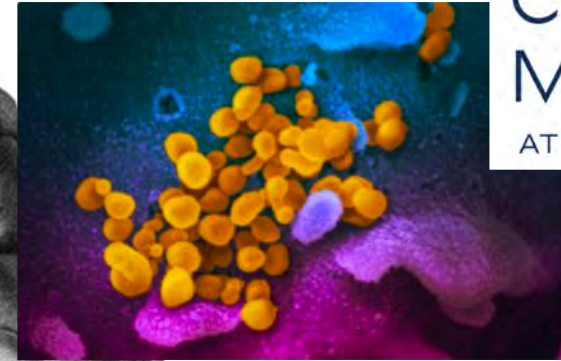
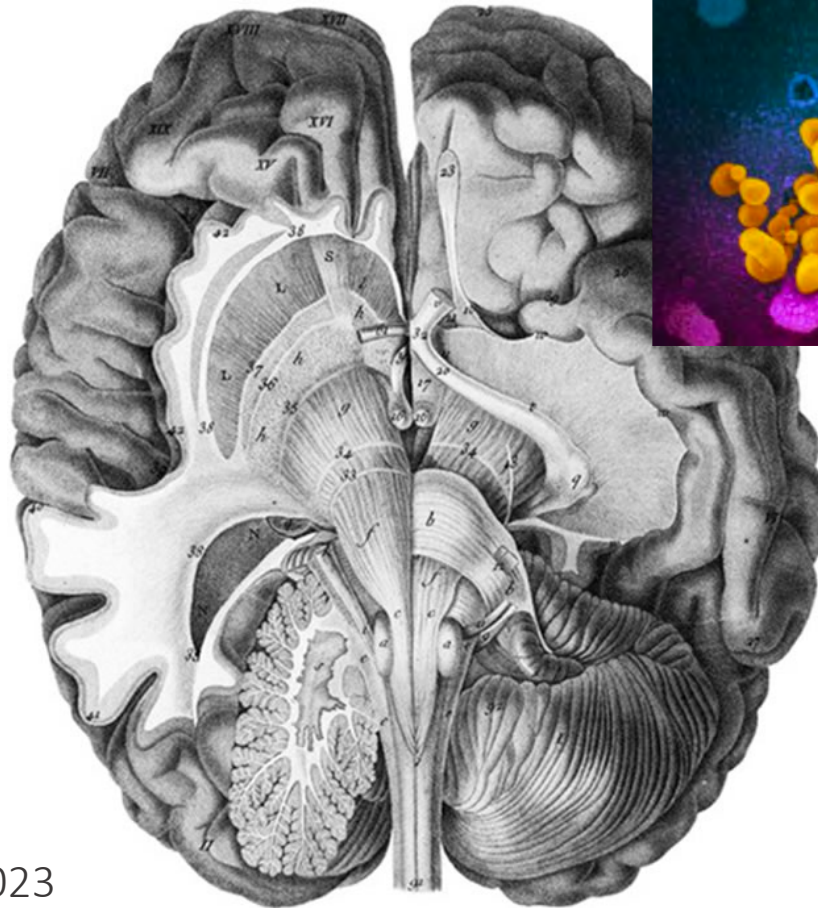


Untangling the Mystery of Nervous System Sequelae of COVID-19: What We Know and What We Need to Learn



THE
COVID
Mind Study
AT YALE



Image credit: NIAID-Rocky Mountain Laboratories

Inflammatory Brain Disorders Conference 2023
May 18, 2023

Serena Spudich, MD
Department of Neurology
Center for Brain & Mind Health
Yale School of Medicine

Neuropsychiatric issues after recovery from acute COVID-19

HEALTH

The New York Times

'I Feel Like I Have Dementia': Brain Fog Plagues Covid Survivors

The condition is affecting thousands of patients, impeding their ability to work and function in daily life.

By Pam Belluck

Science

From 'brain fog' to heart damage, COVID-19's lingering problems alarm scientists

By Jennifer Couzin-Frankel | Jul. 31, 2020, 1:30 PM

Neurologic and Psychiatric Effects of SARS-CoV-2 Meeting

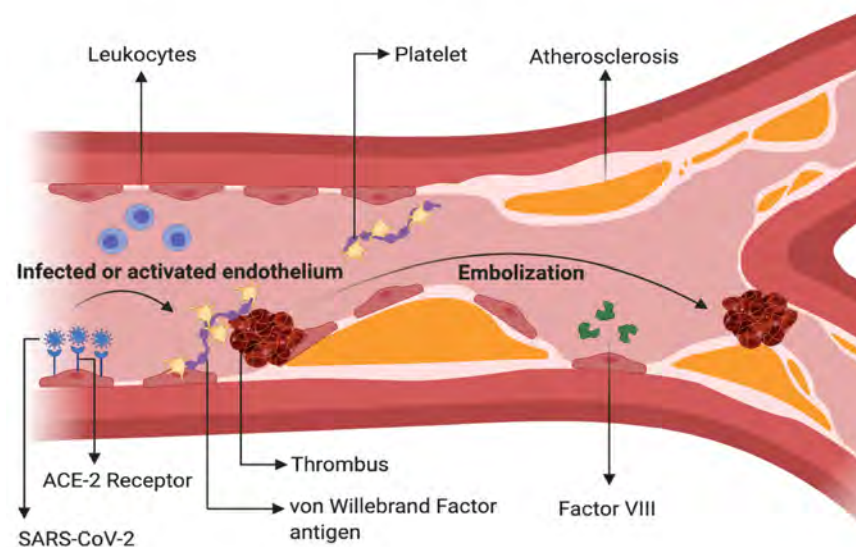
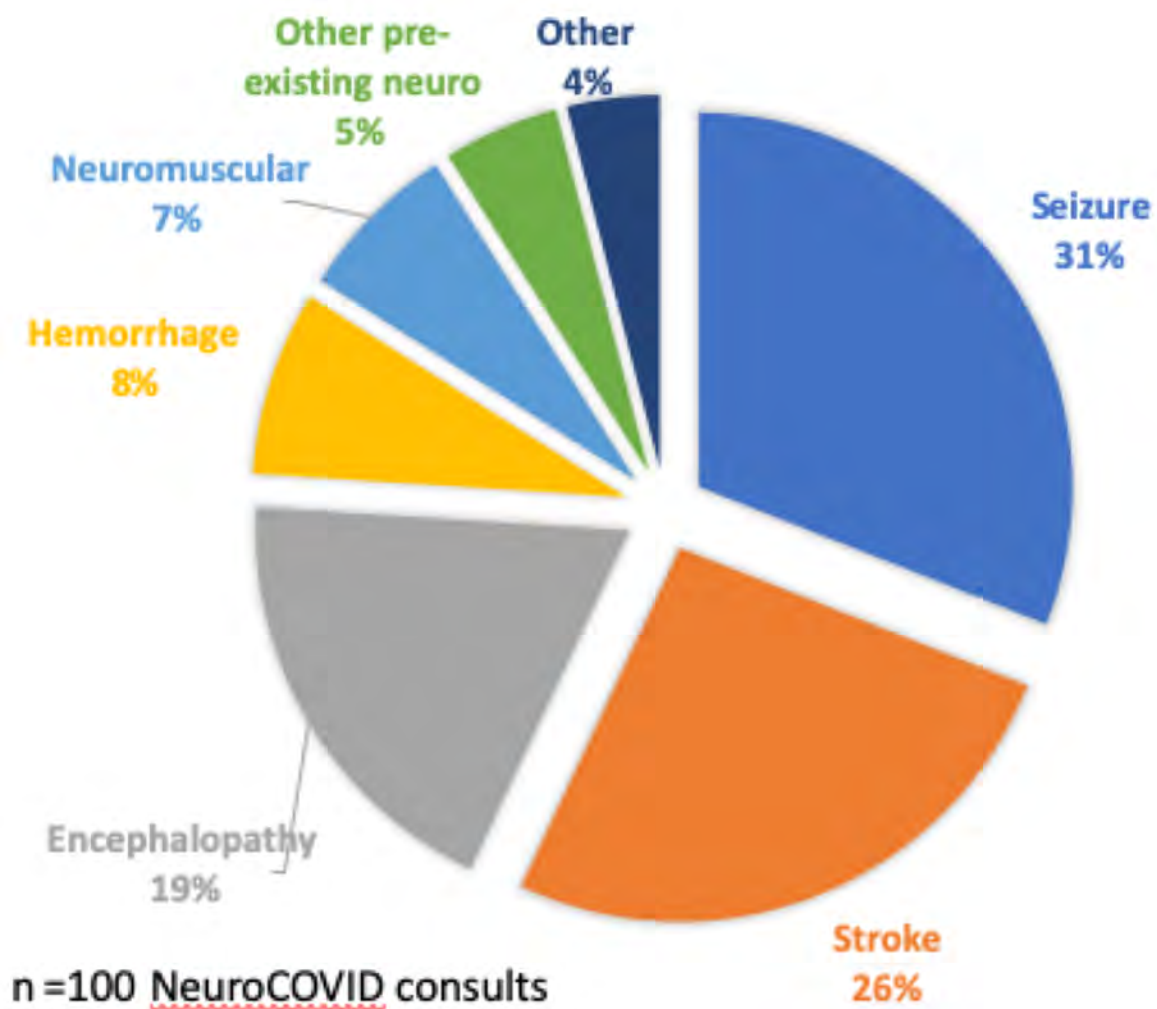


National Institutes
of Health

July 14-15, 2021

Clinical central nervous system complications in acute COVID-19

- Yale Neuro COVID inpatient consult service → wide spectrum of neurological & psychiatric manifestations in patients with acute COVID-19



Encephalopathy, neuromuscular, other –
? perinfectious immune mediated?

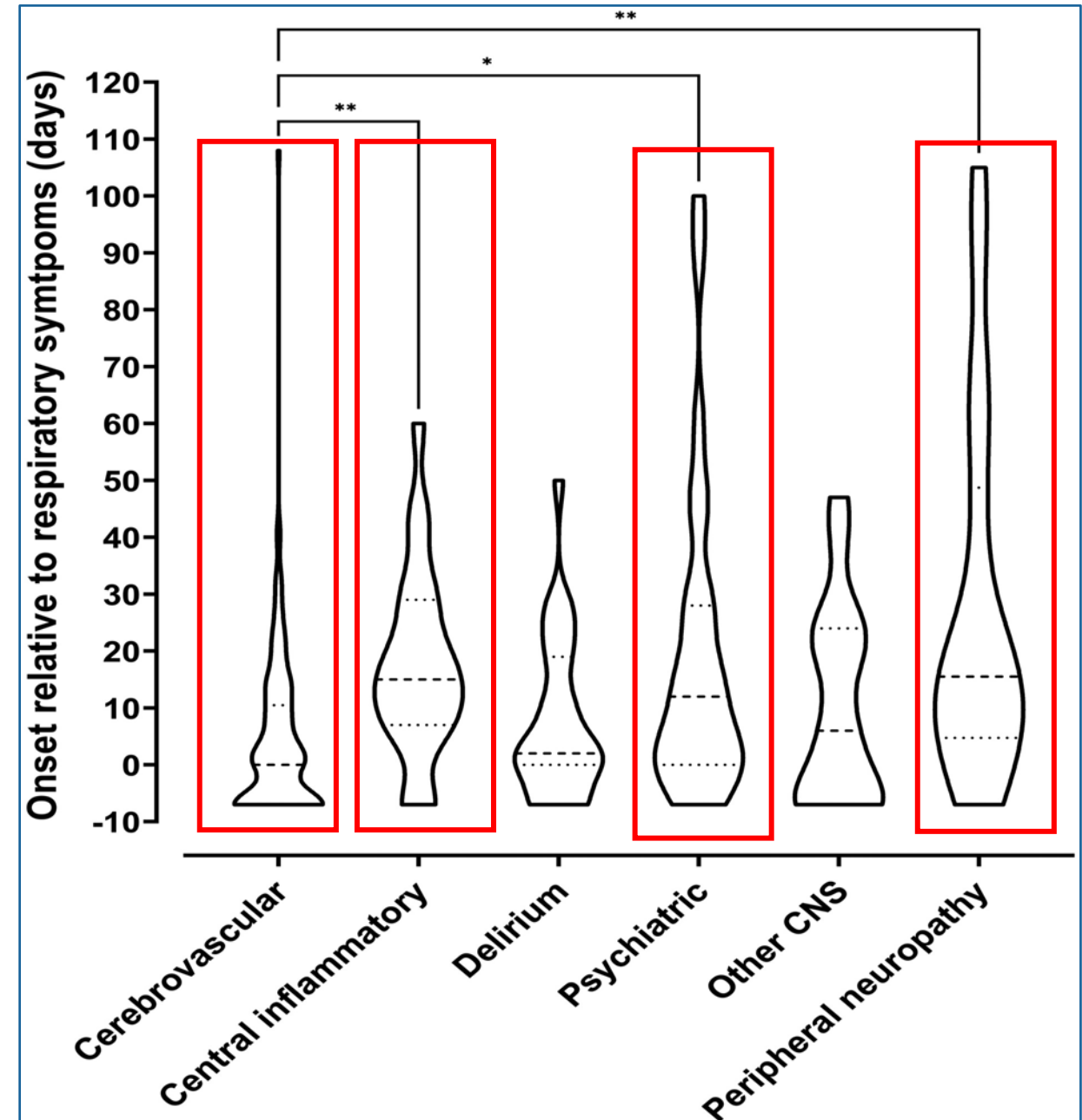
McAlpine et al, *Lancet Neurology*, Oct 2020
Zubair et al, *JAMA Neurology*, May 2020
Farhadian et al, *BMC Neurology*, June 2020
Sheth et al, *JAMA Neurology*, Sept 2020
McAlpine et al, *Stroke*, June 2021

Neurologic complications in acute COVID-19 – Timing of onset suggests diverse pathophysiologies

267 patients hospitalized in UK-wide surveillance study

- In 29%, neuro/psych symptoms predated the onset of COVID-19 symptoms
- In 47%, neuro/psych symptoms occurred after respiratory condition improved
- Longer time to onset was observed in the central inflammatory, psychiatric and peripheral neuropathy diagnoses

Russell Ross et al, *Brain Communications*, Oct 2020

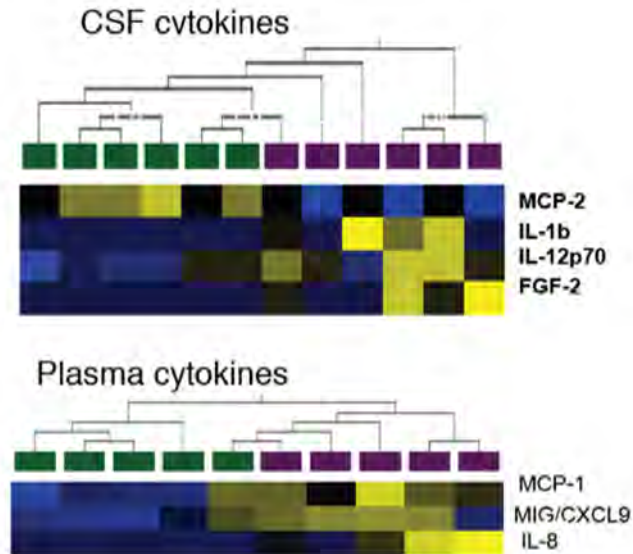


Immune mediated neuropathogenesis in acute COVID-19

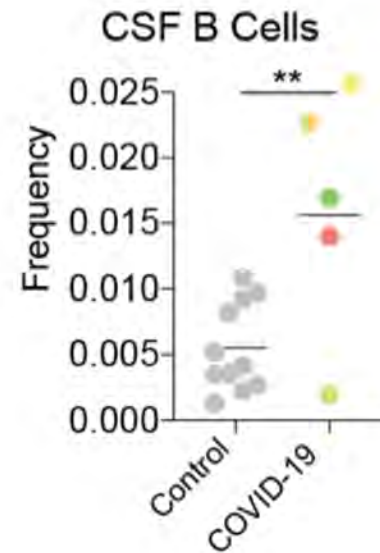
- No detection of SARs-CoV-2 by PCR, metagenomics, culture in CSF samples
- Altered immune responses in CSF compared to healthy controls and compared to blood



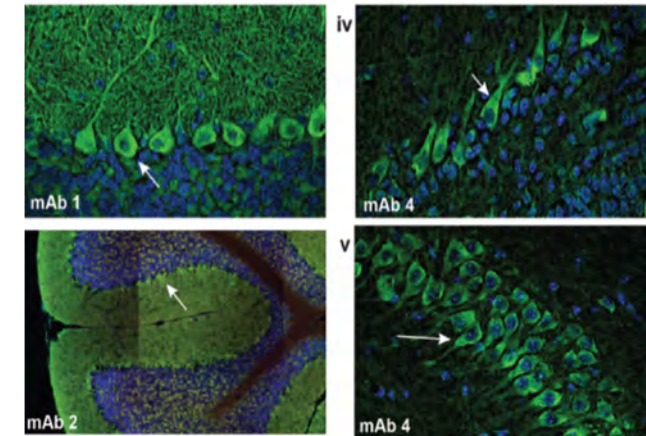
Shelli Farhadian, MD, PhD



Increased CSF cytokines in CSF of COVID-19 (purple) vs controls (green).



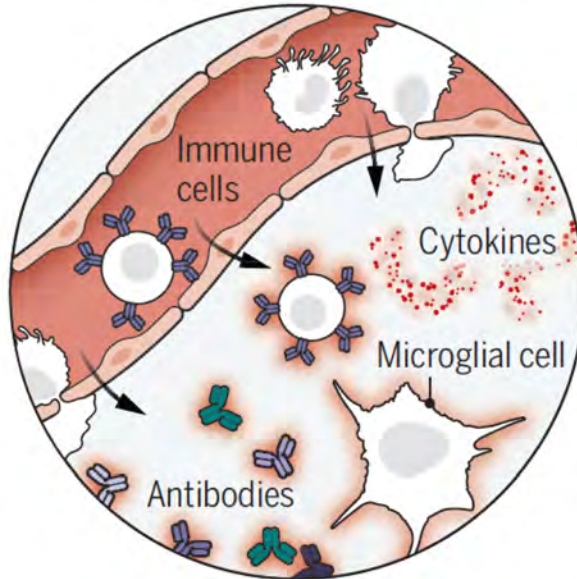
Increased frequency of B cells in CSF in COVID-19.



Anti-SARS-CoV-2 antibodies are detected in CSF and some are autoreactive to brain tissue.

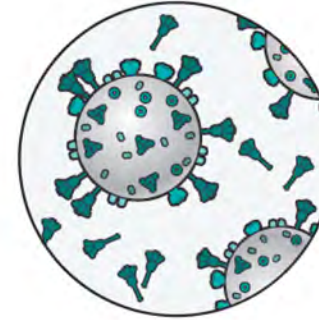
Neuropathogenic effects of acute COVID-19

Generalized **neuroinflammation** with trafficking of immune cells, cytokines, and antibodies into the brain and activation of microglia

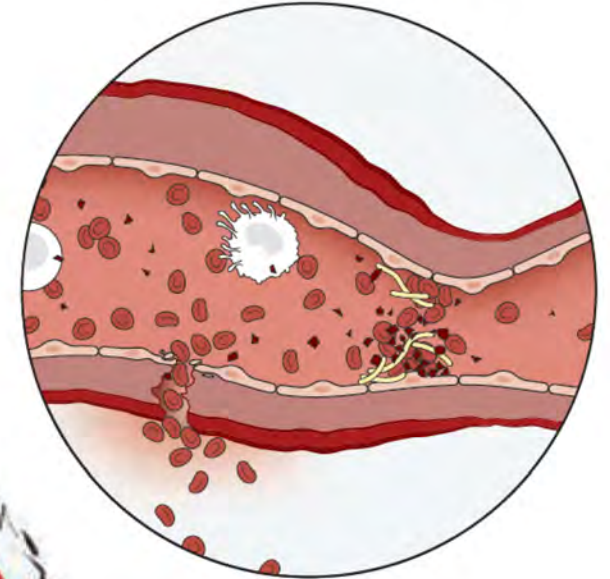


Neuroinflammation is exacerbated by **antibody production**, including antibodies to SARS-CoV-2 and autoantibodies.

Limited presence of SARS-CoV-2 spike protein or viral particles in neurons and other brain cells



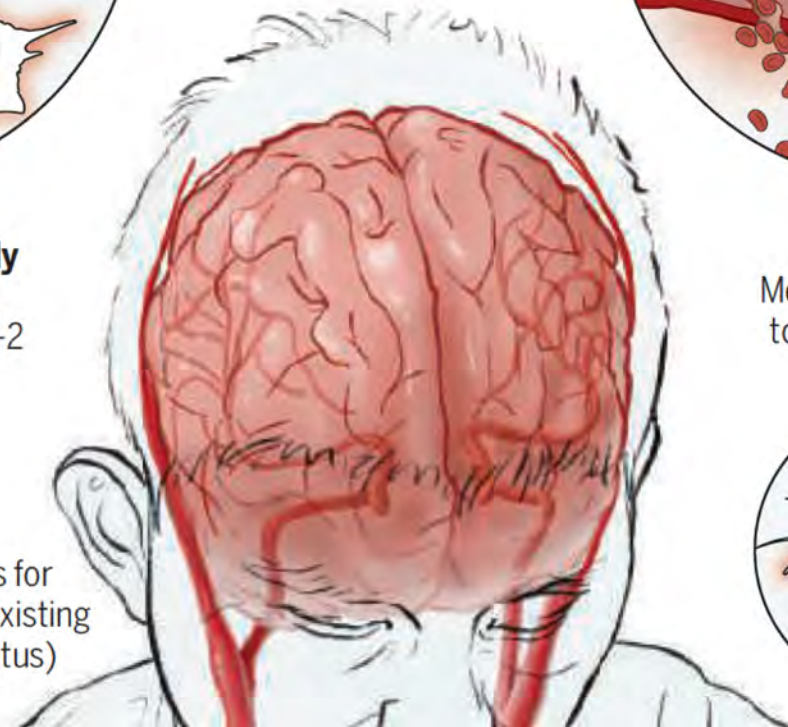
Blood vessels may be damaged by endothelial cell activation and coagulopathy, leading to vascular dysfunction, including microbleeds or stroke.



Mechanisms leading to **neuronal injury** are unknown.



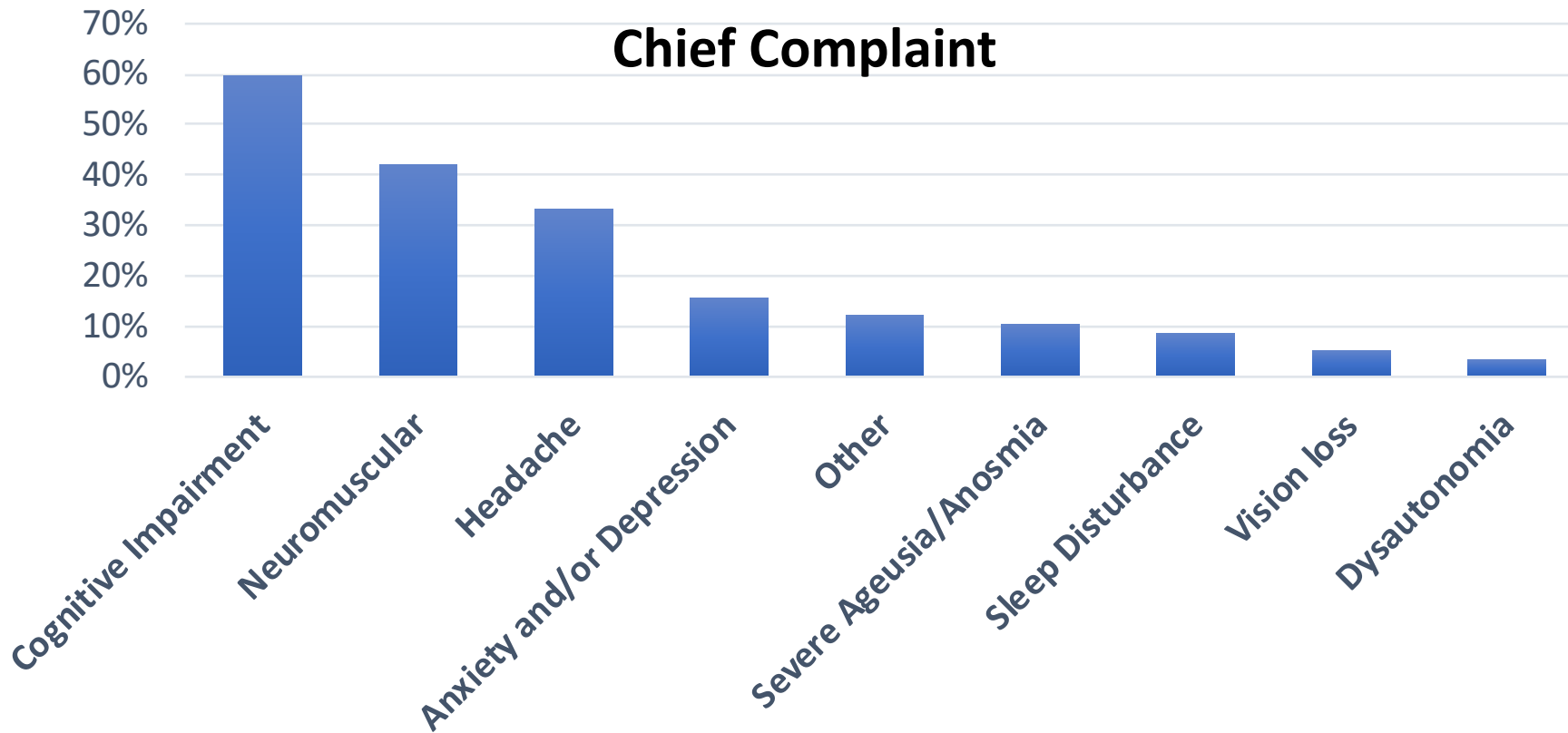
Undetermined host factors for **susceptibility** (genetic, preexisting comorbidities, immune status)



Post-COVID-19 Neurology Clinic experience

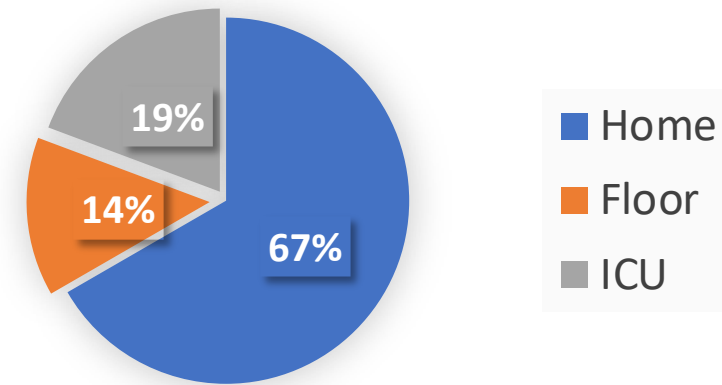


- ~50% of post-COVID referrals to multidisciplinary COVID-19 Recovery Clinic are for primarily neurologic and neuropsychiatric symptoms



~600 patients seen to date
Median Age: 49 (IQR 36-60)
Female (74%) Male (26%)
33% Black and/or LatinX

Highest Level of Care



*Other includes new onset intracranial hypertension, anti-MOG autoimmune encephalitis, vestibular neuritis, debilitating fatigue

Stories from Post-COVID-19 Neurology Clinic at Yale

- 40 yo physician requires notepad to remember all tasks and conversations, unable to follow a familiar recipe to bake bread.
- 62 yo woman with severe headache during initial COVID-19, 9 months later with continued daily headache interfering with job as a nurse.
- 36 yo woman with patchy sensory abnormalities (tingling and burning) on torso, neck, limbs persisting 8 months after COVID-19.
- 30 yo man with no past psychiatric history developed hypersomnolence, paranoia and delusions in first weeks after COVID-19, refractory to antipsychotic medications.

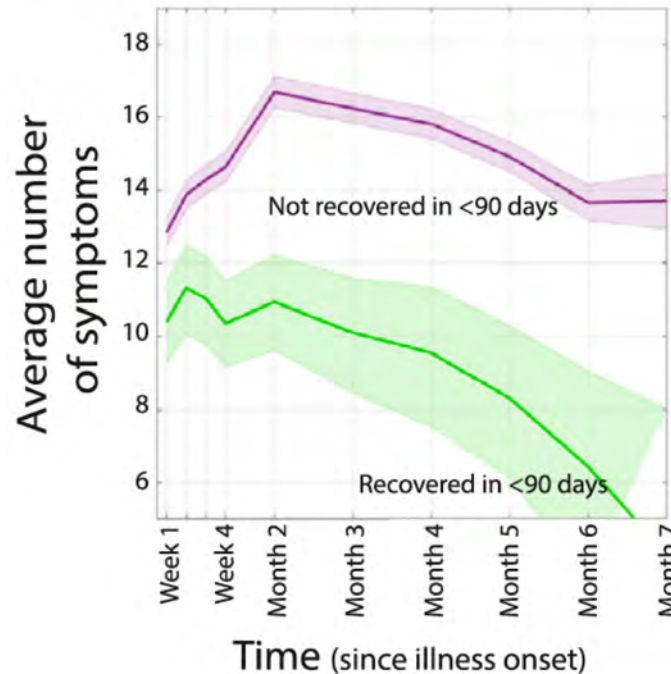
Neuropsychiatric issues after recovery from acute COVID-19



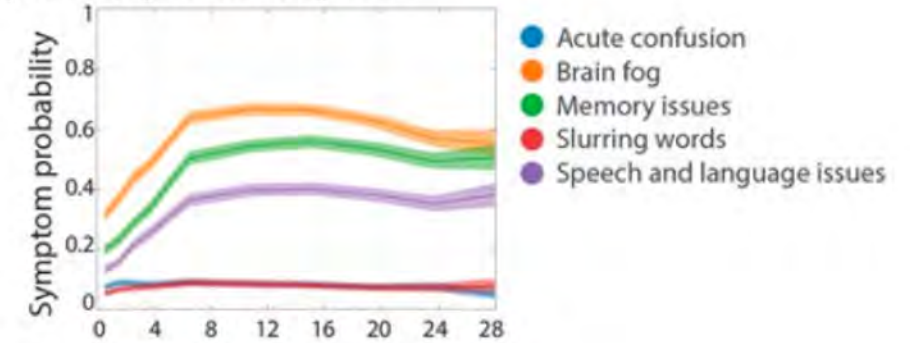
Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

3,762 respondents with confirmed or suspected COVID-19 from 56 countries completed survey online.

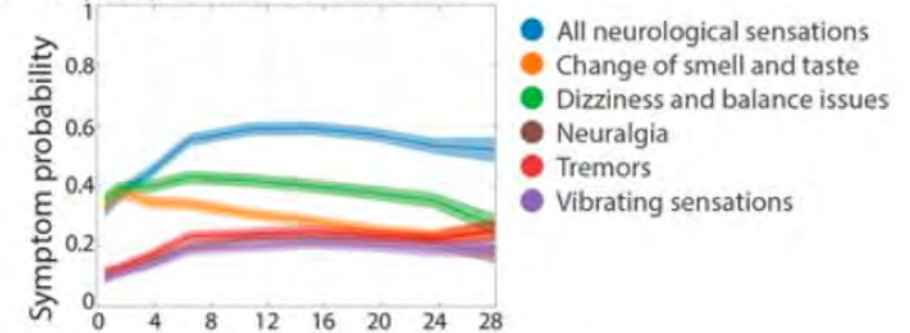
c. Average number of symptoms over time



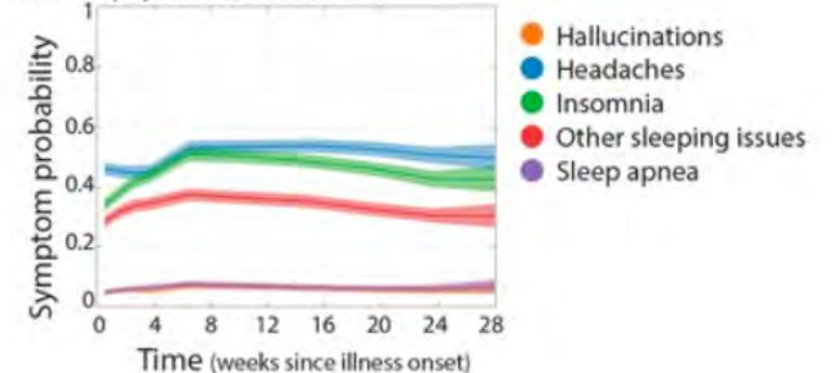
j. Neuropsychiatric - cognitive



k. Neuropsychiatric - sensorimotor



l. Neuropsychiatric - other

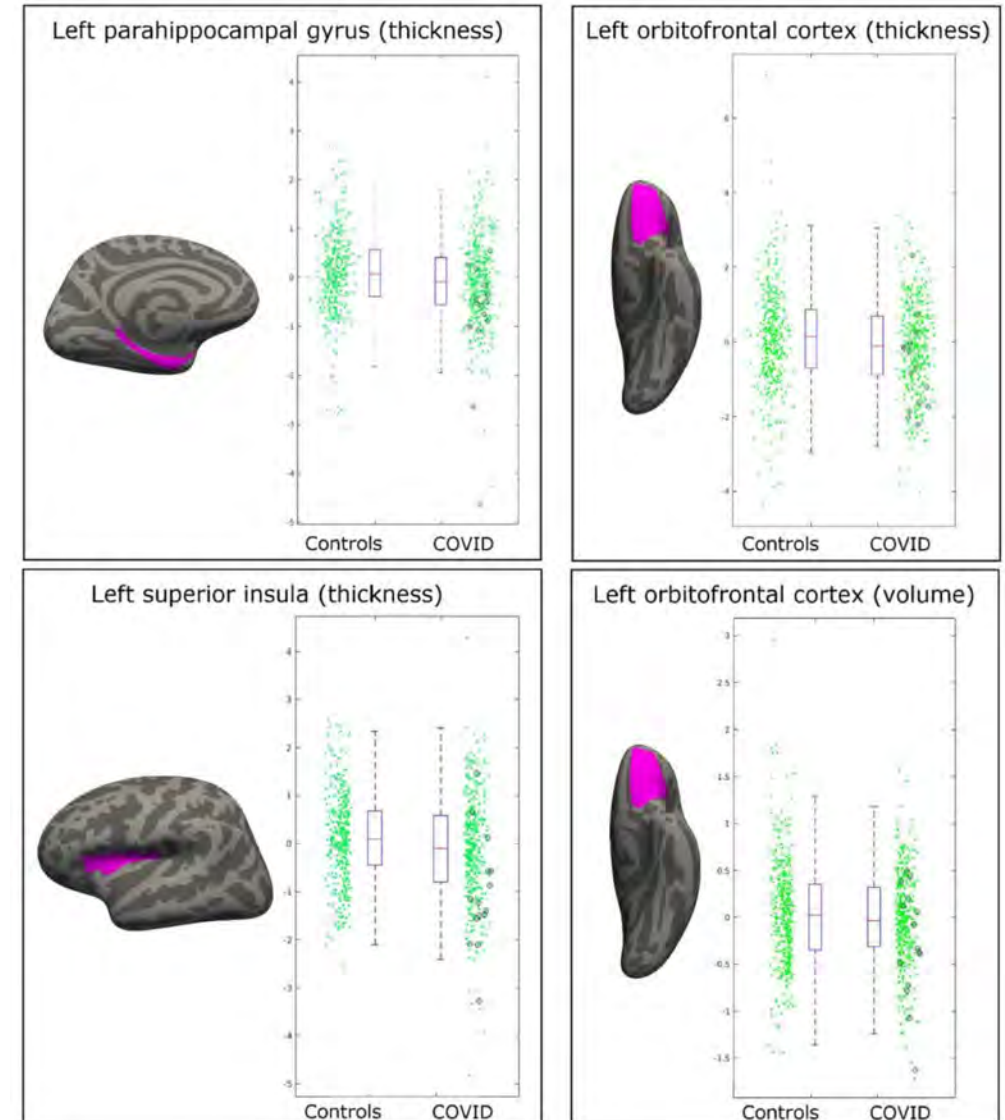


Regional cerebral functional & structural changes post-COVID-19

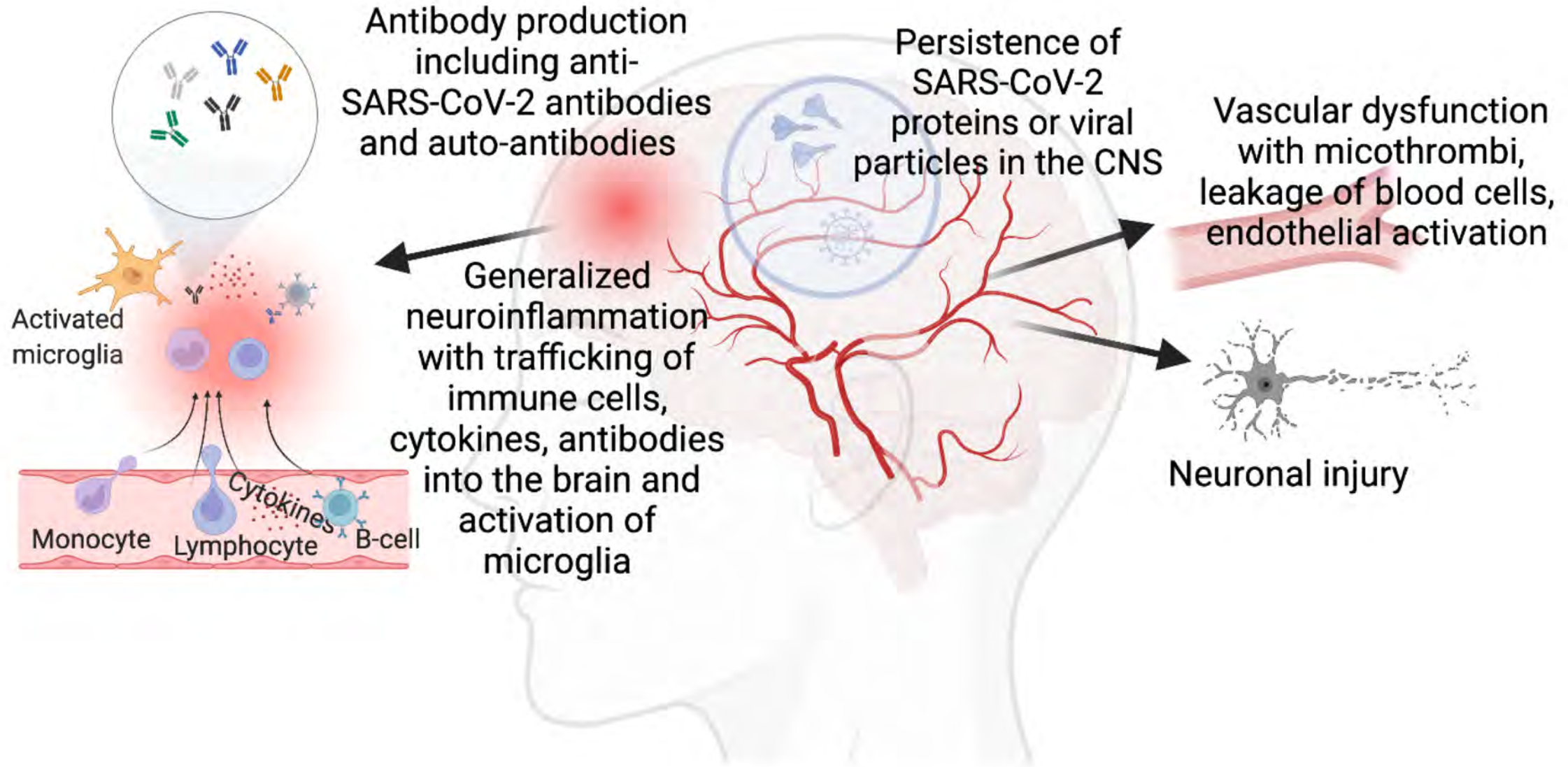
785 participants from the UK Biobank
COVID-19 re-imaging study

- 401 participants tested positive for SARS-CoV-2 between their two scans
- 384 controls matched for age, sex, ethnicity and interval between scans

Loss of gray matter - parahippocampal gyrus, orbitofrontal cortex and insula, anterior cingulate cortex, supramarginal gyrus and temporal pole.

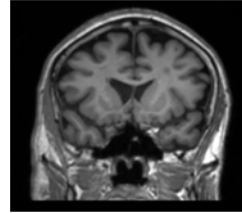


Putative mechanisms for nervous system post-acute sequelae of COVID-19 (NS-PASC)





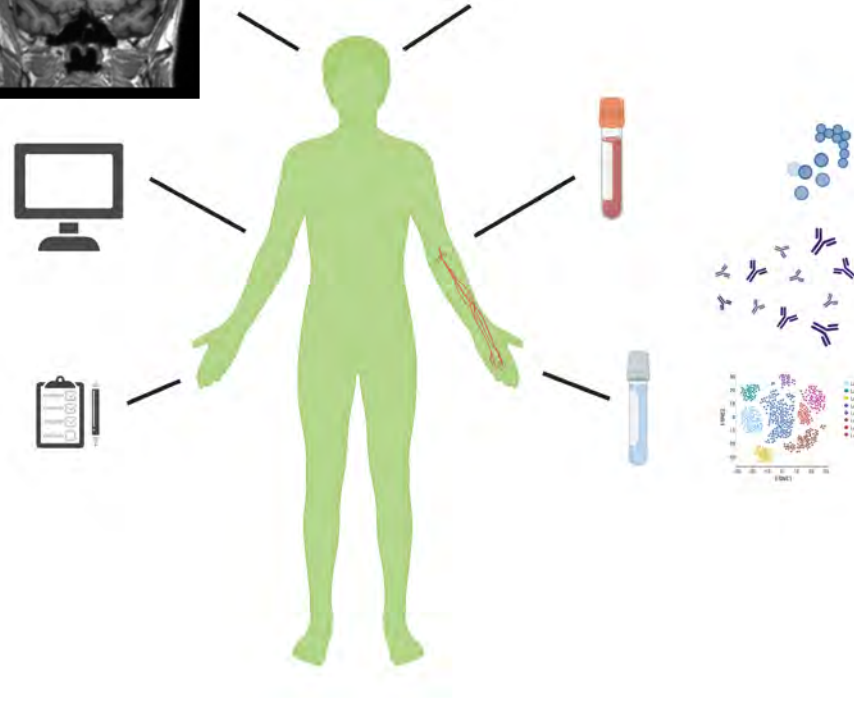
3T MRI Brain – structural, functional, inflammatory & vascular imaging



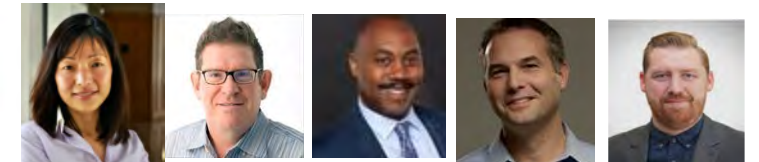
Neuropsychiatric battery – standardized tests of cognition & mood



History and surveys – symptoms, quality of life, medical history



Blood -- immune profiling, neuronal injury, vascular and thrombosis markers



Cerebrospinal fluid – immune profiling, neuronal injury, antibodies, viral persistence

Participants

Post-Acute COVID-19 with
Neurological Symptoms



Pre-Pandemic biobanked controls



Contemporaneous controls
(no COVID)



Study Procedures



COVID-19 symptom
assessment



Large volume LP (30cc)
Blood draw



Neuropsychological
testing



Brain MRI

Aim 1: Assess for CSF and blood markers of immune dysfunction -- including autoimmunity, vascular disturbance, and neuronal disruption

Aim 2: Assess for SARS-CoV-2 persistence in CNS

Aim 3: Integration of immune and viral markers (Aims 1&2) with objective assessments of nervous system dysfunction (MRI, CSF proteins, neurocognitive)

Preliminary demographic and clinical parameters



Neuro-PASC = participants
with nervous system post-
acute sequelae of COVID-19

Control = pre-pandemic
controls (n = 21)
+ contemporaneous
control (n = 1)

Enrollment Characteristics	Neuro-PASC (n=38)	Control (n = 22)	p-value
Age (Median, IQR)	48.5 (38.5 - 59.8)	51.5 (38.8 - 56.8)	0.91
Race/Ethnicity			
White	76%	23%	0.0002**
Black	13%	45%	0.013*
Hispanic	11%	27%	0.19
Asian	0%	5%	0.78
Female Gender	74%	32%	0.0012**
Education	16 (13.5 - 17.25)	12 (12-15.5)	0.029*
Comorbidities			
Alcohol	0%	33%	0.0001**
Smoking	5%	59%	0.0001**
Hypertension	29%	18%	0.36
Type 2 Diabetes	11%	14%	0.72
Obesity	18%	5%	0.13
Antidepressant Use	45%	14%	0.013*

Median (interquartile range) or number (%) are shown.

Preliminary demographic and clinical parameters

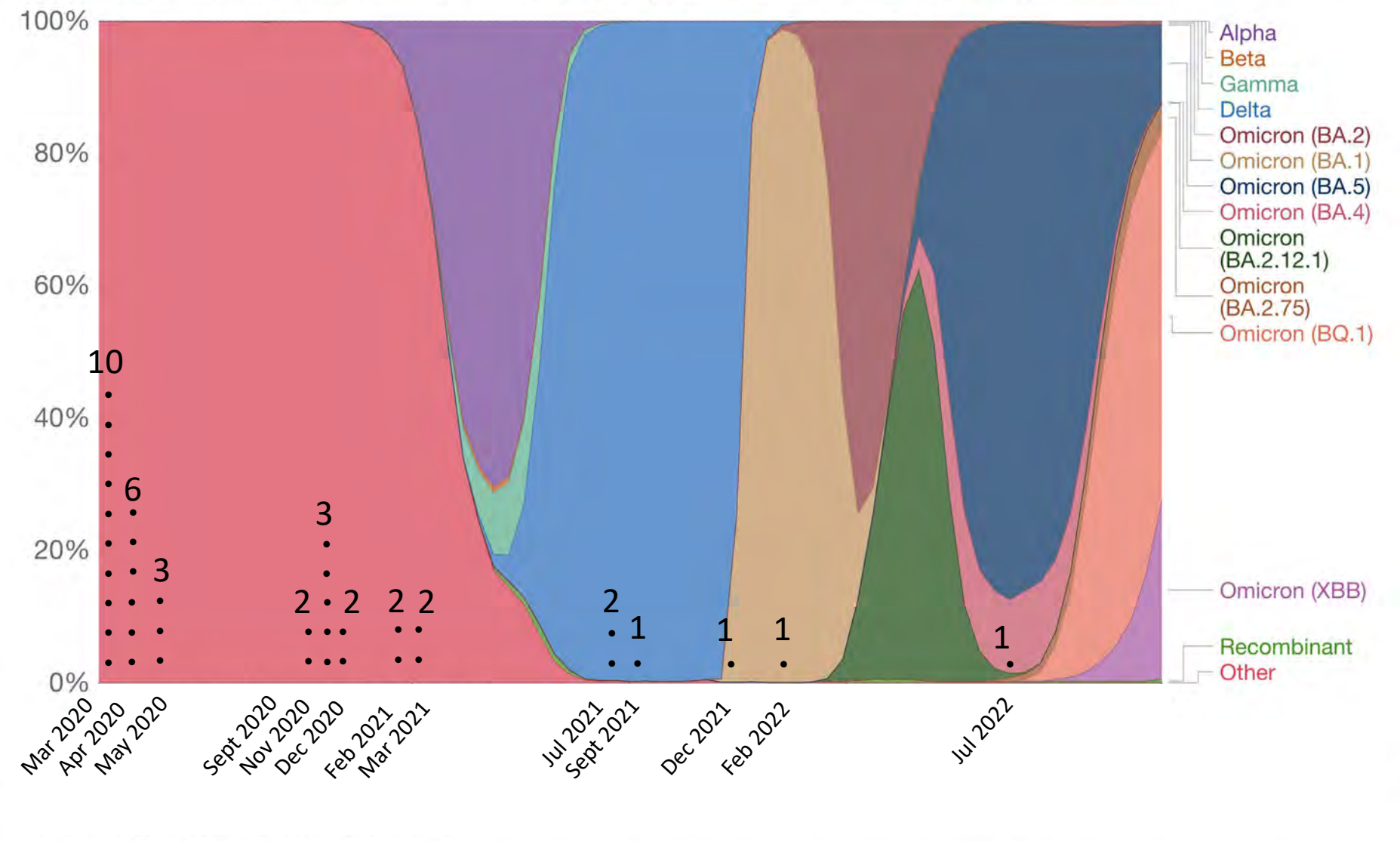


Neuro-PASC = participants
with nervous system post-
acute sequelae of COVID-19

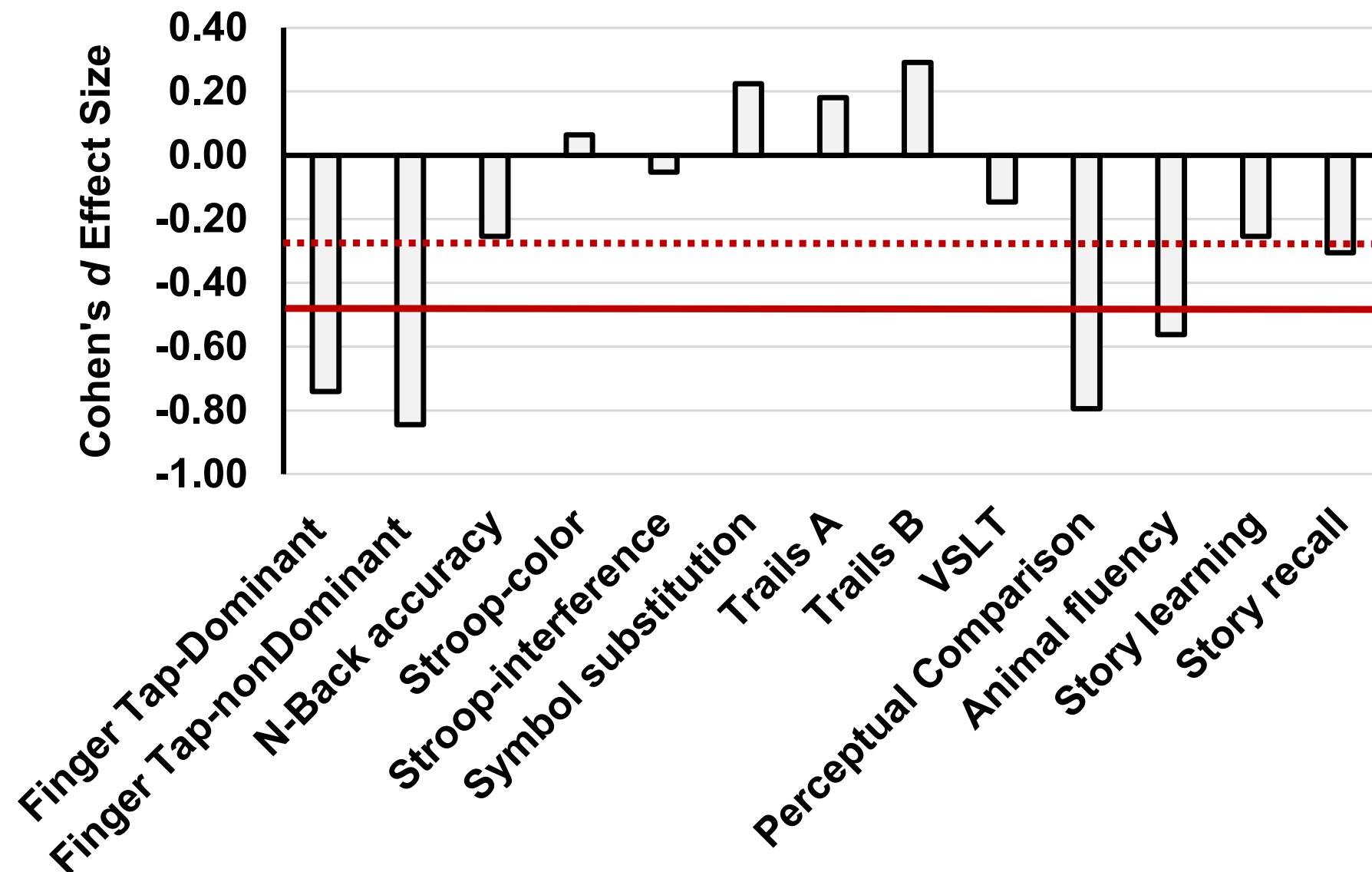
Acute COVID-19 Illness		Neuro-PASC (n = 38)
Days between symptom onset and research visit		310 (223 - 422)
Acute Illness Level of Care		
Home		84%
Hospital Floor		21%
ICU		8%
Acute Illness Treatment		n = 10
Steroids		5
Hydroxychloroquine		4
Azithromycin		4
Tocilizumab		3
Remdesivir		1
Anti-Retroviral Therapy		1
Monoclonal Antibodies		1

Median (interquartile range), number or % are shown.

COVID-19 Strains



Preliminary findings – Neuropsychological testing



Cohen's d comparing performance in NS-PASC (n = 20) versus Controls (n = 23).

Preliminary findings – Neuropsychiatric symptoms

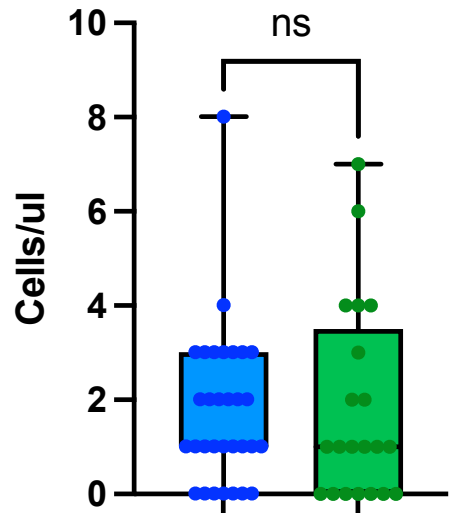
	Test Range	NS- PASC (n = 20)	Controls (n = 23)	p value
Cognitive Failures Questionnaire (CFQ)	0-100	48.4 (21.3)	24.5 (11.4)	<0.001
Patient Health Questionnaire-9 (PHQ-9)	0-27	15.0 (11.7)	1.9 (3.1)	<0.001
Temporal Experience of Pleasure Scale (TEPS) [†]	18-108	79.0 (10)	84.0 (19.5)	0.74
Social Anhedonia Scale-Short Form (SAS-15)	0-15	3.8 (3.3)	3.5 (2.6)	0.80
Rumination Response Scale (RRS)	22-88	55.2 (14.7)	36.9 (9.4)	<0.001
Apathy Evaluation Scale (AES)	18-72	39.5 (8.7)	30.4 (5.1)	<0.001
Generalized Anxiety Disorder Assessment (GAD-7)	0-21	11.2 (6.6)	1.7 (2.8)	<0.001
Perceived Stress Scale (PSS-10)	0-40	22.7 (5.9)	9.6 (5.7)	<0.001
Intolerance of Uncertainty Scale-Short Form (IUS-12)	12-60	29.1 (8.5)	29.4 (7.0)	0.94

Neuropsychiatric symptoms are presented as mean (standard deviation).

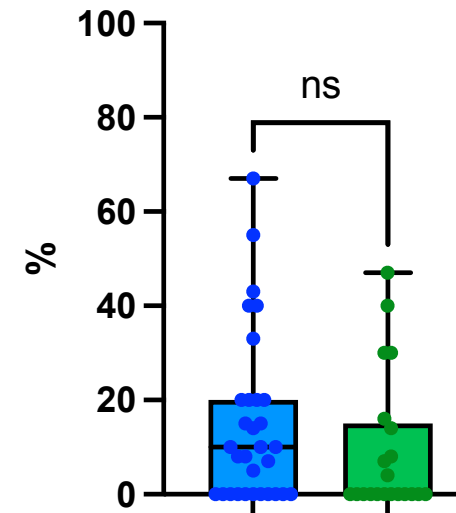
Higher scores = more problems except that marked with †

Normal clinical CSF parameters in Neuro-PASC

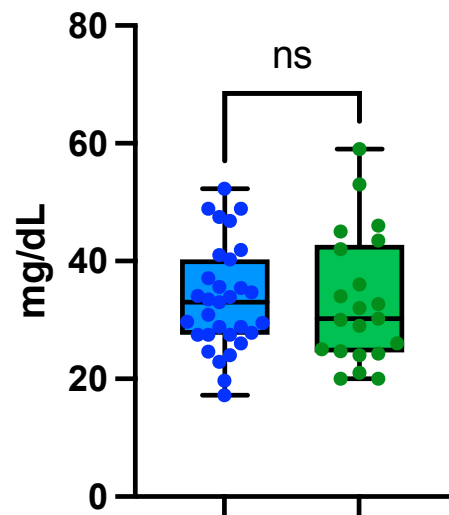
White Blood Cells



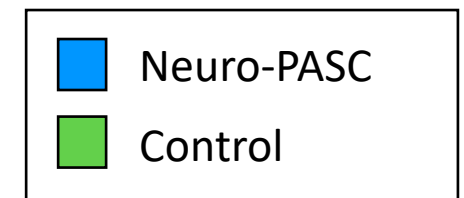
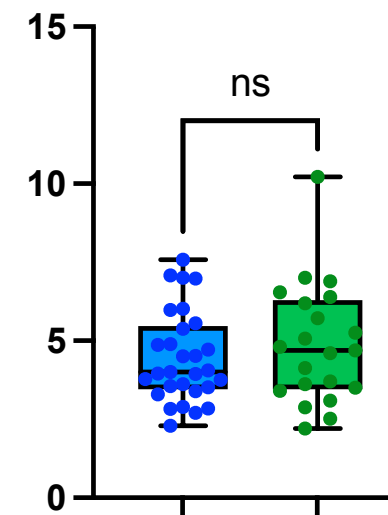
Monocytes



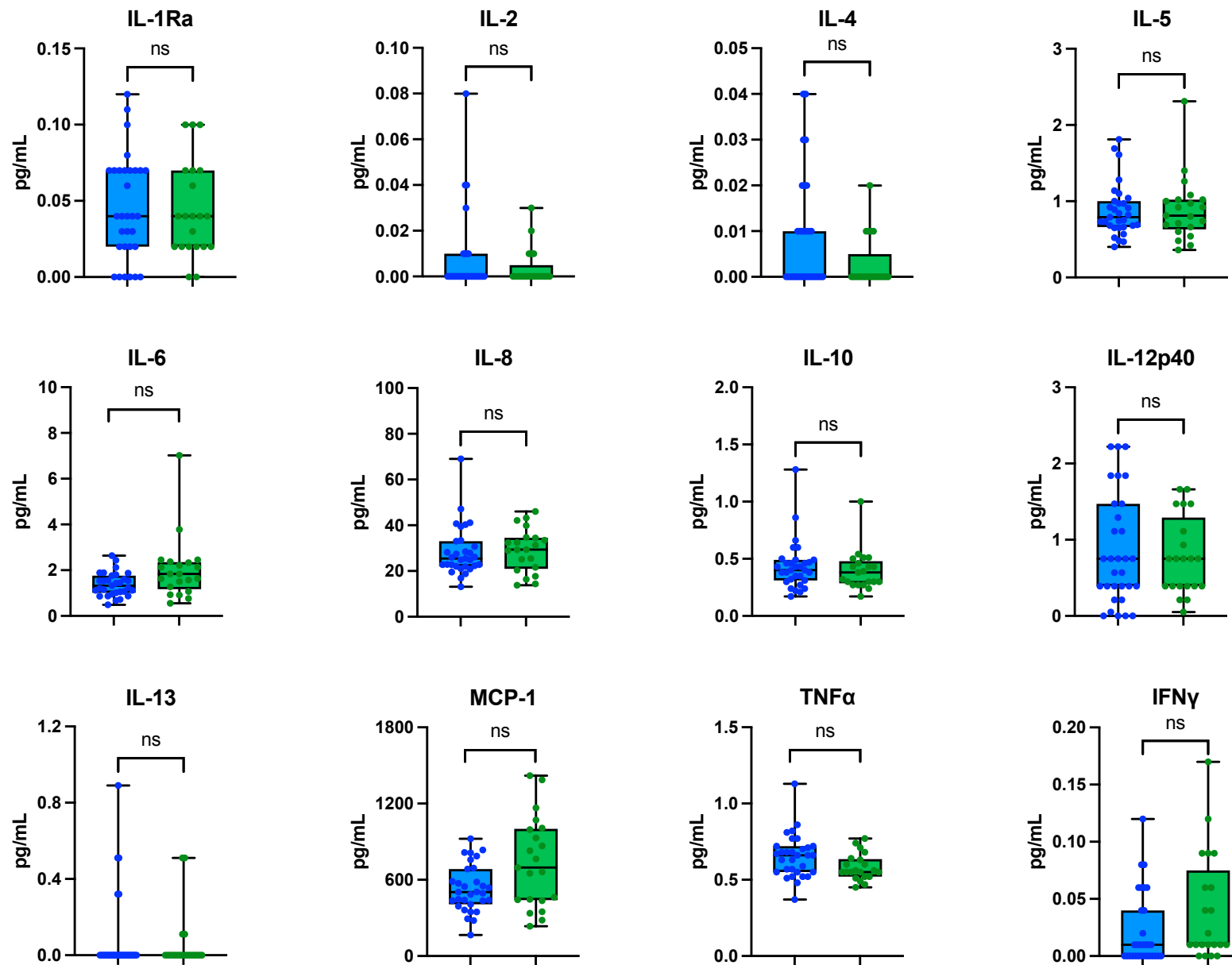
Protein



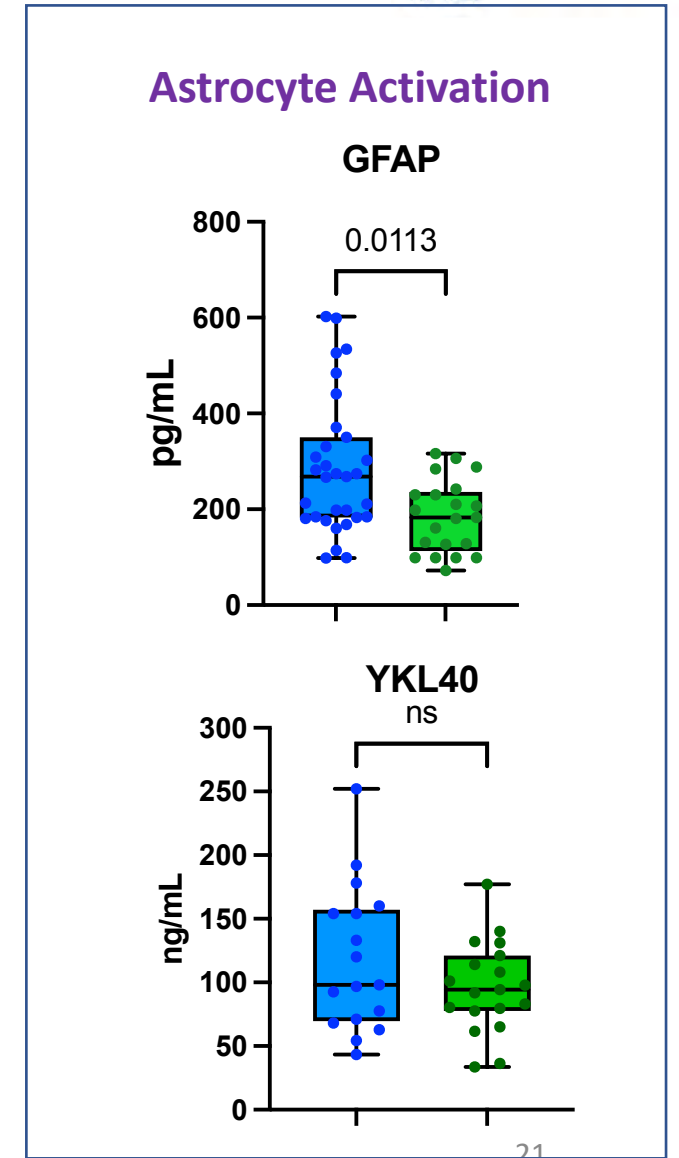
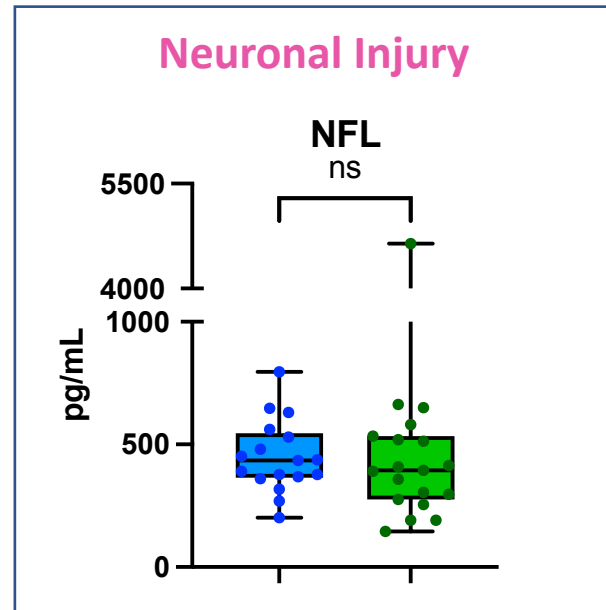
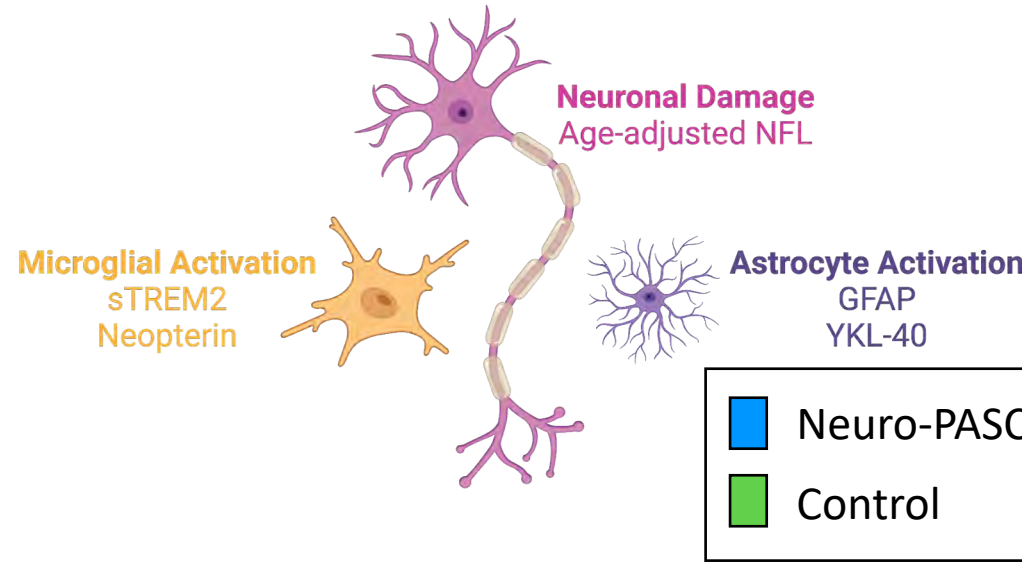
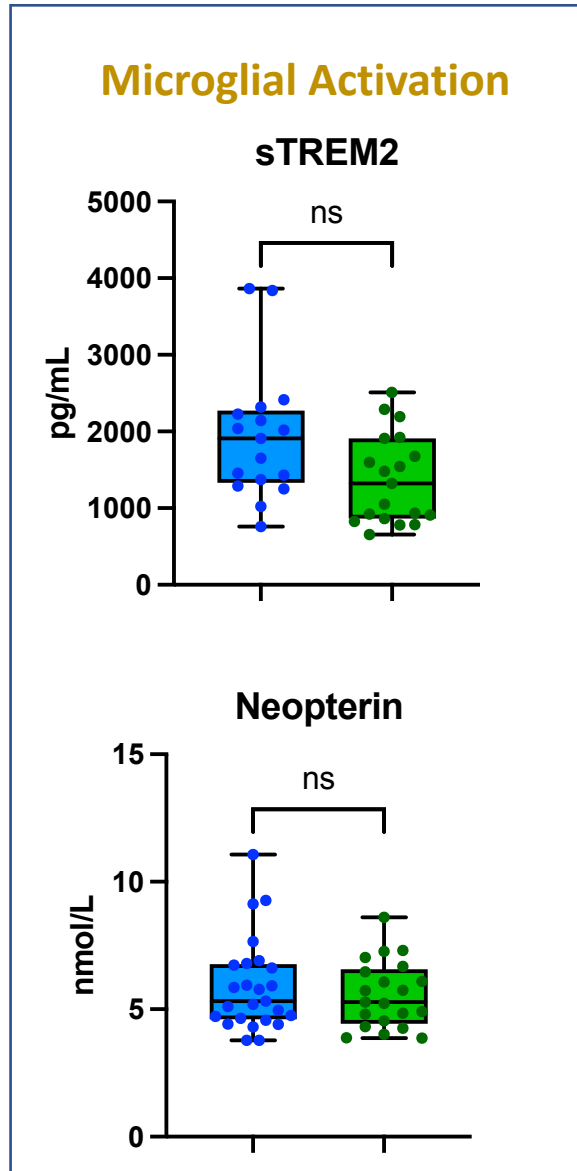
CSF/Plasma Albumin Ratio



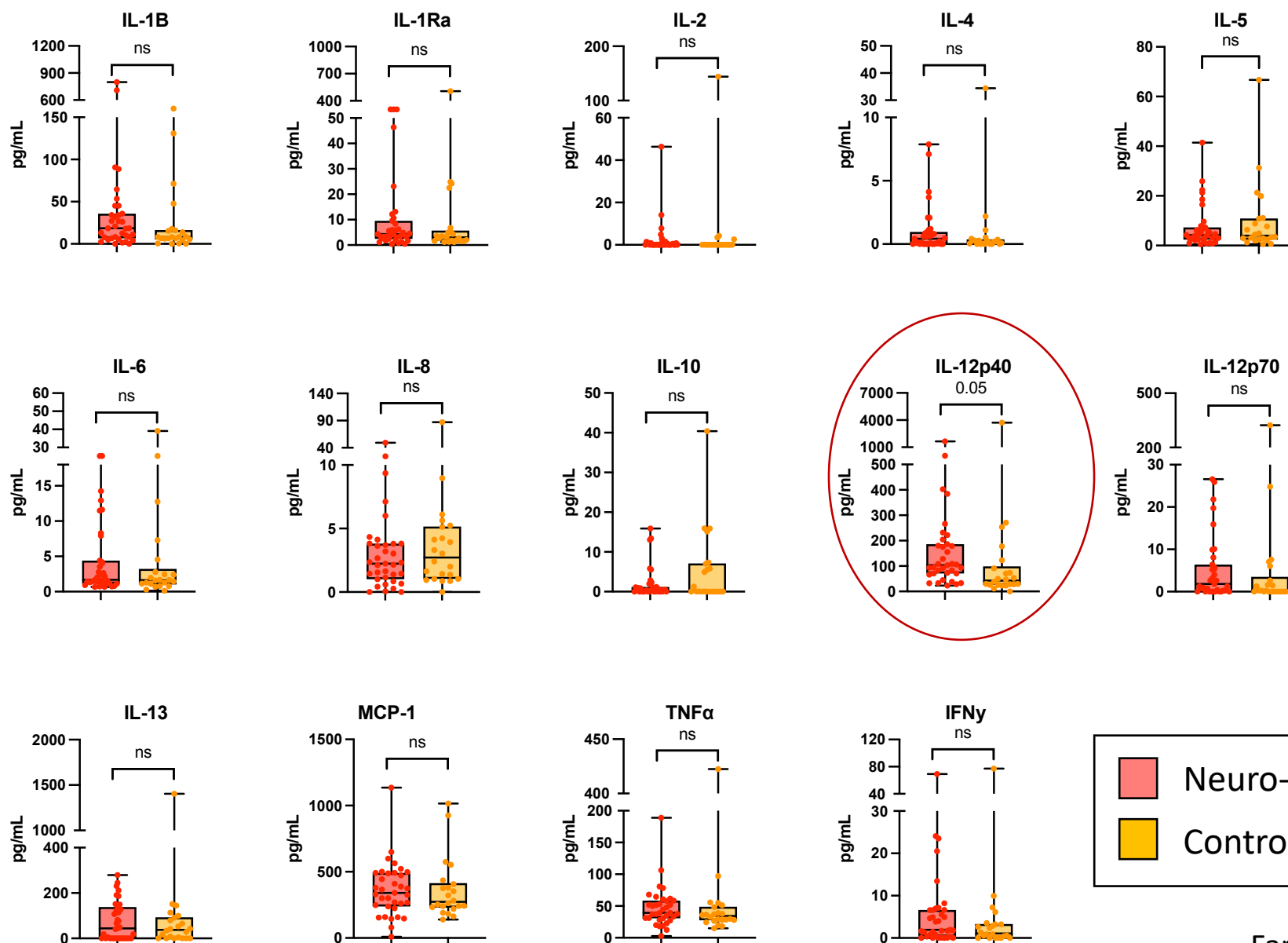
No difference in CSF cytokines in Neuro-PASC



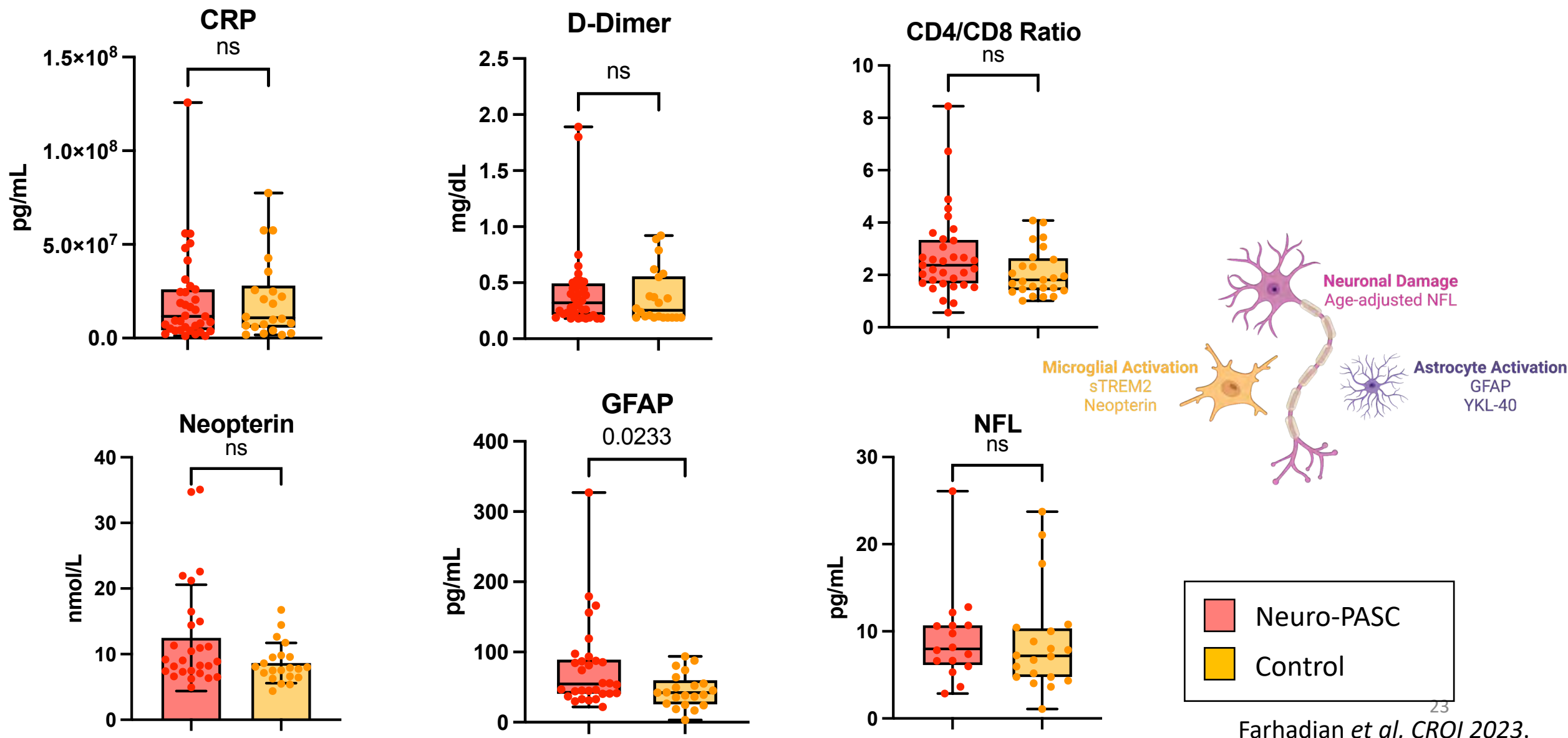
No CSF evidence of neuroinflammation or neuronal injury, mild astrocyte activation in Neuro-PASC



Plasma IL12-p40 is elevated in neuro-PASC

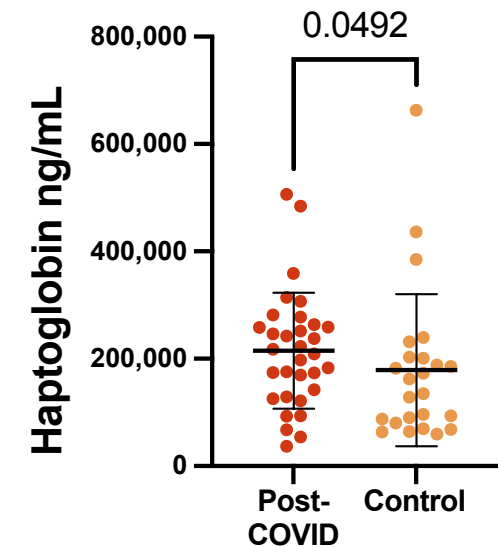
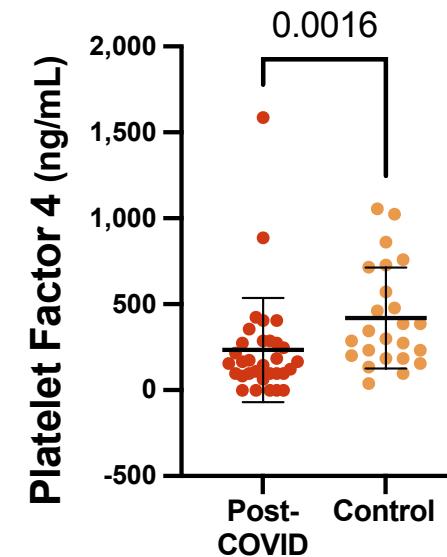
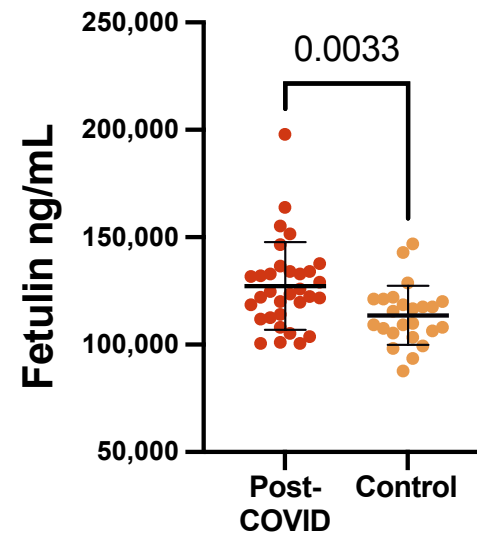
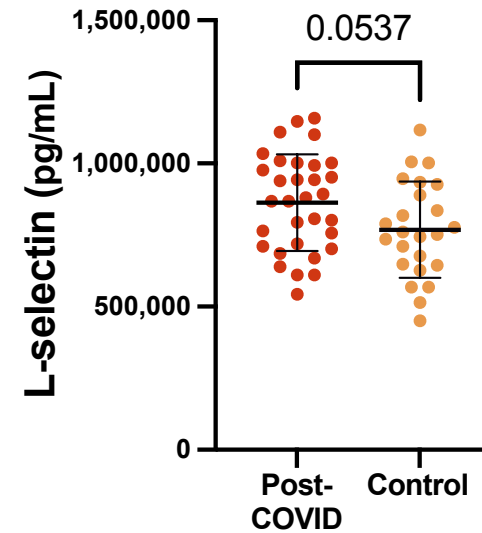
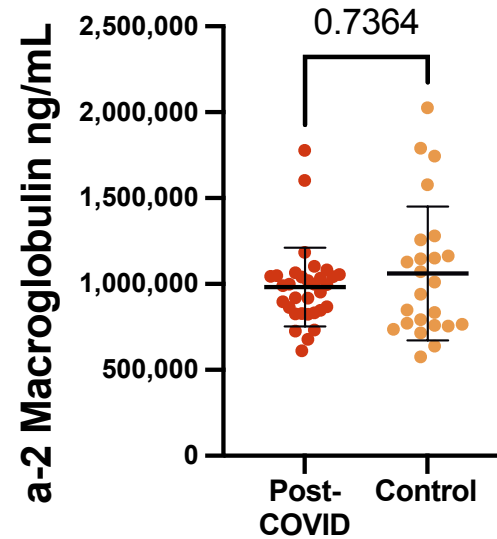
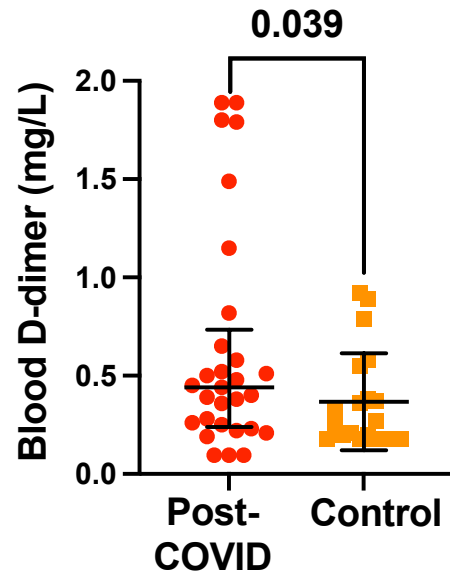


Plasma marker of astrocyte activation is elevated in neuro-PASC

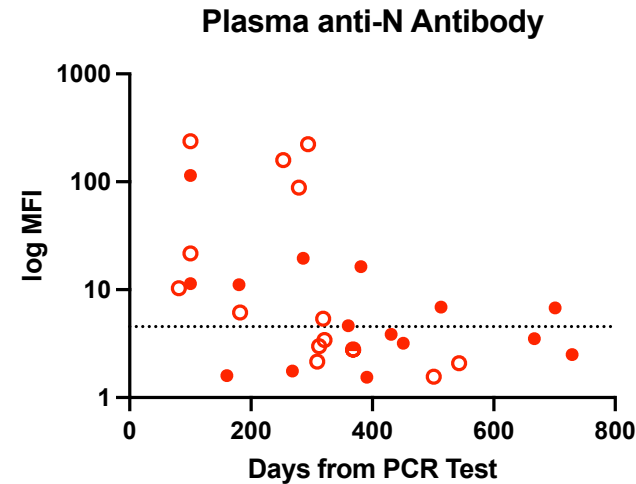
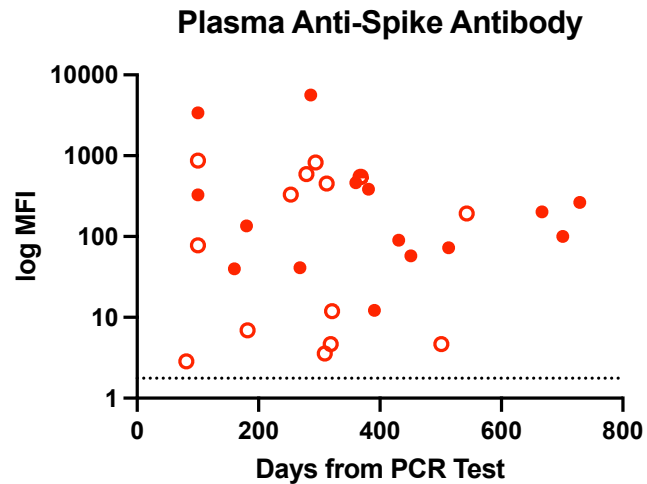
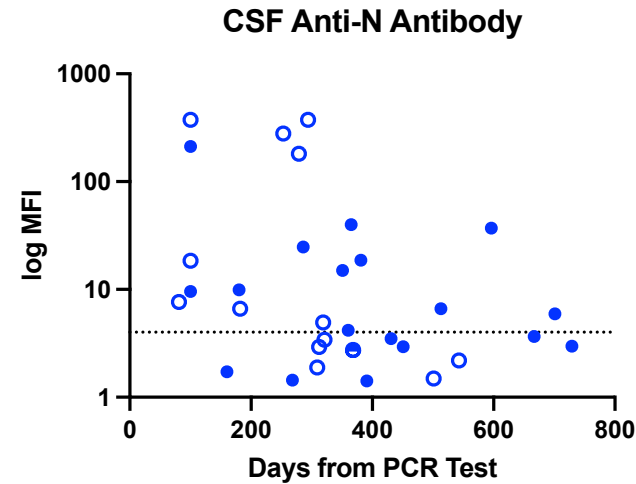
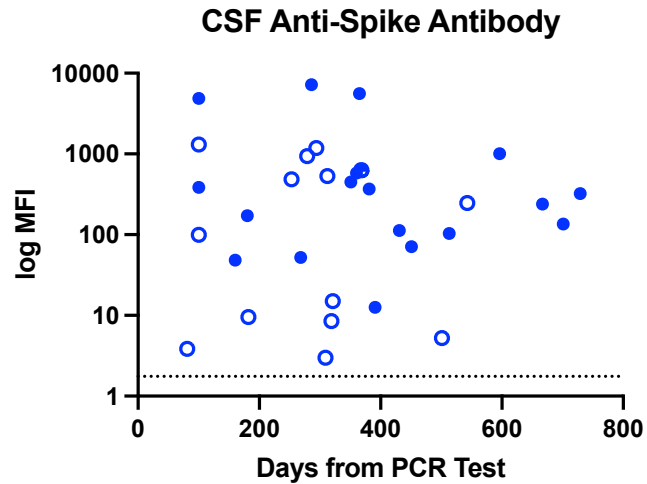


Plasma markers of vascular function are abnormal in neuro-PASC

Vascular measures



Persistence of anti-SARS-CoV-2 antibodies in blood and CSF



CSF: 32 individuals (100%) were positive for anti-spike and 19 individuals (59%) were positive for anti-N antibodies.

Plasma: 29 individuals (100%) were positive for anti-spike and 16 individuals (55%) were positive for anti-N antibodies

Open dots = unvaccinated at study visit
Closed dots = vaccinated at study visit

With M Wilson, S Pleasure, C Bartley UCSF

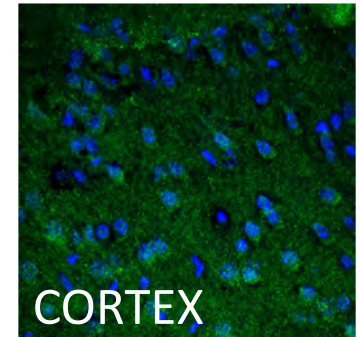
Preliminary study findings

Unique study participant:

30 yo man with abrupt onset psychosis post COVID-19

- Normal clinical CSF measures, clinical MRI imaging, negative clinical autoimmune panels from CSF and blood.
- CSF IgG slightly elevated (4.6 mg/dL)
- Clinical management: intravenous immune globulin → resolution of psychosis
- Mouse immunostaining method to detect novel autoantibodies revealed a novel auto-antibody in CSF → presumed autoimmune mediated psychosis

Post-
COVID
Psychosis



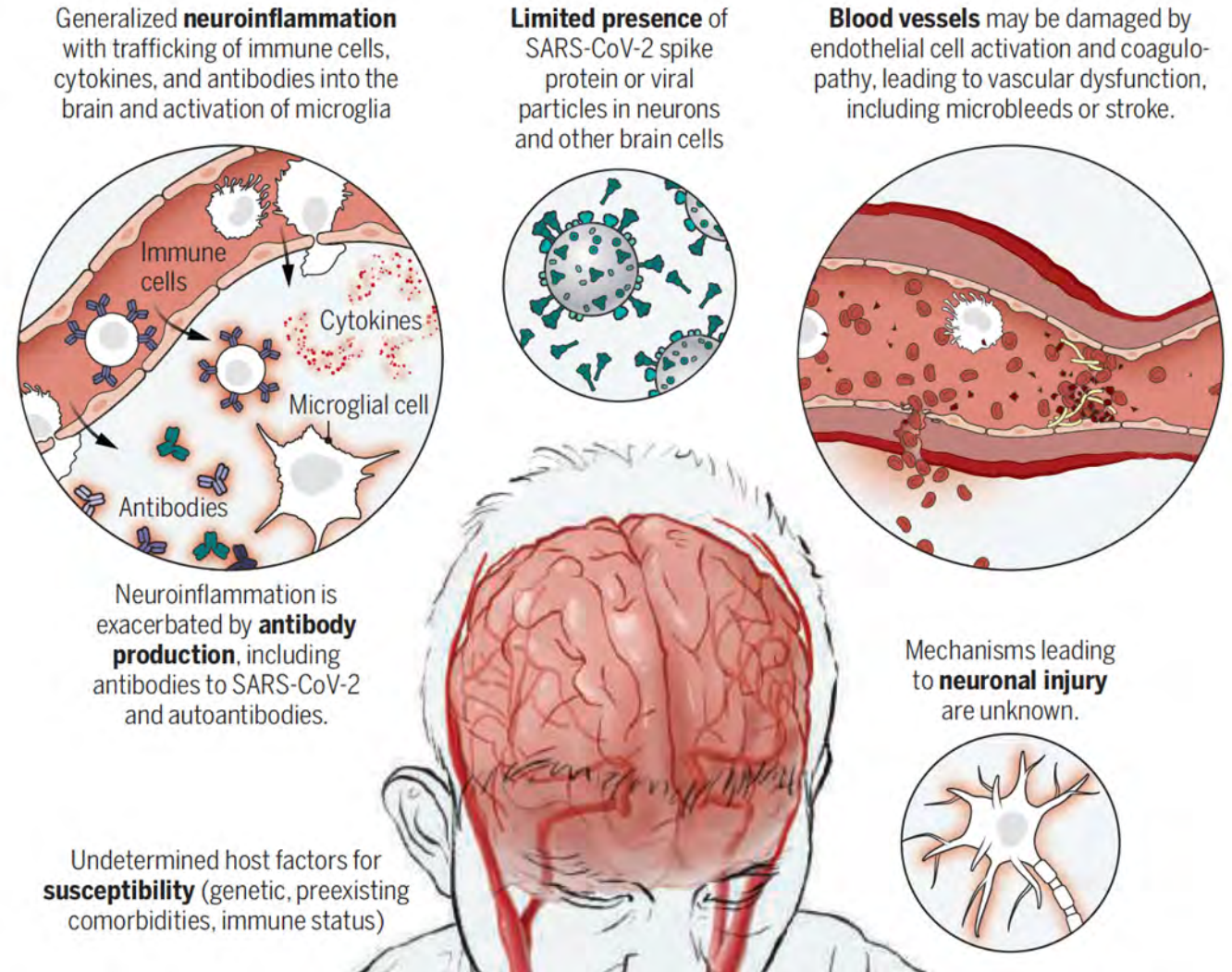
Negative
Control



Key questions related to nervous system post-acute sequelae of COVID-19 (NS-PASC)

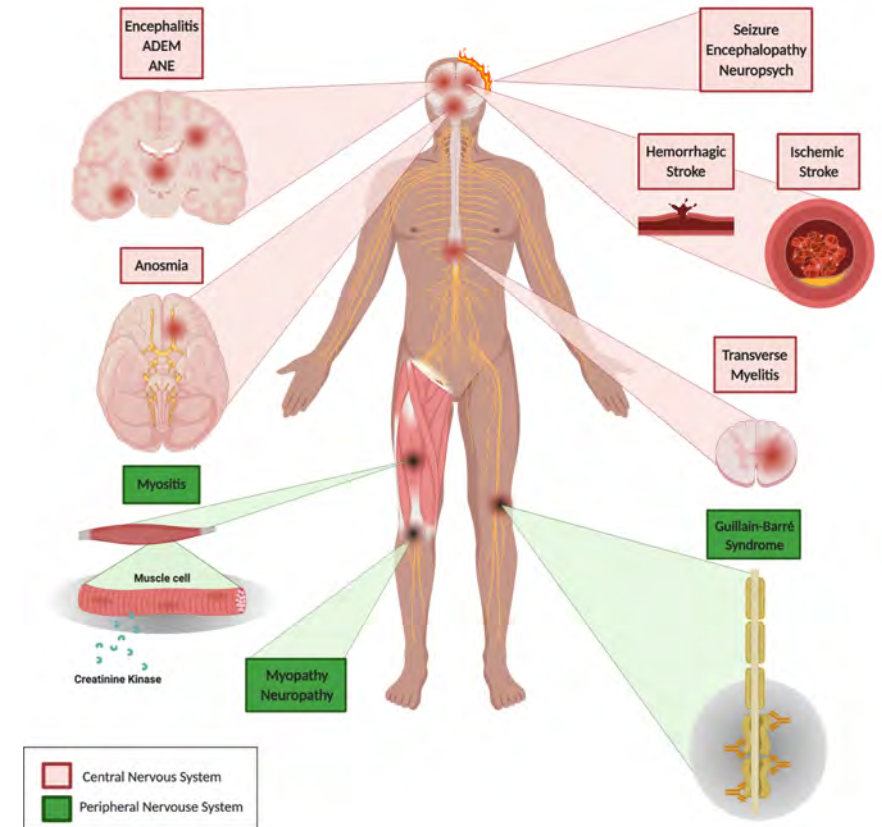
What are the underlying biological mechanisms of ongoing neurologic and psychiatric syndromes after COVID-19?

- Injury accrued during acute infection?
- Ongoing perturbations in systemic and neuro inflammation, autoimmune responses
- Vascular inflammation, microvascular compromise, impact on regional blood flow
- Persistence of low level viral antigen in the CNS or other tissues (? Blood, ?gut)



Key Challenges: Nervous system post-acute sequelae of COVID-19 (Neuro-PASC)

- Heterogeneity of NS-PASC clinical presentations
- Consensus definitions of NS-PASC are still lacking
- Lack of abnormalities on clinical tests (exception: detection of small fiber nerve injury)
- No definitive biomarkers of NS-PASC
- To date, lack of signal in most pathobiology investigations
- Urgent medical/public health need – (understandable) pressure for clinical trials and clinical interventions



Acknowledgements

Study Participants

Shelli Farhadian, MD, PhD – Co-Principal Investigator – infectious disease

Lindsay McAlpine, MD –neuro-infection/neuro-immunology fellow

COVID Mind Study Team

Jennifer Chiarella – Research Program Manager

Allison Nelson -- Clinical Research Nurse

Hailey Reisart -- Study Coordinator



COVID Mind Study Yale Collaborators

Todd Constable, MD - MRI radiology

Akiko Iwasaki, PhD - immunology

COVID Mind Study External Collaborators

Leah Rubin, MA, MPH, PhD – neuropsychology (Johns Hopkins)

Samuel Pleasure, MD, PhD – neurology (UCSF)

Michael Wilson, MD – neurology (UCSF)

Debanjana Chakravarty – neurology (UCSF)

PeiXi Chen – neurology (UCSF)

Christopher Bartley, MD, PhD – psychiatry (NIH/NIMH)

Magnus Gisslen, MD, PhD – infectious diseases (U Gothenburg)

Henrik Zetterberg, MD, PhD – biochemistry (U Gothenburg)

Michael Corley, PhD – genomics (Weill Cornell)

Joshua Cyktor, PhD – virology (U Pitt)

John Mellors, MD – virology (U Pitt)



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<https://medicine.yale.edu/neurology/research/covid-mind-study/>