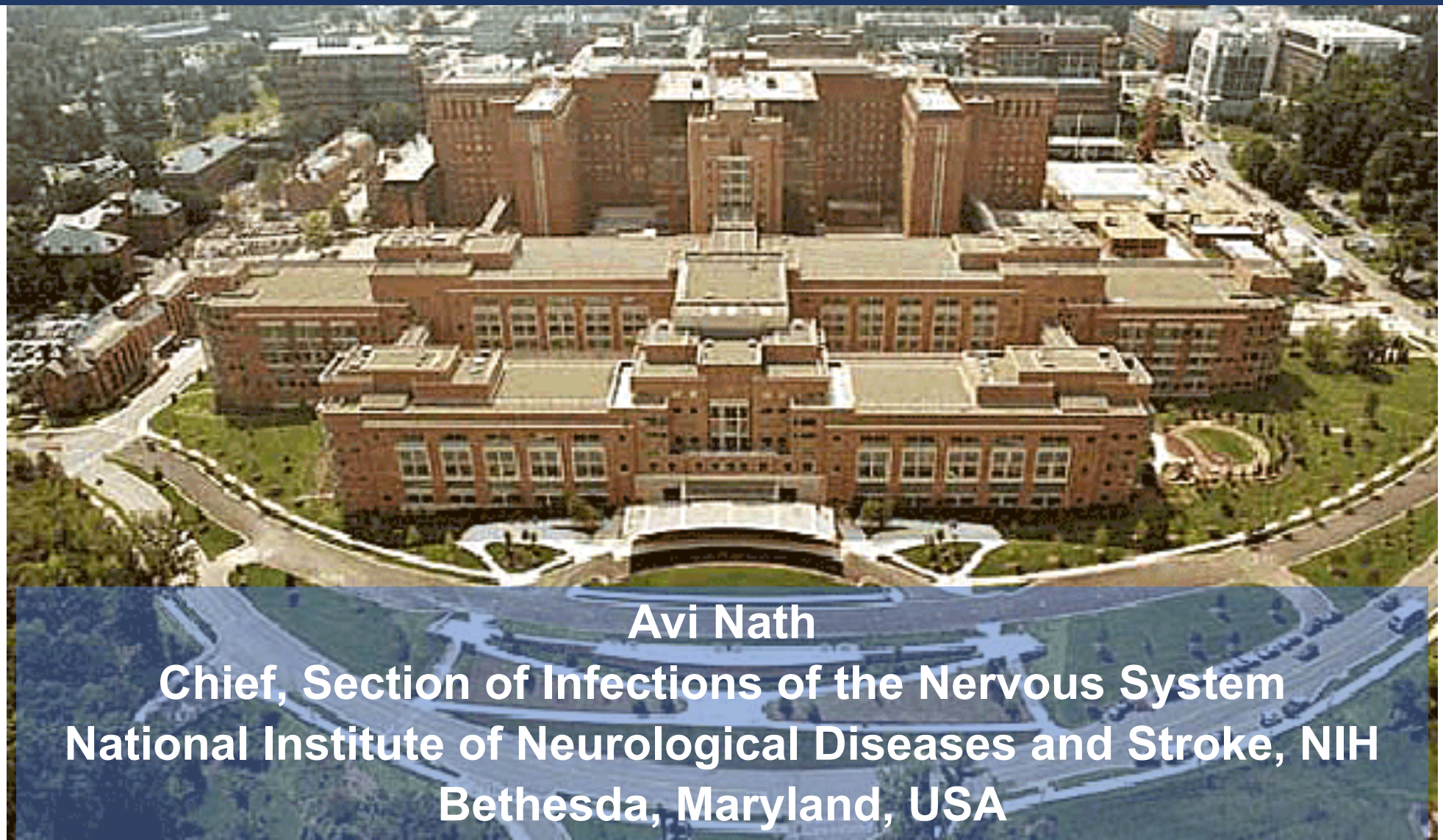
Pathophysiology of Neuropsychiatric Complications of COVID



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Disclosures

None

Objectives

1. **To recognize the acute and long-term complications of COVID.**
2. **To describe the neuropathology and pathophysiological mechanisms of COVID and the gaps in knowledge.**
3. **To develop a rational approach for identifying therapeutic targets for Long-COVID.**

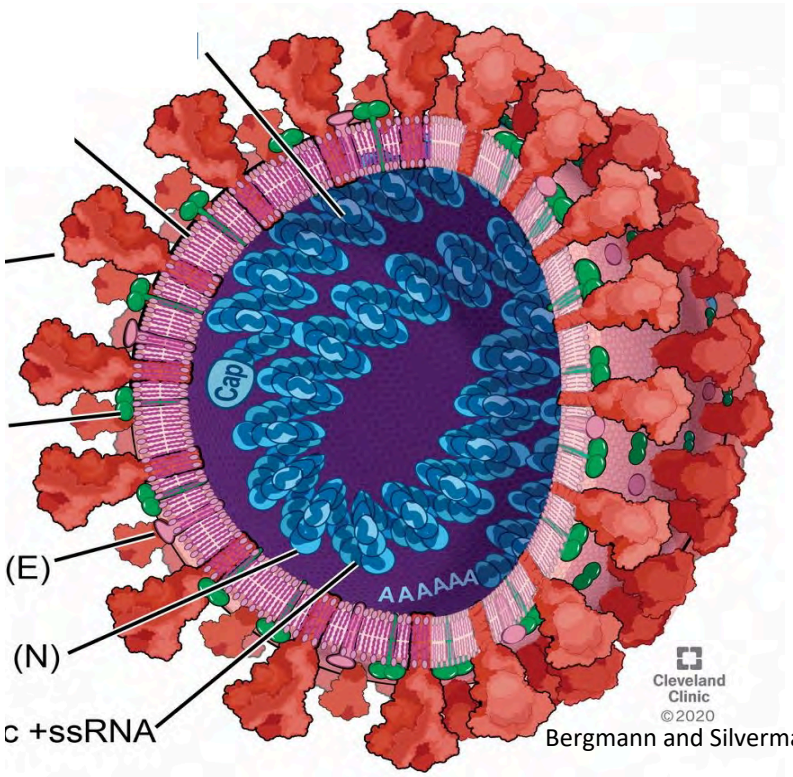
“Humanity has but three great enemies: fever, famine [climate change], and war; of these by far the greatest, by far the most terrible, is **fever**.”

—Sir William Osler, 1896

Social Unrest

AIDS quilt

COVID-19



Bergmann and Silverman 2020

Global Infections: 900 Million
Global Deaths: 60 Million

US Infections: 100 Million
US deaths: 1,000,000; 2-4,000/day

All coronaviruses can cause neurological complications

Human Coronavirus	Genus	Receptor
HCoV-OC43	betacoronavirus	O-acetylated Sialic Aicd (Protein Receptor Unknown)
HCoV-229E	alphacoronavirus	APN
HCoV-HKU1	betacoronavirus	O-acetylated Sialic Aicd (Protein Receptor Unknown)
HCoV-NL63	alphacoronavirus	ACE2
SARS-CoV-1 and 2	betacoronavirus	ACE2
MERS-CoV	betacoronavirus	DPP4

Totura & Bavari 2019. DOI:10.1080/17460441.2019.1581171

Variants of Concern

Alpha

Beta

Gamma

Delta

Omicron

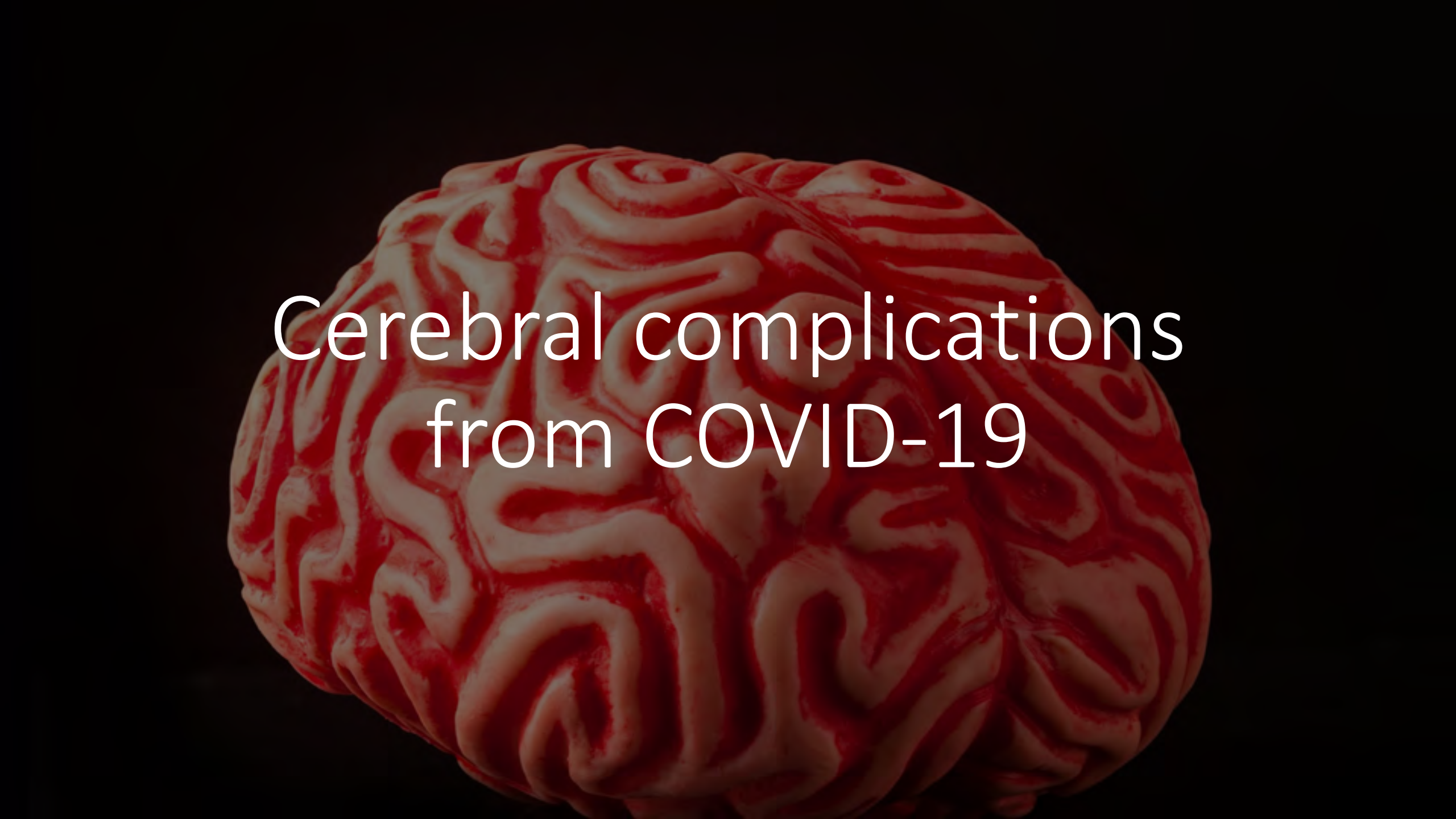
BA.1 to BA.5

B1, XBB1.5

The variants have become more transmissible

Neurological complications seem similar with all of them

More infectious less virulent



Cerebral complications from COVID-19

Acute

Anosmia

Metabolic/hypoxic encephalopathy

Strokes

Viral Encephalitis (rare)

Sudden death (Ondine's curse)

Vertigo and tinnitus

Subacute

Inflammatory Syndromes

Acute disseminated encephalomyelitis

Acute necrotizing hemorrhagic encephalopathy

Limbic encephalitis

Guillian Barre Syndrome

Multisystem Inflammatory Syndrome

Unmasking of Autoimmune Syndromes

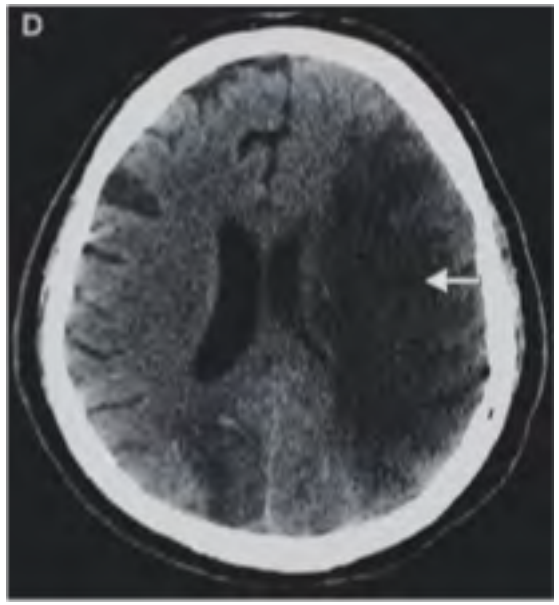
Chronic

Long COVID

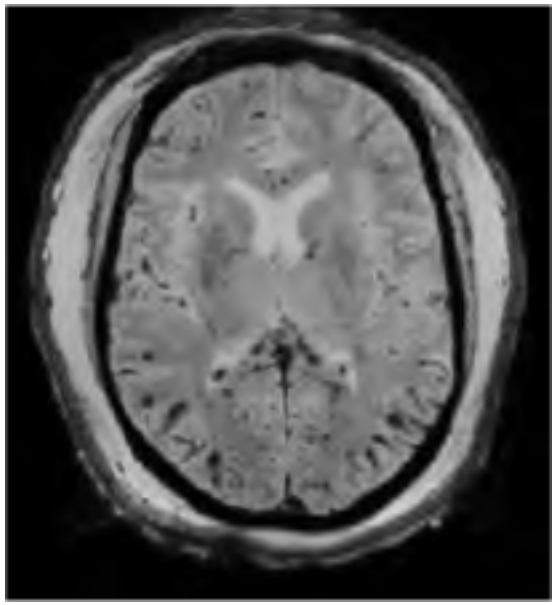
Neurodegenerative Diseases

ACUTE VASCULAR INJURY

Strokes and vascular disease with COVID-19



Berlin et al., NEJM 2020
DOI: 10.1056/NEJMcp2009575



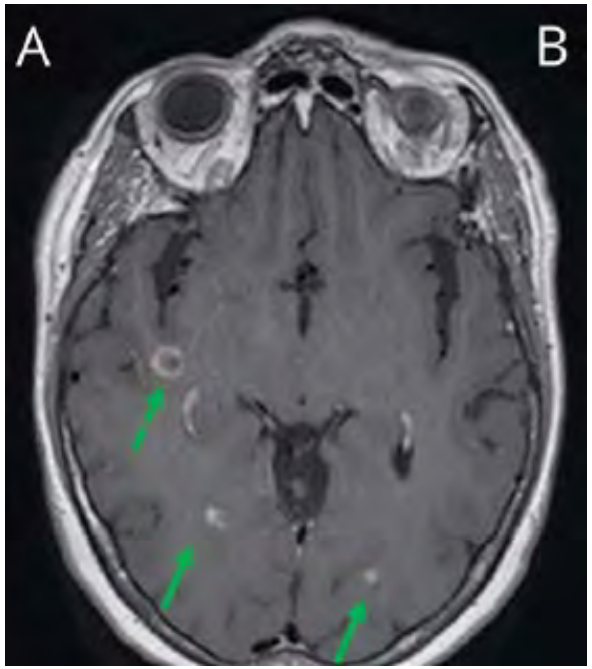
Coolen et al., MedRxiv 2020
DOI:10.1101/2020.10.18.20214221v1

ECHMO (external heart lung machine)

Abdalkader et al., J Stroke and Cerebrovascular Diseases 2021
DOI:10.1016/j.jstrokecerebrovasdis.2021.105733

Subacute NEURO-INFLAMMATION

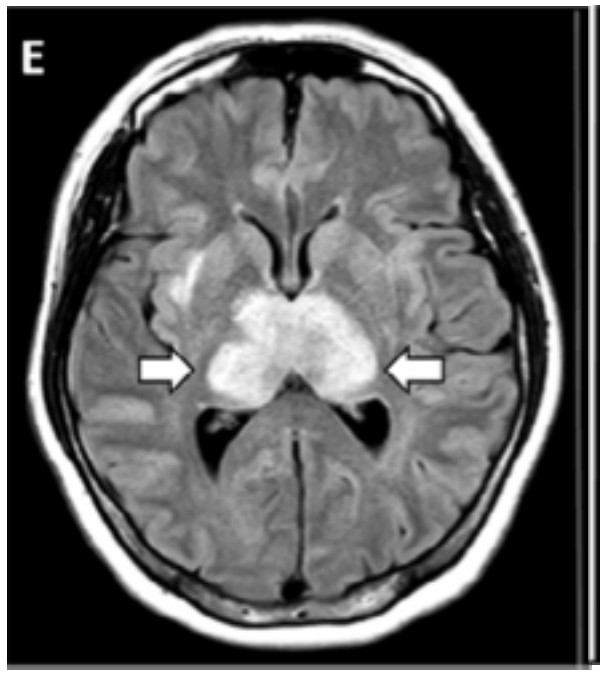
Types of inflammation in the brain

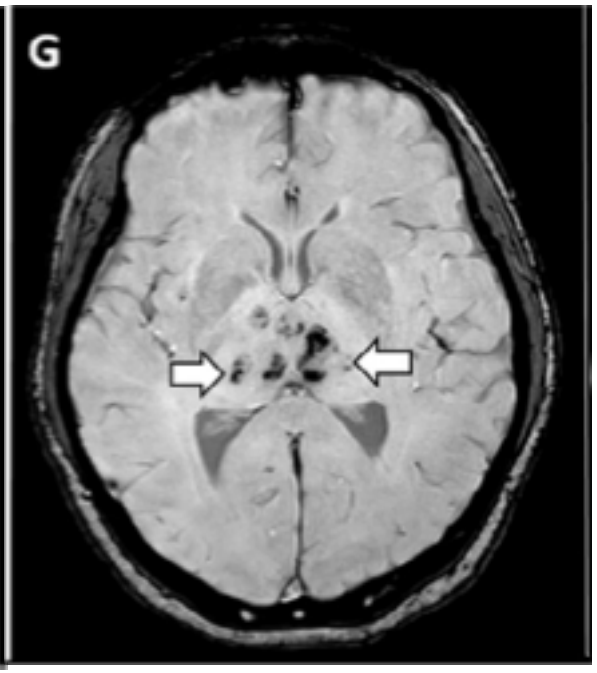


Acute disseminated encephalomyelitis

T-cell mediated

Novi et al., Neurol Neuroimmunol Neuroinflamm 2020





Acute necrotizing hemorrhagic encephalopathy

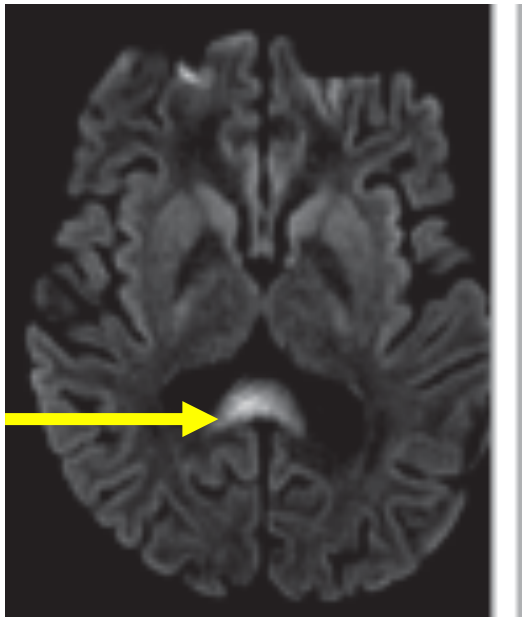
Cytokine mediated

Poyiadji et al., Radiology 2020

Multi-system Inflammatory Syndrome with COVID-19 (MIS-C) in Children

Fever, dyspnea, rash, vomiting, circulatory failure

2 weeks later
Encephalopathy
Difficulty with speech and swallowing
Generalized flaccid weakness



CSF normal
Pericardial effusion (small)
CRP: 29 mg/dL
D-dimer 1479 ug/ml
Ferritin 48,142 ng/ml
LDH: 4331 U/L

Dexamethasone
IVIG
Partial response

Restricted diffusion on DWI in Splenium of Corpus Callosum

Abdel-Mannan et al.,
JAMA Neurol 2020

Chronic
Long-COVID

Attempts at Defining Long-COVID
(Diagnostic criteria)

Long-COVID:

Patients

PASC (Post-acute sequelae of COVID-19)

National Institutes of Health

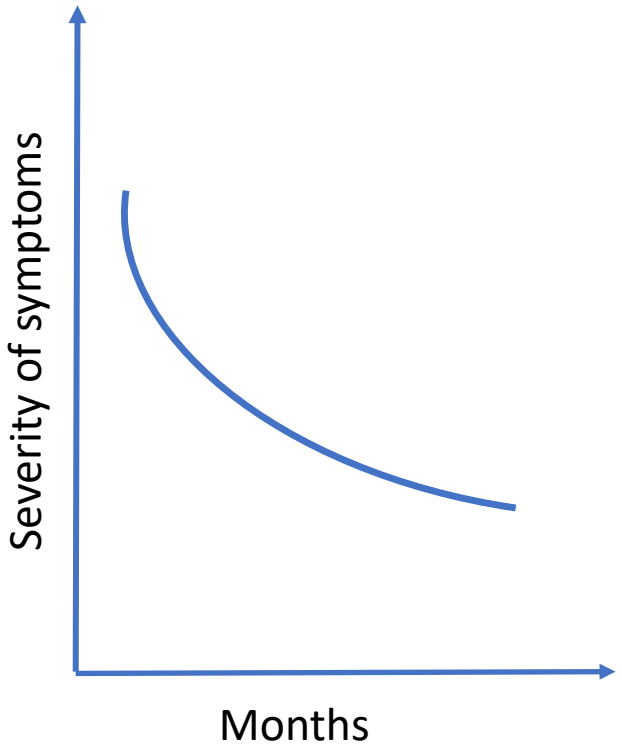
Post-COVID-19

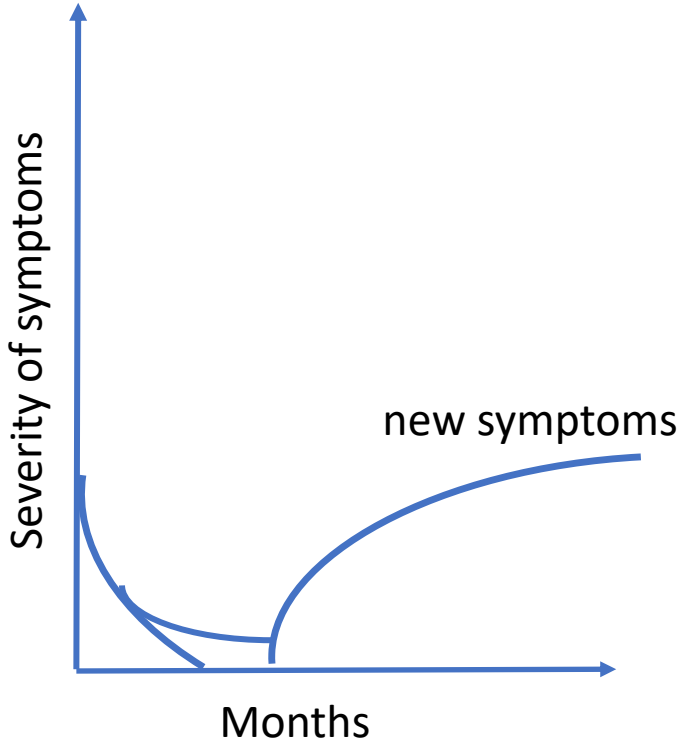
World Health Organization

WHO definition of Post-COVID

- *Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time*

PATTERNS OF LONG-COVID

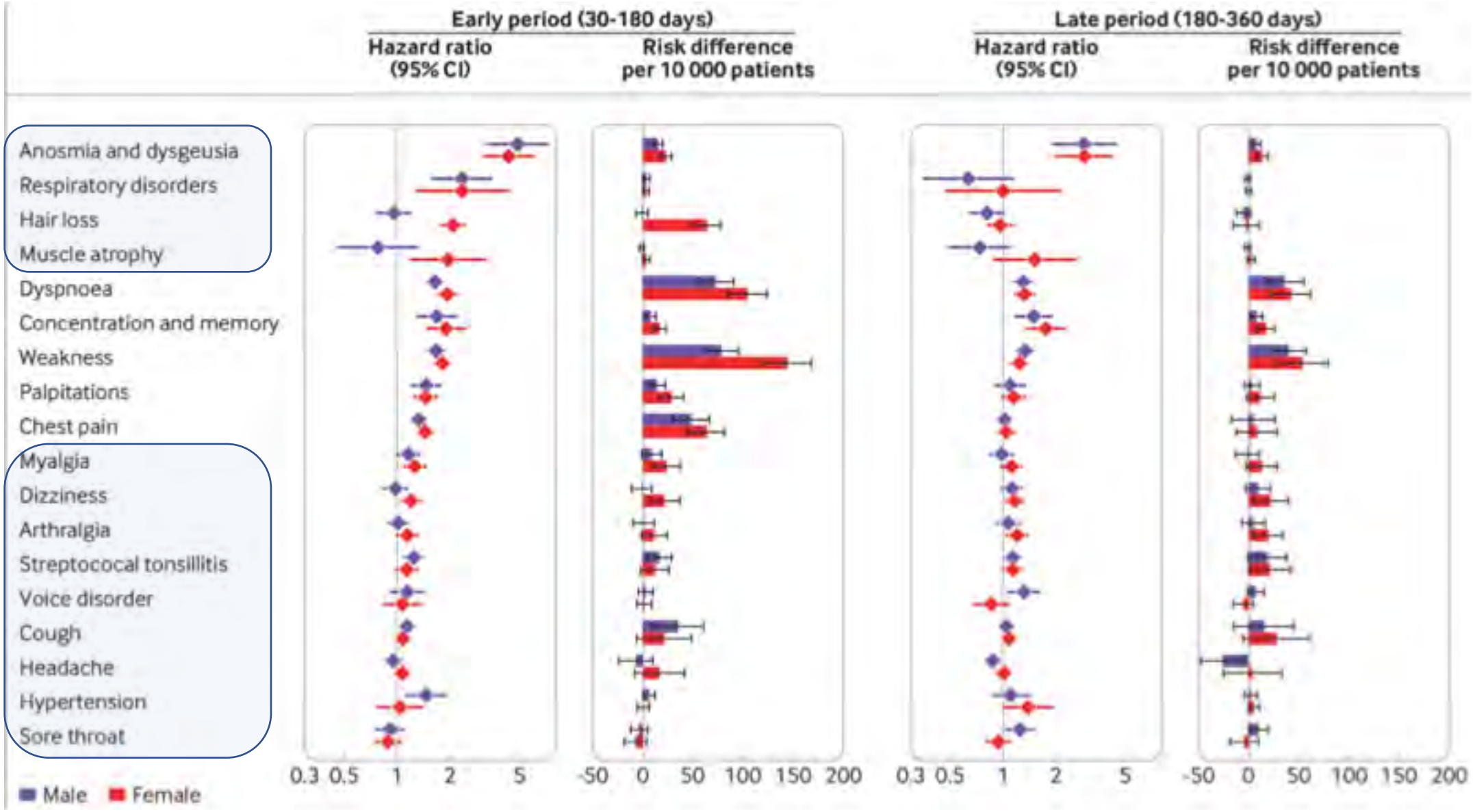




Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study

Mizrahi et al., BMJ 2023

N=229.008 unvaccinated patients



Feb 2023

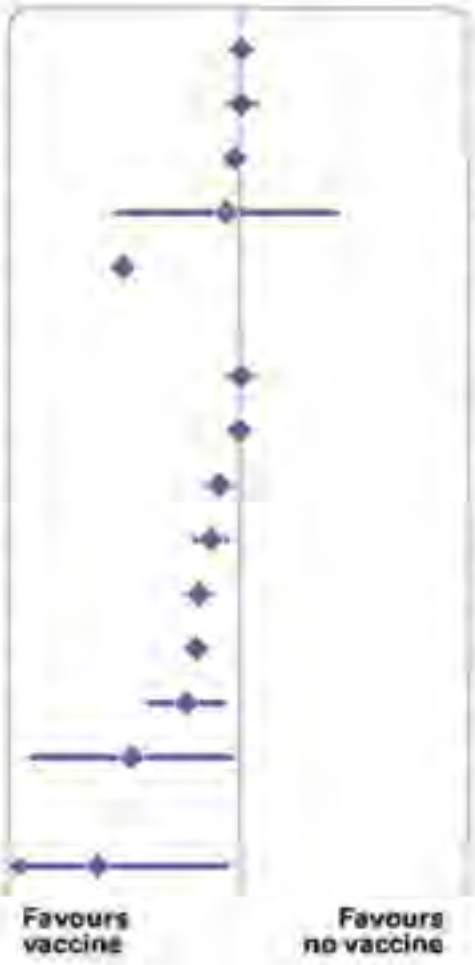
bmjmedicine

Check for updates

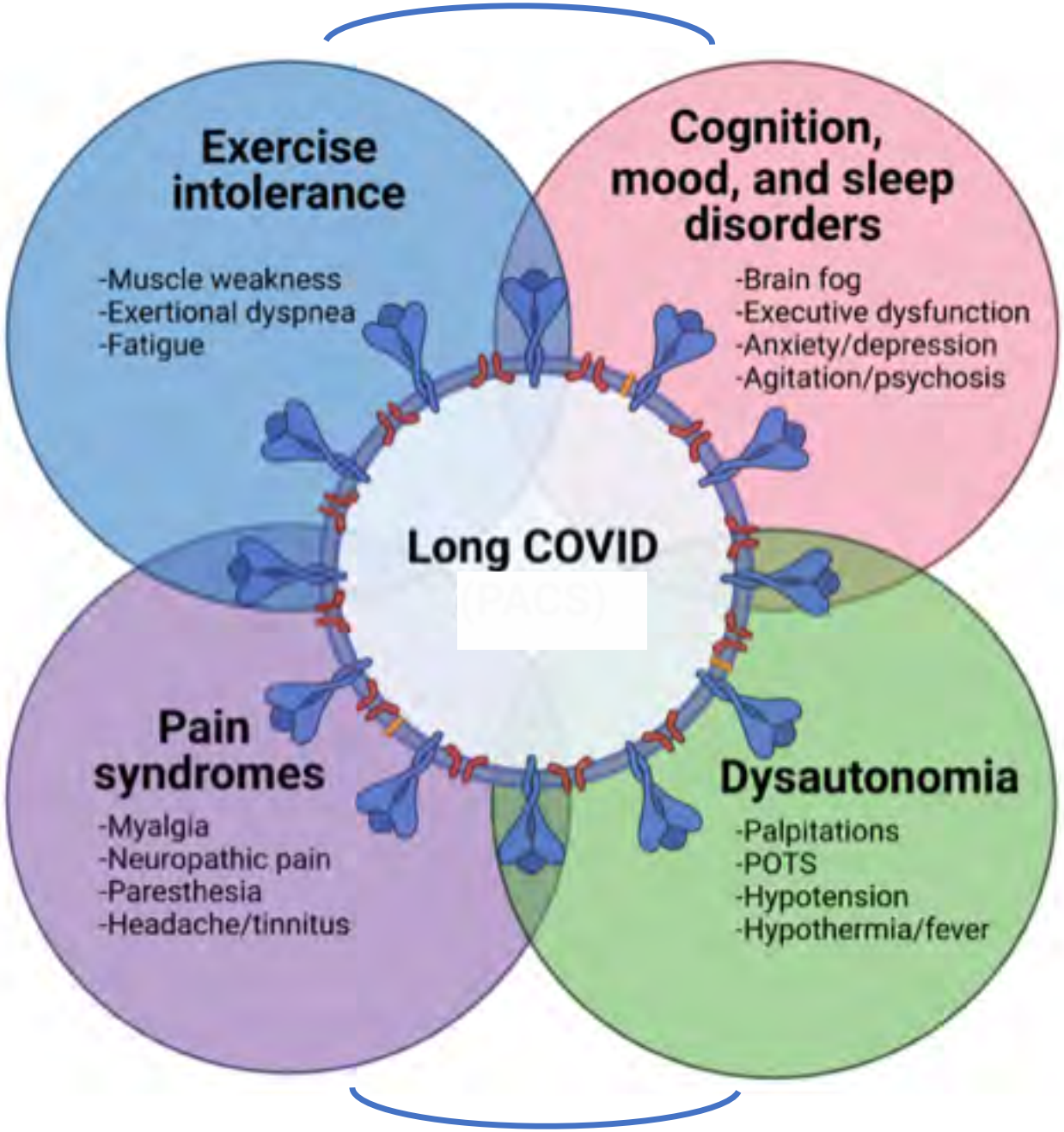
Effect of covid-19 vaccination on long covid: systematic review

Oyungerel Byambasuren [1], Paulina Stehlik [1], Justin Clark [1], Kylie Alcorn,[2] Paul Glasziou [1]

Study or subgroup	Log (odds ratio)	Standard error	Odds ratio IV, random (95% CI)
One dose before infection			
Ioannou 2022[23]	0.030	0.041	1.03 (0.95 to 1.12)
Antonelli 2022[20]	0.030	0.098	1.03 (0.85 to 1.25)
Taquet 2021[27]	-0.041	0.039	0.96 (0.89 to 1.04)
Azzolini 2022[22]	-0.151	0.719	0.86 (0.21 to 3.52)
Simon 2021[31]	-1.514	0.049	0.22 (0.20 to 0.24)
Two doses before infection			
van der Maaden 2022[28]	0.020	0.093	1.02 (0.85 to 1.22)
Taquet 2021[27]	0.000	0.026	1.00 (0.95 to 1.05)
Ioannou 2022[23]	-0.249	0.070	0.78 (0.68 to 0.89)
Mohr 2022[24]	-0.357	0.096	0.70 (0.58 to 0.84)
Ayoubkhani 2022[21]	-0.528	0.084	0.59 (0.50 to 0.70)
Tannous 2022[26]	-0.545	0.056	0.58 (0.52 to 0.65)
Antonelli 2022[20]	-0.673	0.238	0.51 (0.32 to 0.81)
Azzolini 2022[22]	-1.386	0.650	0.25 (0.07 to 0.89)
Three doses before infection			
Azzolini 2022[22]	-1.833	0.854	0.16 (0.03 to 0.85)



Post-Intensive Care Syndrome



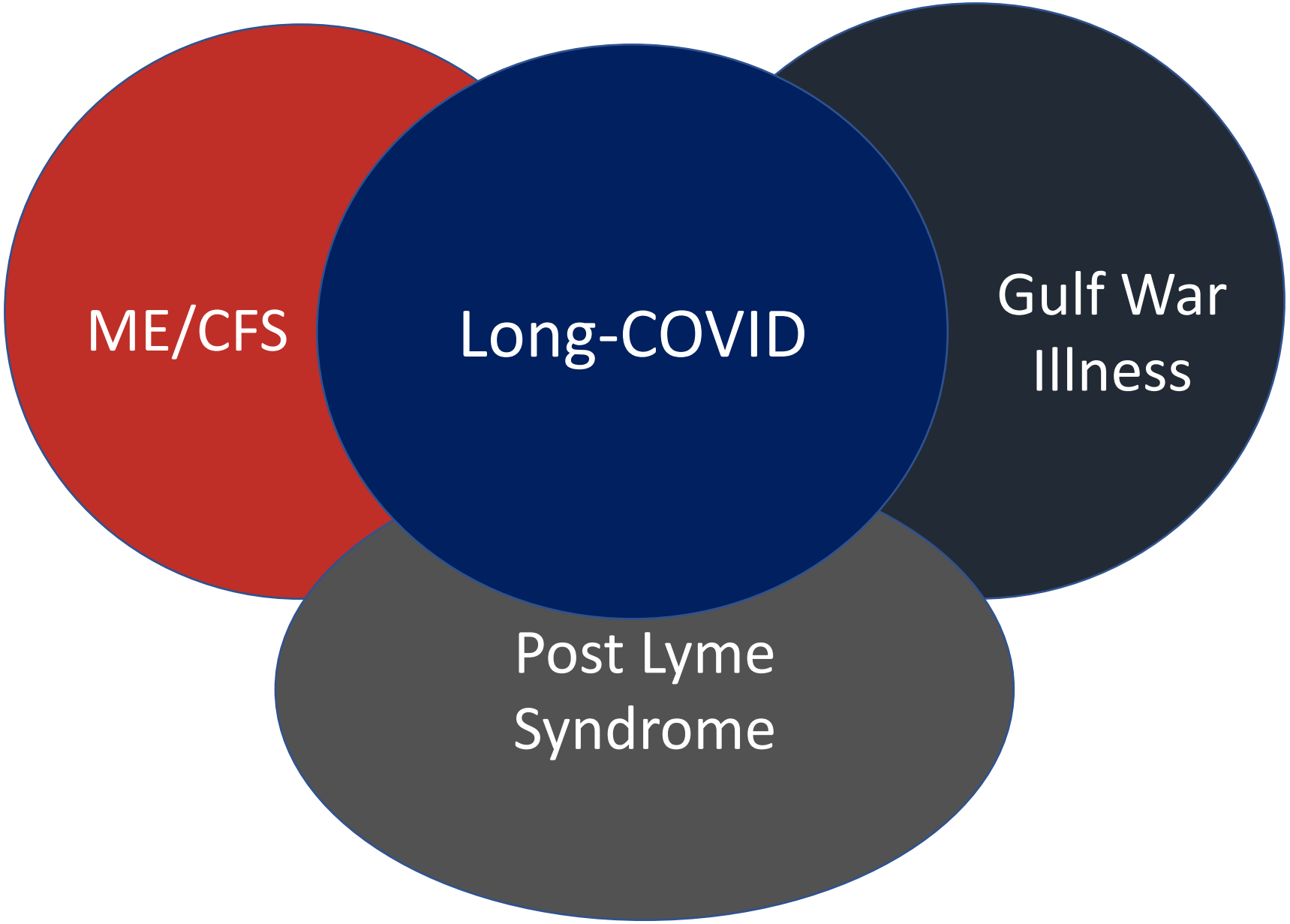
Balcom, et al., Brain 2021

Brain Fog: FADE IN MEMORY

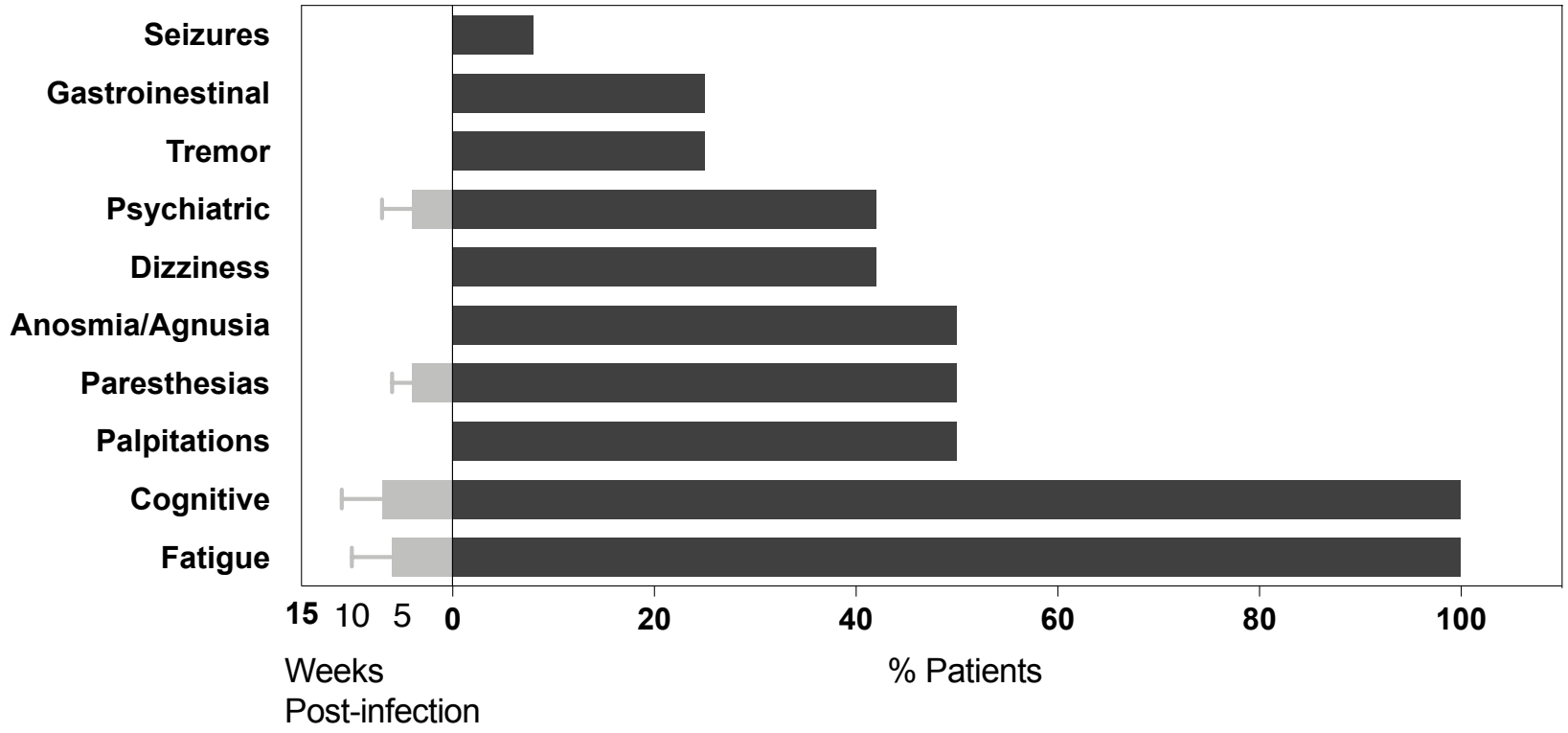
- **F**atigue
- **F**luency
- **A**ttention deficit
- **D**epression
- **E**xecutive dysfunction
- **In**formation processing
- **Memory** impairment; subcortical

Dubey et al., J Alzheimers Dis Rep 2023

Biggest Mysteries of Medicine

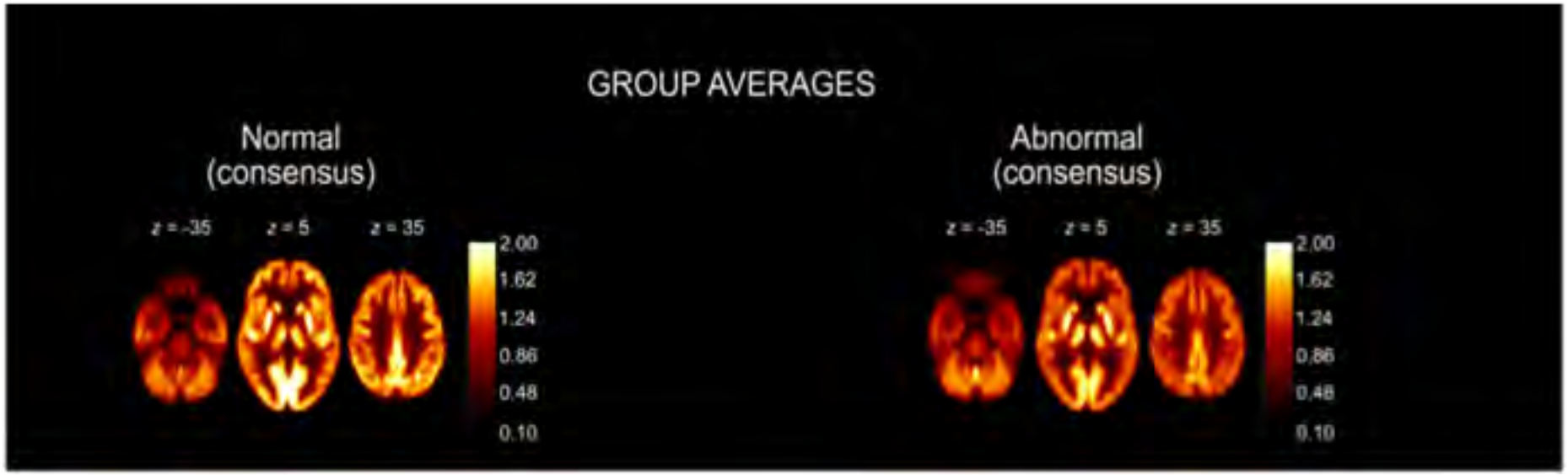


Neurological Symptoms following Mild COVID



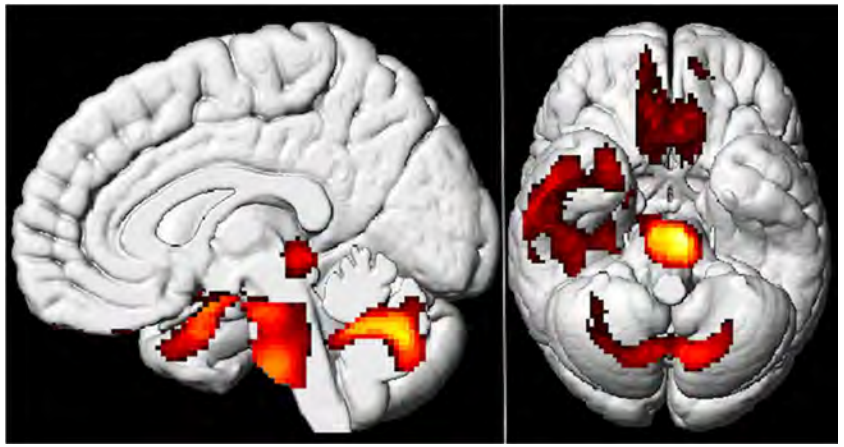
Mina et al., in press 2023

^{18}FDG PET scans in subacutely ill hospitalized patients with COVID-19



Hosp et al., Brain 2021

^{18}FDG PET scans in long-COVID patients with COVID-19



Regions of hypometabolism
(n=44)

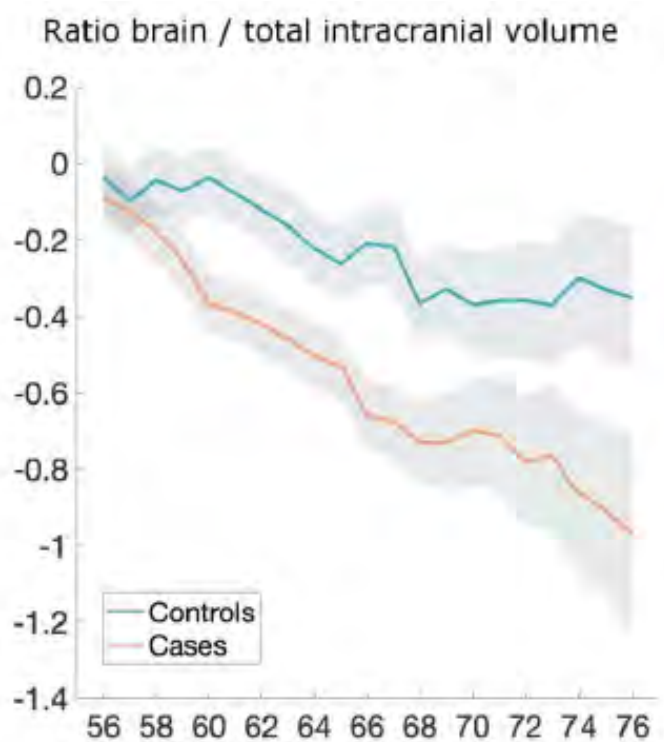
Guedj et al., European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2823–2833

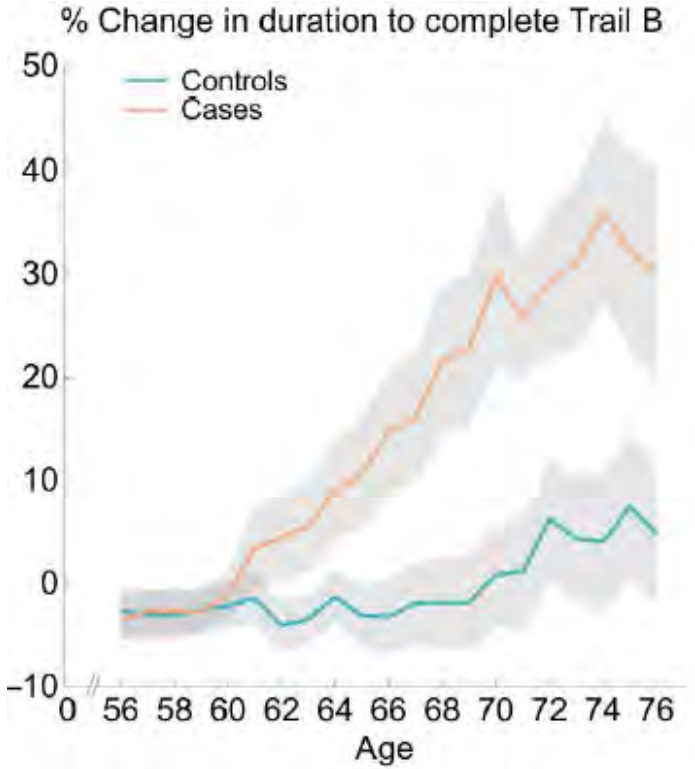
nature

https://doi.org/10.1038/s41586-022-04569-5

Accelerated Article Preview

SARS-CoV-2 is associated with changes in brain structure in UK Biobank

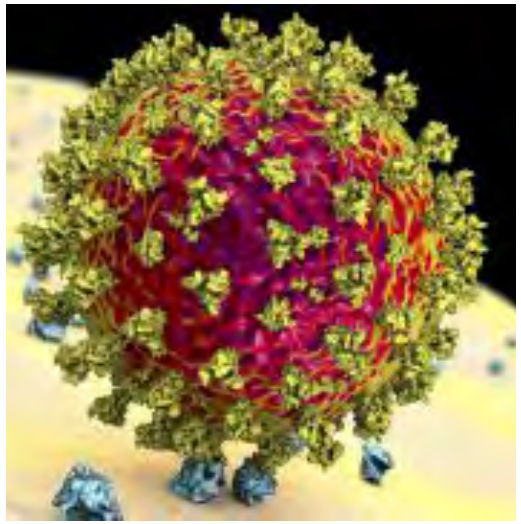




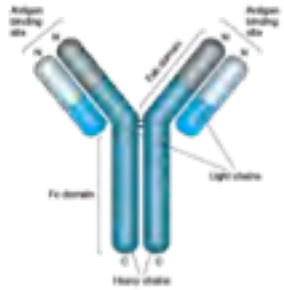
COVID cases: 401
Controls: 384

Douaud et al., 2022

Persistent viral infection



Immune dysregulation

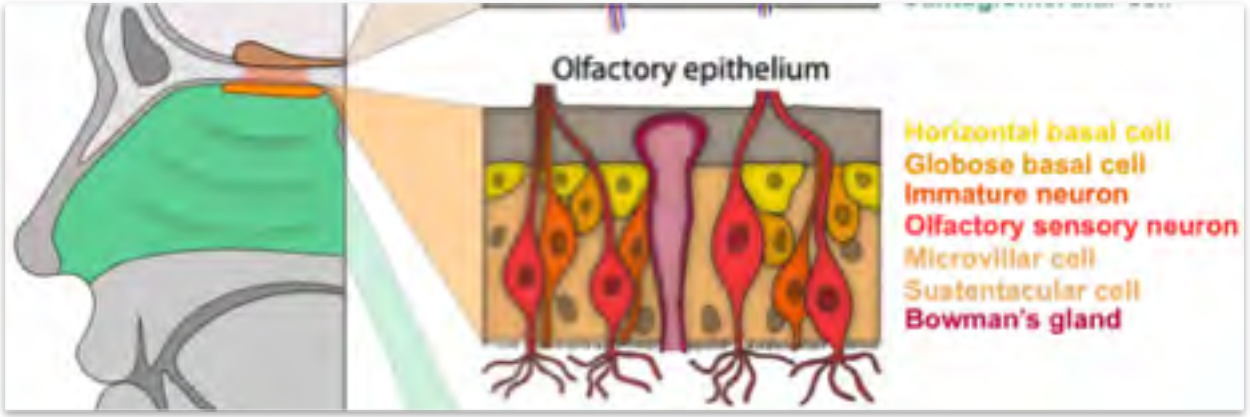


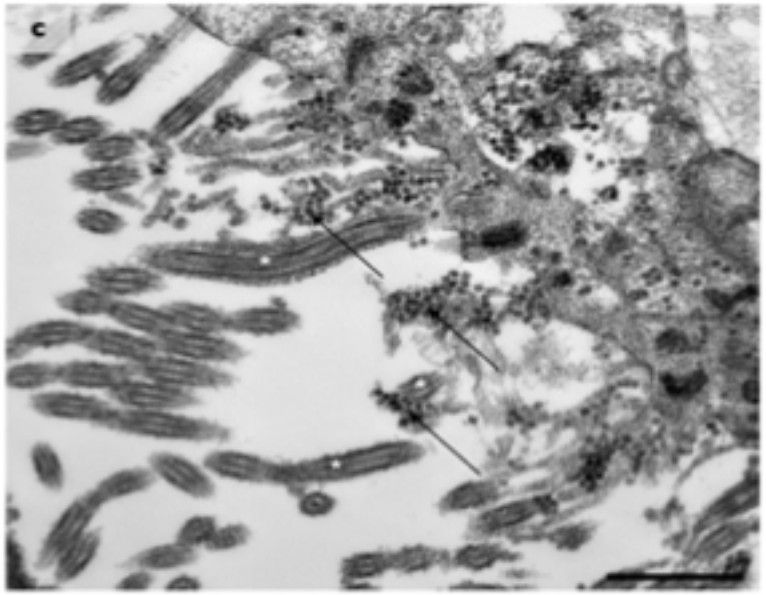
Antibodies

Macrophages

Can the virus enter the brain through the olfactory pathways?

Virus infects Sustentacular cells



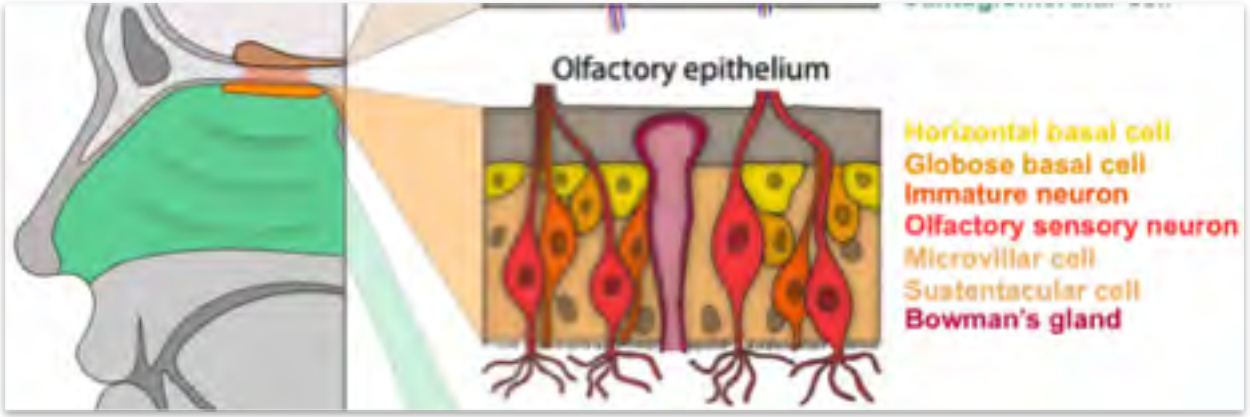


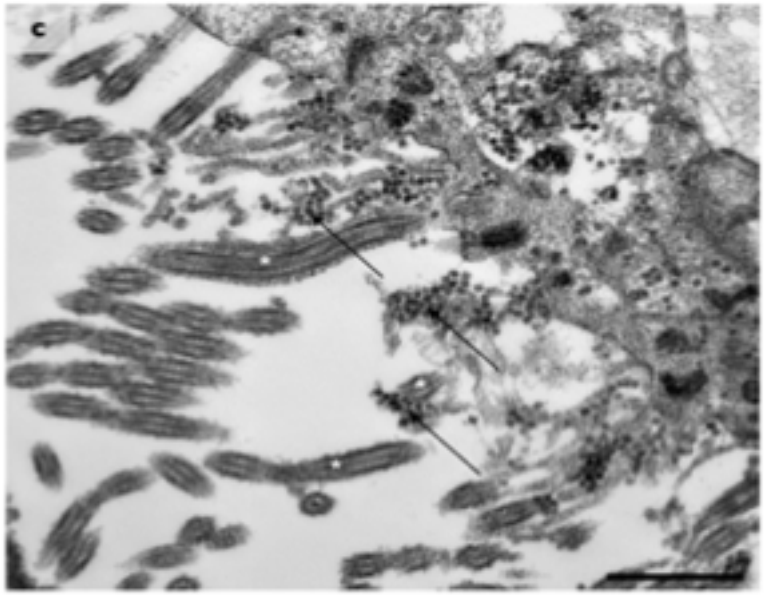
Images: McQuaid et al., 2021 DOI: 10.1186/s12987-021-00267-y;
Brann et al., 2020 DOI:10.1126/sciadv.abc5801

Images: Meinhardt et al., 2020 DOI:0.1038/s41593-020-00758-5

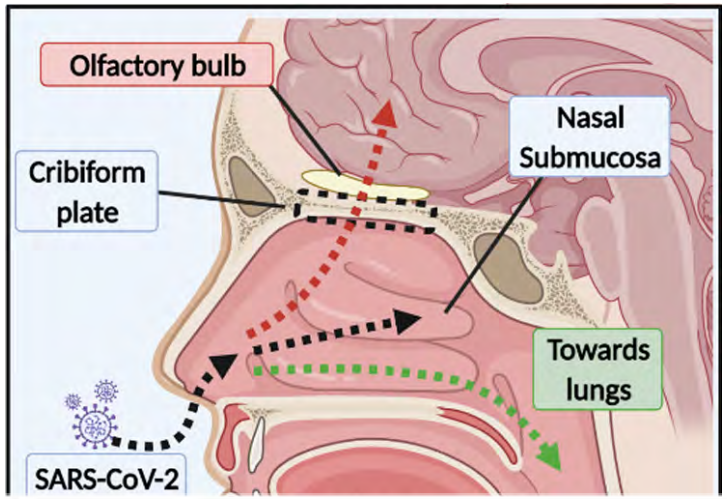
Can the virus enter the brain through the olfactory pathways?

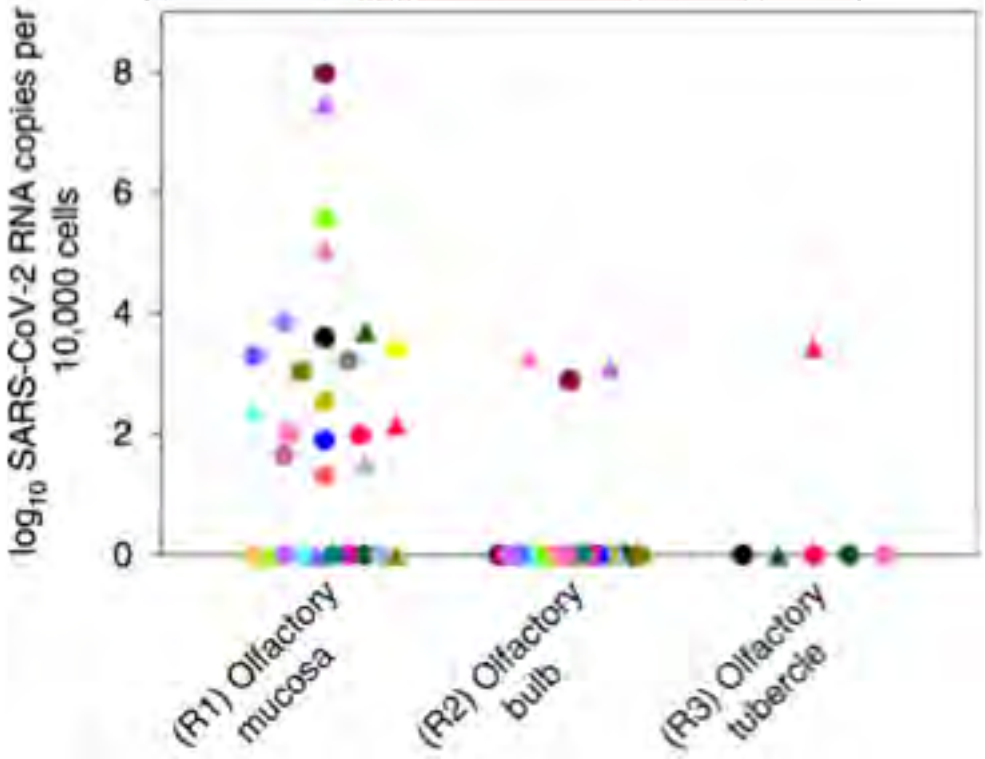
Virus infects Sustentacular cells





Images: McQuaid et al., 2021 DOI: 10.1186/s12987-021-00267-y;
Brann et al., 2020 DOI:10.1126/sciadv.abc5801





Images: Meinhardt et al., 2020 DOI:0.1038/s41593-020-00758-5

Detection of virus in brain at autopsy

- Rarely detected; in small quantities
- We and others have not been able to detect virus by
  - Immunostaining
  - PCR
  - RNA in situ hybridization
  - RNA sequencing
  - RNA hybridization followed by PCR

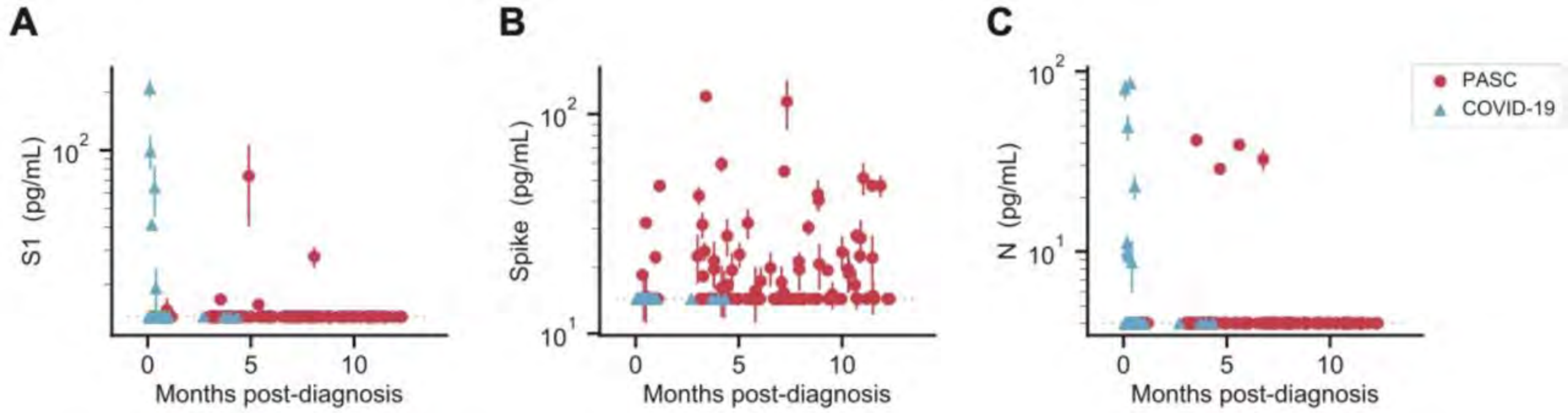
Lee et al., NEJM 2021

SARS-CoV-2 persistence in human body

Tissue Category	DOI (days)	Avg. N gene copies/ng RNA (SD)
Respiratory Tract	≤14	9,210.10 (43,179.20)
	15-30	19.67 (77.98)
	≥31	0.65 (2.61)
Cardiovascular	≤14	38.75 (106.08)
	15-30	0.59 (3.43)
	≥31	0.47 (2.51)
Lymphoid	≤14	30.01 (157.86)
	15-30	0.35 (1.28)
	≥31	0.73 (3.83)
Gastrointestinal	≤14	24.66 (99.37)
	15-30	0.87 (4.38)
	≥31	0.24 (2.17)
Renal & Endocrine	≤14	12.76 (59.01)
	15-30	0.03 (0.16)
	≥31	0.04 (0.33)
Reproductive	≤14	0.36 (0.58)
	15-30	1.87 (6.72)
	≥31	0.01 (0.02)
Muscle, Nerve, Adipose, & Skin	≤14	27.50 (101.13)
	15-30	50.65 (264.46)
	≥31	0.54 (3.03)
Ocular	≤14	57.40 (242.40)
	15-30	0.07 (0.24)
	≥31	0.03 (0.12)
Central Nervous System	≤14	32.93 (121.69)
	15-30	2.37 (7.34)
	≥31	0.39 (1.40)

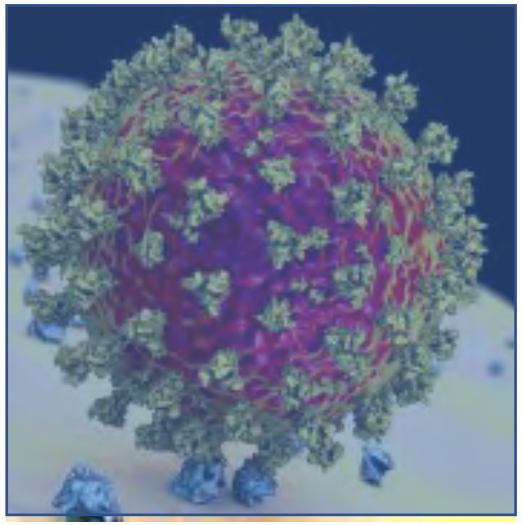
Chertow et al., Research Square 2021

Detection of Spike protein in blood of patients with PASC (Long-COVID): Restricted viral replication

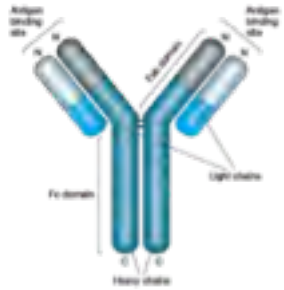


Swank et al., MedRxiv 2022

Persistent viral infection



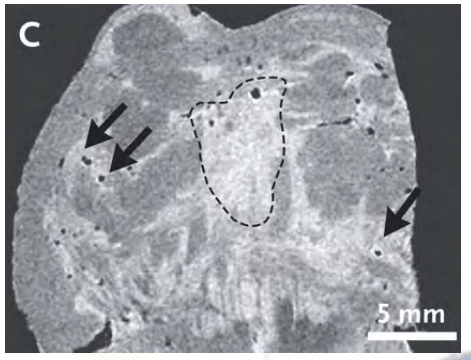
Immune dysregulation

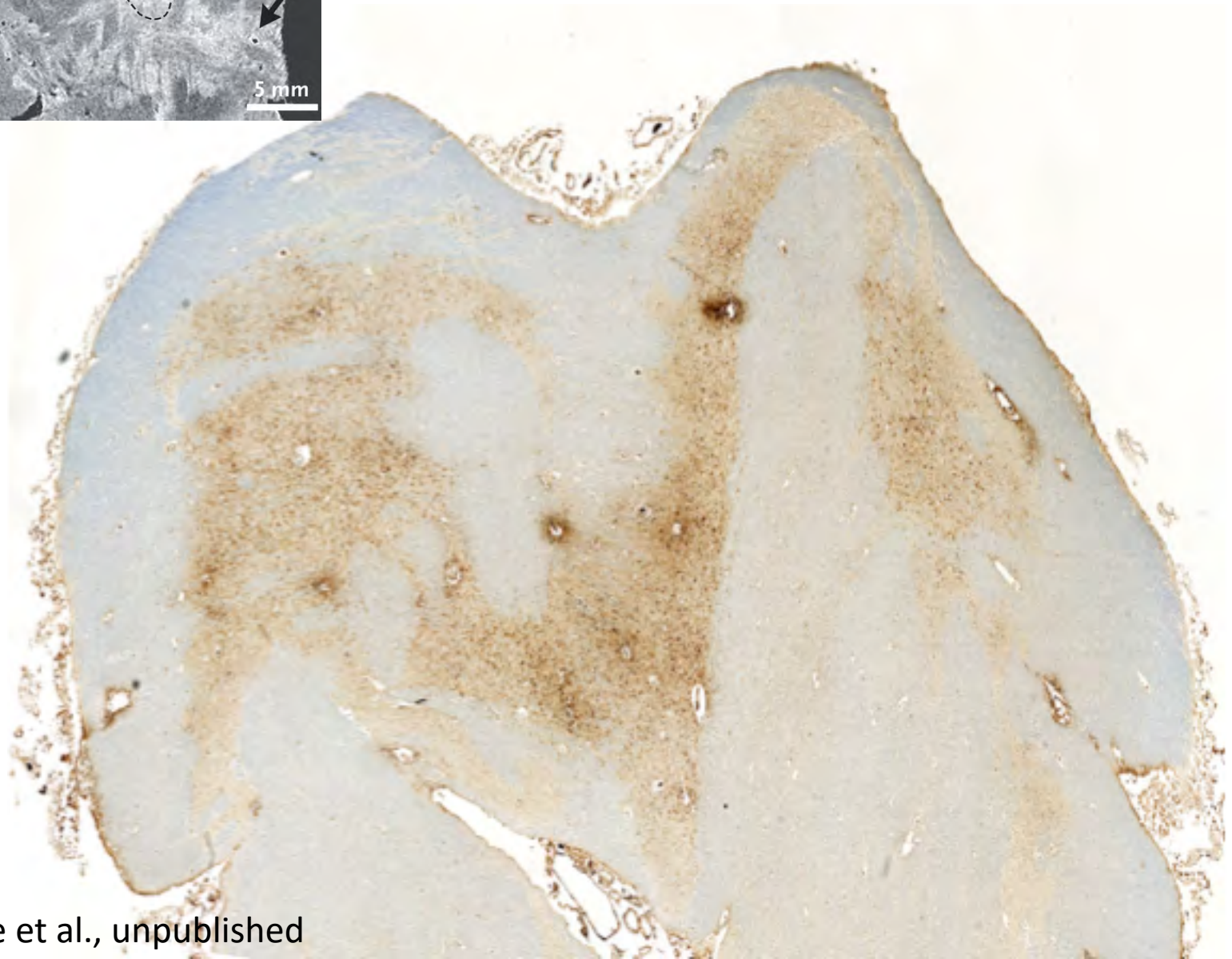


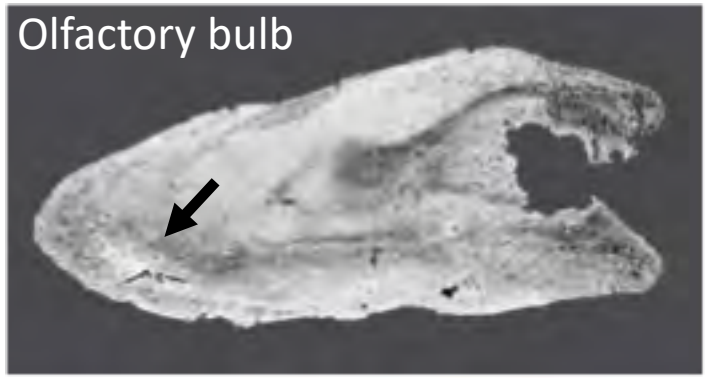
Antibodies

Macrophages

Perivascular fibrinogen leakage indicates vascular injury







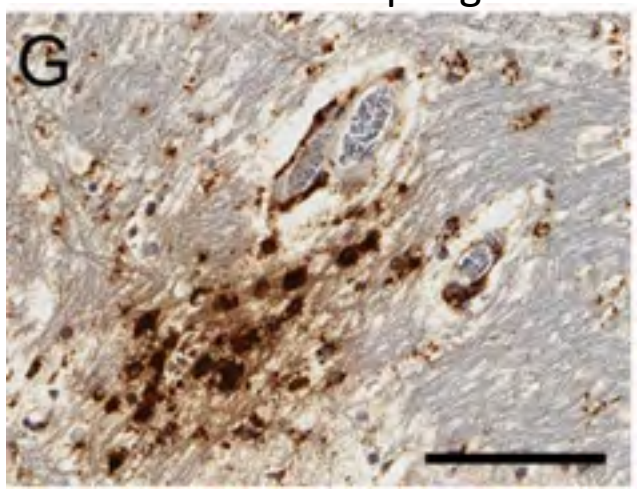
Lee et al., unpublished

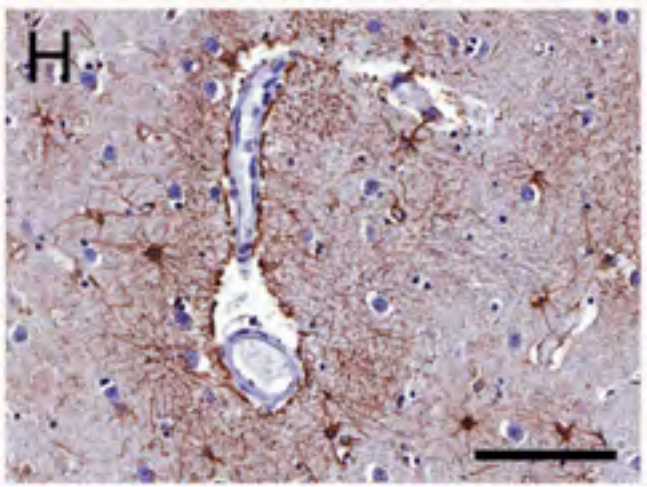
CD68: Macrophages

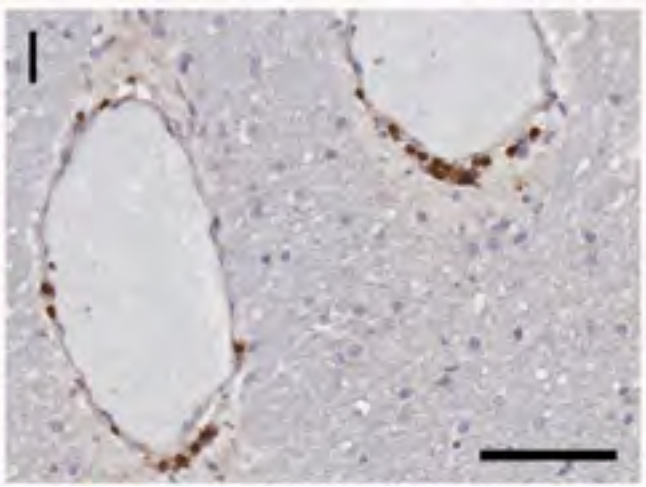
GFAP: Astrocytes

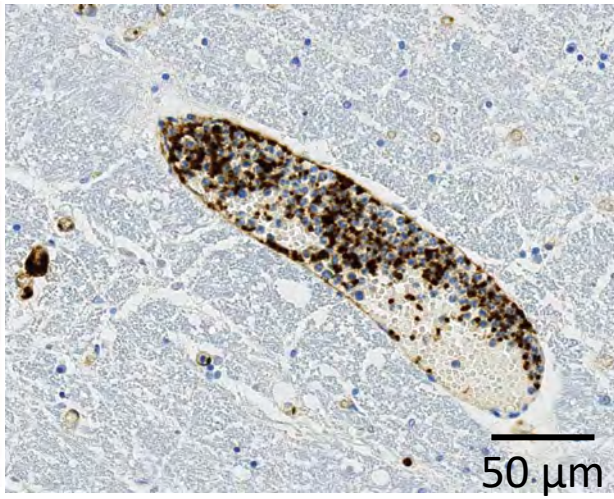
CD3 T cells

CD61: Activated platelets









Perivascular activated macrophages

Perivascular activated astrocytes

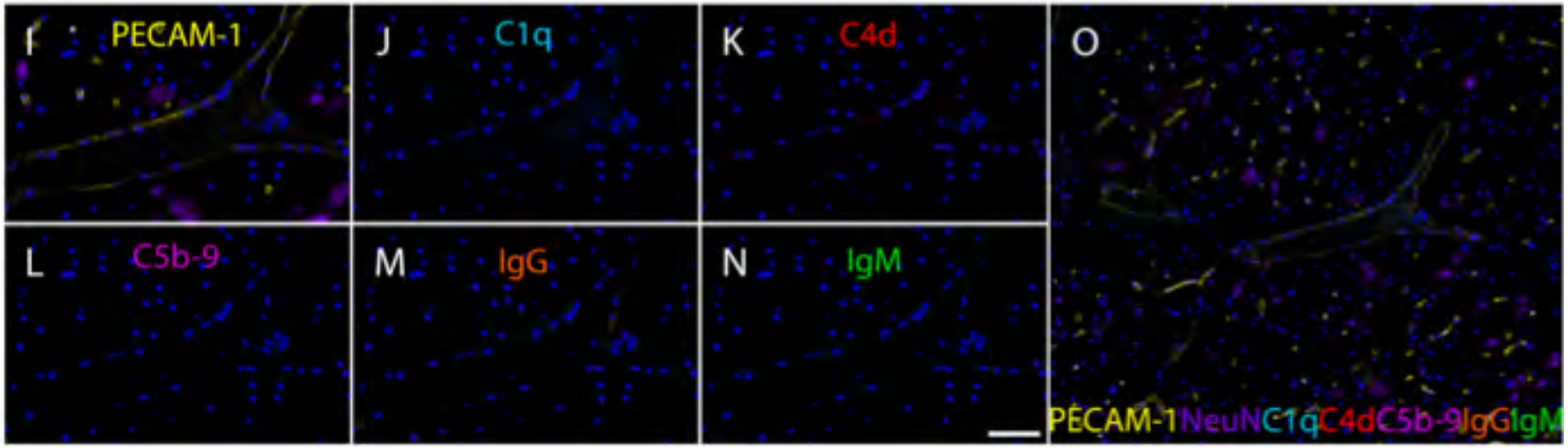
Very few T cells and confined to the blood vessels

Platelets are sticking to endothelial cells and forming clots

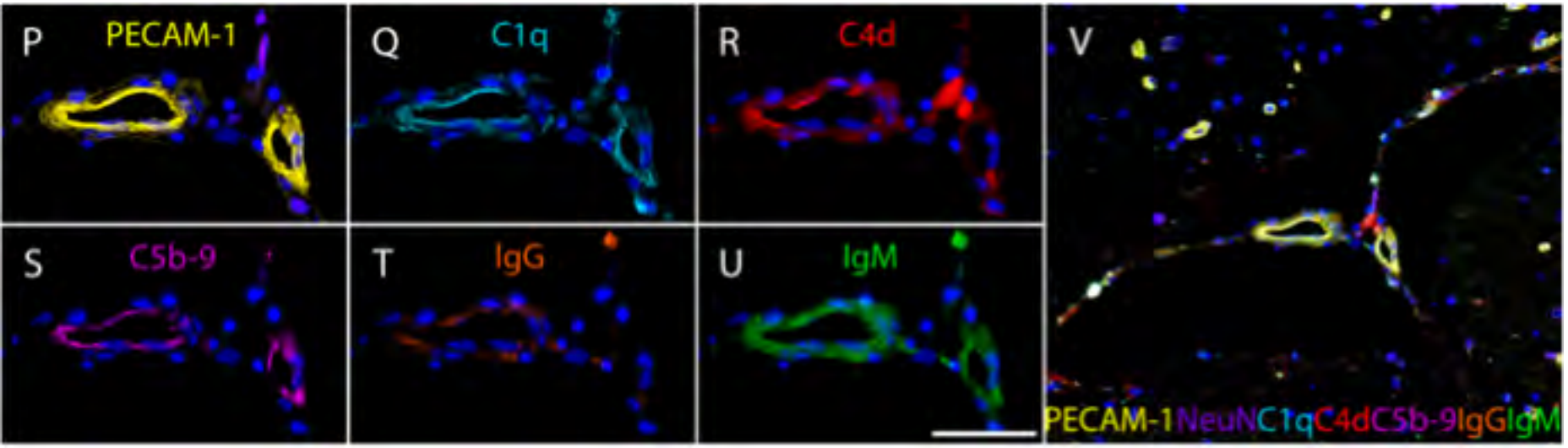
Lee et al. Brain 2022

Lee et al., NEJM 2021

Control



COVID-19



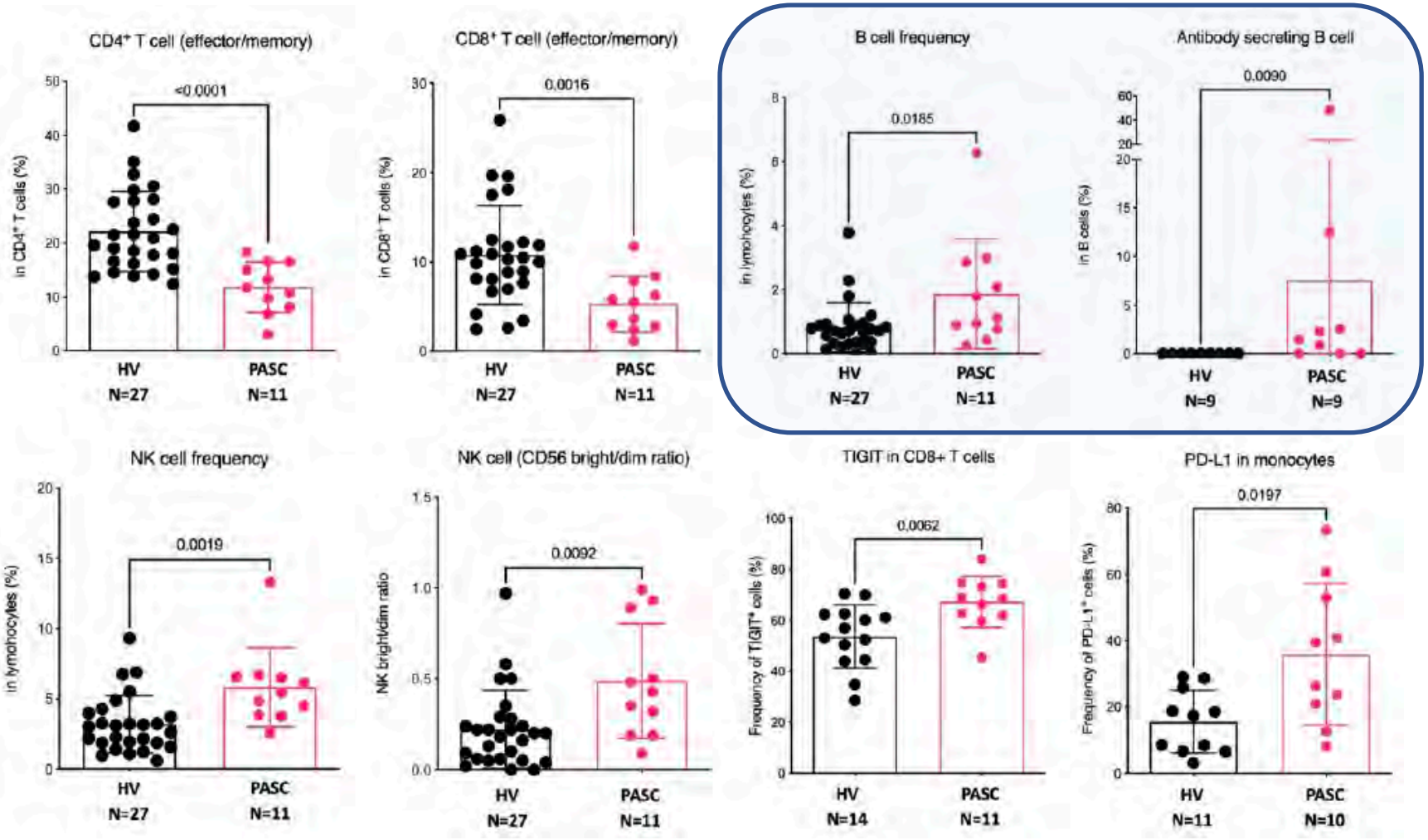
Activation of endothelial cells (PECAM-1)

Deposition of complement

Deposition of IgG and IgM

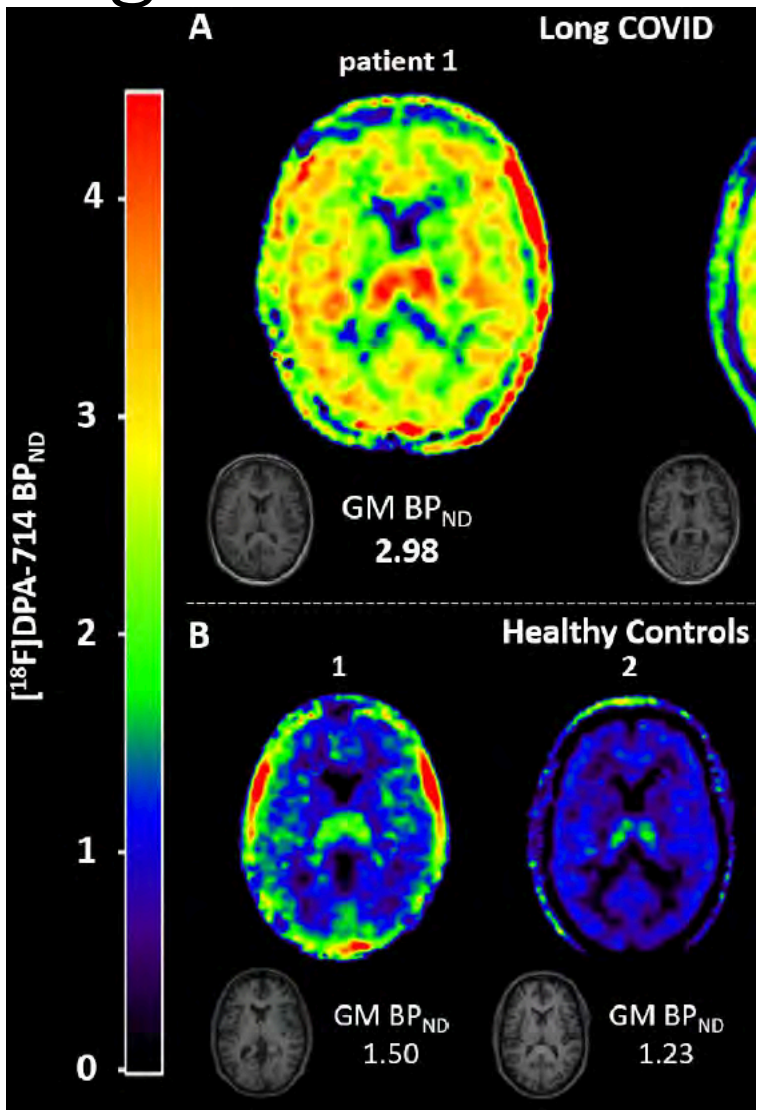
Lee at al., Brain 2022

Increased plasma B cells in Long-COVID



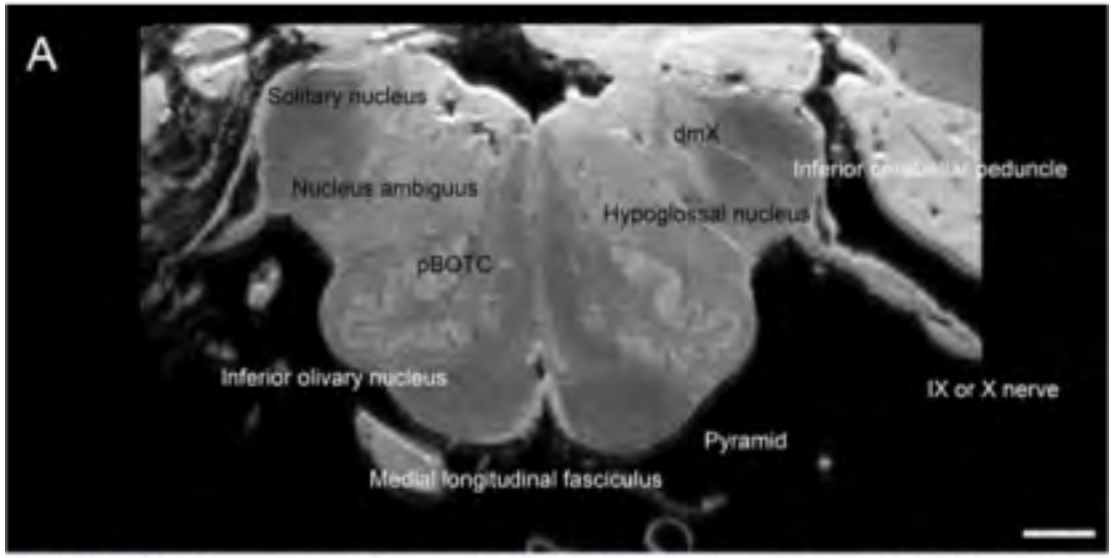
Mina et al., In press

Diffuse microglial cell activation in Long-COVID

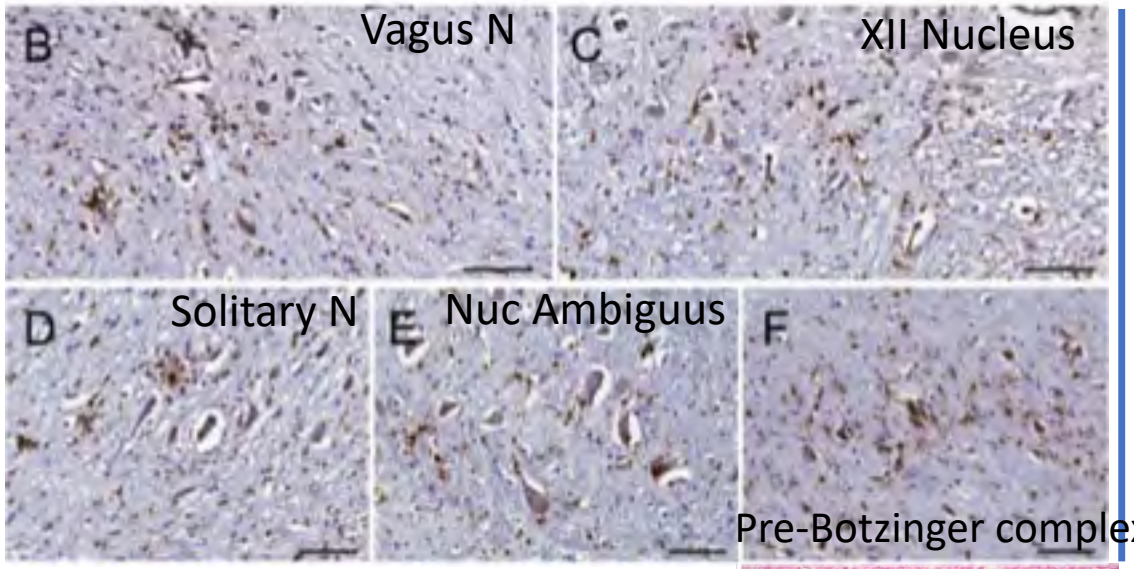


Visser et al., Med Rxiv 2022

Neuronal Injury in Brainstem

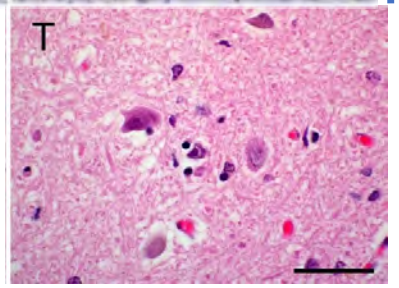


Post-mortem MRI
(11.4T scanner)
100 micron sections



CD68

Pre-Botzinger complex



Pre-Botzinger complex

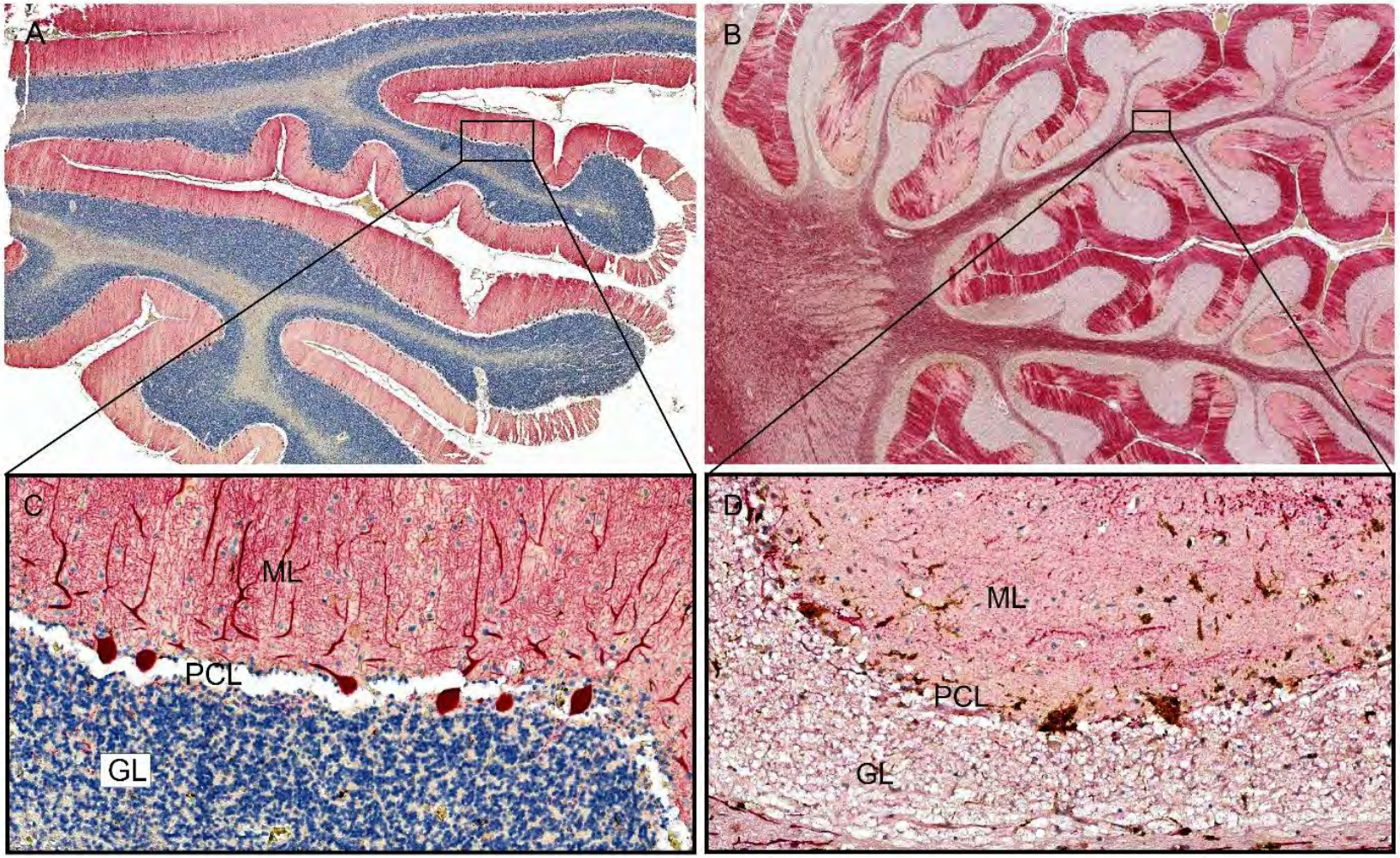
Neuronophagia

Lee et al., NEJM 2021

Loss of Purkinje cells in cerebellum

Control cerebellum

COVID-19



Lee et al., Brain 2022

Can SARS-CoV-2 infection accelerate Neurodegenerative Diseases?

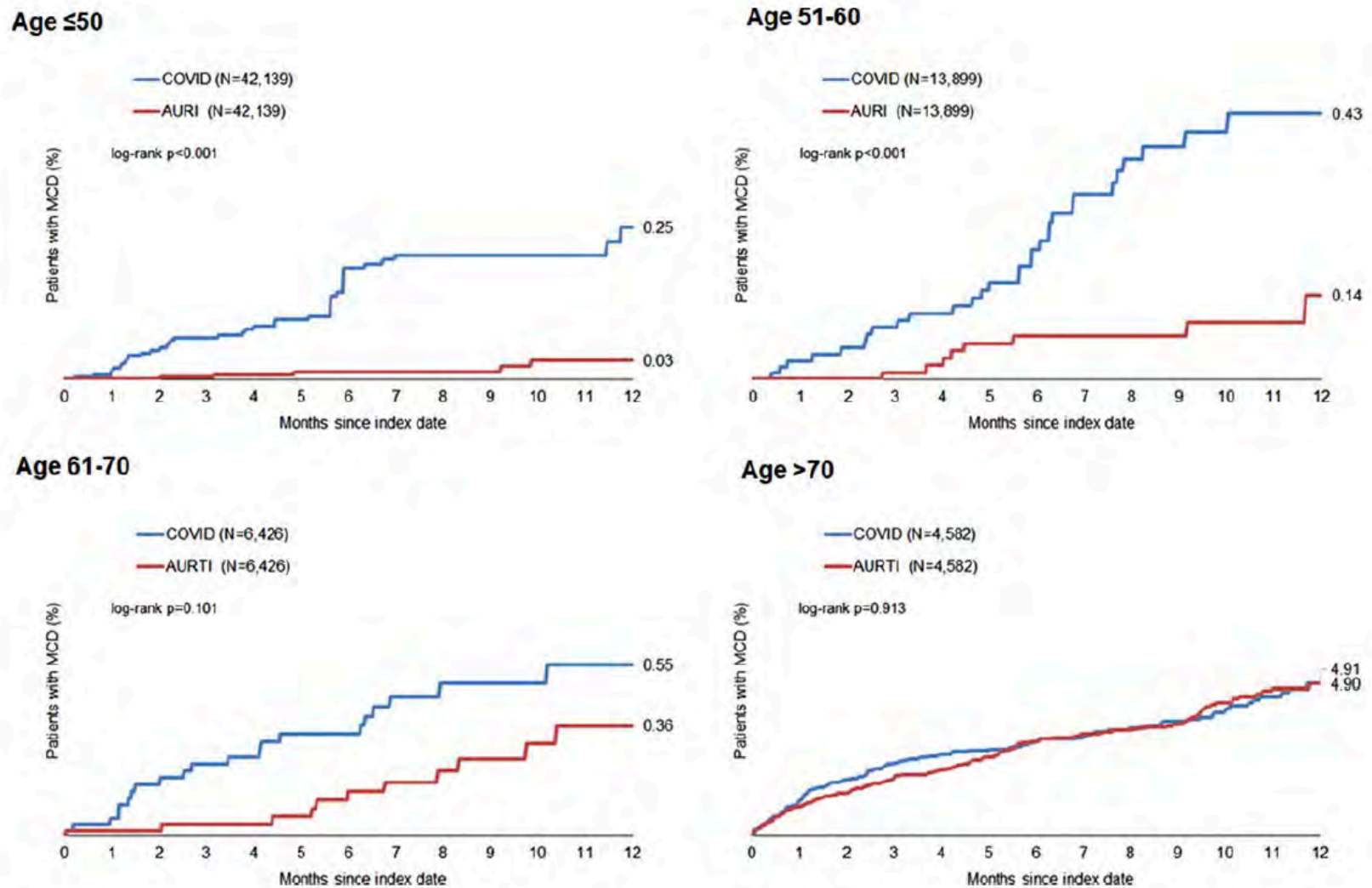
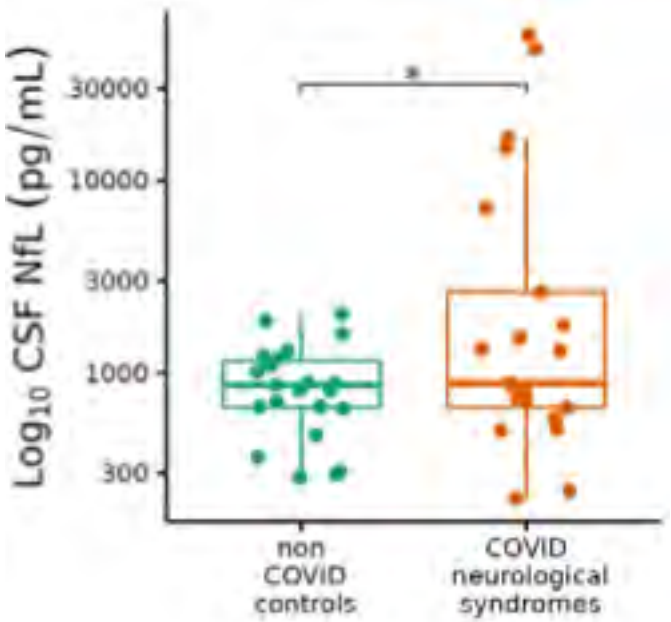
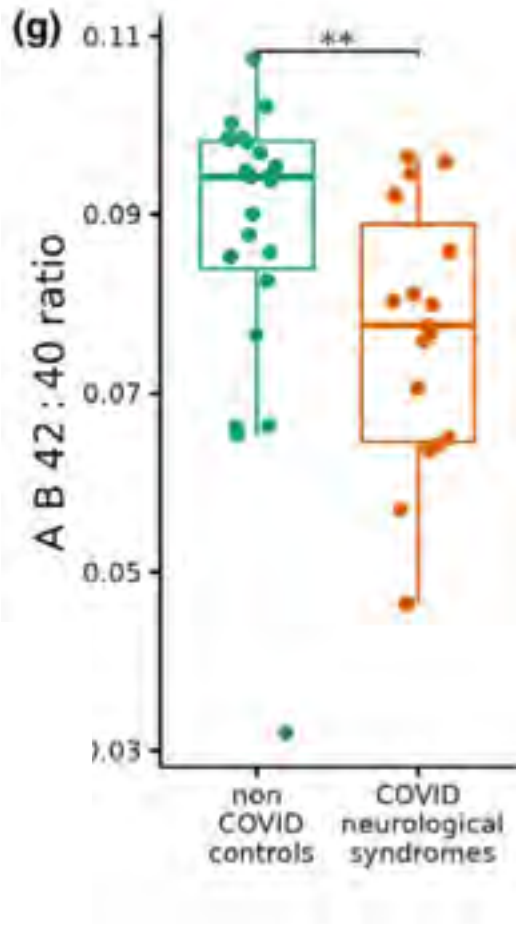


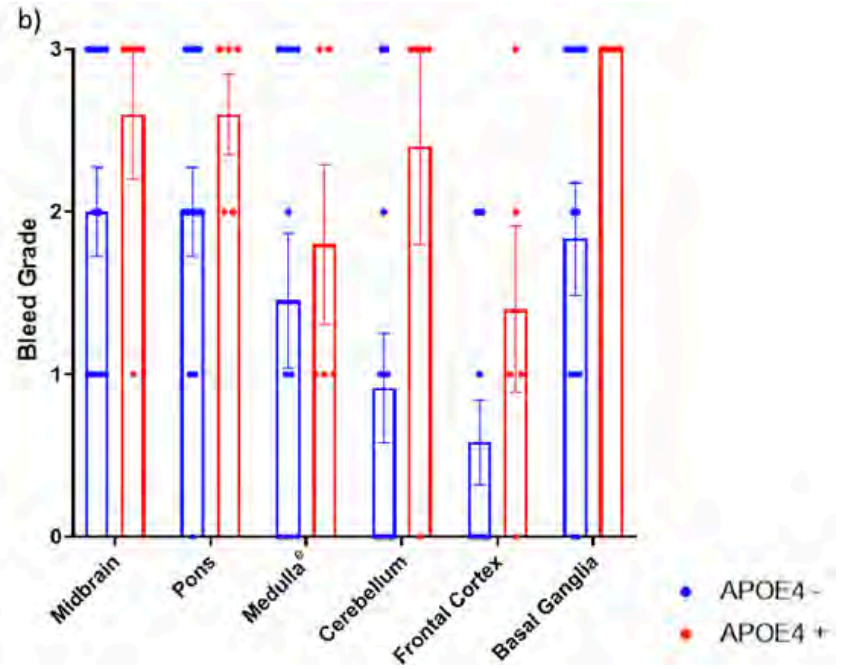
Fig. 2. Kaplan-Meier curves for incidence of mild cognitive disorder in patients with COVID-19 versus patients with upper respiratory tract infection.

Bohelken et al., J Alzheimers Dis Rep 2022

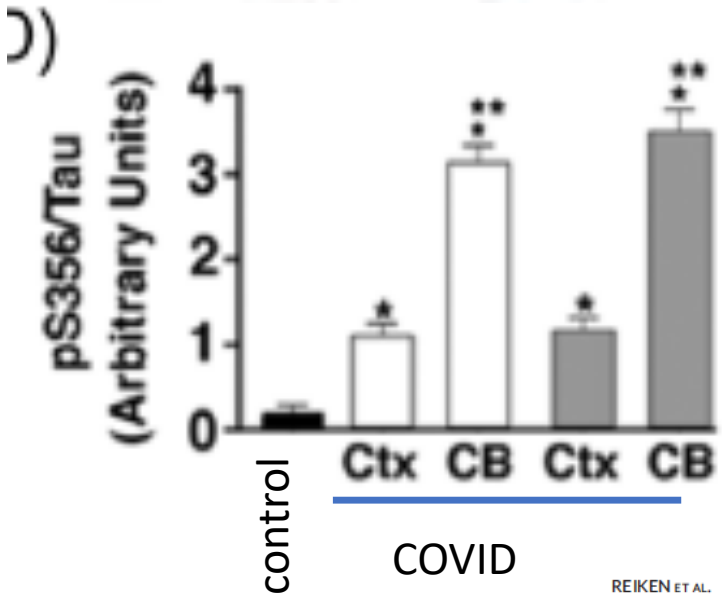
MARKERS OF NEURONAL INJURY and ALZHEIMER's DISEASE





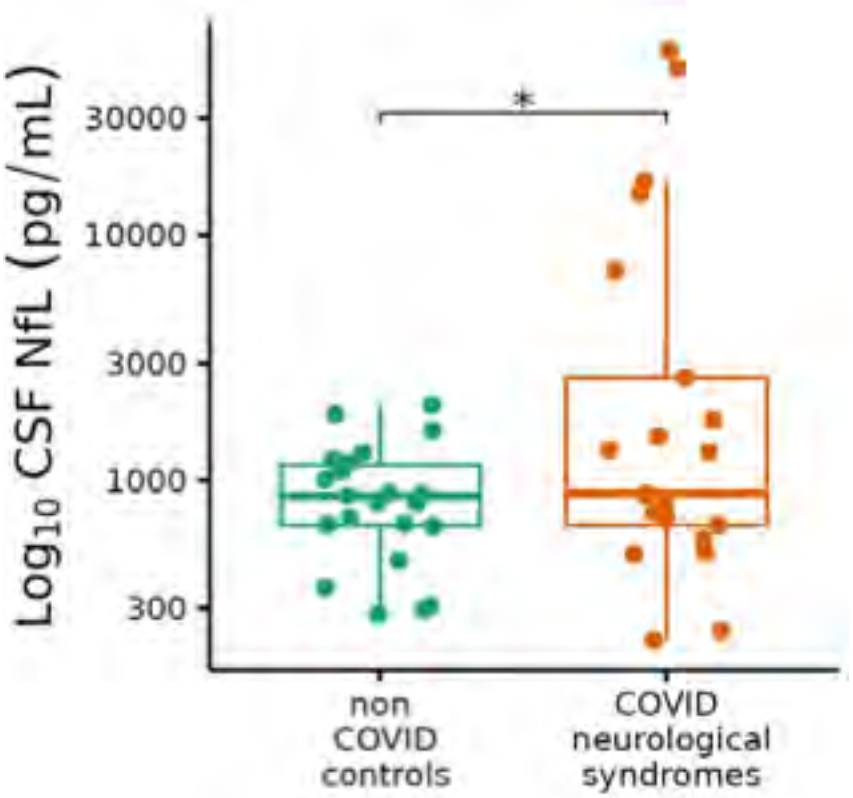


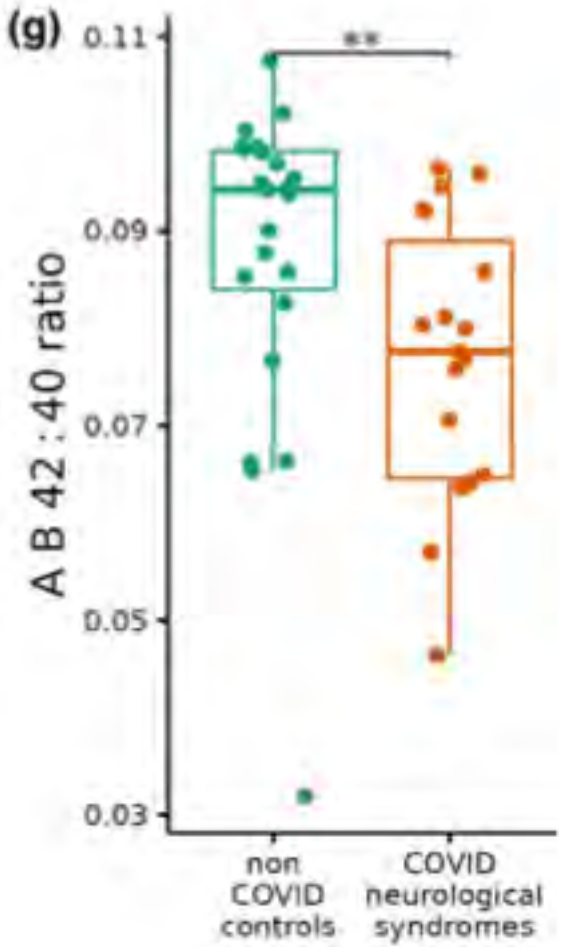
Kurki *et al.*
Acta Neuropathologica Communications (2021) 9:199

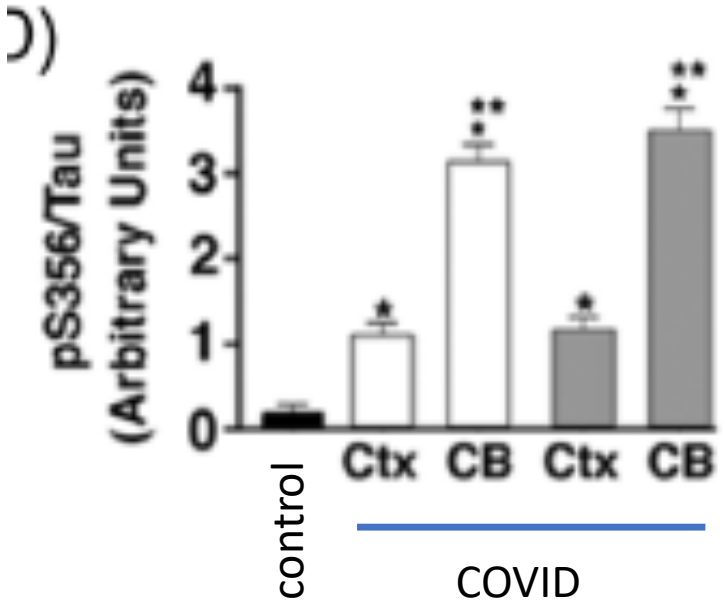


Ziff et al., J Neurochem 2021

MARKERS OF NEURONAL INJURY and ALZHEIMER's DISEASE

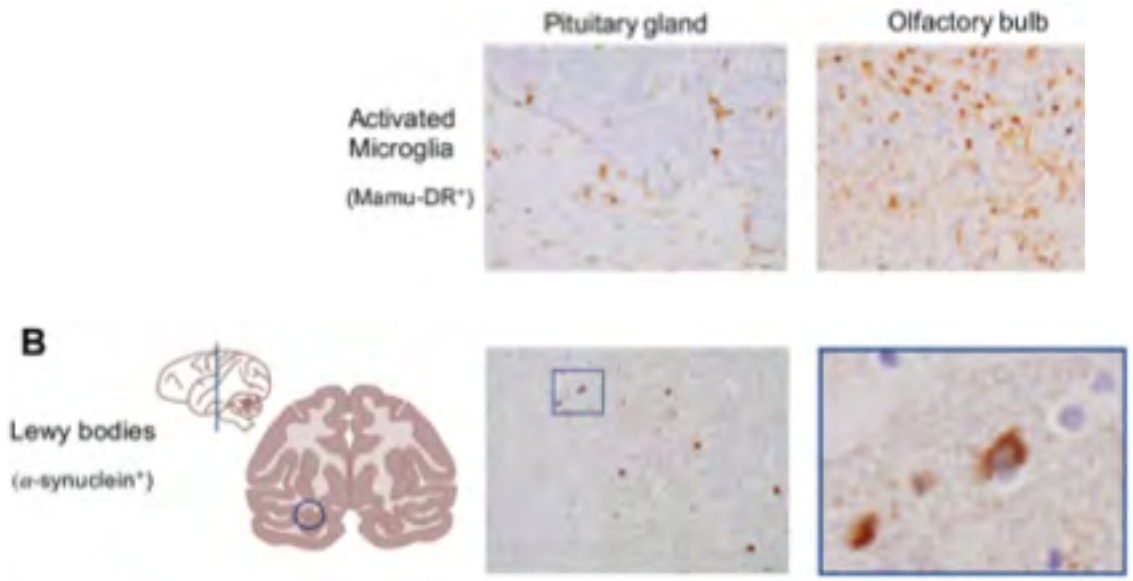






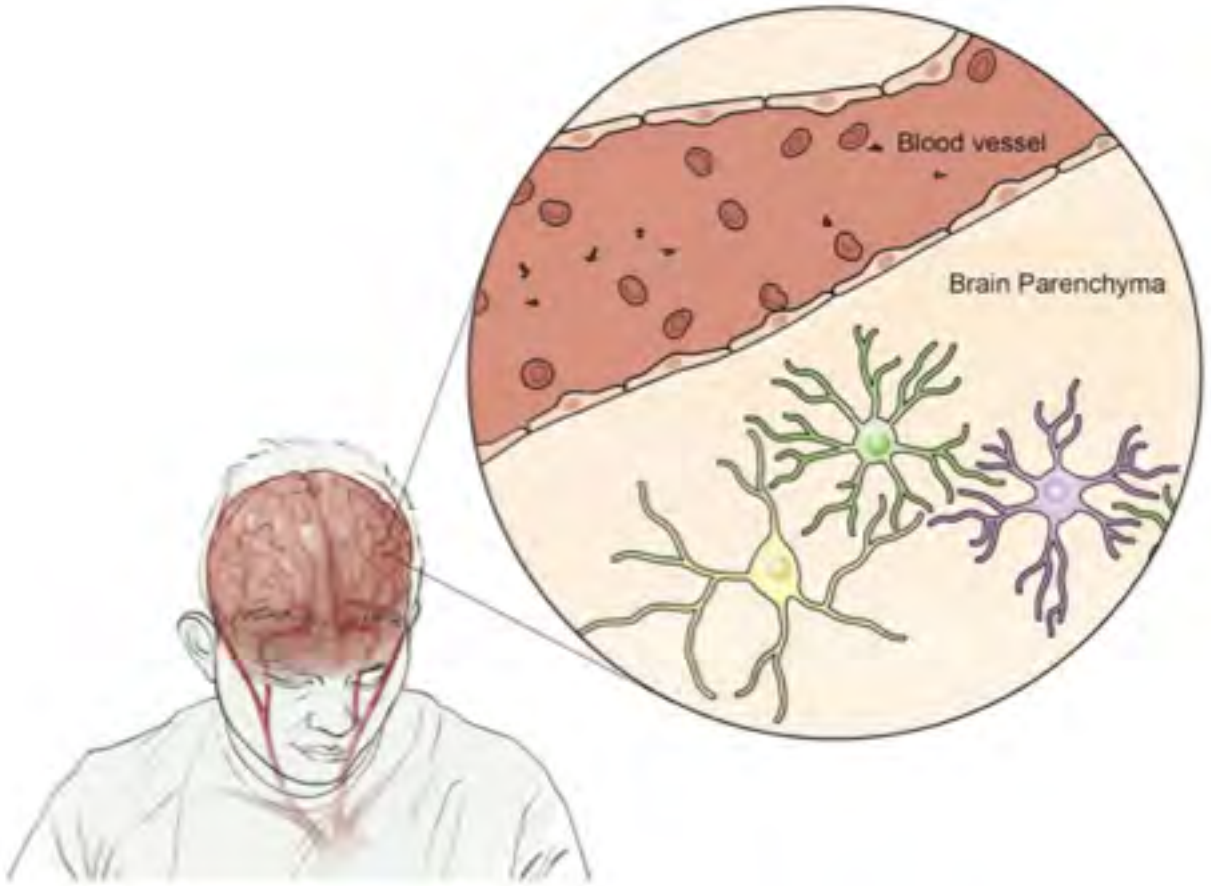
Ziff et al., J Neurochem 2021

SARS-CoV-2 causes brain inflammation and induces Parkinson's Disease pathology in macaques



Philippens et al.,

Neuropathogenesis of LONG-COVID



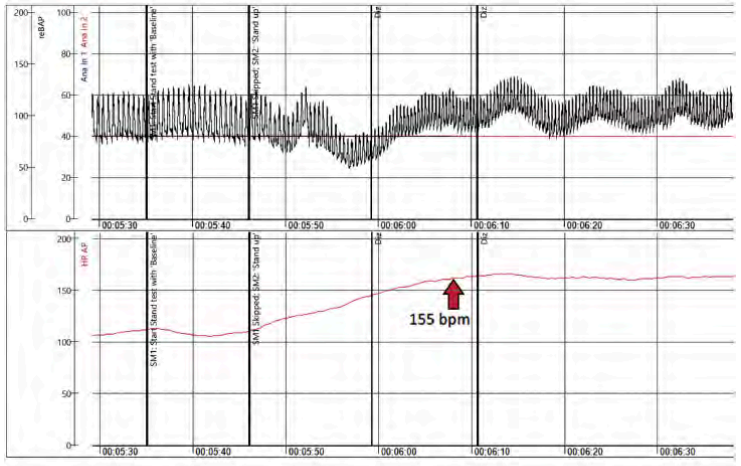
Spudich and Nath Science 2022

Credit: Myounghwa Lee, NINDS

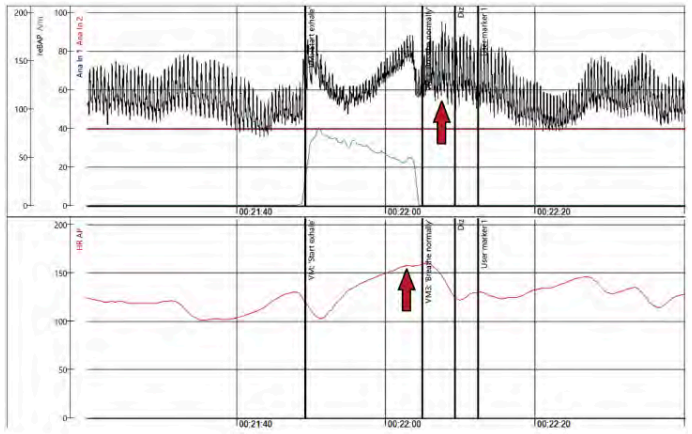
Long-Haul Post–COVID-19 Symptoms Presenting as a Variant of Postural Orthostatic Tachycardia Syndrome

The Swedish Experience

Madeleine Johansson, MD, PhD,[a,b,*] Marcus Ståhlberg, MD, PhD,[c,d,*] Michael Runold, MD, PhD,[e] Malin Nygren-Bonnier, PhD, PT,[f,g] Jan Nilsson, MD, PhD,[a] Brian Olshansky, MD,[h] Judith Bruchfeld, MD, PhD,[i,j,†] Artur Fedorowski, MD, PhD[a,b,†]



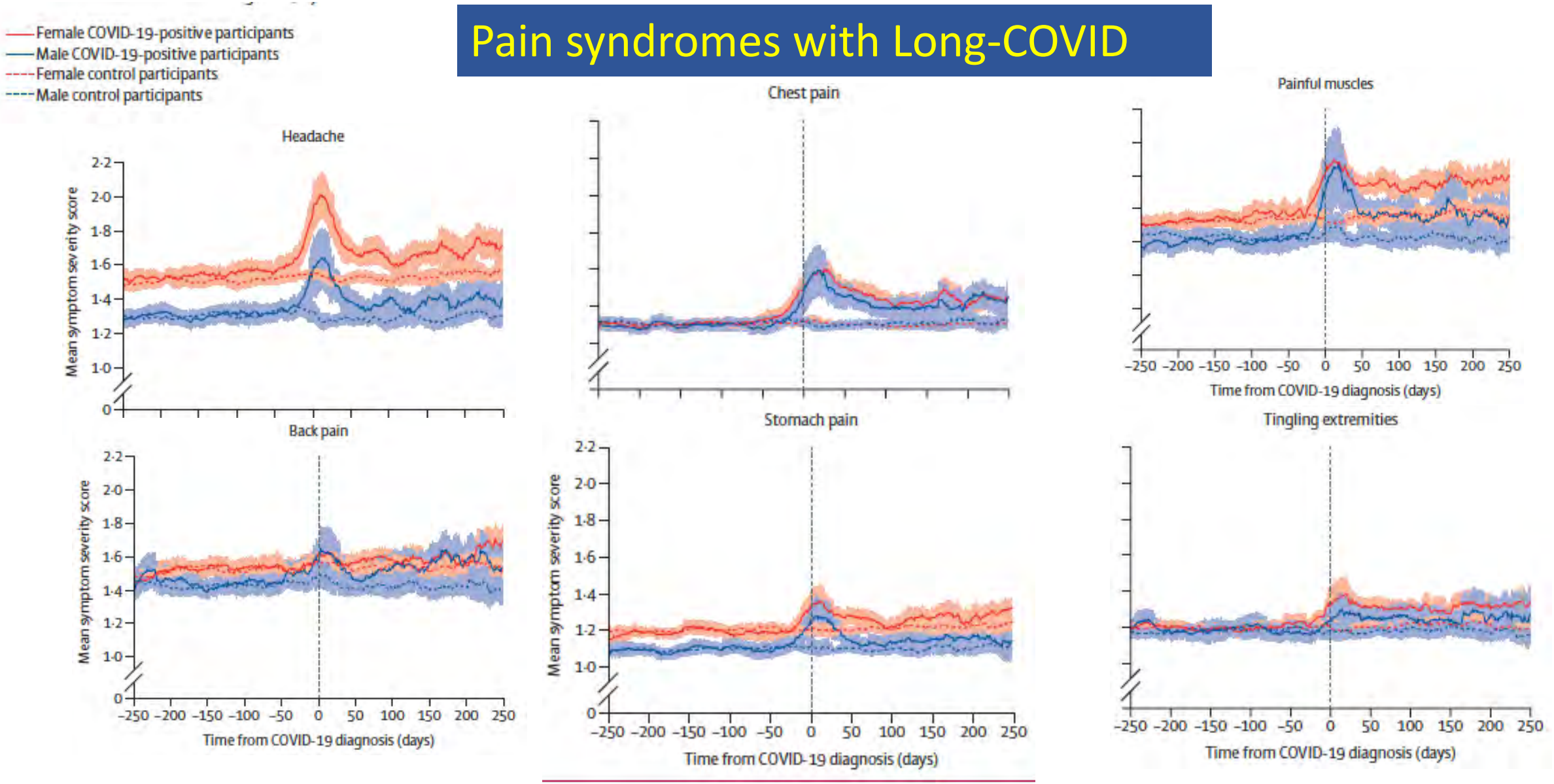
Active standing test demonstrating initial orthostatic hypotension and POTS in a 42-year-old woman (Patient #1) with long-haul post-coronavirus disease-2019 symptoms, with **red arrow** indicating the marked increase in heart rate during orthostasis. Abbreviations as in Figures 1 and 2.



Hyperadrenergic Valsalva maneuver in a 42-year-old woman (Patient #1) with long-haul post-coronavirus disease 2019 symptoms, with **red arrows** indicating the marked increase in heart rate and blood pressure (hyperadrenergic response). Abbreviations as in Figure 2.

Peripheral neuropathies

Pain syndromes with Long-COVID



COVID (N=4231)

Controls (N=8462)

Ballering et al. Lancet; 400: 452-61; 2022

Potential Therapeutic Targets for Clinical Trials

- Antivirals
- Innate immune responses:
  - IVIg; anti-IL-1 and anti-IL-6 antibodies; BTK inhibitors, GM-CSF inhibitors
- Reverse immune exhaustion
  - Checkpoint inhibitors
- Anti-B cell therapies
  - Rituximab
- Non-specific immune modulators
  - Corticosteroids

Challenges

Subjective endpoints

Natural history unknown

Conclusions

- Direct invasion of the brain by SARS-CoV-2 is rare and does not explain the neurological complications
- Neuroimmune dysfunction is driven by activation of innate immunity, immune exhaustion and antibody mediated phenomenon
- Clinical trials with immunotherapies could be considered in patients with Long-COVID

Acknowledgements

Marco Hefti *(University of Iowa)*

Rebecca Folkerth *(NY medical examiner)*

Daniel Perl *(USUHS)*

Eliezer Masliah *(NIA)*

Serena Spudich (Yale U)

NINDS, NIH

Myoughwa Lee, Wenxue Li, Dragan Marac (Neuropath)

Yair Mina, Farinaz Safavi, Bryan Smith, Brain Walitt, David Goldstein, Stave Jacobson, Amanda Weibold Ladifatou Fouanta

Govind Nair, Alan Koretsky, Helen Murray (MRI)

Walter Koroshetz