# Analyzing the biological mechanisms of CCL11 in cognitive impairments following COVID-19 infection and populations at greater risk

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**SUMMARY** "Brain fog", an informal term that encapsulates various neurological symptoms including impaired attention, concentration, speed of information processing, memory, and executive functions, is a persistent symptom common among a quarter of COVID-19 survivors. While severe COVID-19 causes multi-organ disease, even mild COVID-19 can result in neuroinflammatory responses and subsequent brain fog. SARS-CoV-2 infection has been shown to also increase the risks of later developing other neurodegenerative disorders such as Alzheimer's disease. Considering the continued prevalence of COVID-19 around the globe and emerging variants such as Omicron, these neurological symptoms present a major public health concern. Recent studies have detected elevated levels of pro-inflammatory chemokine CCL11 only in those experiencing cognitive impairments after SARS-CoV-2 infection, establishing a strong link between CCL11 and the central nervous system (CNS). CCL11 plays a major role in eosinophilic inflammation, and has been shown to limit neurogenesis and contribute to other cognitive and psychiatric illnesses, such as multiple sclerosis, Alzheimer's, major depression, bipolar disorder, and schizophrenia. However, the biological mechanisms of CCL11 over-expression as a result of SARS-CoV-2 infection remain poorly understood. This article will investigate the mechanism behind SARS-CoV-2-driven CCL11 upregulation from infection to CCL11 entry into the CNS across the blood-brain barrier, outlining the sources of CCL11 and targets within the plasma and CNS. Additionally, it will discuss the subsequent pathological effects of CCL11 on the CNS, including eosinophil degranulation, activation of microglia, inhibition of oligodendrocyte precursors, and production of reactive oxygen species. It will also investigate which demographics are more vulnerable to the adverse effects of CCL11 and risks of long COVID. These inquiries play a key role in understanding CCL11 functions within the brain and evaluating the potential of CCL11 as a new therapeutic target. If this therapeutic strategy is successful, it will improve health outcomes not only for post-COVID brain fog, but also for other neurological disorders related to inflammatory dysregulation.

## INTRODUCTION

Post COVID-19 condition, commonly known as long-COVID, refers to symptoms that persist after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has cleared from the body, and can encompass adverse pathophysiological outcomes affecting multiple organ systems (1, 2). Approximately 17.2% of Canadians previously infected with SARS-CoV-2 experience long-COVID, and of those affected, 47.3% experience symptoms for one year or longer, and 21.3% report that their symptoms often or always limit their daily activities (3). In particular, neurological symptoms related to impaired attention, concentration, speed of information processing, memory, and executive functions have been shown to affect approximately one in four individuals previously infected with COVID-19, even after a mild acute phase (4, 5). These cognitive deficits are often referred to as "brain fog", and have been observed to persist even two years after initial infection (6). The biological milieus involved in these cognitive impairments remain in question, and there are currently no available diagnostic tests or treatments in Canada (7). Given the global

prevalence of COVID-19, these cognitive impairments and the associated knowledge gaps present a major public health concern.

Recent evidence has revealed that SARS-CoV-2 infection can lead to neuroinflammation and subsequent brain damage, resulting in brain fog (8). Specifically, it was observed that only the long-COVID patients that were experiencing brain fog symptoms exhibited elevated levels of the pro-inflammatory C-C motif chemokine 11 (CCL11) in their serum, which was absent in long-COVID patients without brain fog symptoms (8). CCL11, also known as eotaxin-1, has shown to play a significant role in mediating inflammation and has previously been associated with limited neurogenesis and various other cognitive and psychiatric illnesses, such as multiple sclerosis, Alzheimer's disease, major depression, bipolar disorder, and schizophrenia (9). Research has found that higher levels of CCL11 are correlated with late-stage progression of bipolar disorder, as well as reduced gray matter, declined memory functioning, and higher severity of symptoms in schizophrenia patients, thereby establishing a strong connection between CCL11 and the CNS. Additionally, studies have found an increased risk of new diagnoses of Alzheimer's within 360 days of the initial COVID-19 diagnosis (10-12). These findings suggest that CCL11 may act as a mediator of not only brain fog but also other neurological and psychiatric disorders that can manifest downstream of SARS-CoV-2. Given that the Omicron (B.1.1.529) variant presents with greater transmissibility and similarly high risks of neurological and psychiatric outcomes as the Delta (B.1.617.2) variant despite significantly lower death rates, there is an urgent need to better understand the biological activities of CCL11 within the CNS (6).

## PROPOSED RESEARCH QUESTIONS

Fernández-Castañeda et al. demonstrated through mouse models that SARS-CoV-2 infection can induce elevated levels of CCL11 in the hippocampus, concomitant with impaired neurogenesis (8). An in-depth exploration of the complex biophysiological networks involved in this process could potentially reveal new therapeutic targets, such as CCL11 or its interacting molecules. The development of a drug that could re-establish CNS homeostasis by reversing the effects of CCL11-mediated neuroinflammation could possibly serve as a multifunctional treatment for not only long-COVID, but also other neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis. Furthermore, understanding the mechanisms of CCL11 may reveal demographics most susceptible to its adverse effects. Prior studies have established that long-COVID is more prevalent in certain groups, such as young, female, Hispanic individuals with a history of mood and thought disorder or depression (13). It is plausible that certain populations similar to the aforementioned demographics are more vulnerable to the effects of CCL11 and thus may be predisposed to the associated neurological and psychiatric disorders. The identification of these populations may represent a significant step towards improving clinical care for these groups.

## PROPOSED PROJECT NARRATIVE

**What is the biological pathway of SARS-CoV-2 mediated CCL11 activity, and what are the pathological effects on the CNS?** When a SARS-CoV-2 virion infects host cells via its spike protein, chemokines are secreted by the host immune systems to recruit leukocytes and initiate an inflammatory response. The secreted chemokines then bind to G protein-coupled receptors on the surface of leukocytes and activate signaling cascades that lead to shape rearrangement and cell movement mediated by integrins (14, 15). CCL11 of the CC chemokine family is an eosinophil chemoattractant that acts through C-C motif receptor 3 (CCR3). In the plasma, CCL11 is produced by eosinophils, B-cells, fibroblasts, macrophages, chondrocytes, and endothelial cells during systemic inflammation (Fig. 1), and although CCL11 is able to also bind to the CCR2 and CCR4 receptors as well, it binds with highest affinity to CCR3 (16-18). In the blood, CCR3 is expressed on mast cells, eosinophils, Th2 lymphocytes, and keratinocytes (Fig. 1) (18). When Th2 lymphocytes bind with CCL11 via CCR3, they are able to release additional cytokines such as interleukin-4 (IL-4), IL-5, and IL-13, complement factors, and immune complexes that induce further CCL11 production by

other cells (19). The plasma CCL11 can also travel to the CNS, where they bind to CCR3 expressed on microglia, astrocytes, and brain endothelial cells to initiate neuroinflammation (Fig. 1) (20). The molecular mechanisms behind how CCL11 traverses the brain vasculature and enters the brain parenchyma are currently uncertain, but studies have shown that CCL11 is able to cross the blood-brain barrier (BBB) without disruption (21).
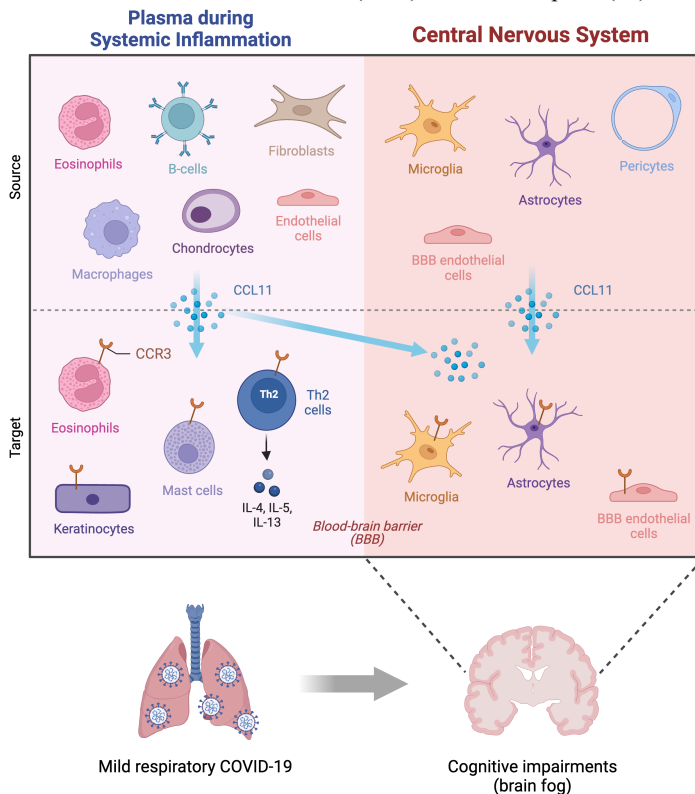


**FIG. 1** CCL11 sources and targets within the plasma and CNS during mild respiratory COVID-19 infection and following cognitive impairments.

To investigate how CCL11 travels to and from the brain parenchyma through the BBB, Erickson et al. treated mice with CCL11 and CCR3 inhibitor SB328437 and observed the effects on CCL11 uptake. In high concentrations of SB328437, the mean tissue to perfusate ratio significantly increased, indicating CCL11 accumulation in the brain. Two possibilities were presented: the first idea (Fig. 2A) is that CCL11 receptors in the CNS and transporters at the BBB are distinct and competing entities, and inhibition of CCR3 within the CNS allows for increased transport of CCL11 across the BBB. The second idea (Fig. 2B) is that CCR3 mediates only the efflux of CCL11 across the BBB from the CNS, and thus inhibition of CCR3 would lead to CCL11 accumulation in the brain. Both ideas suggest that although CCL11 is able to cross the BBB, CCR3 is not a predominant influx transporter (21).
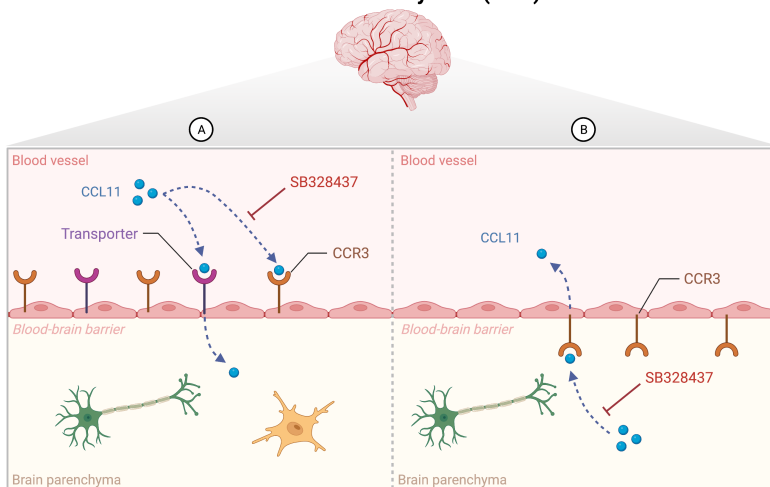


**FIG. 2** CCL11 uptake and efflux across the blood brain barrier. (A) CCL11 receptors in the CNS and transporters at the BBB are distinct and competing entities. (B) CCR3 mediates only the efflux of CCL11 across the BBB from the CNS.

Within the CNS, inflammatory stimuli also induce CCL11 production by choroid plexus epithelial cells, pericytes, astrocytes, and microglia (22). In studies observing CCL11 in inflammatory diseases such as asthma, accumulated CCL11 has shown to bind with CCR3 receptors expressed on the cell surface of eosinophils, and activate a series of intracellular signaling cascades that recruit further eosinophils. The eosinophils then release granular proteins and growth factors that lead to tissue damage and remodeling (9). However, COVID-19 patients have shown lower levels of eosinophils in the blood, known as eosinopenia, despite increased CCL11 in serum, lung tissue, and cerebrospinal fluid even at 7-weeks following SARS-CoV-2 infection (8). Studies suggest that CCL11 produced via SARS-CoV-2 infection initiates the degranulation of eosinophils and subsequent release of eosinophil-derived neurotoxins (EDN), which corresponds to both the observed eosinopenia and elevated levels of eosinophil-related granule contents in COVID-19 patients (23, 24). EDN is known to severely alter the white matter of the cerebellum and form vacuoles within the myelin sheaths of axons by separating the lamellae (Fig. 3A) (25). This aligns with the recent findings of decreased myelinated axon density in the subcortical white matter 7 weeks after SARS-Cov-2 infection, thus highlighting the impaired neural circuit function and axon health in COVID-19 patients (8).
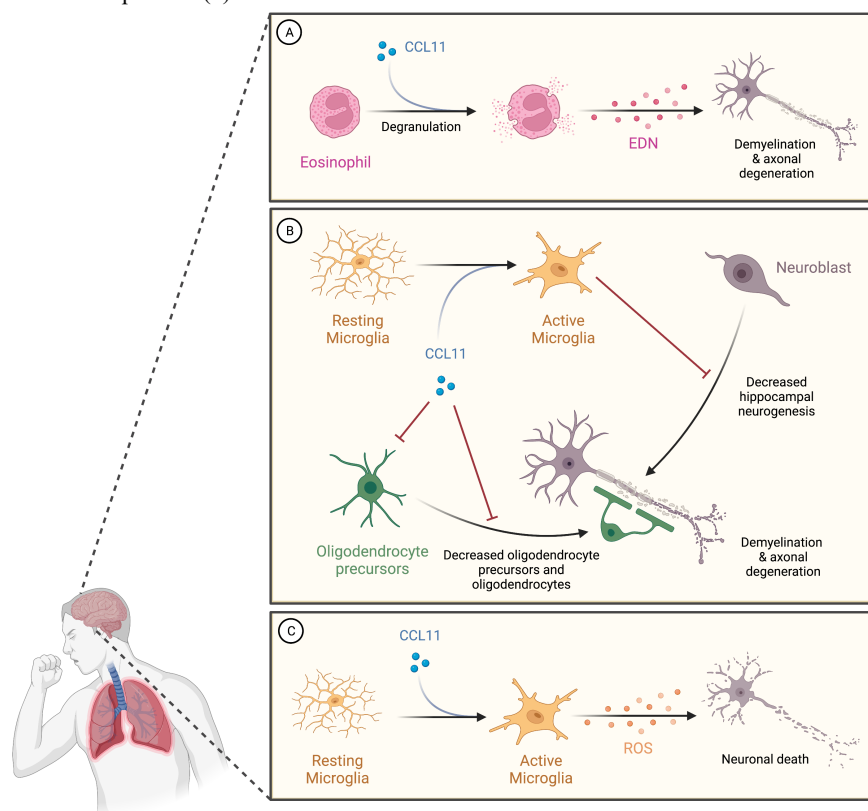


**FIG. 3** CCL11 pathways and effects in the CNS. (A) CCL11 produced in COVID-19 infection promotes eosinophil degranulation and release of EDN, which causes decreases in myelin sheaths and axonal degeneration. (B) CCL11 produced in COVID-19 infection activates microglia, leading to decreased hippocampal neurogenesis. CCL11 also reduces oligodendrocyte precursors and following oligodendrocytes, further contributing to the loss of axon myelination. (C) Microglia activated by CCL11 in other inflammatory diseases can release ROS, which potentiates neuronal death.

In addition to eosinophil degranulation, CCL11 has been shown to promote microglia and macrophage migration and reactivity, which inhibits neurogenesis in hippocampal white matter (Fig. 3B) (8). Elevated CCL11 levels in COVID-19 patients are also correlated with a mild decrease in the number of oligodendrocyte precursor cells and the corresponding decrease in mature oligodendrocytes. Fernández-Castañeda et al. found that within 7 days of COVID-19 infection, mature oligodendrocytes were depleted by ⅓ in patients, and this persisted until at least 7 weeks after initial SARS-CoV-2 infection (Fig. 3B) (8). Studies on other inflammatory disorders have also found that when activated by CCL11, microglia subsequently produce reactive oxygen species (ROS) by upregulating nicotinamide adenine dinucleotide phosphate-oxidase 1 (NOX1), which potentiates glutamate-induced neuronal death (Fig. 3C) (26). When treated microglia with NOX1 inhibitor ML-171, microglial ROS production was significantly reduced (26). Given the novel discovery of CCL11 upregulation in long-COVID patients, the biological and cellular processes understood previously in other CCL11-associated inflammatory diseases are yet to be confirmed in SARS-CoV-2 infection.

However, past findings provide valuable background context on CCL11 profiles to suggest how similar pathways may cause the long-lasting cognitive dysfunctions in COVID-19 patients, and potential pathways for early diagnosis and treatment.

**Which populations are more vulnerable to the adverse effects of CCL11 and risks of long-COVID?** Despite higher incidence of brain fog and long-COVID in female patients, Fernández-Castañeda et al. found that male patients have significantly higher levels of CCL11 (8, 13). Patients with a history of autoimmune disease also had greater levels of CCL11 in the serum, but age, body mass index, and duration of time since symptom onset did not account for variability in CCL11 levels among long-COVID patients (8). However, this contradicts the existing literature demonstrating a correlation between older age and onset of neurological symptoms following COVID-19 infection, as well as the age-related increase in CCL11 in healthy patients and the corresponding cognitive decline (27-29). High BMI and depression have also previously been associated with increased CCL11 in circulation, and have also shown to be risk factors of long-COVID, further contradicting Fernández-Castañeda et al.'s findings (13, 28, 30). In summary, the current literature suggests plasma levels of CCL11 may not be the sole determinant for the development of long-COVID, and additional factors such as inflammatory mediators may contribute to the biological mechanisms. Research in Alzheimer's disease have also found that the A23T mutation in the CCL11 receptor-binding domain can modulate CCL11 signaling and neuroinflammation, thus suggesting a potential avenue of research into CCL11 polymorphisms and their relationship to brain fog vulnerability (31).

## POTENTIAL IMPACT/CONCLUSIONS

Recent evidence has found that patients infected with the Omicron variant had a slight increase in plasma CCL11 levels (65.2 pg/ml) compared to the Delta variant (51.0 pg/ml), pressing concerns about possibility of greater brain fog susceptibility (32). It is important to understand the physiological principles behind CCL11's long-lasting effects within the CNS to develop strategies that will prevent and treat brain fog in COVID-19 patients. There is currently a gap in the literature addressing the mechanisms of CCL11 inhibition and the contributing factors to brain fog development. Early phase clinical trials have been conducted using CCR3 antagonists for asthma and therapeutic antibodies against CCL11 (Bertilimumab) for allergic rhinitis (33, 34). Their efficacy and effectiveness in brain fog patients and in other neurocognitive diseases with similar CCL11 profiles, such as multiple sclerosis, Alzheimer's, major depression, bipolar disorder, and schizophrenia currently remain in question (9). Future research groups could also study whether other neuroinvasive viruses such as Zika or West Nile cause similar upregulation of CCL11 within the brain, and if a single therapeutic or multi-drug regimen could act as a multifunctional treatment for these diseases along with COVID-19. The novel development of mouse-adapted models of SARS-CoV-2 provide an excellent resource for the hopeful acceleration of new discoveries in the relationship between SARS-CoV-2, CCL11, and brain fog (34). In summary, this article provides a detailed overview of the current line of knowledge regarding the biological pathways of CCL11 within the brain and the affected populations, and highlights the need for further research in order to develop a drug applicable to a broader range of diseases.

## ACKNOWLEDGEMENTS

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