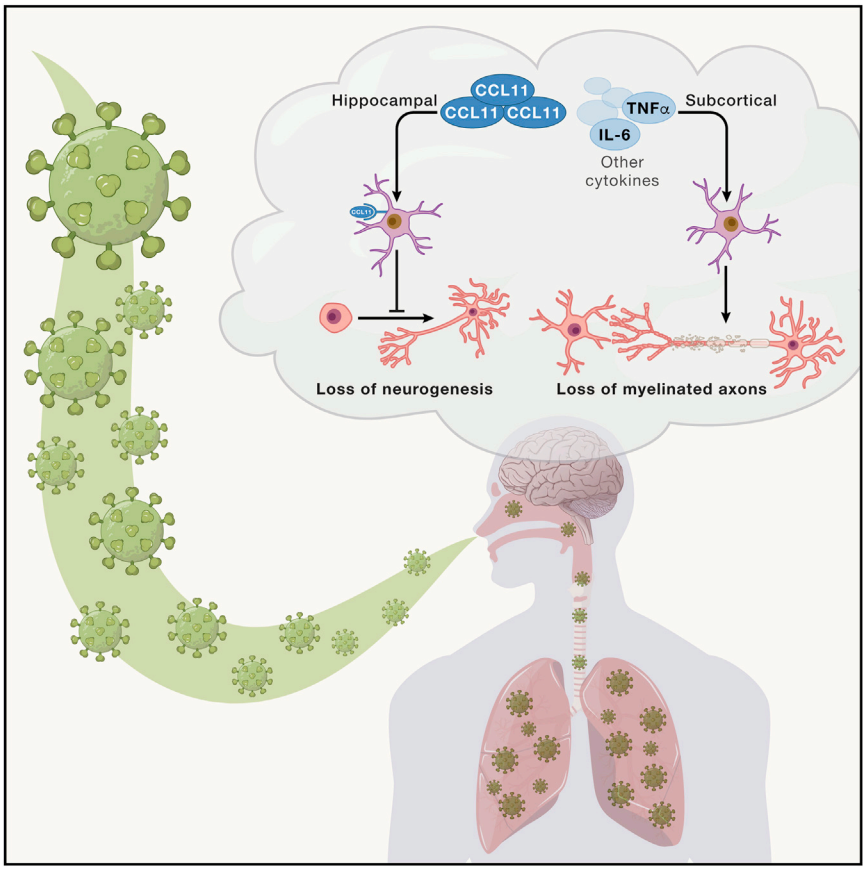

Figure 1. The neuroinflammatory basis of COVID fog
Acute mild respiratory COVID-19 infection can lead to a more chronic cognitive syndrome known as brain fog. Suggested pathways for brain fog include cytokine-induced activation of regional microglia, causing decreased hippocampal neurogenesis and a loss of myelinated subcortical axons.

reactive microglia and decreased numbers of new neurons in these mice suggest a causal role for CCL11 in COVID fog pathology. These CCL11-induced outcomes were restricted to the hippocampus, suggesting that particular cytokines can have circuit-specific effects.

Another way in which CCL11 and/or reactive microglia might impact cognition is via effects on white matter. In CRCI, reactive microglia impair the formation of myelin-forming oligodendrocytes and myelin plasticity (Geraghty et al., 2019; Gibson et al., 2019). Similarly, the authors found reduced numbers of oligodendrocytes and their precursor cells, as well as decreased axon myelination in the subcortical white matter, several weeks following infection in mice. Although behavior was not assessed in this study, it is nonetheless reasonable to assume that such changes would alter cognitive function following mild respiratory COVID in mice, as it does in other disease contexts (Geraghty et al., 2019; Gibson et al., 2019). Since myelination regulates the speed and timing of communication between neurons, dysregulation of oligodendroglial lineage cells following infection might slow neural processing, disrupt brain synchrony, and impair cognition (Steadman et al., 2020).

The principle that inflammatory challenges may induce glial dysregulation and consequent neural circuit dysfunction is not specific to COVID-19. Many systemic infections are associated with lasting cognitive impairments. For instance, similar to COVID-19, the Spanish flu of 1918 (caused by H1N1 influenza virus infection) was associated with brain fog. In the current study, the authors compared the effects of mild respiratory SARS-CoV-2 infection with a mouse model of mild respiratory H1N1 influenza. Similar to SARS-CoV-2 infection, they found persistently elevated CCL11 in the H1N1 influenza infection. Therefore, CCL11-driven neuroinflammatory changes and cellular deficits may represent a common pathway to cognitive deficits in both mild respiratory COVID-19 and H1N1 influenza disease (as well as perhaps in other contexts, including aging).

However, different systemic infections can also have non-overlapping outcomes. For instance, whereas risk for anxiety and depression appears to be elevated in COVID-19, Spanish flu was associated with increased prevalence of psychosis (Honigsbaum, 2013). What accounts for these differences? One clue emerges from the current study. While CCL11 was elevated following SARS-CoV-2 and H1N1 influenza infection, a subset of cytokines was differentially regulated in these two conditions. It is likely that these non-overlapping cytokines (and their potentially non-overlapping circuit effects) might differentiate these diseases in terms of elevated risks for particular neuropsychiatric outcomes.

If cytokines have circuit-specific effects, should we consider cytokine profiling as a way to inform our treatment strategies for viral-induced/non-viral induced cognitive syndromes? Future research will no doubt address this and other outstanding questions. For instance, how are these effects mitigated by vaccination, administered before or after infection? And, perhaps most significantly, might interventions that block inducers of these cytokines or reset reactive microglia prove useful in treating COVID fog?

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Breaking down a gut-to-brain circuit that prevents malabsorption

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The ileal brake is an important reflex that ensures proper absorption of nutrients. This involves intestinal GLP-1 release, which recruits an enteric-sympathetic-spinal pathway to inhibit gastric motility and appetite. This visceral alarm system could be targeted to treat obesity and gastrointestinal dysfunction.

The transit of food through the gastrointestinal tract must be properly timed so that nutrients can be safely and efficiently absorbed. During a normal meal, most macronutrients are absorbed before they reach the most distal part of the small intestine, known as the ileum. However, this normal pattern of digestion can be disrupted by bariatric surgery, certain diseases, or the rapid consumption of very large meals. In these scenarios, the accumulation of excess food in the ileum triggers an alarm reflex known as the "ileal brake" that decreases gastrointestinal motility and powerfully inhibits appetite, thereby allowing time for nutrients to be absorbed (Maljaars et al., 2008). In this issue of *Cell*, Zhang et al. identify the neural circuit that mediates this response to digestive emergencies in a mouse model. In doing so, they reveal a web of interactions between gut hormones and enteric, sympathetic, and spinal neurons that together regulate gastric emptying and aversive responses to food (Zhang et al., 2022; Figure 1).

The hormone GLP-1 is released by enteroendocrine cells in the intestine in response to the detection of ingested nutrients and functions to inhibit gastric emptying and food intake (Figure 1, enteroendocrine cells in blue). Although GLP-1 is expressed at many sites in the intestine, it is enriched in the ileum, making it an attractive candidate to mediate the ileal brake (Larsson et al., 1975). Indeed, Zhang et al. show that direct infusion of GLP-1 into the ileum can decrease gastric motility and appetite and cause a remarkable doubling of stomach volume. They further showed, using either optogenetics or chemogenetics, that these responses are phenocopied by direct stimulation of the ileal cells that produce GLP-1, indicating that endogenous GLP-1 release from the ileum is sufficient to mimic the ileal brake.

The authors next investigated how the release of ileal GLP-1 triggers these responses. Vagal afferents, which are sensory neurons that densely innervate the intestine and provide a direct link from the gut to brain, are thought to be the principal gut sensors of GLP-1 (Brierley and de Lartigue, 2022). However, Zhang et al. show that ileal GLP-1 is instead detected by enteric neurons (the resident neurons of the gastrointestinal tract) and specifically by a specialized subset of enteric neurons known as intestinofugal cells that project to the abdominal sympathetic ganglia (Figure 1, shown in red). These ganglia provide sympathetic input