”Brain fog” syndromes: neural-immune interactions in cognitive impairment after COVID

Michelle Monje MD PhD
Stanford University
Howard Hughes Medical Institute

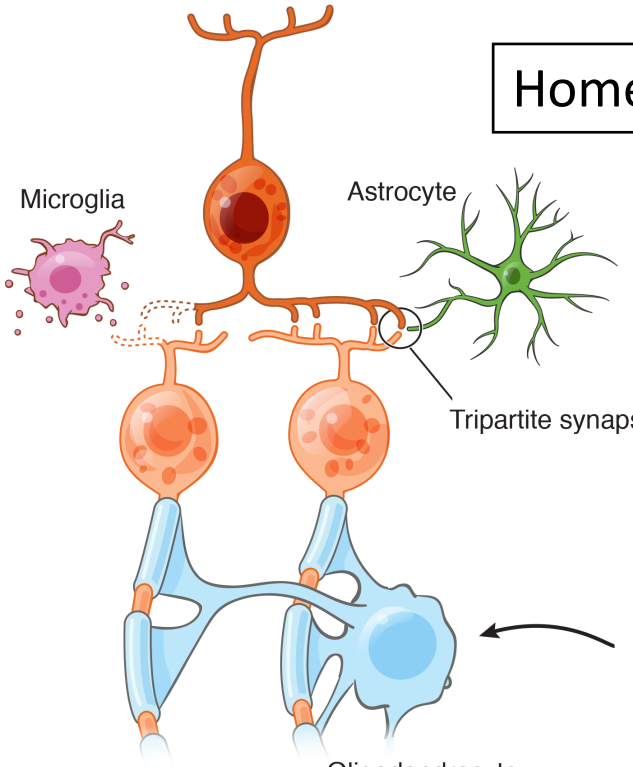
Disclosures

- None related to the talk
- TippingPoint Biosciences SAB
- Members of my family hold equity in MapLight Therapeutics and Syncopation Life Sciences

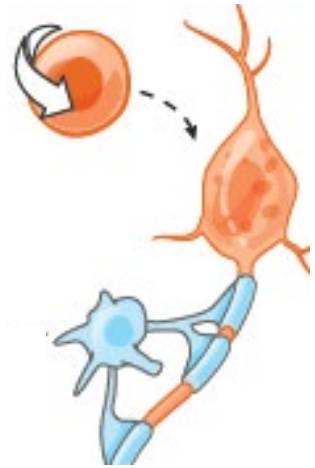
Healthy cognitive function depends on intact mechanisms of neural homeostasis and plasticity

Plasticity of synapse structure and function

Homeostatic astrocyte function



Hippocampal Neurogenesis



Myelin plasticity and homeostasis

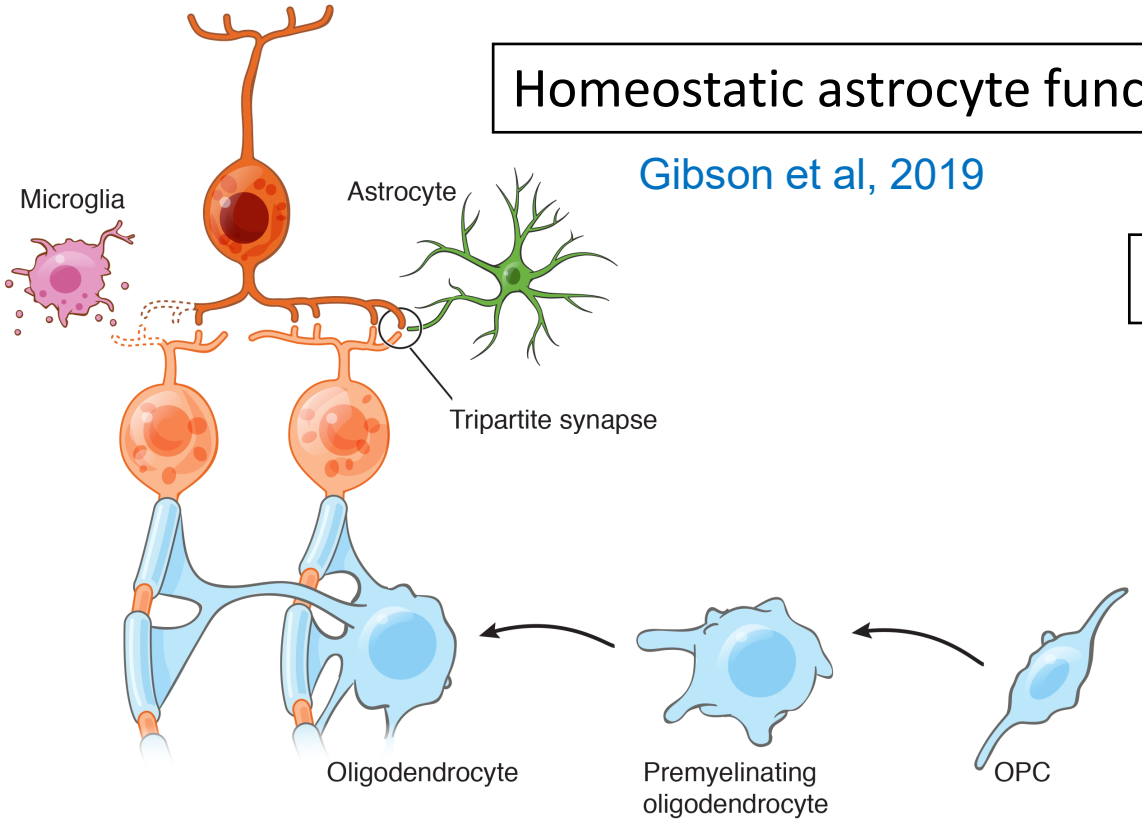
In cancer therapy-related cognitive impairment, microglial reactivity can impair mechanisms of neural homeostasis and plasticity

Plasticity of synapse structure and function

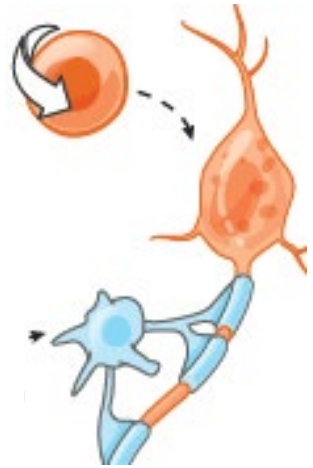
Andres et al, 2014
Parihar et al, 2013
Kempf et al, 2014

Homeostatic astrocyte function

Gibson et al, 2019



Hippocampal Neurogenesis



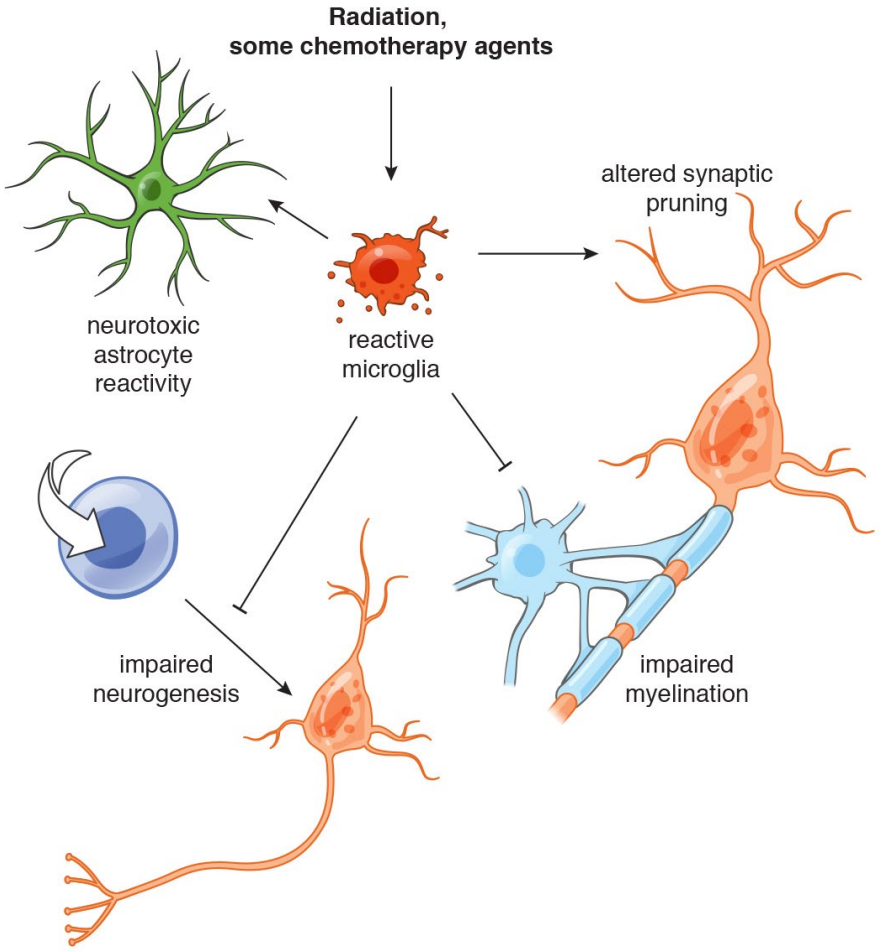
Tada et al 1999
Monje et al 2002
Monje et al 2003
Dietrich et al., 2006
Monje et al 2007
Seigers et al 2009

Myelin plasticity and homeostasis

Gibson et al, 2019
Geraghty et al, 2019

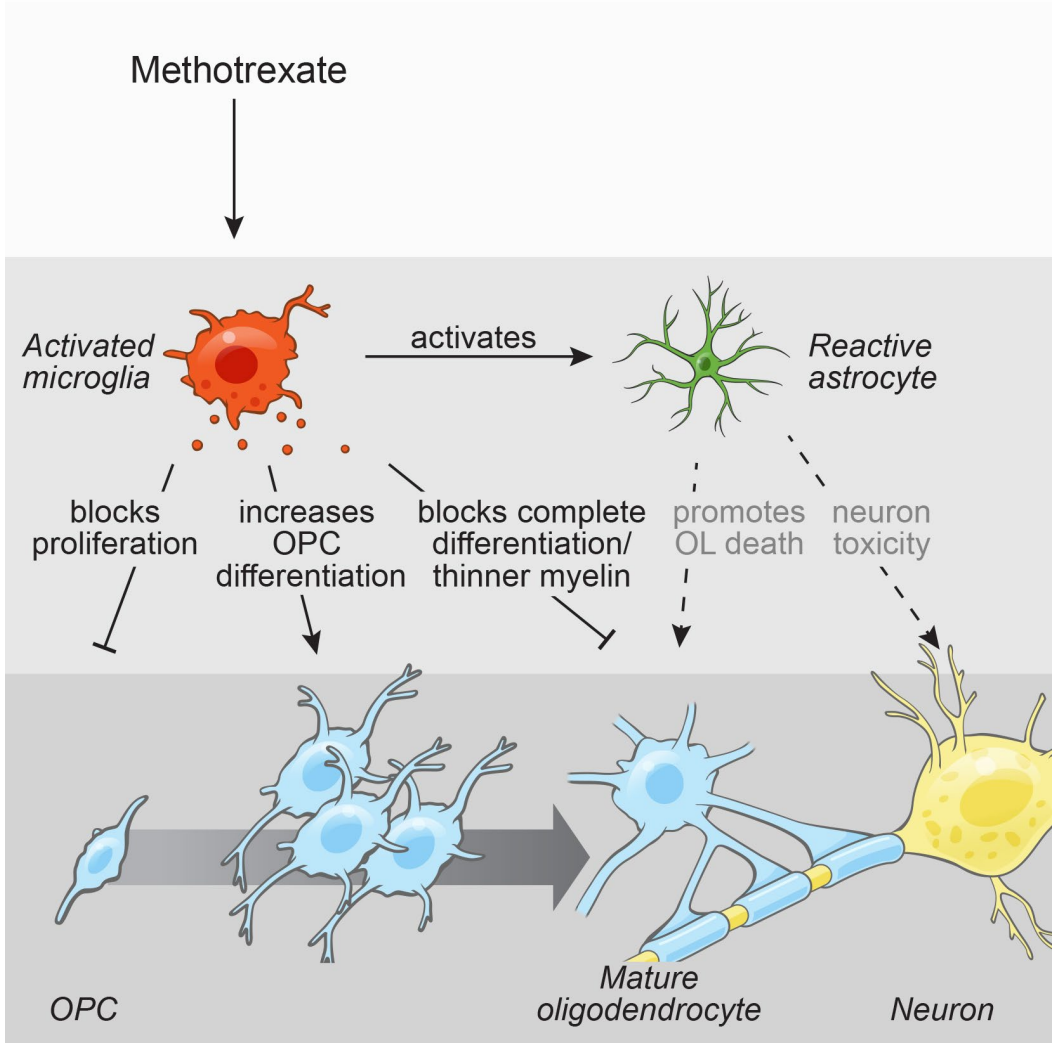
Cancer therapy-related cognitive impairment (CRCI)

- Impaired attention, concentration, memory, speed of information processing, multi-tasking
- In many cases, standard neuroimaging is unremarkable but advanced imaging reveals subtle white matter aberrations and decreased hippocampal volume
- Affects a large proportion of cancer survivors to a variable extent

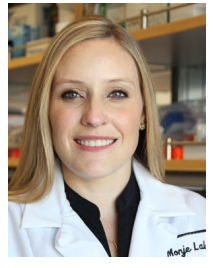


Filbin and Monje, 2019 *Nat Med*

“Chemo fog”: multi-lineage glial dysregulation underlies methotrexate chemotherapy-induced cognitive impairment



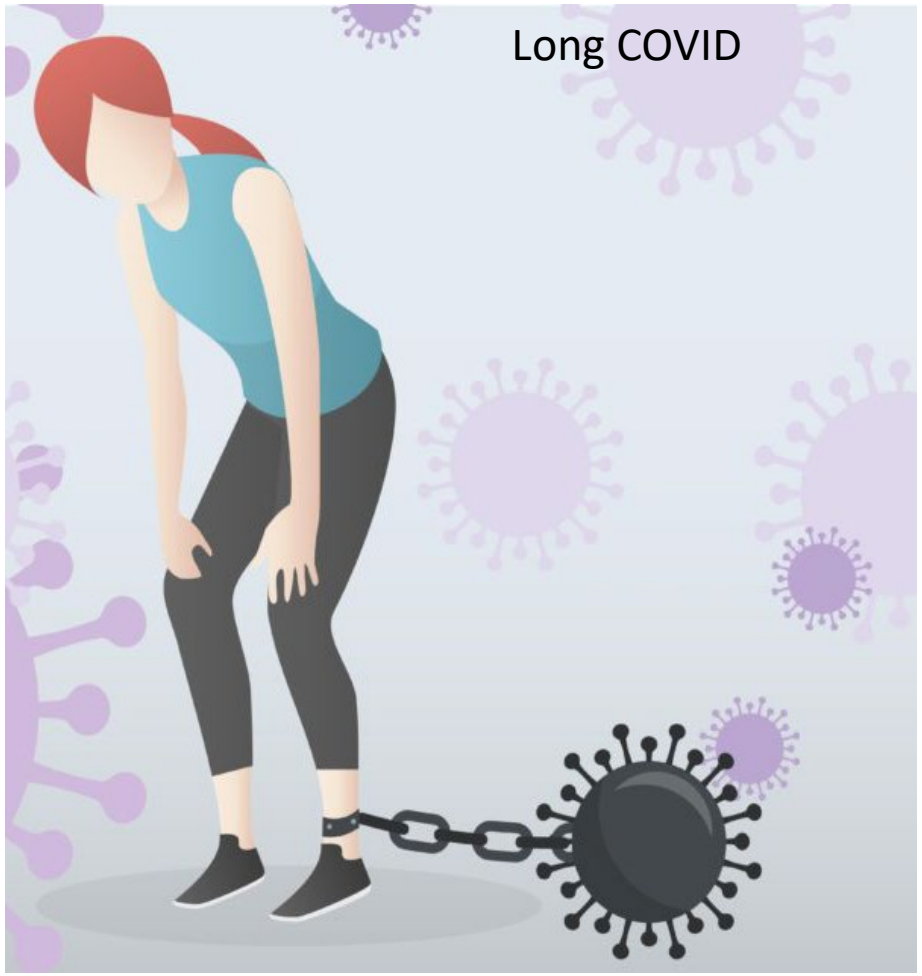
- Systemic methotrexate chemotherapy directly activates white matter microglia,
  - which in turn activate astrocytes
- Myelin homeostasis and plasticity are disrupted
- Microglial depletion using a CSF1R antagonist restores myelination and rescues cognition in mice



Gibson et al. (2019) *Cell*
Geraghty et al. (2019) *Neuron*

Striking clinical parallels between “chemo-fog” and “COVID-fog”

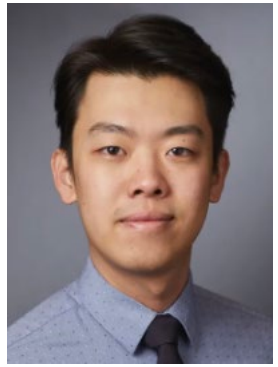
- Impaired attention, concentration, memory, speed of information processing, multi-tasking
- In many cases, standard neuroimaging is unremarkable but advanced imaging reveals subtle white matter aberrations and decreased volume of limbic and olfactory structures
- Affects a large proportion of COVID survivors
  - A meta-analysis of nearly 10,000 subjects found that 25% of people experience persistent cognitive dysfunction (Nasserie et al., 2021)
  - The risk of cognitive dysfunction is higher with severe COVID, but a significant portion of people with mild COVID-19 experience lasting cognitive impairment.
  - Breakthrough infections in vaccinated people may be at somewhat lower risk for Long COVID, but not as much as hoped



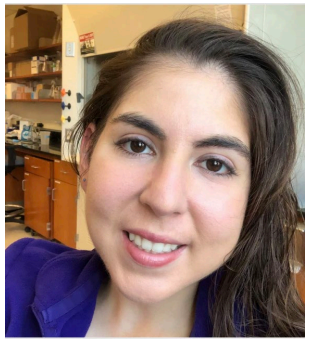
Might similar glial dysregulation contribute to cognitive symptoms after COVID?

Akiko Iwasaki



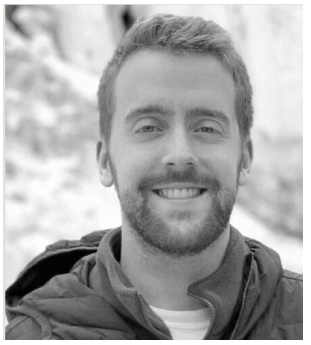







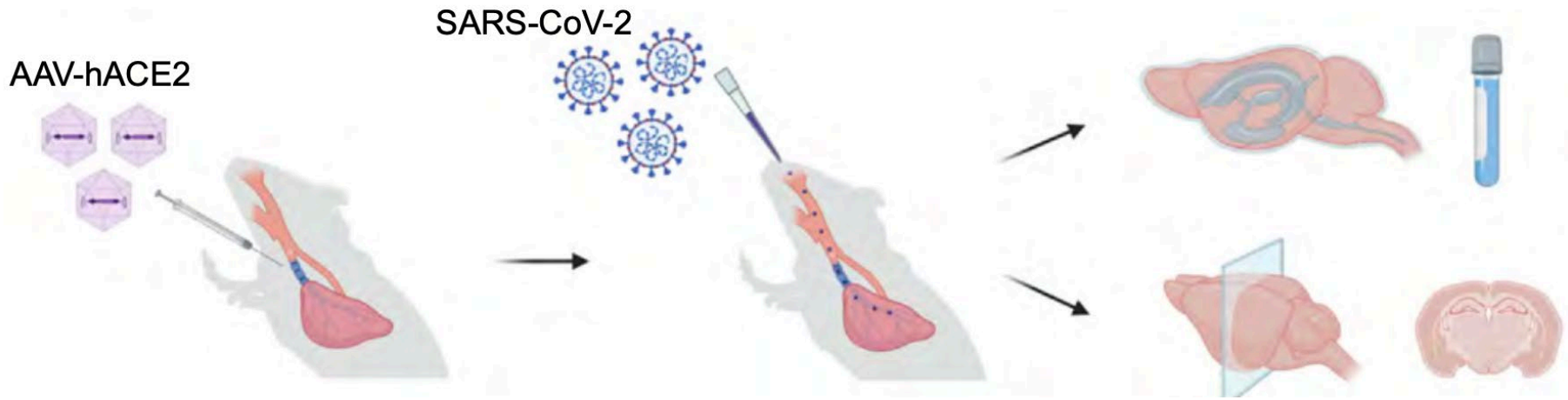
Avindra Nath

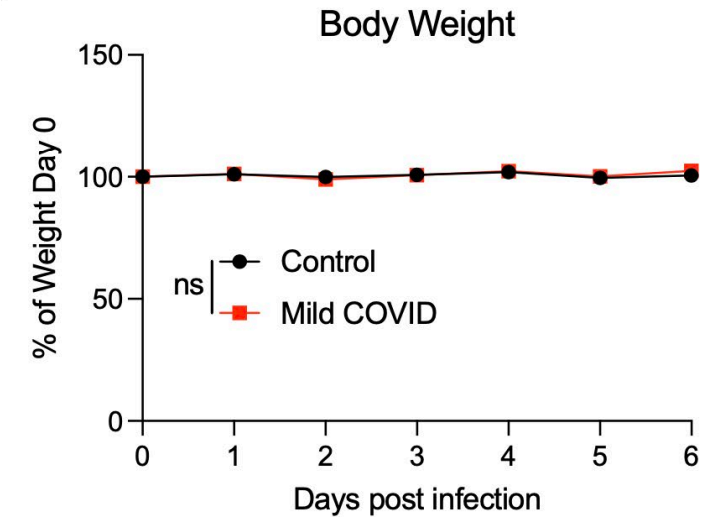
Myounghwa Lee

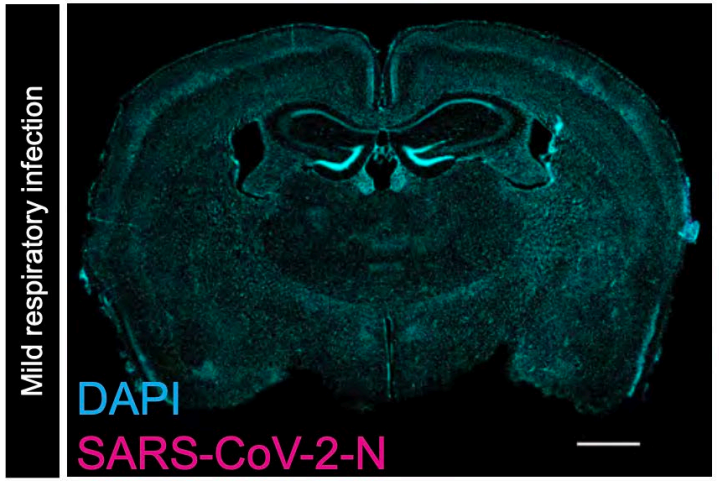



….and many others!

Mouse model of mild respiratory SARS-CoV-2 infection





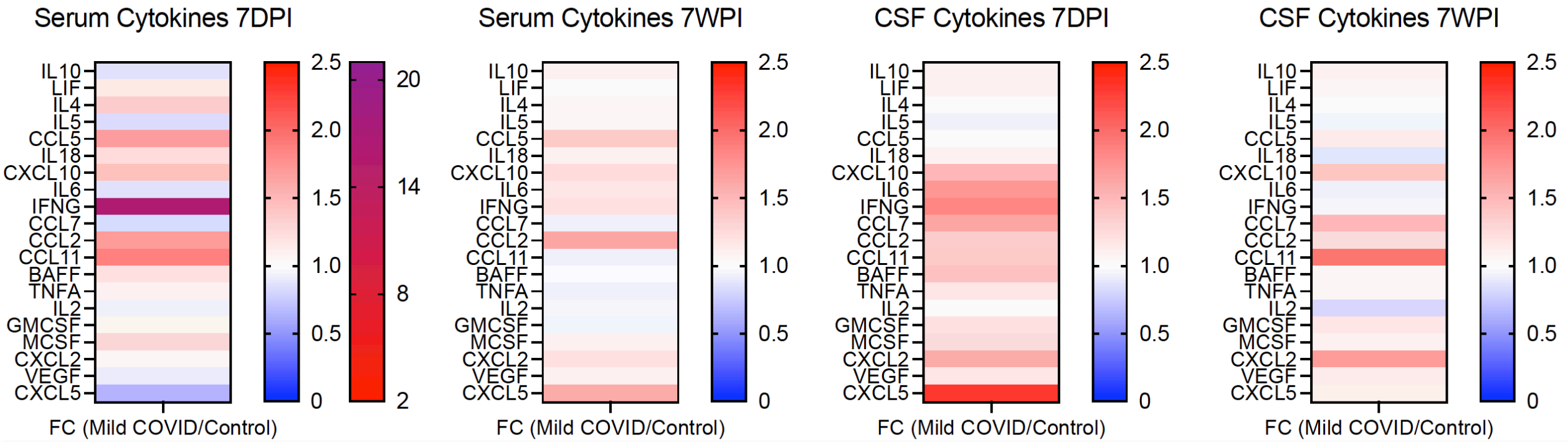


No brain infection

With Akiko Iwasaki

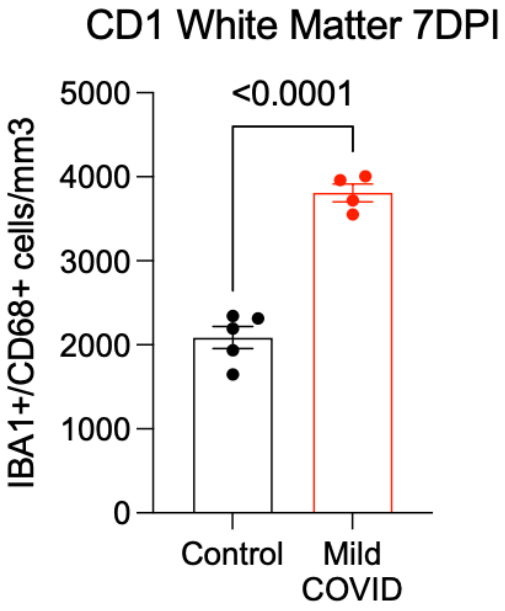
Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

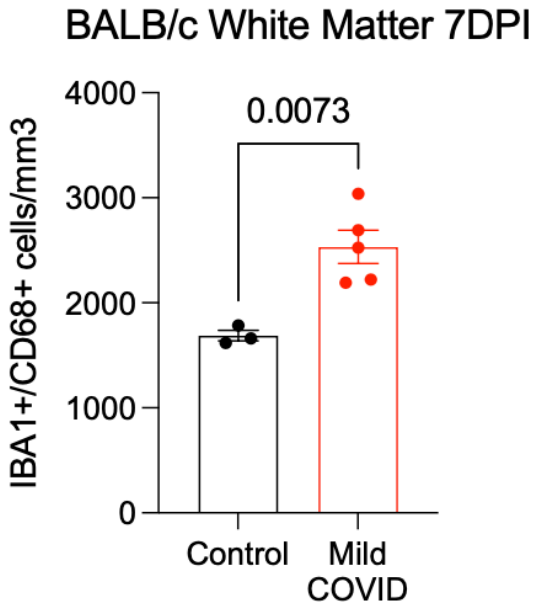
Mild respiratory SARS-CoV-2 infection persistently elevates cytokine/chemokine levels in serum and CSF

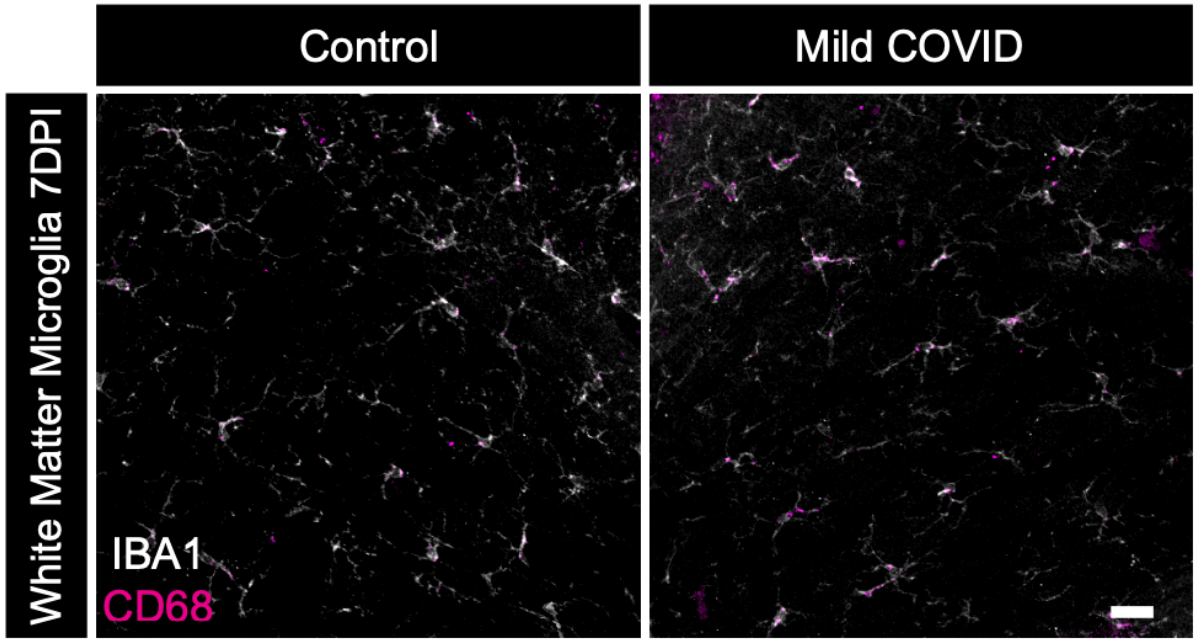


Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

Subcortical white matter microglial reactivity after mild respiratory SARS-CoV-2 infection in mice

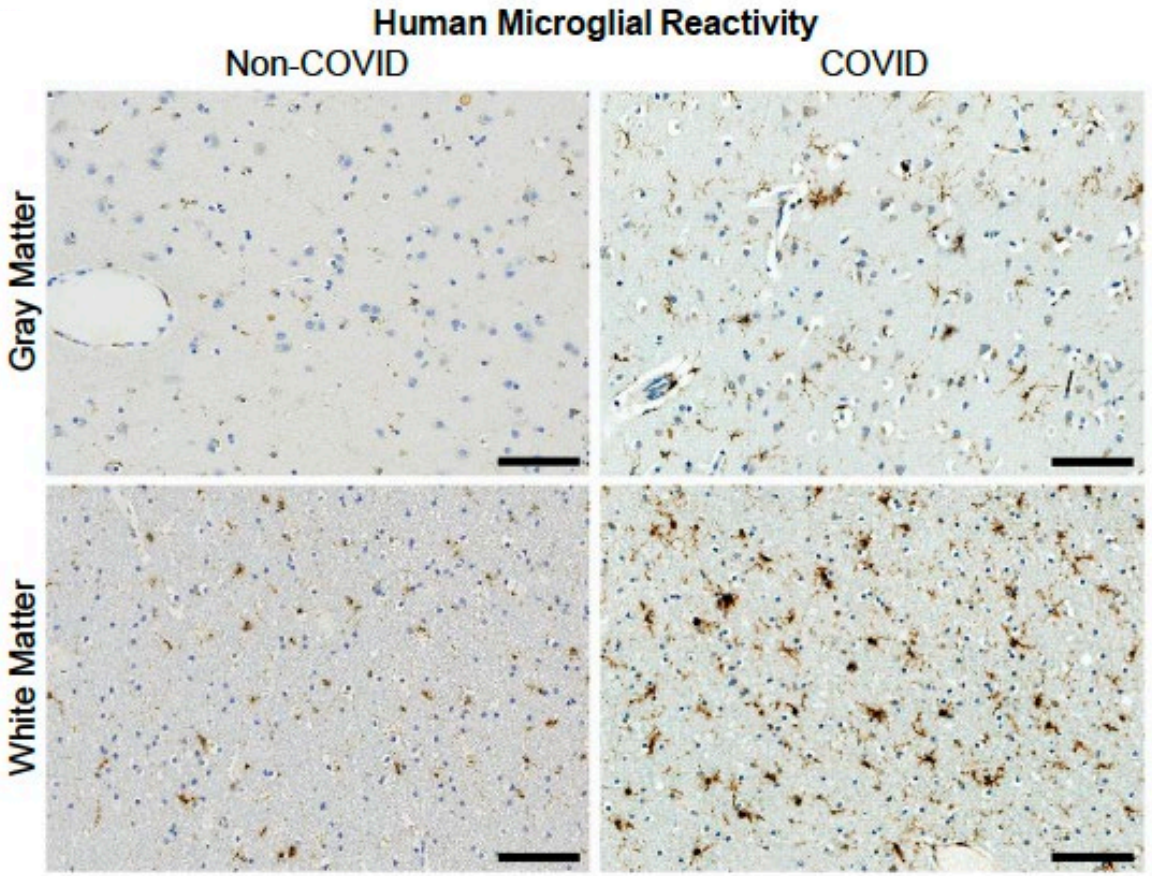


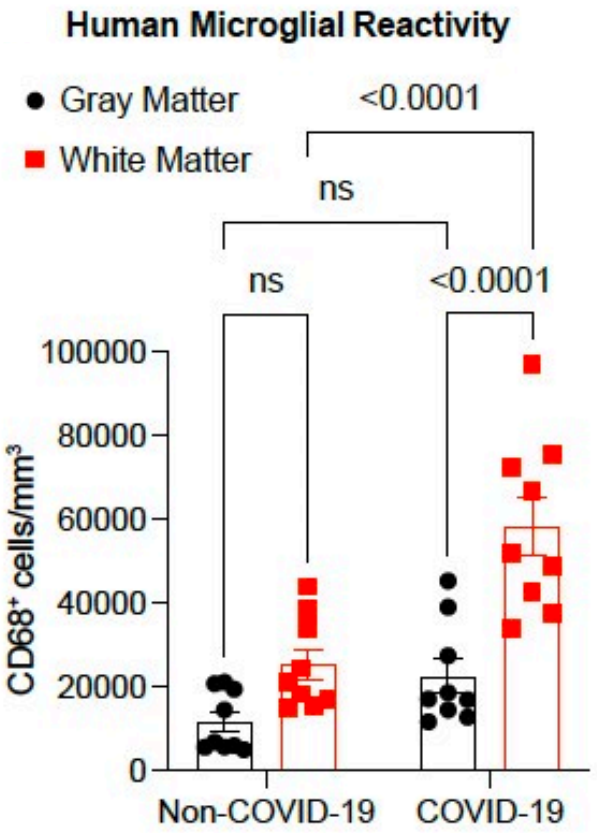




Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

White matter microglial reactivity in humans with COVID

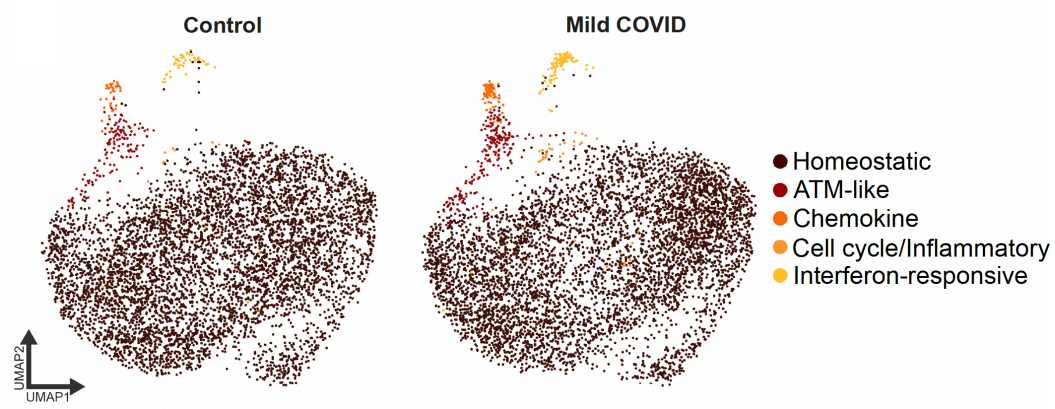


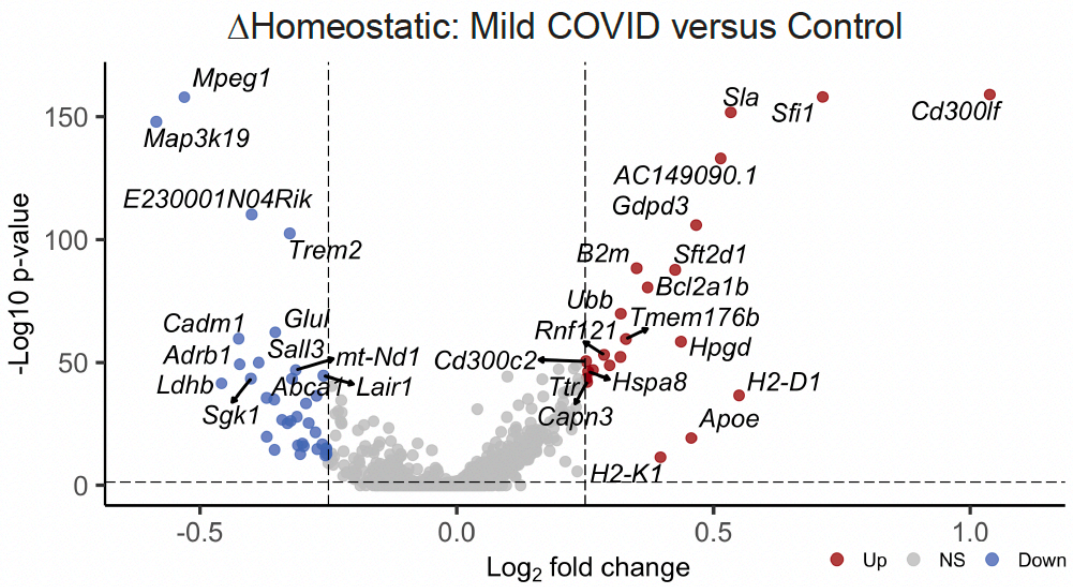


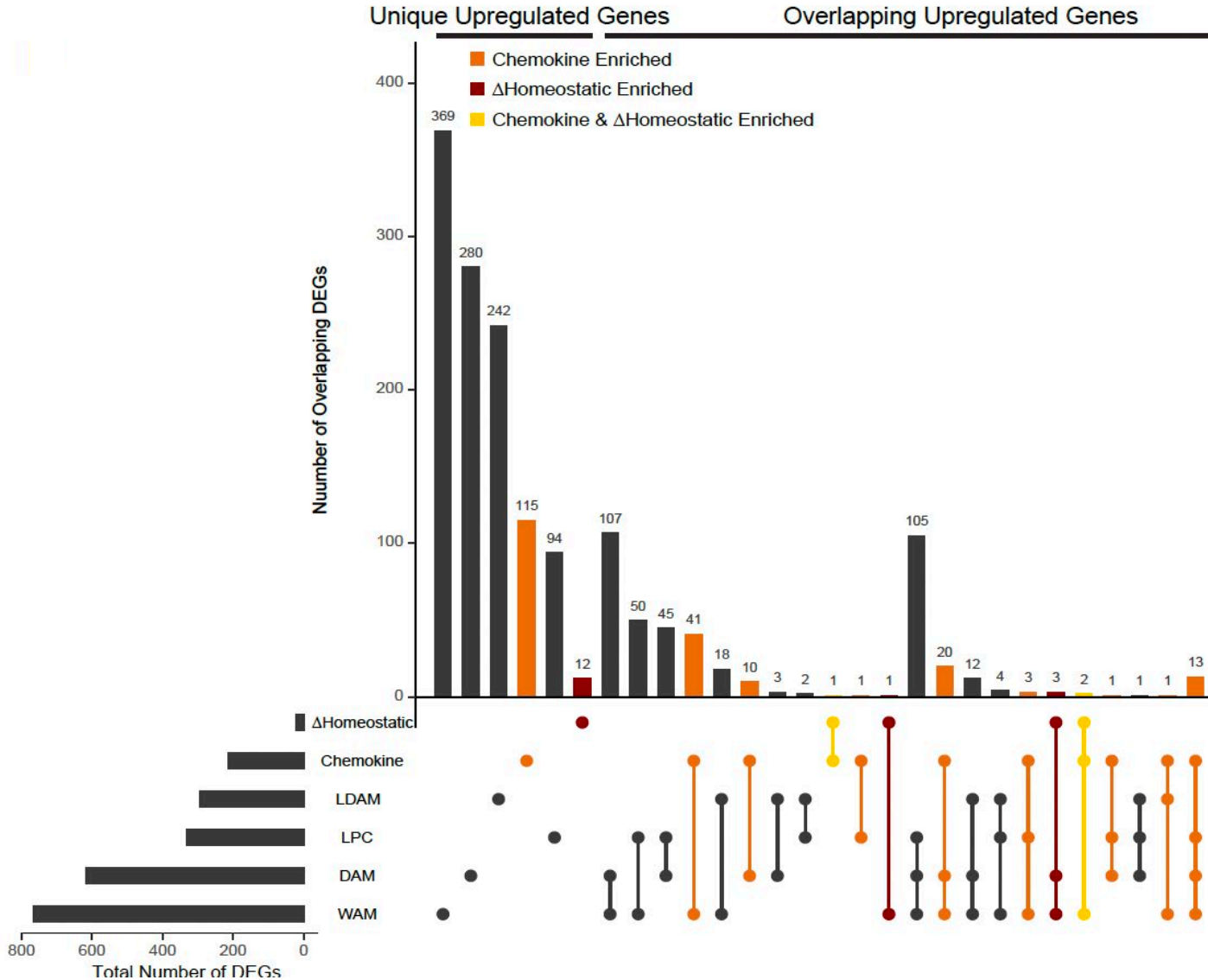
With Myounghwa Lee and Avi Nath

Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

Mild respiratory COVID alters microglial states



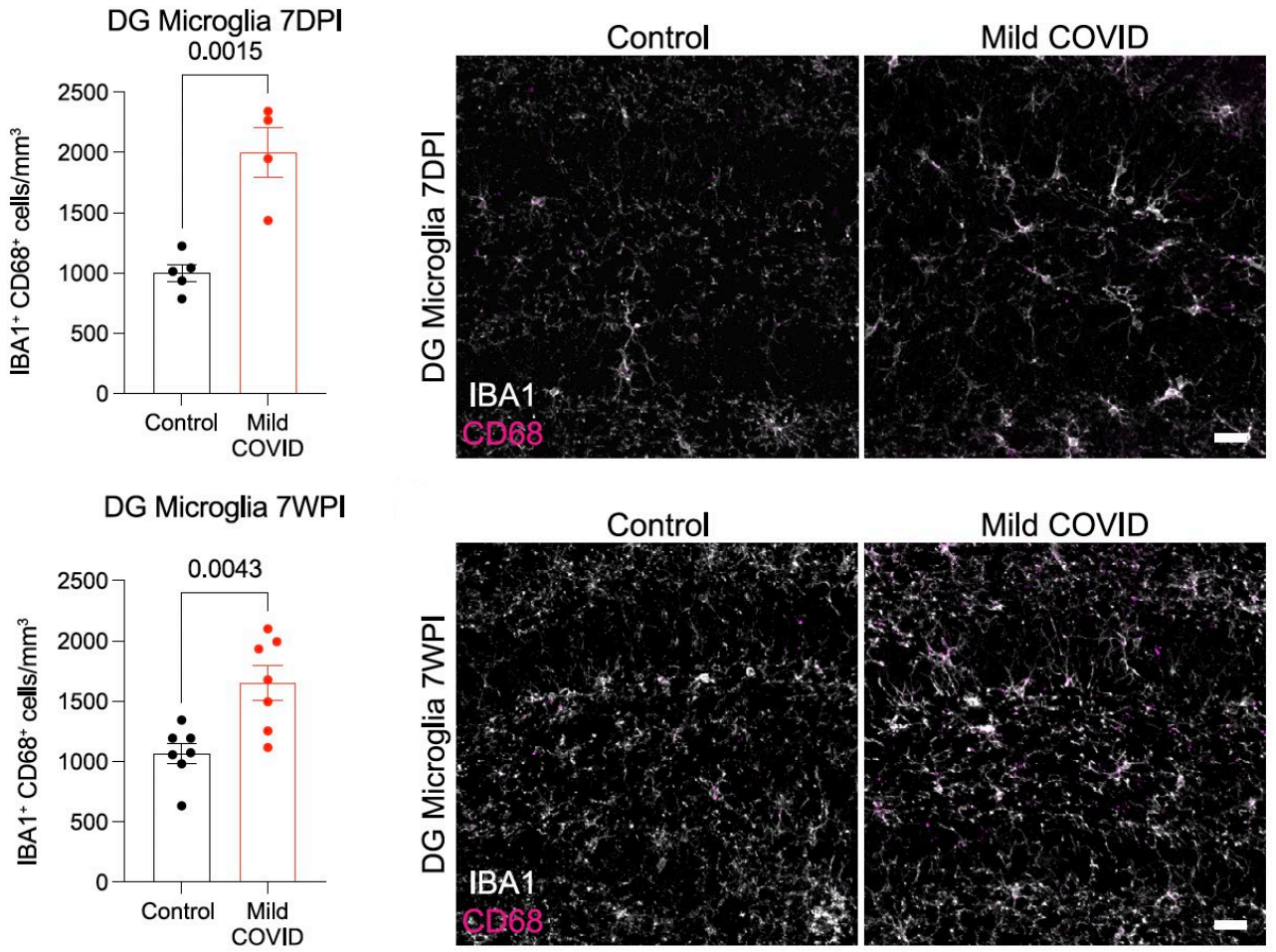




With Michael O'Dea and Shane Liddelow

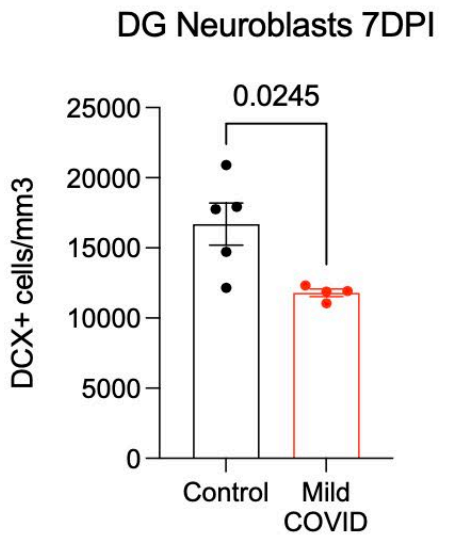
Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

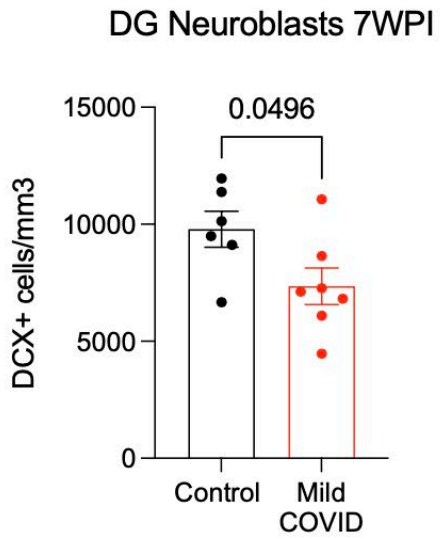
Hippocampal white matter microglial reactivity after mild respiratory SARS-CoV-2 infection

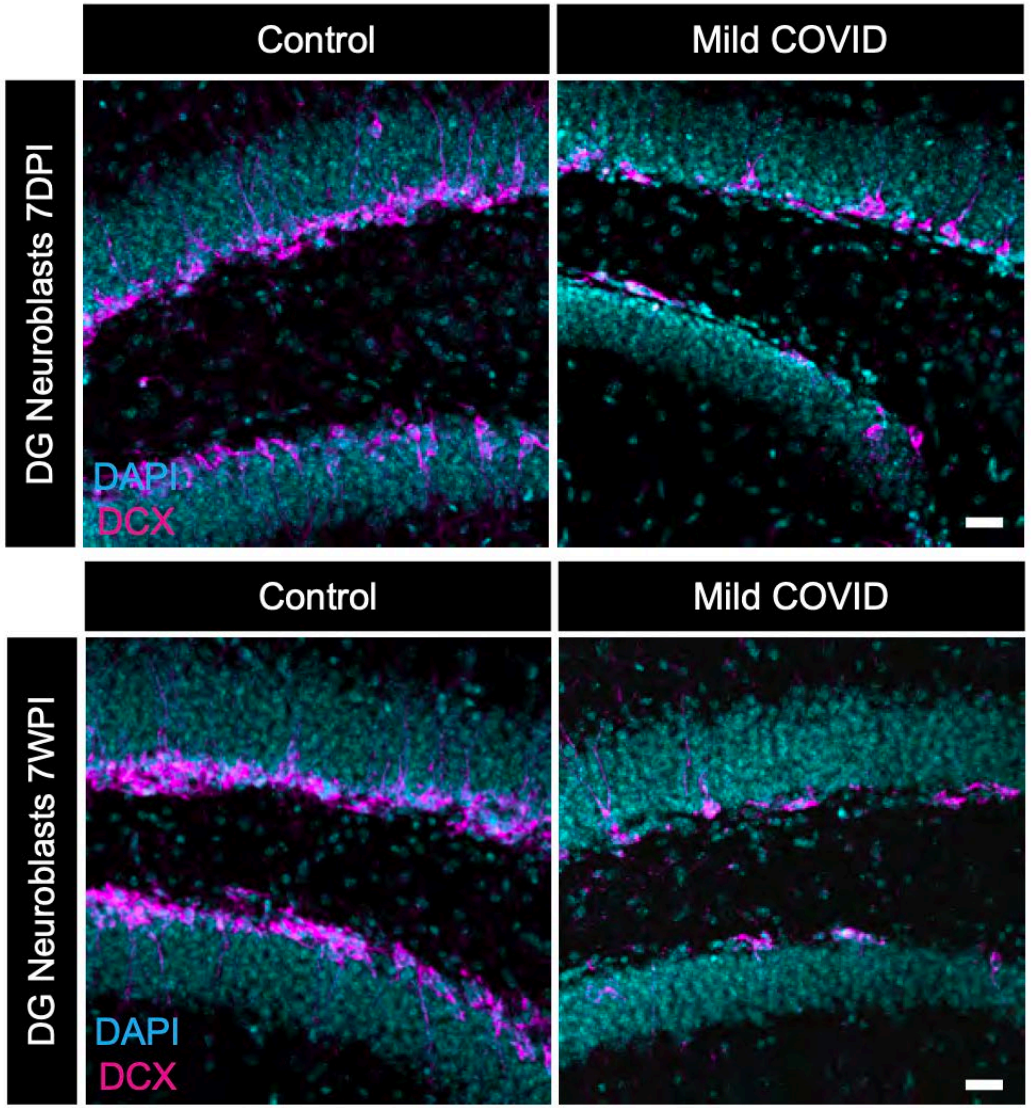


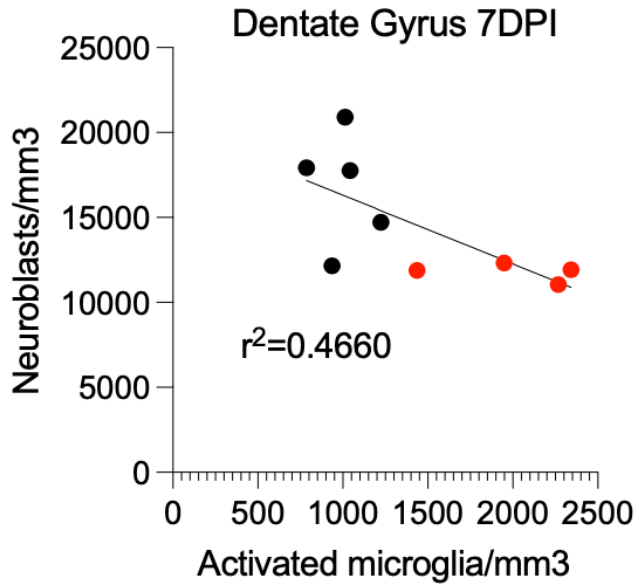
Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

Mild respiratory SARS-CoV-2 infection impairs hippocampal neurogenesis



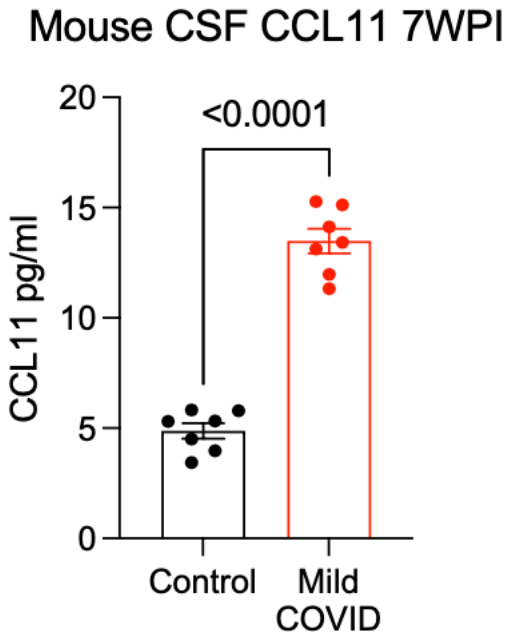






Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

Role for elevated CCL11 levels in cognitive symptoms of Long COVID?

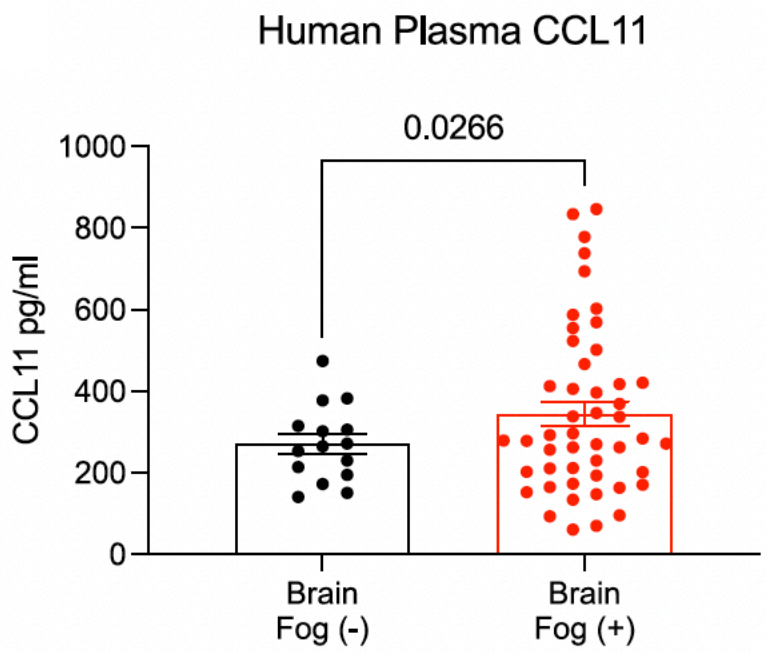


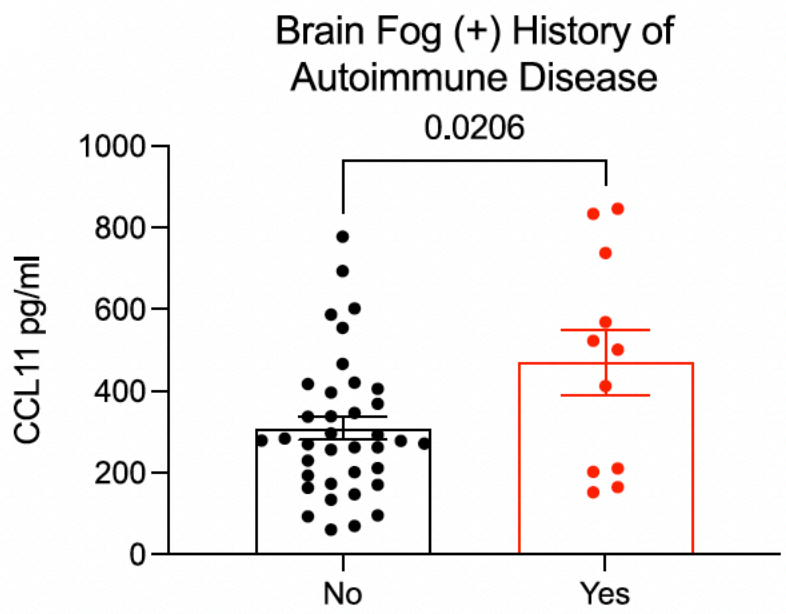
- CCL11 readily crosses the BBB
- Plasma levels of CCL11 correlates with reduced neurogenesis in aging
- CCL11 is necessary and sufficient for decreased neurogenesis and memory impairment in mice

Villeda et al 2011

Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

Elevated CCL11 levels in patients with cognitive symptoms of Long COVID

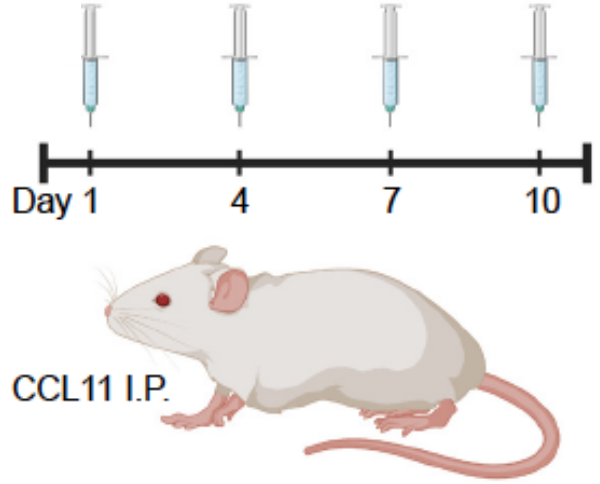


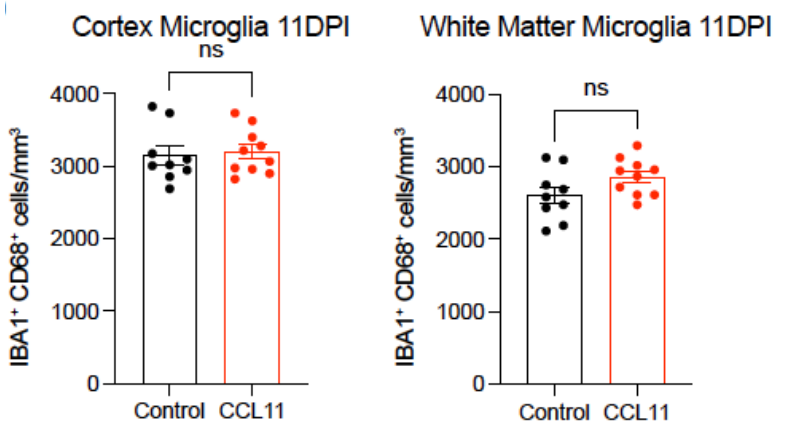


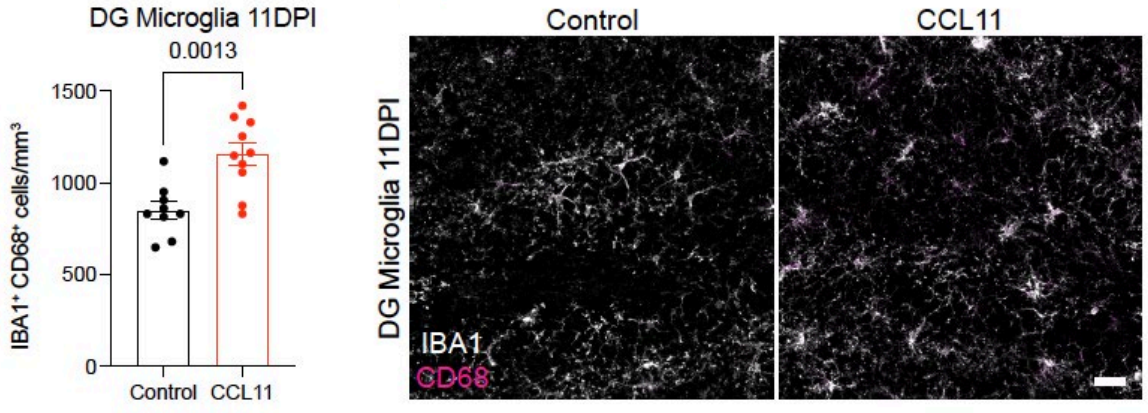
With Akiko Iwasaki and David Putrino

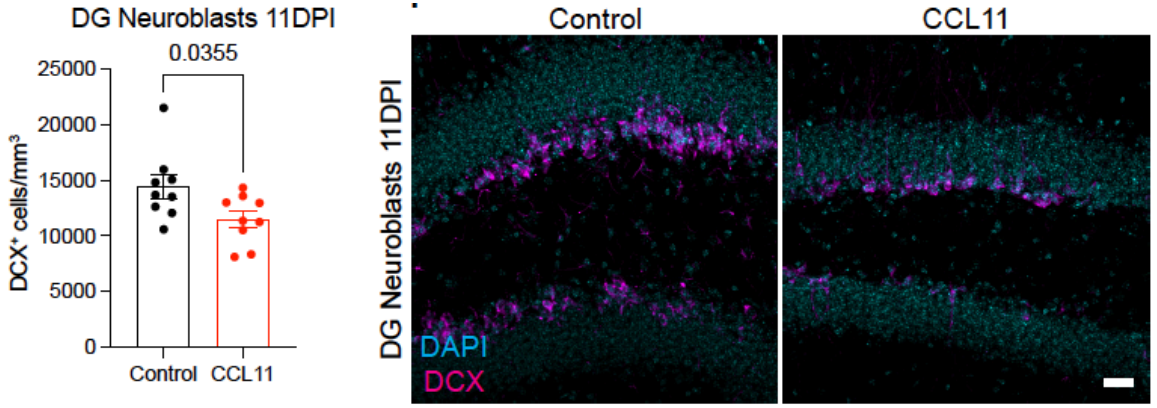
Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

CCL11 induces microglia reactivity *only* in the hippocampus and inhibits neurogenesis



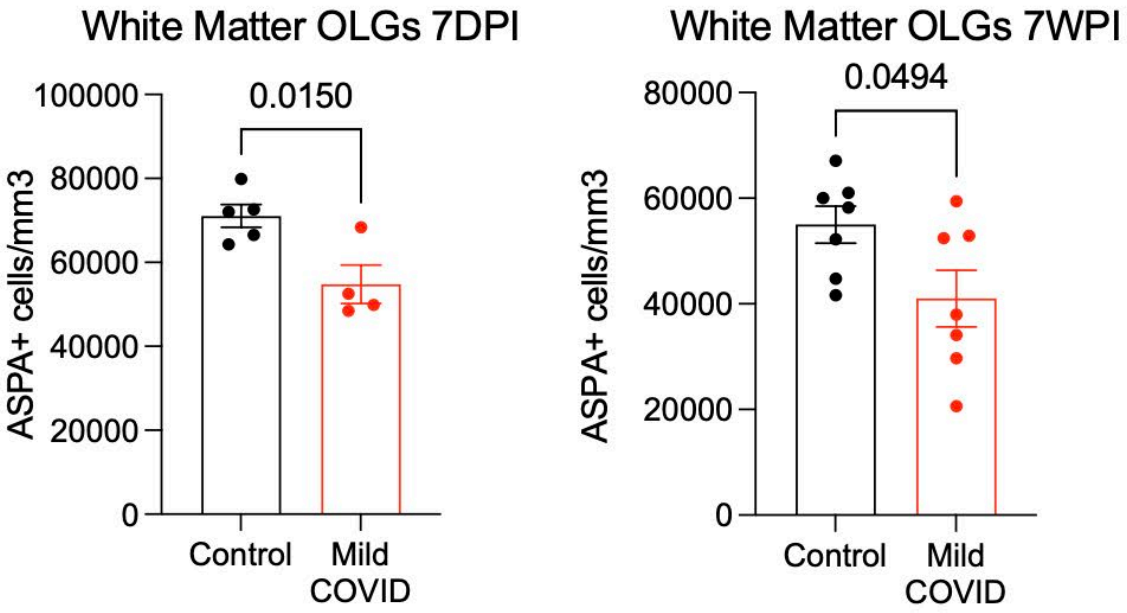


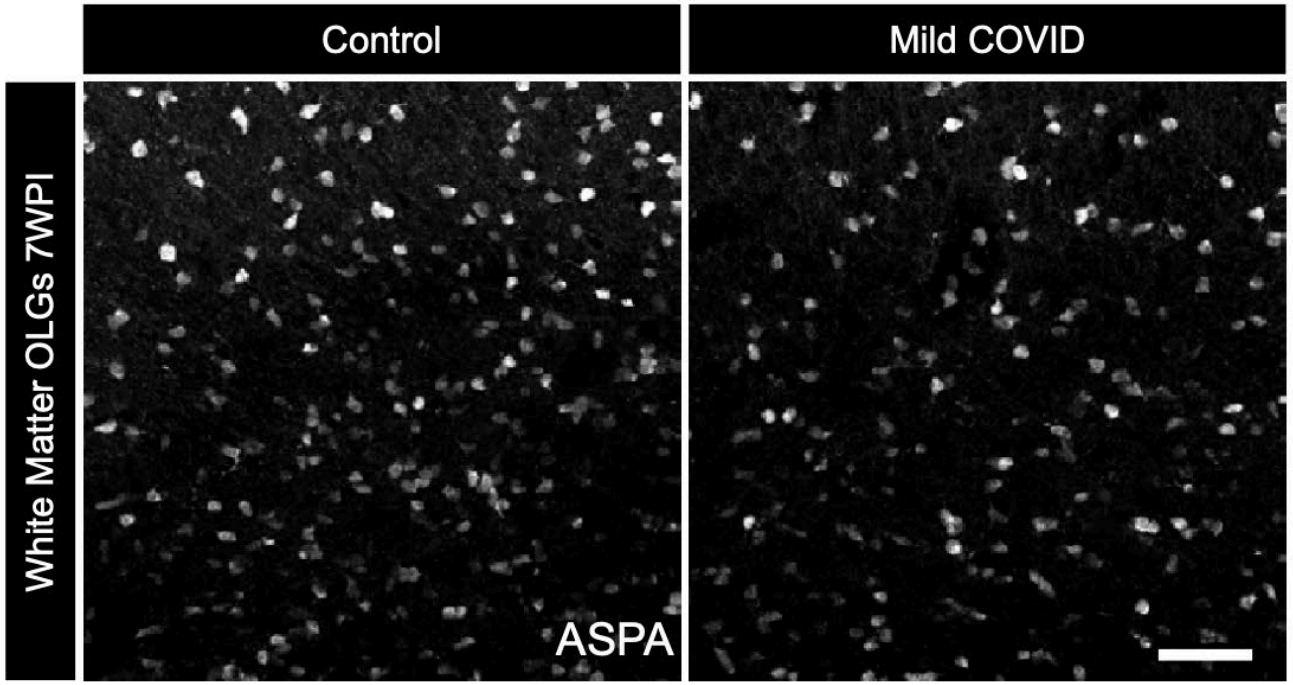




Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

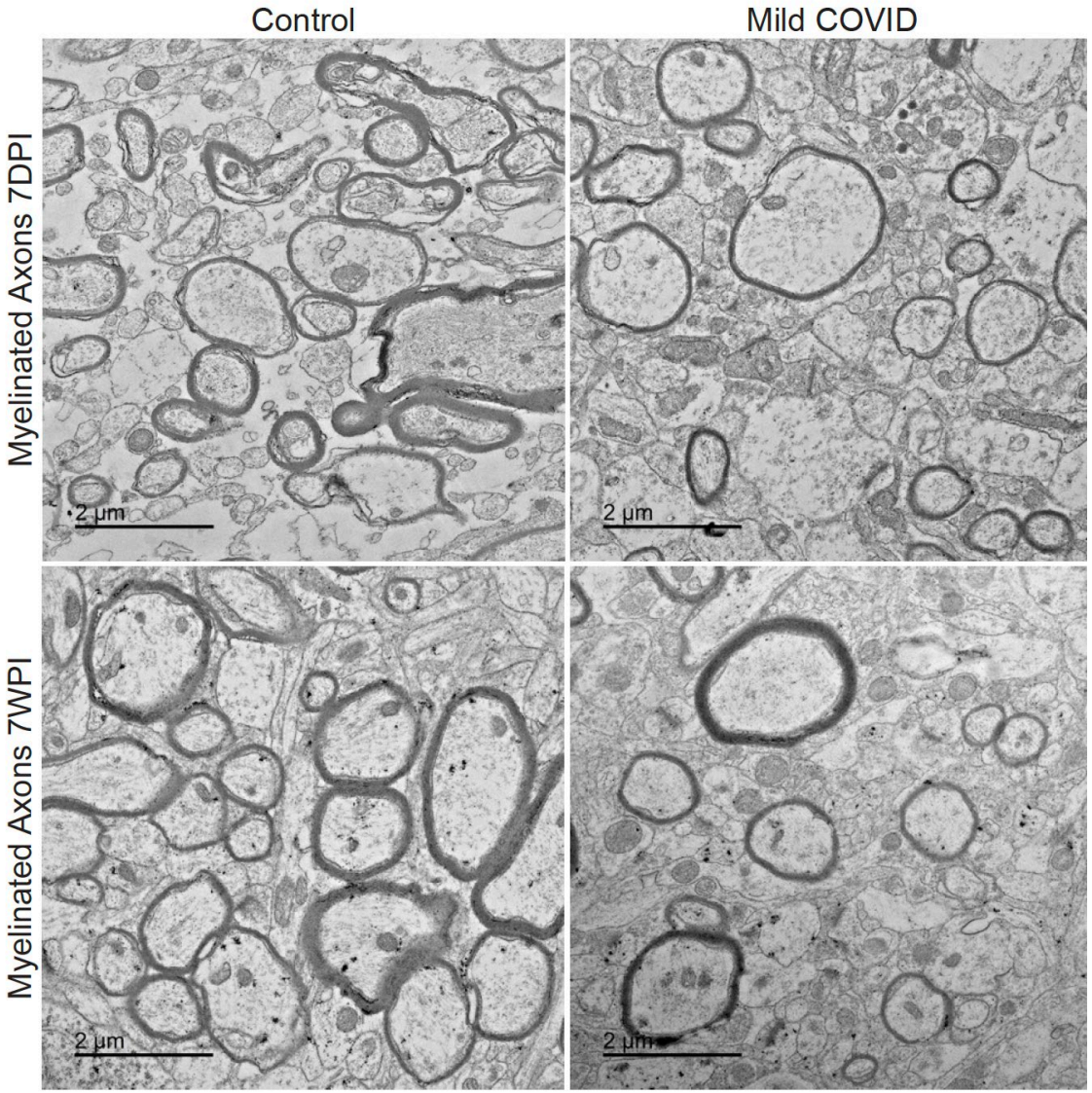
Oligodendrocyte loss after mild respiratory SARS-CoV-2 infection in mice

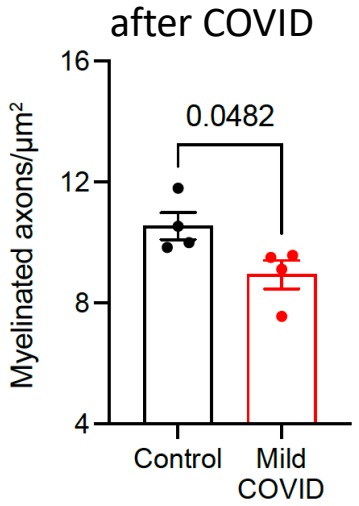


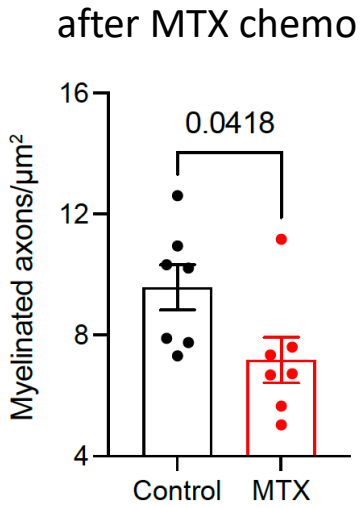


Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

Mild respiratory COVID can cause myelin dysregulation

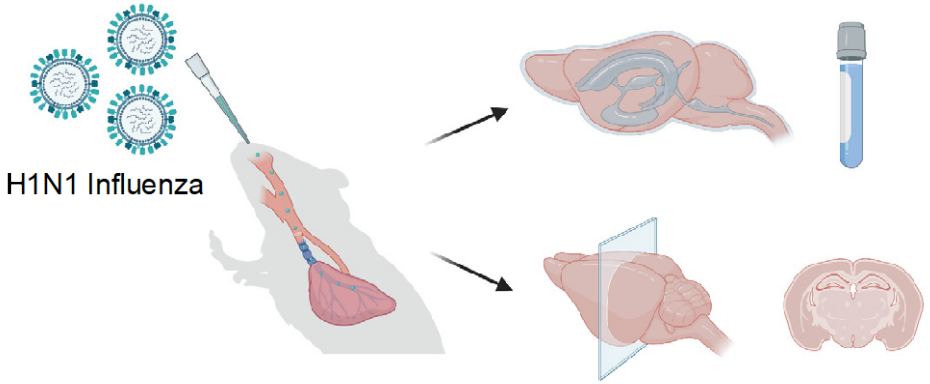


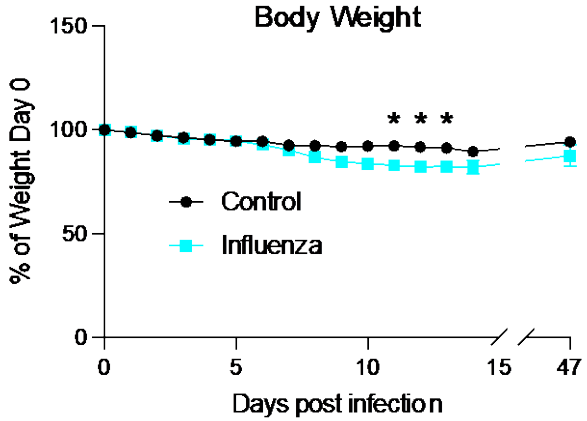




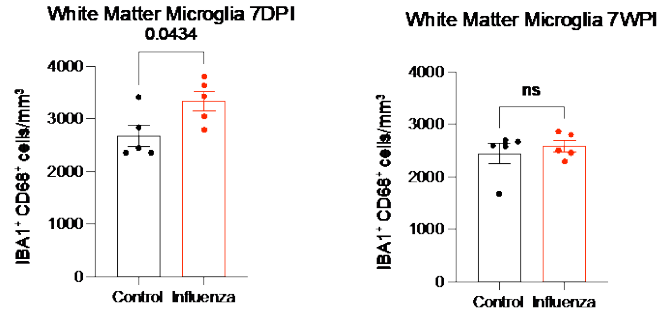
Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

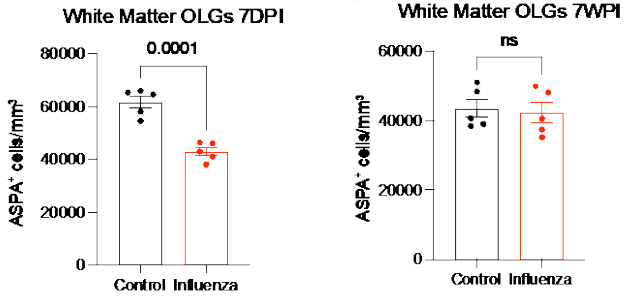
H1N1 influenza: transient subcortical white matter changes, persistent hippocampal pathology



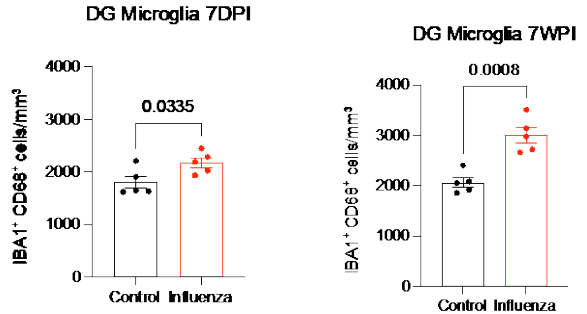


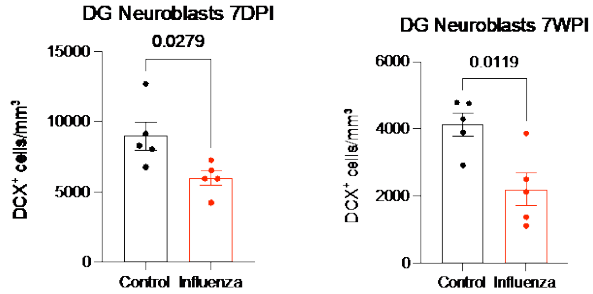
*Transient subcortical white matter microglial reactivity and oligodendrocyte loss





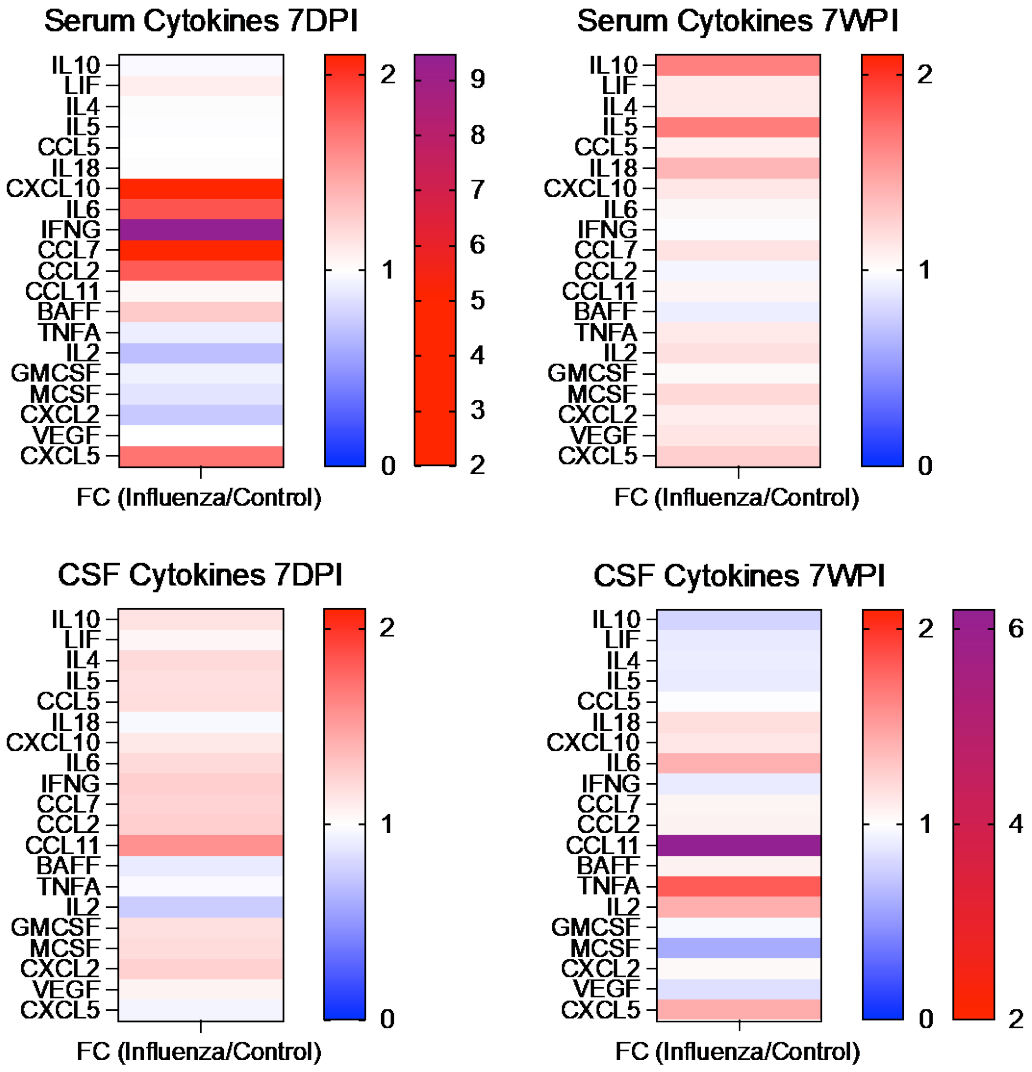
*Persistent hippocampal white matter microglial reactivity and neurogenesis loss

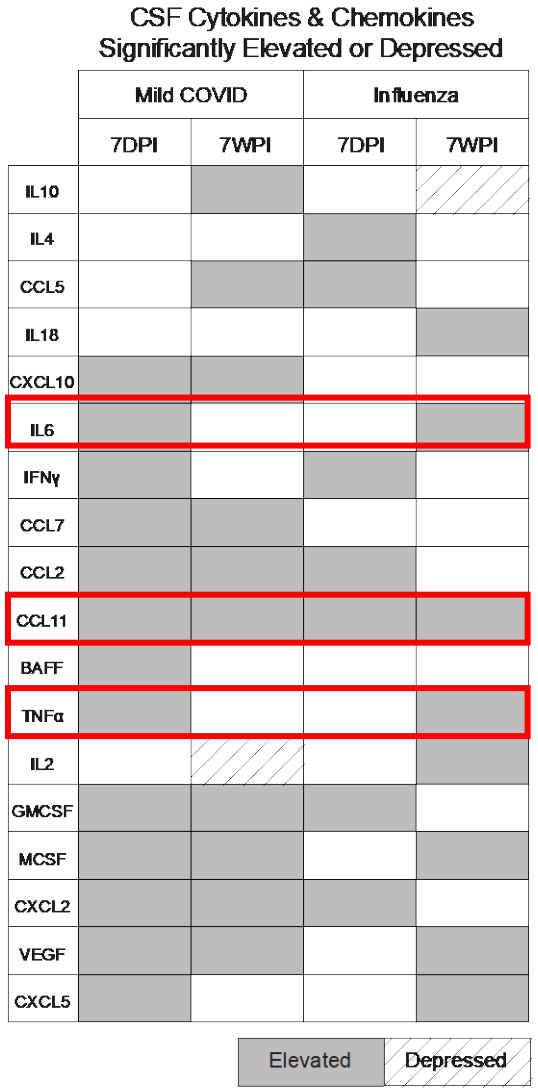




Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

H1N1 influenza: shared and distinct CSF cytokine/chemokine changes



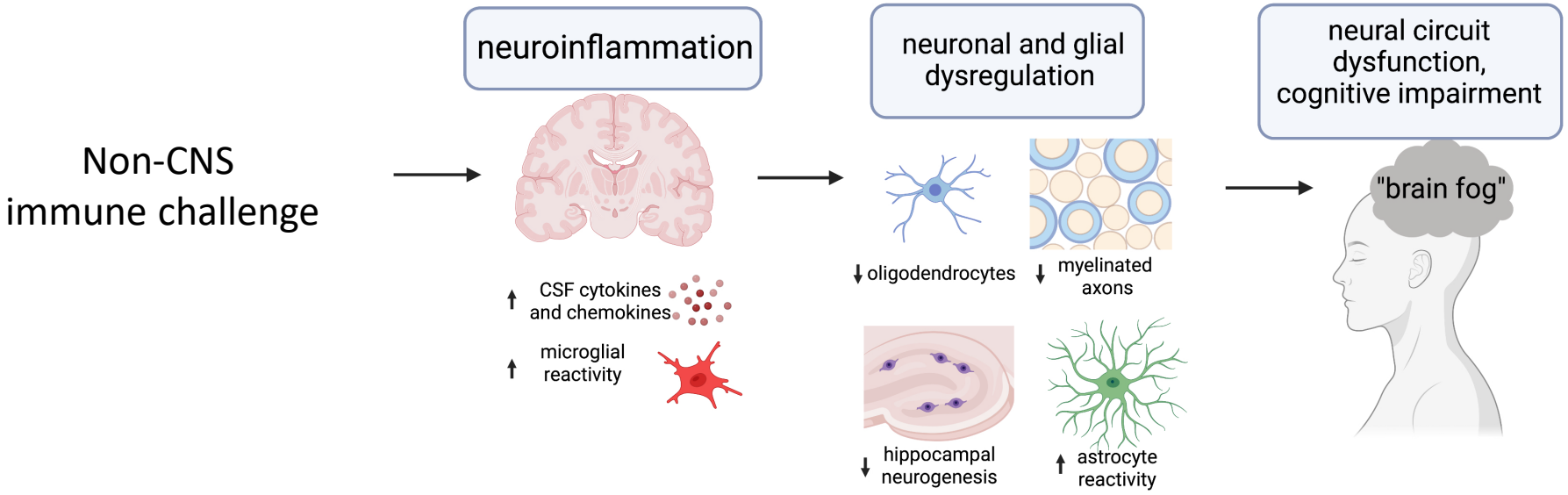


Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

Emerging principle of “brain fog” syndromes

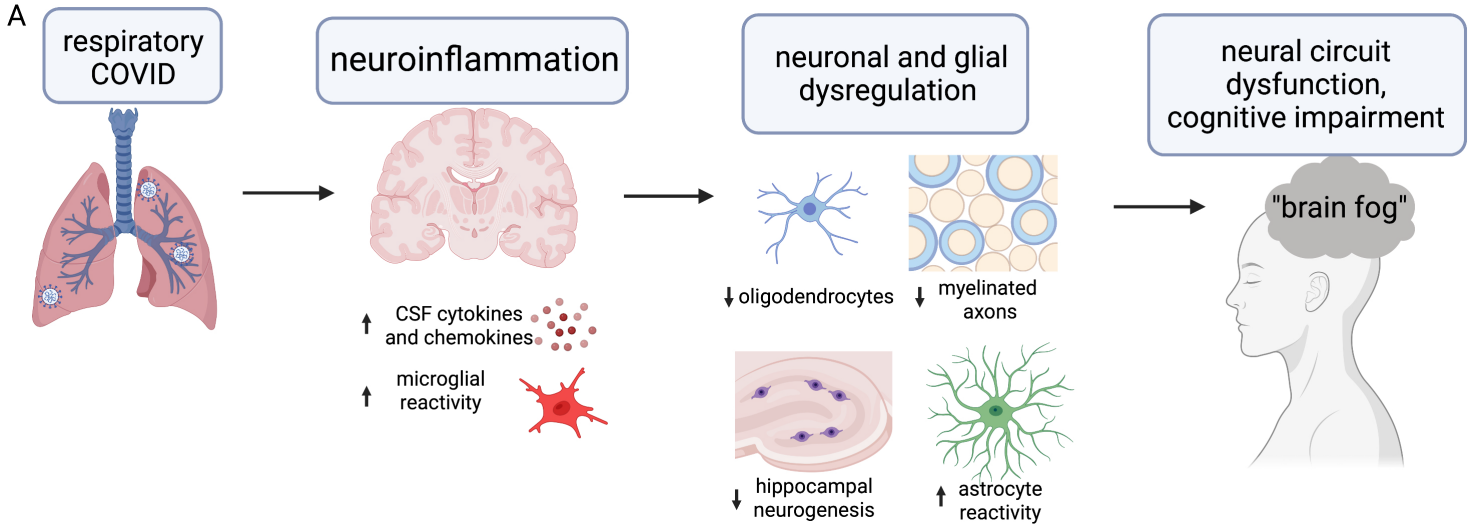
Neuroinflammation, especially reactive microglia in particular states, can cause multi-lineage neural cell dysregulation that contributes to cognitive impairment following:

- Cancer chemotherapy
- CAR T-cell immunotherapy
- COVID



Possible mechanisms contributing to cognitive impairment in Long COVID

likely the most common mechanism

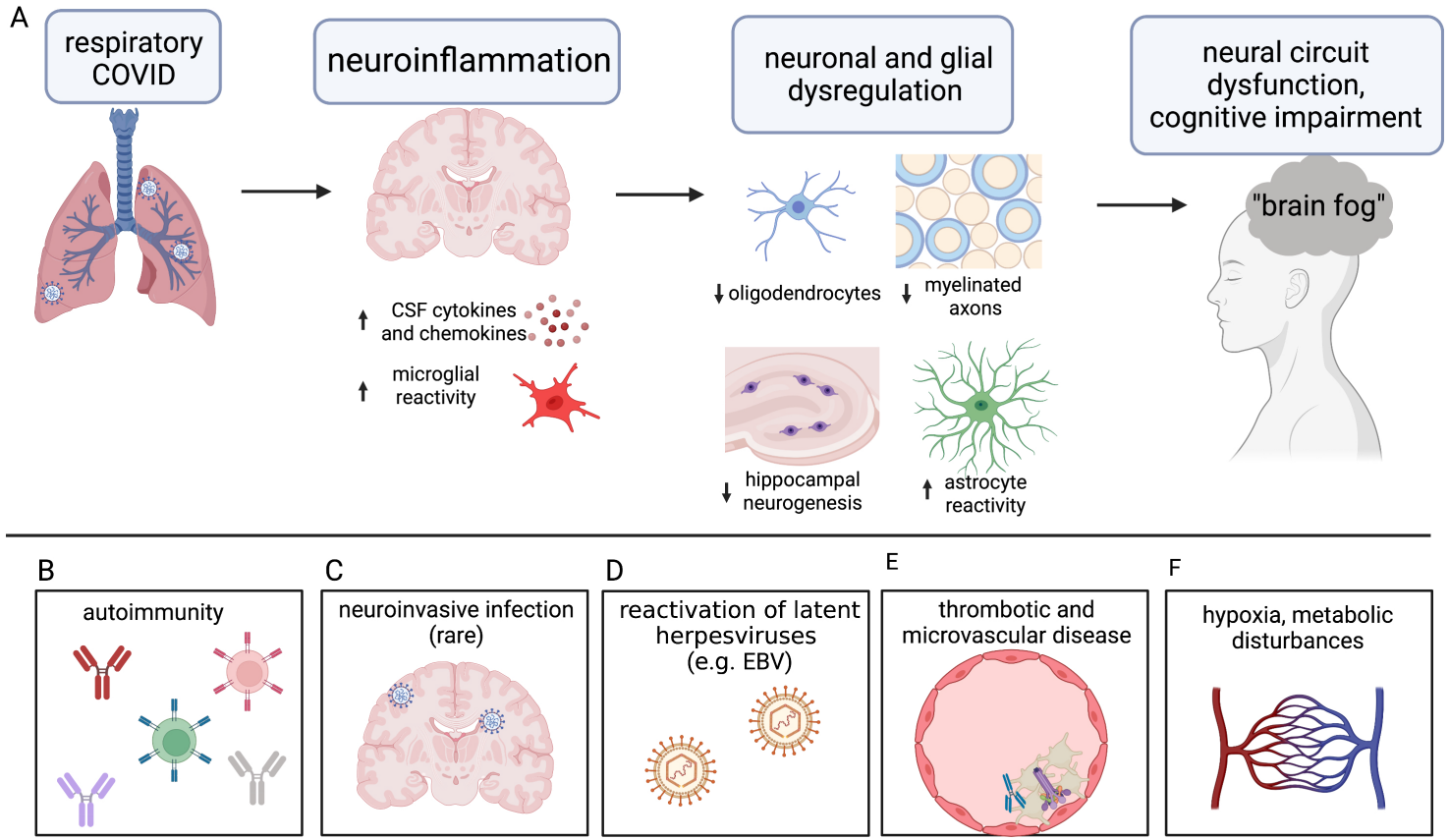


Monje and Iwasaki, 2022 *Neuron*

Possible mechanisms contributing to cognitive impairment in Long COVID

likely the most common mechanism

additional mechanisms that can also occur



Monje and Iwasaki, 2022 *Neuron*

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Collaborators

Akiko Iwasaki
Peiwen Lu
Eric Song
David Putrino
Avi Nath
Myoung Lee
Rebecca Folkerth
Marco Hefti
Daniel Perl
Shane Liddelow
Michael O'Dea
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Angus Martin Shaw Toland
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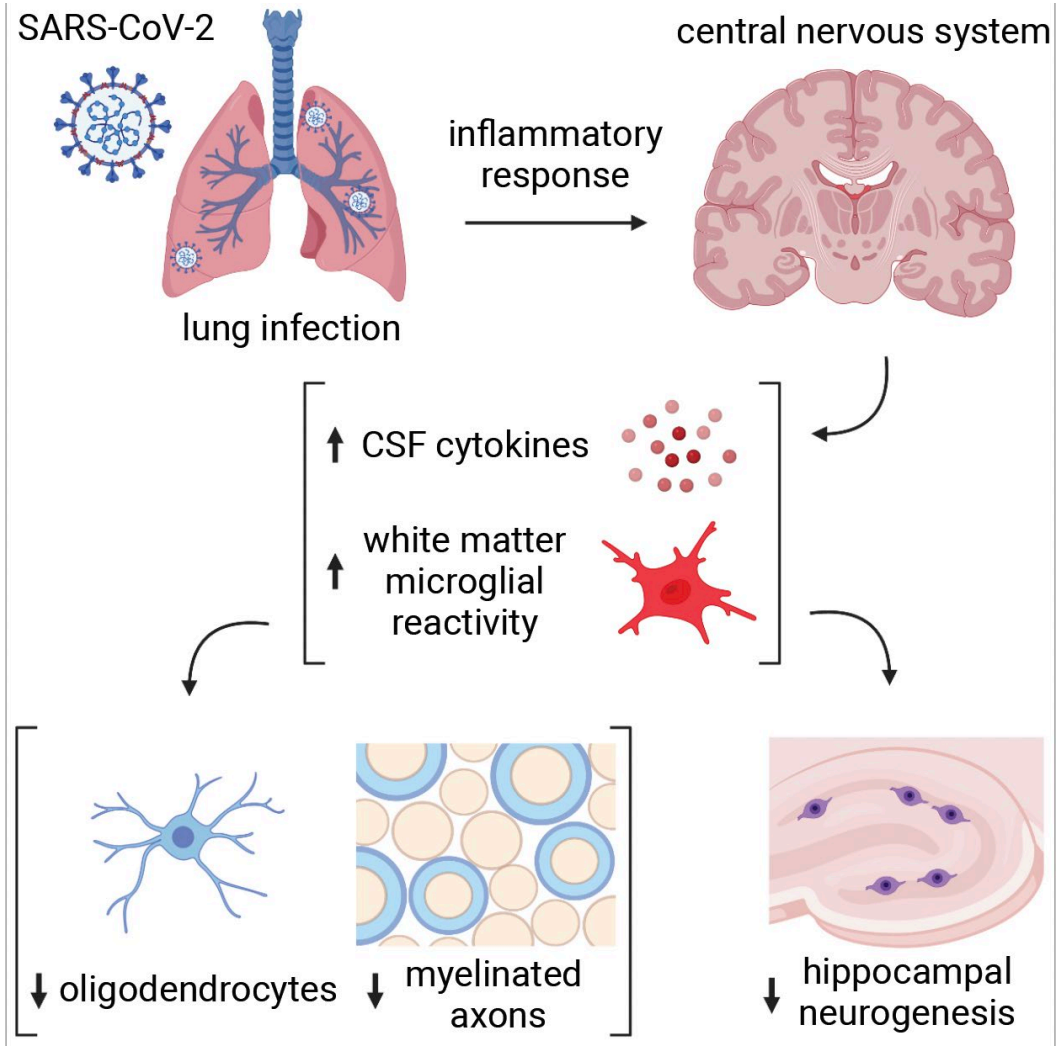
Conclusions

- Systemic immune challenges can cause neuroinflammatory changes, consequent glial dysregulation and neural circuit dysfunction that impairs cognitive function

- H1N1 influenza causes similar but less persistent neuropathology, as well as both overlapping and distinct cytokine changes

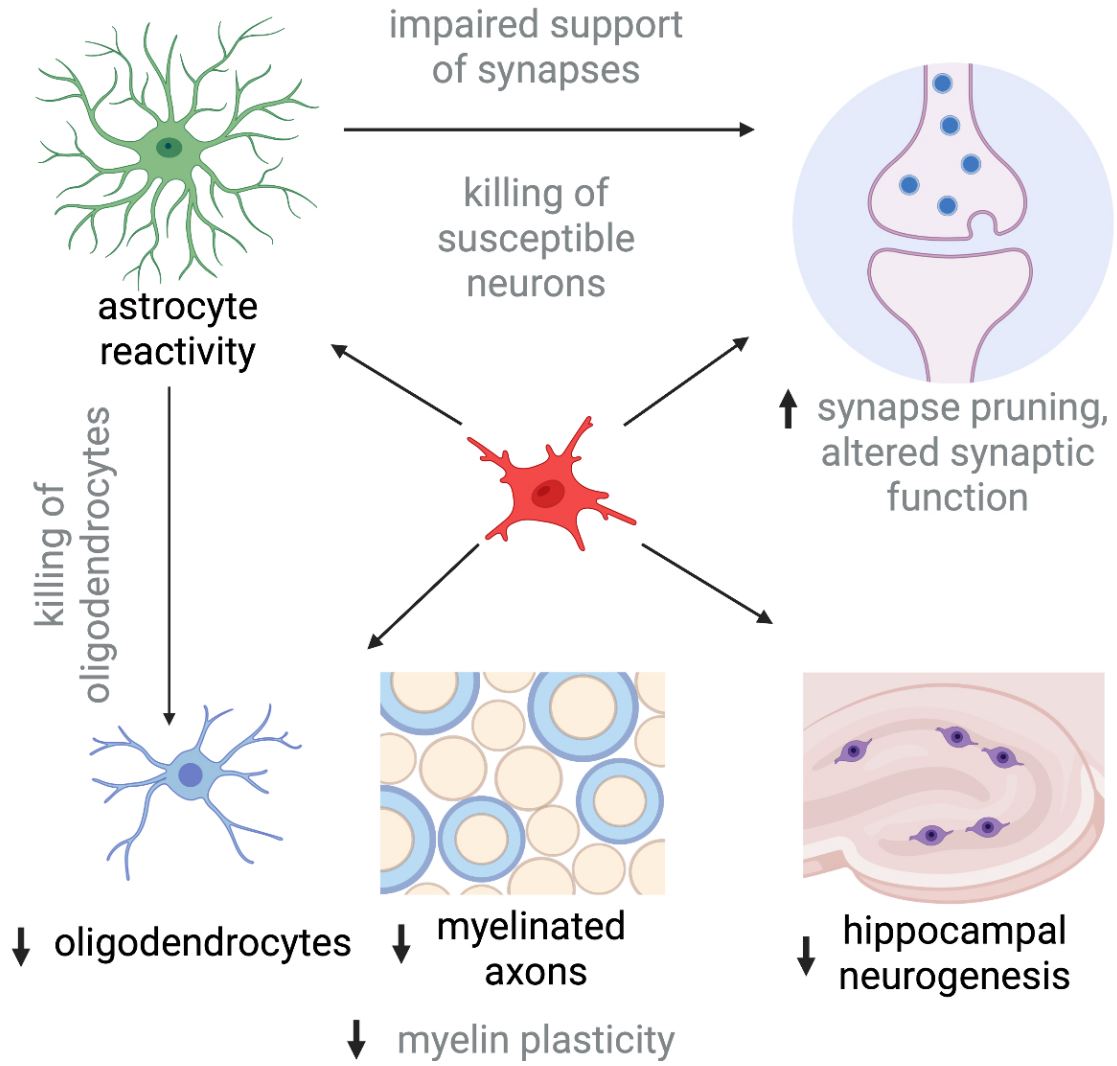
- CCL11 causes region/circuit-specific microglial reactivity
  - Various immune challenges, eliciting different cytokine profiles, may increase risk for overlapping yet distinct constellations of neurological and psychiatric symptoms

Mild respiratory COVID induces multi-lineage cellular dysregulation and myelin loss in the brain



Fernandez-Casteneda, Lu, Geraghty, Song et al. (2022) *Cell*

Demonstrated and hypothesized consequences of glial dysregulation after COVID

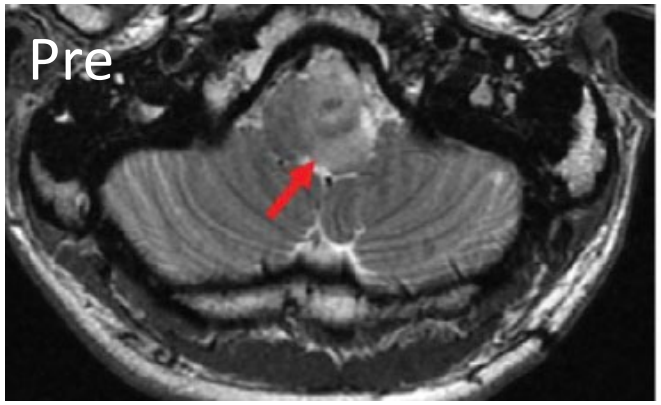


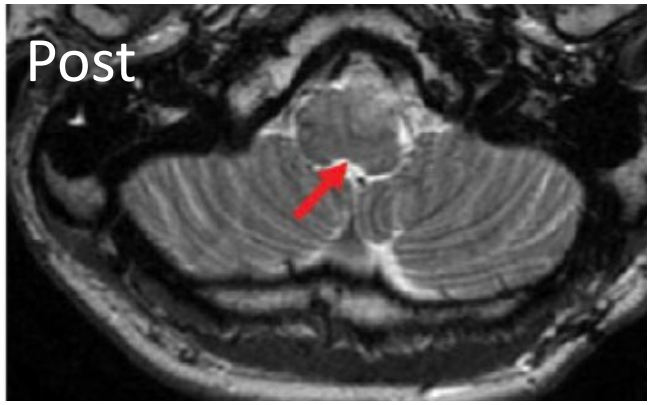
Astrocyte reactivity in severe COVID demonstrated by Yang et al., 2021

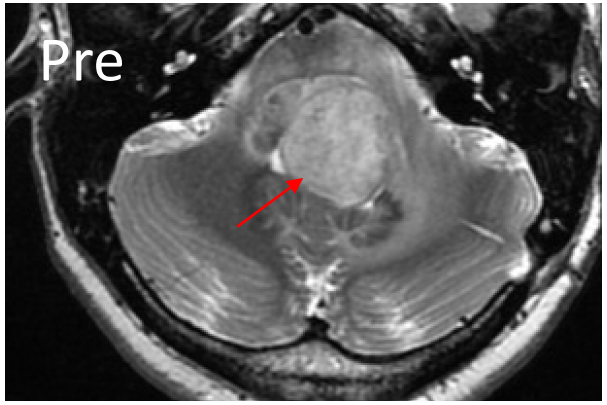
Monje and Iwasaki, 2022 *Neuron*

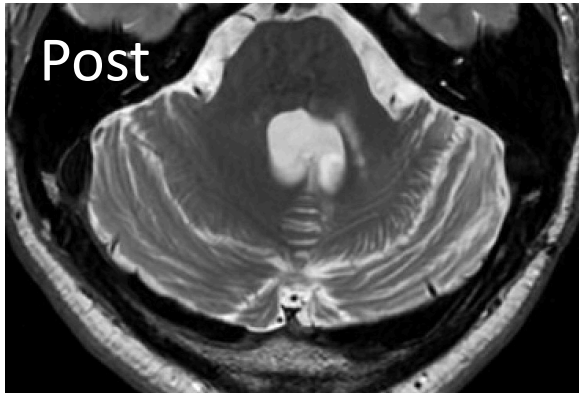
NCT04196413: Phase 1 Clinical Trial of Autologous GD2 Chimeric Antigen Receptor (CAR) T cells for Diffuse Intrinsic Pontine Gliomas (DIPG) and Spinal Diffuse Midline Glioma (DMG)

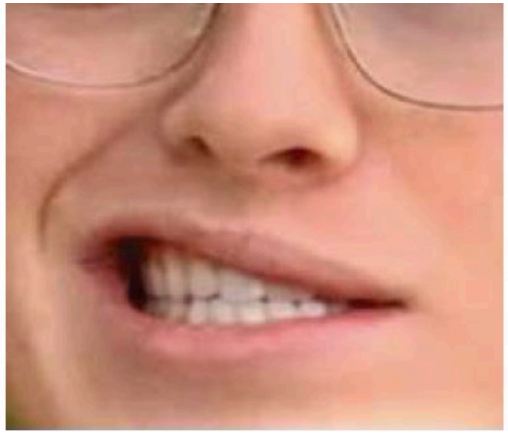
PI: Michelle Monje; IND Holder: Crystal Mackall

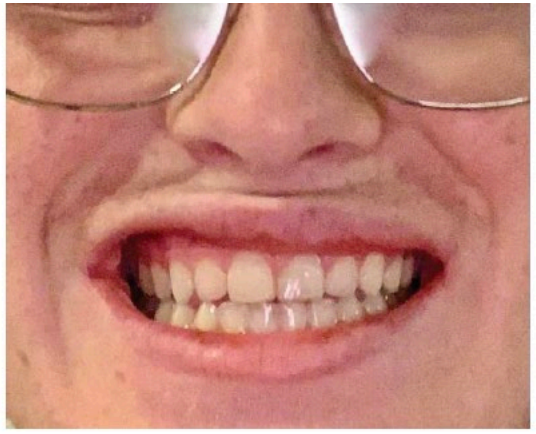












Complete response, durable >1 year

unpublished

(For this historically fatal brain cancer,
I am grateful to have the chance to
worry about long-term cognitive outcomes)

Majzner, Ramakrishna…Mackall & Monje *Nature* (2022)