Clinical Manifestations and pathophysiology of Long-COVID

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Disclosures

None

Attempts at Defining Long-COVID
(Diagnostic criteria)

Long-COVID:

Patients

PASC (Post-acute sequelae of COVID-19)

National Institutes of Health

Post-COVID-19

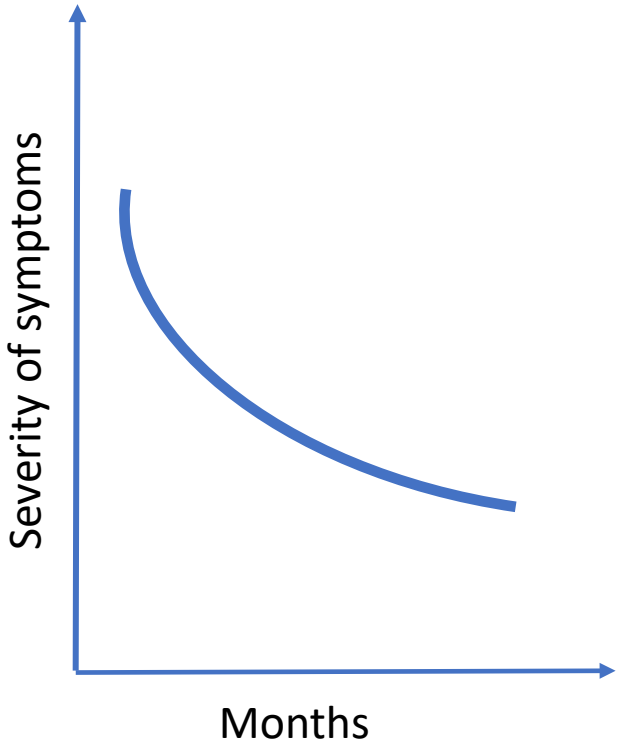
World Health Organization

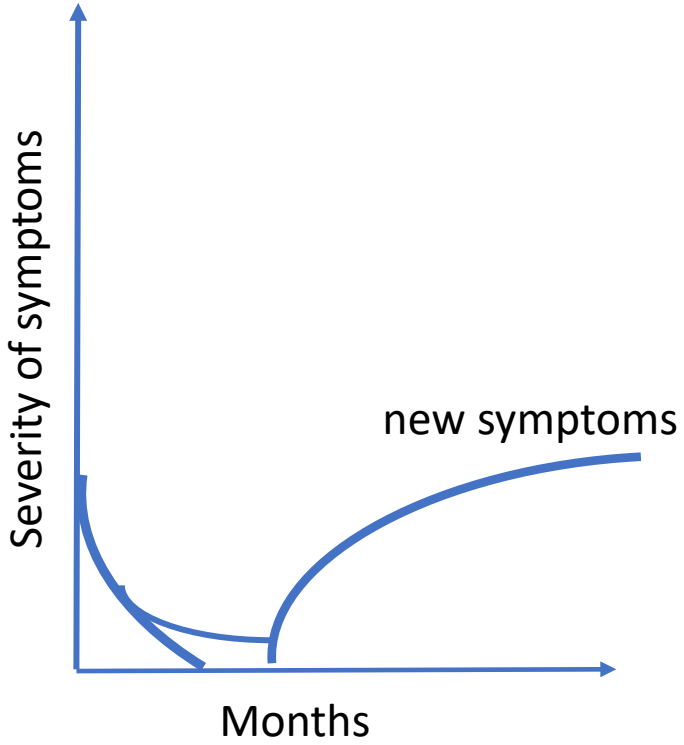
WHO definition of Post-COVID-19

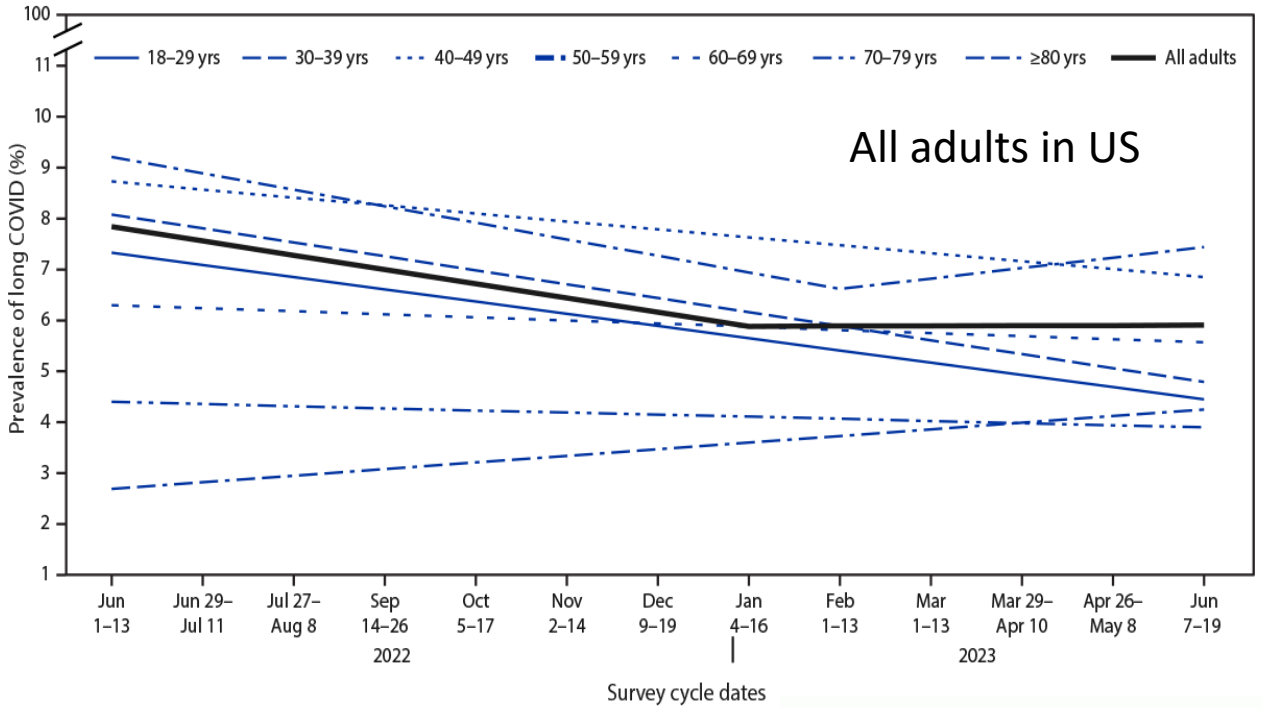
The continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation.

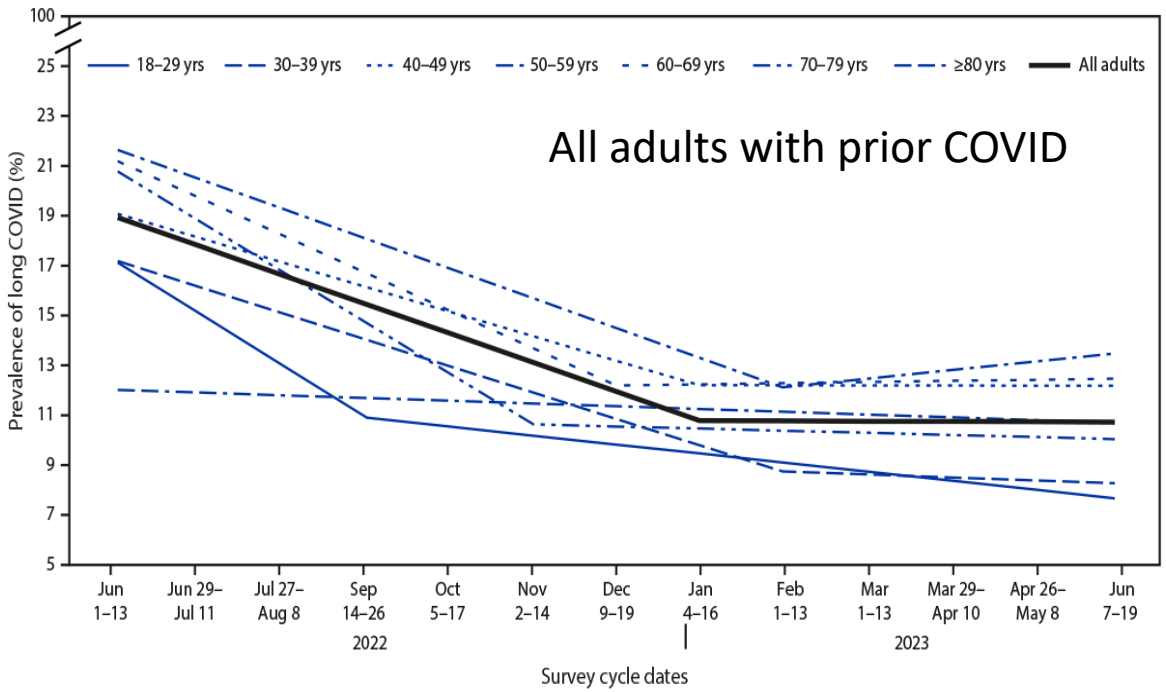
Dec 7, 2022

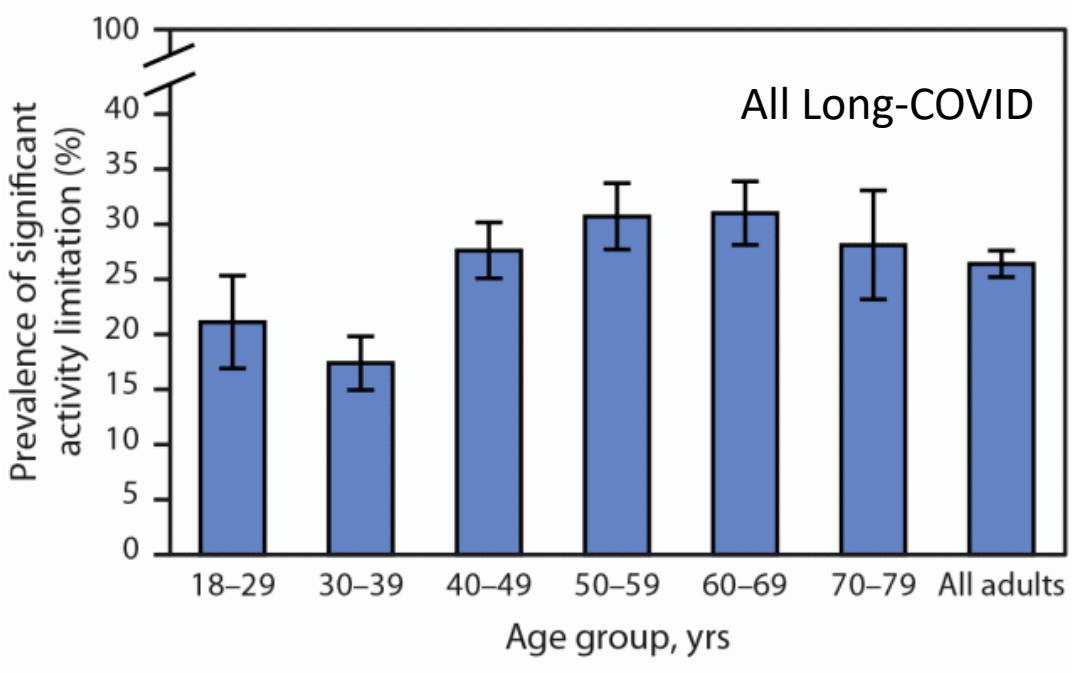
PATTERNS OF LONG-COVID





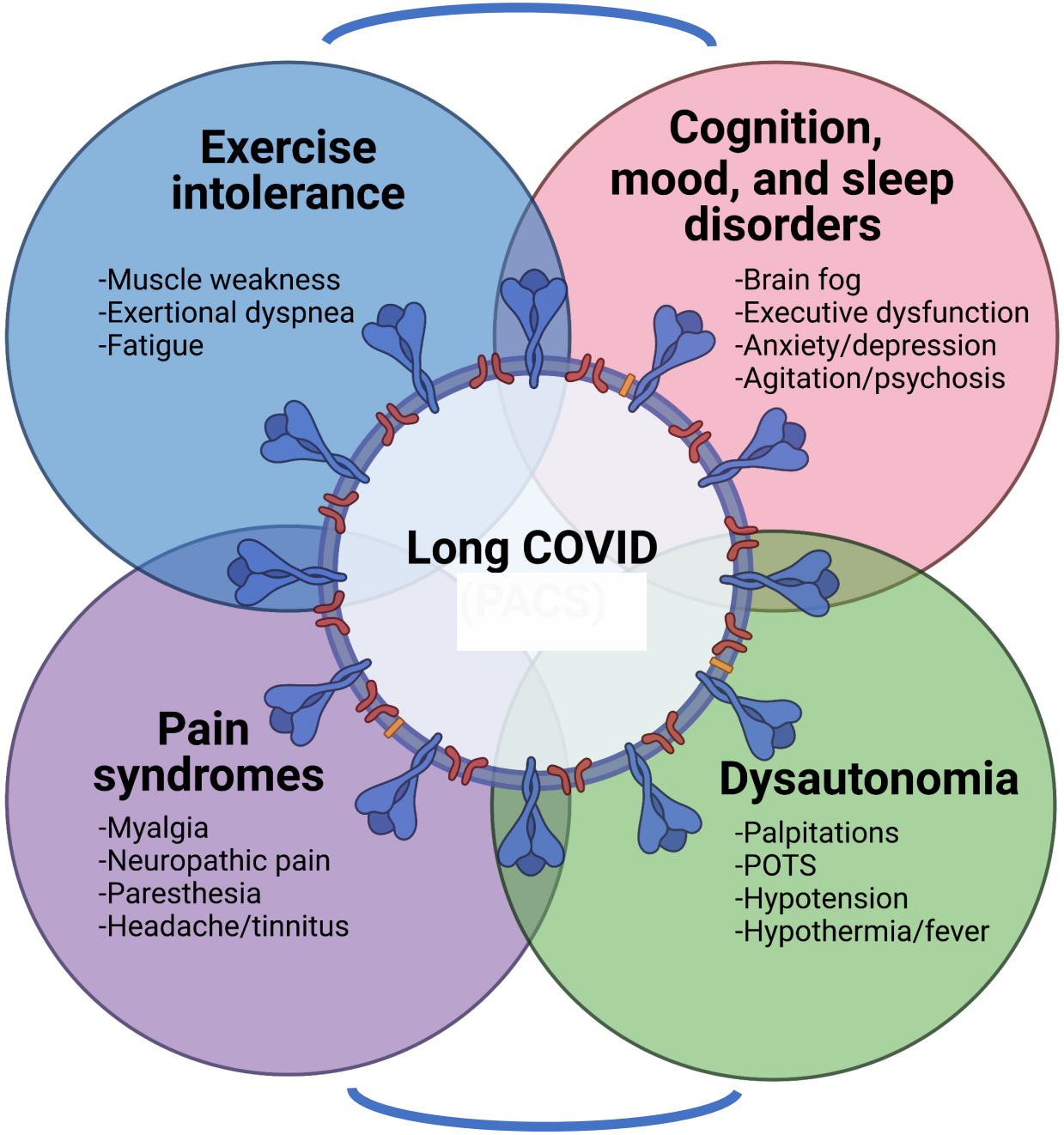






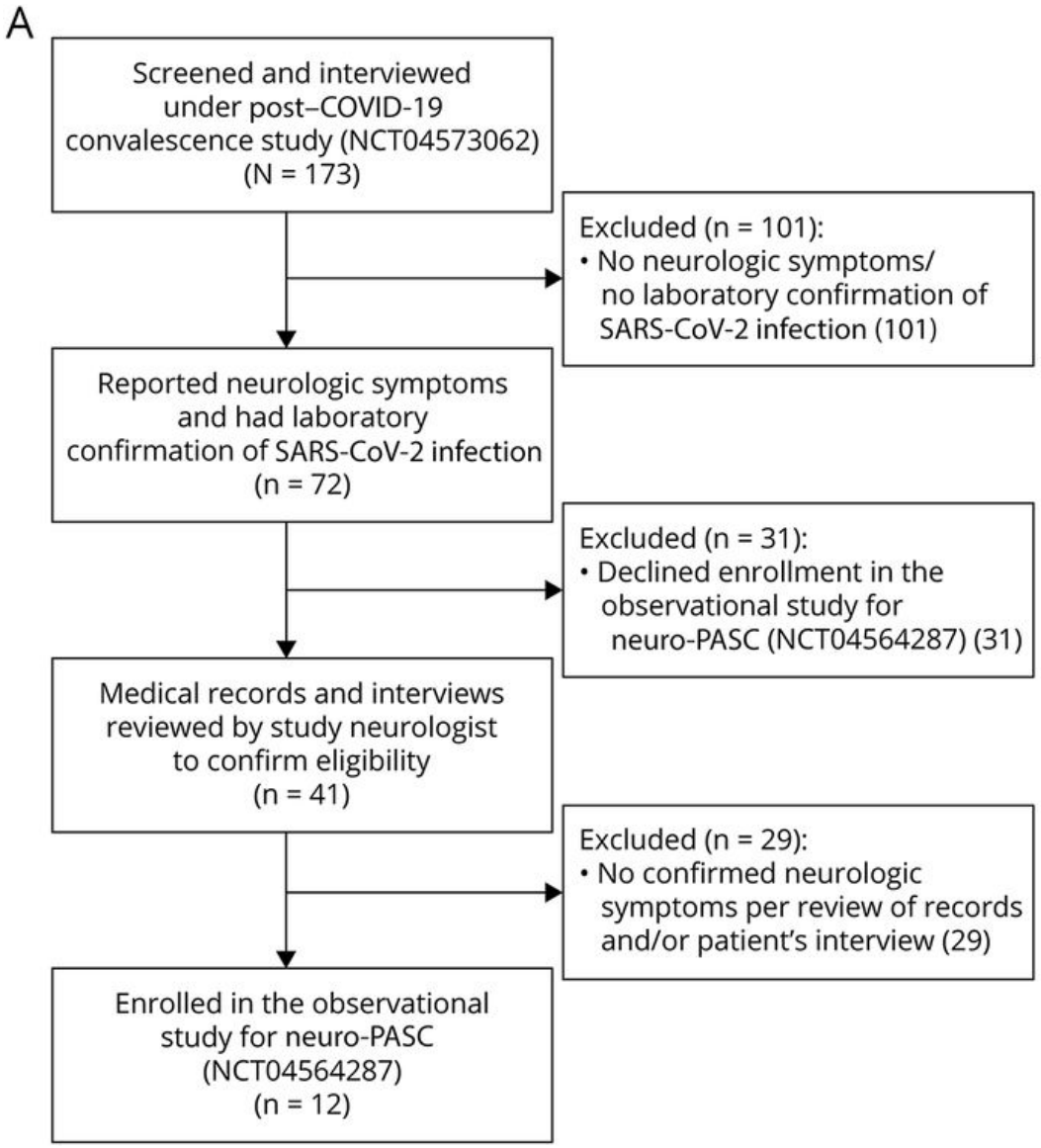
MMWR Aug 2023 (CDC)

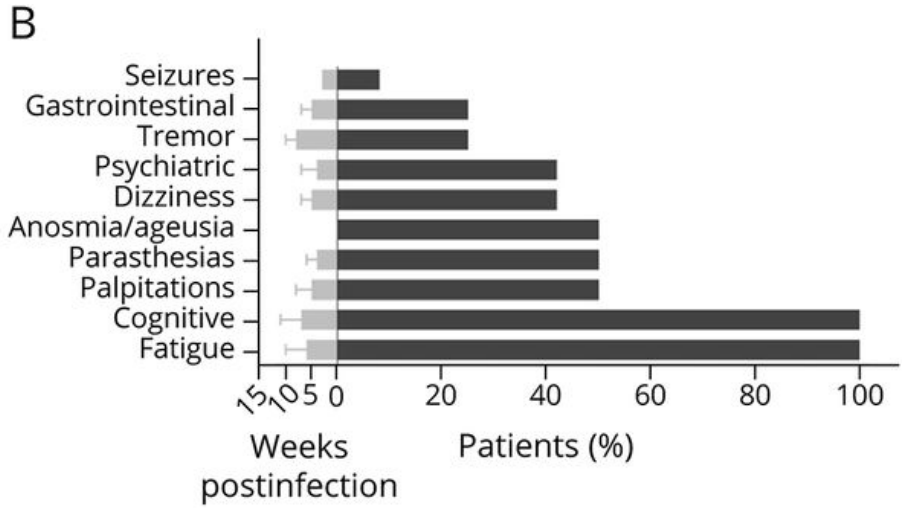
Post-Intensive Care Syndrome

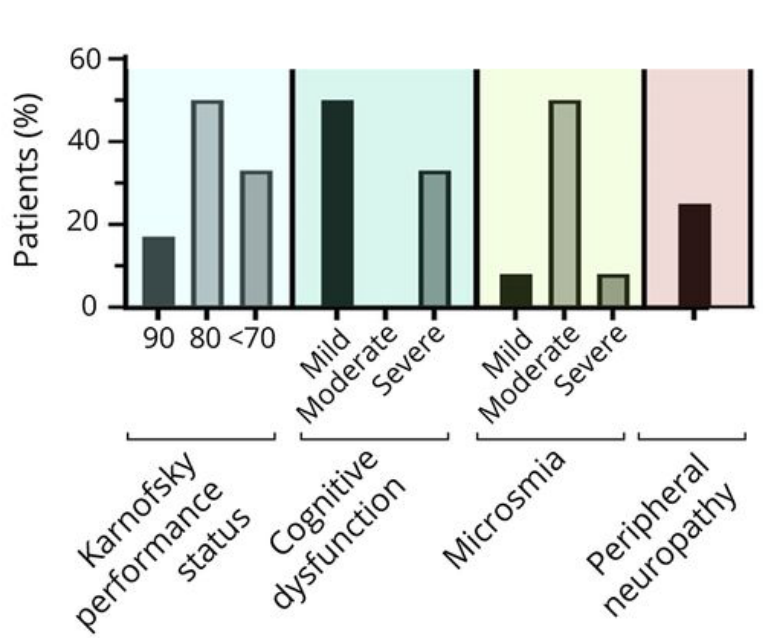


Balcom, et al., Brain 2021

Neurologic Postacute Sequelae of SARS-CoV-2 Infection (Neuro-PASC)







Yair Mina et al. Neurol Neuroimmunol Neuroinflamm 2023;10:e200097

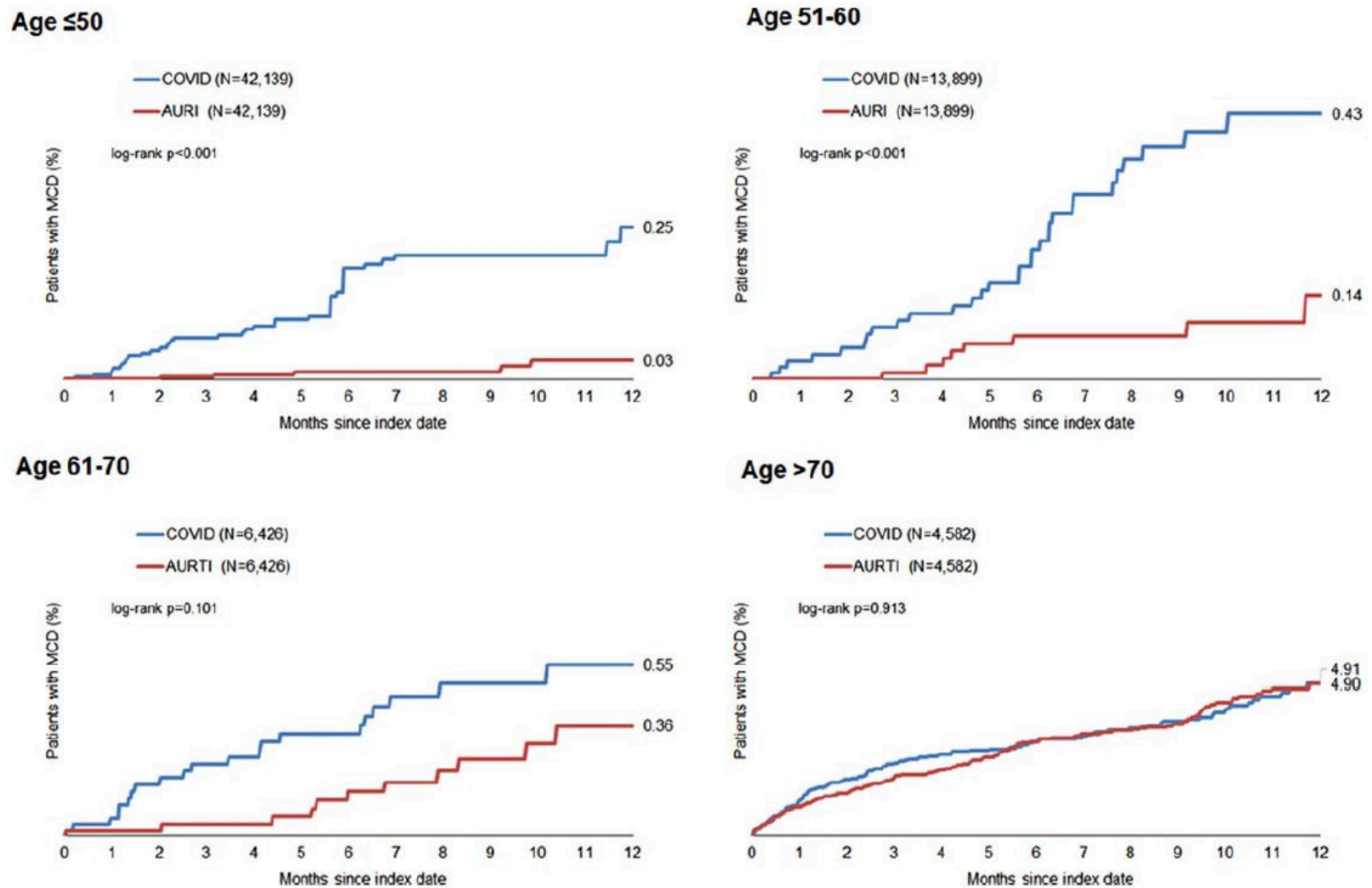


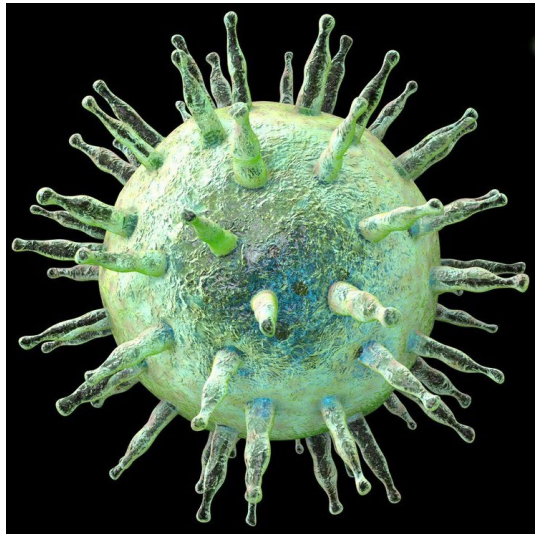
Fig. 2. Kaplan-Meier curves for incidence of mild cognitive disorder in patients with COVID-19 versus patients with upper respiratory tract infection.

Bohelken et al., J Alzheimers Dis Rep 2022

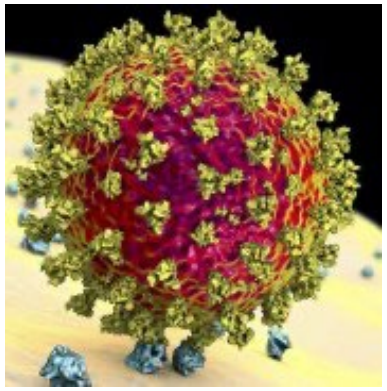
Viral reactivation

Persistent viral infection

Immune dysregulation

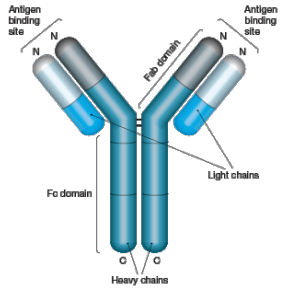


EBV



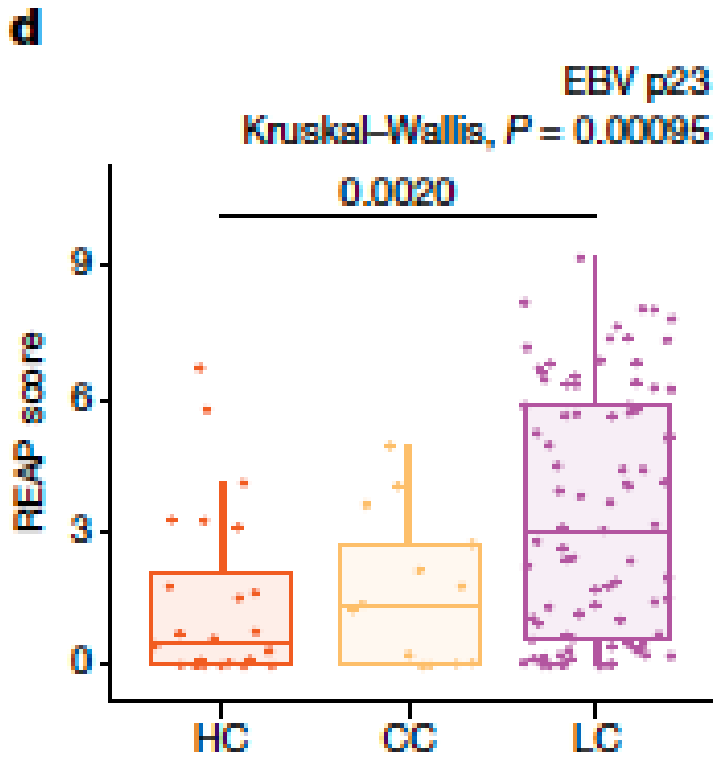
SARS-CoV-2 antigen

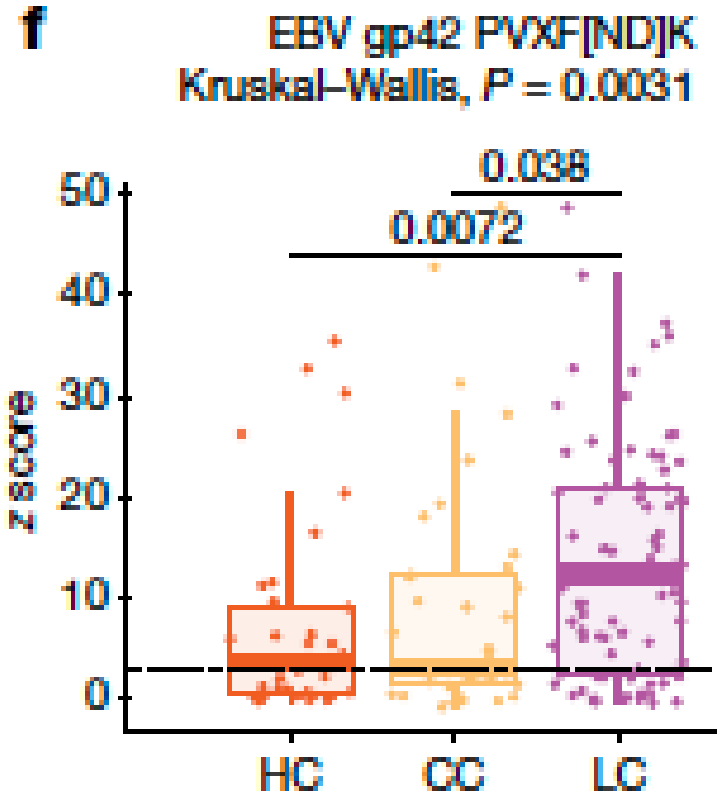
Macrophages



Antibodies

Reactivation of EBV in Long-COVID: Antibody responses to EBV



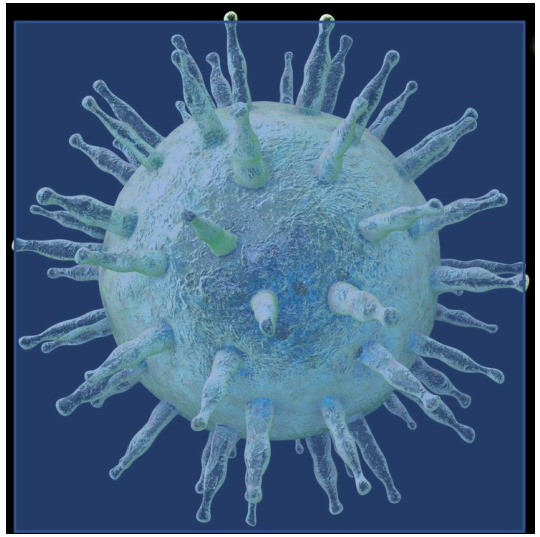


Klein et al., Nature 2023

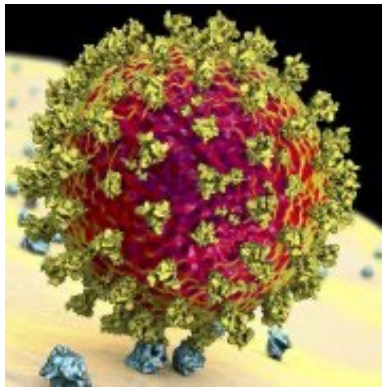
Viral reactivation

Persistent viral infection

Immune dysregulation

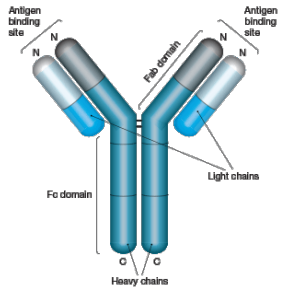


EBV



SARS-CoV-2 antigen

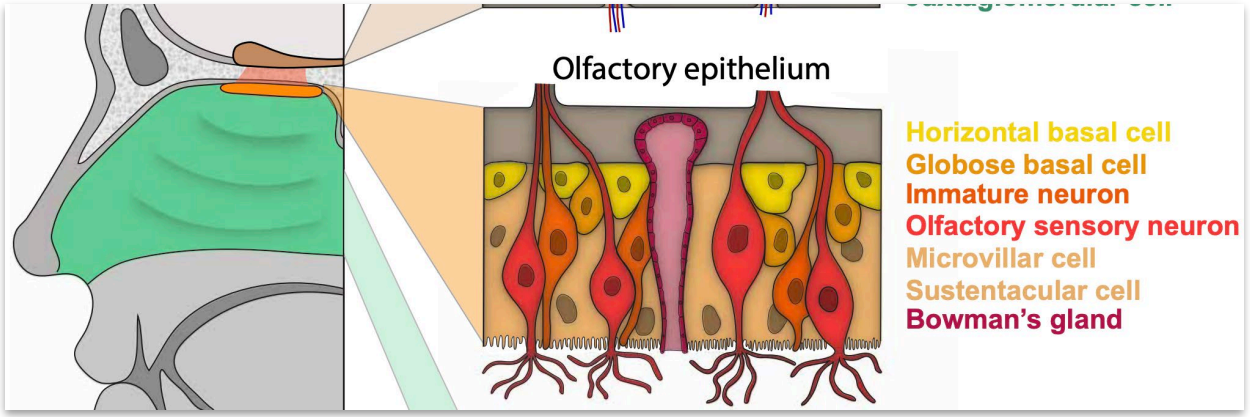
Macrophages

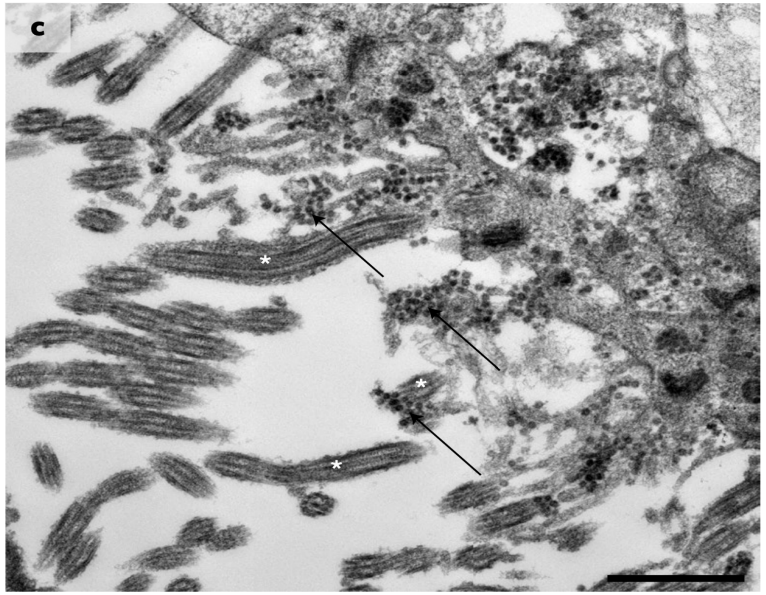


Antibodies

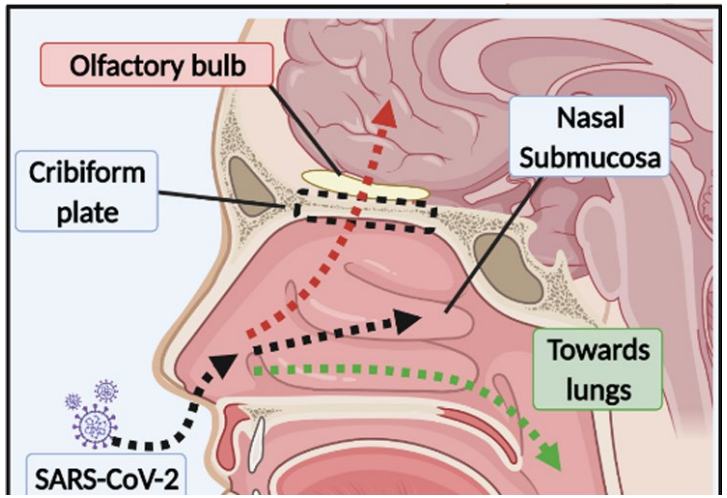
Can the virus enter the brain through the olfactory pathways?

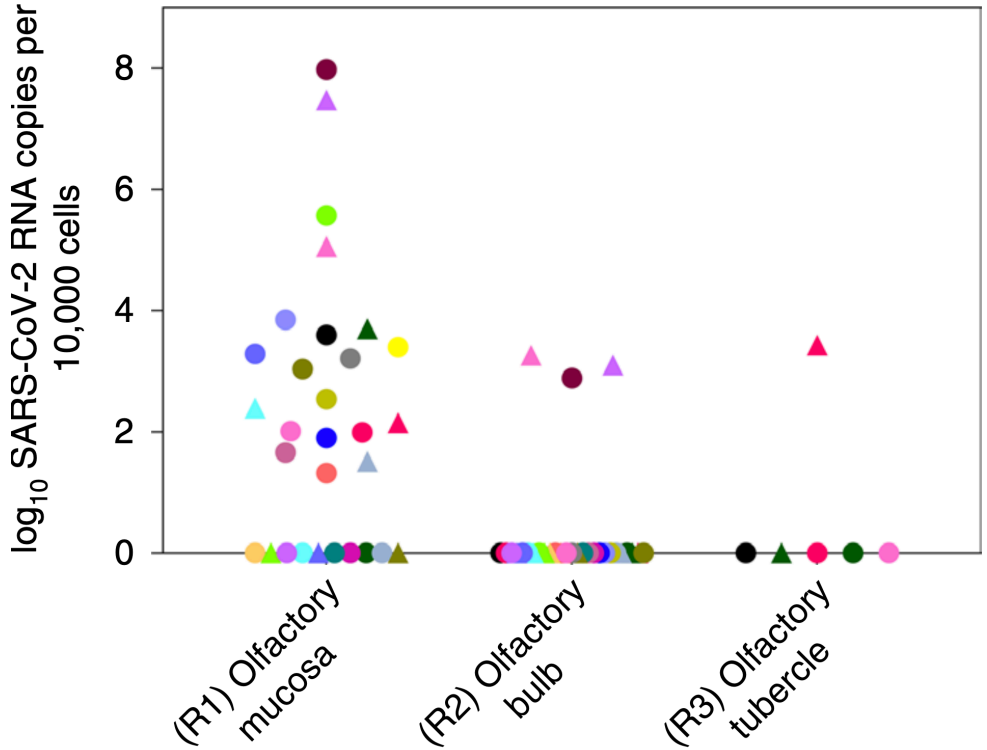
Virus infects Sustentacular cells





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

SARS-CoV-2 infection and persistence in the human body and brain at autopsy

https://doi.org/10.1038/s41586-022-05542-y

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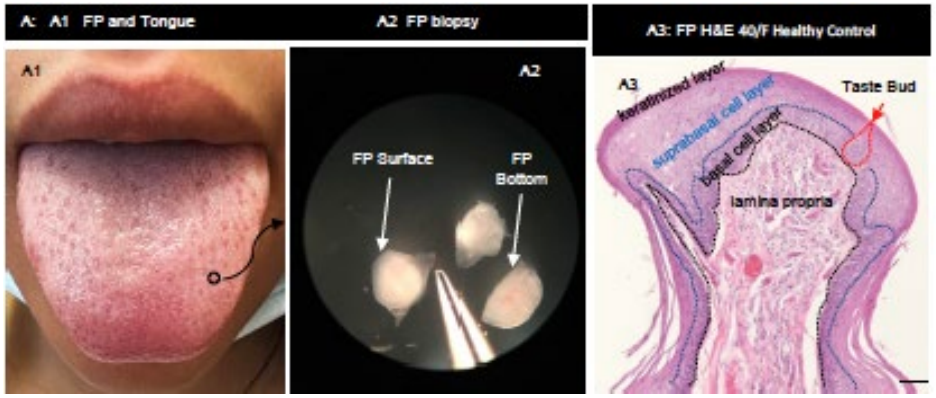
Check for updates

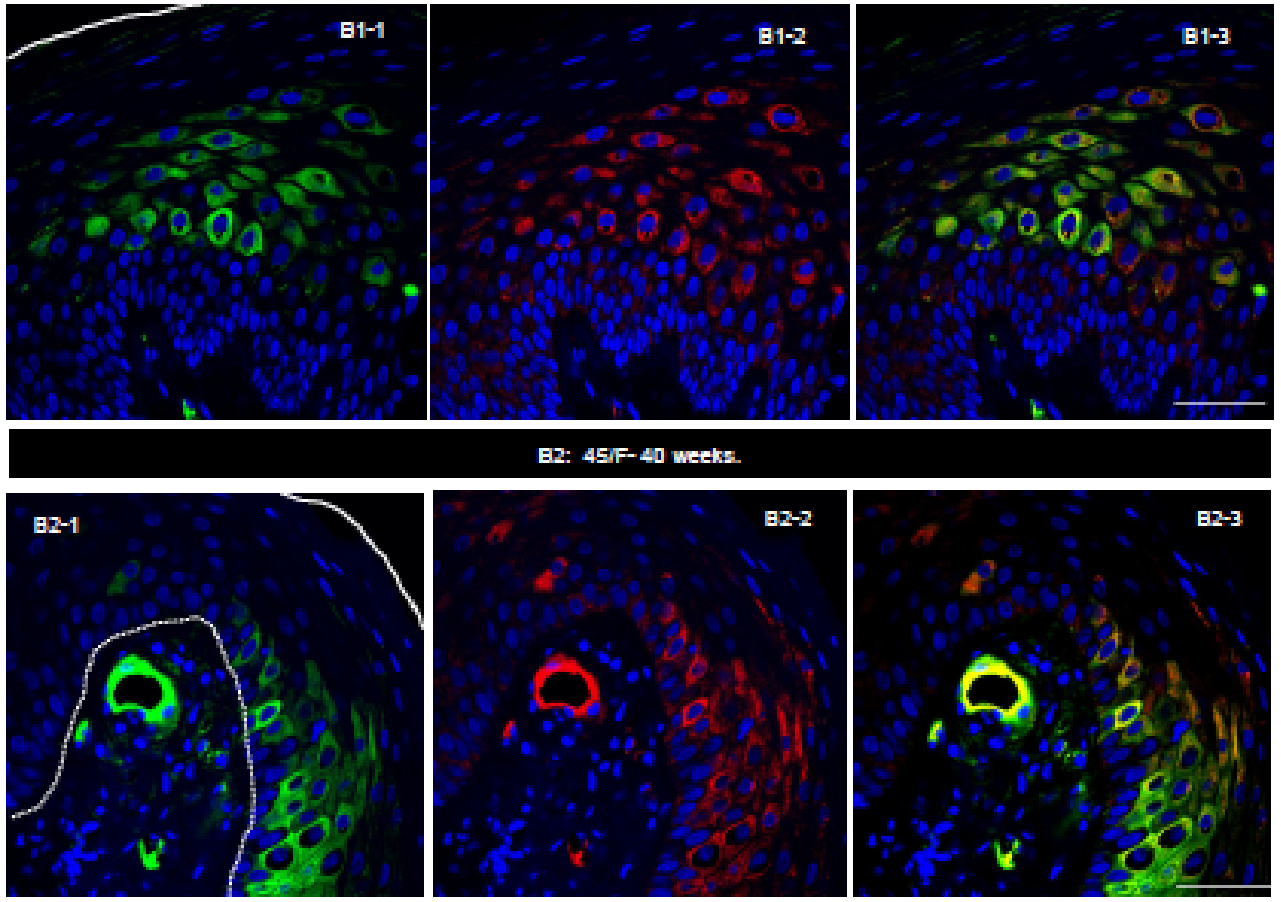
Sydney R. Stein[1,2], Sabrina C. Ramelli[3], Alison Grazioli[4], Joon-Yong Chung[5], Manmeet Singh[6], Claude Kwe Yinda[6], Clayton W. Winkler[7], Junfeng Sun[3], James M. Dickey[1,2], Kris Ylaya[5], Sung Hee Ko[8], Andrew P. Platt[1,2], Peter D. Burbelo[9], Martha Quezado[5], Stefania Pittaluga[5], Madeleine Purcell[10], Vincent J. Munster[6], Frida Belinky[8], Marcos J. Ramos-Benitez[1,2,11], Eli A. Boritz[8], Izabella A. Lach[1,2], Daniel L. Herr[12], Joseph Rabin[13], Kapil K. Saharia[14,15], Ronson J. Madathil[16], Ali Tabatabai[17], Shahabuddin Soherwardi[18], Michael T. McCurdy[17,19], NIH COVID-19 Autopsy Consortium*, Karin E. Peterson[7], Jeffrey I. Cohen[20], Emmie de Wit[6], Kevin M. Vannella[1,2], Stephen M. Hewitt[5], David E. Kleiner[5] & Daniel S. Chertow[1,2]✉

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	0.42 (2.51)
Lymphoid	≤14	30.01 (157.86)
	15-30	0.35 (1.28)
	≥31	0.73 (3.83)
Gastrointestinal	≤14	24.68 (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 (284.46)
	≥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)

Research Gate 2021

SARS-CoV-2 in taste papillae

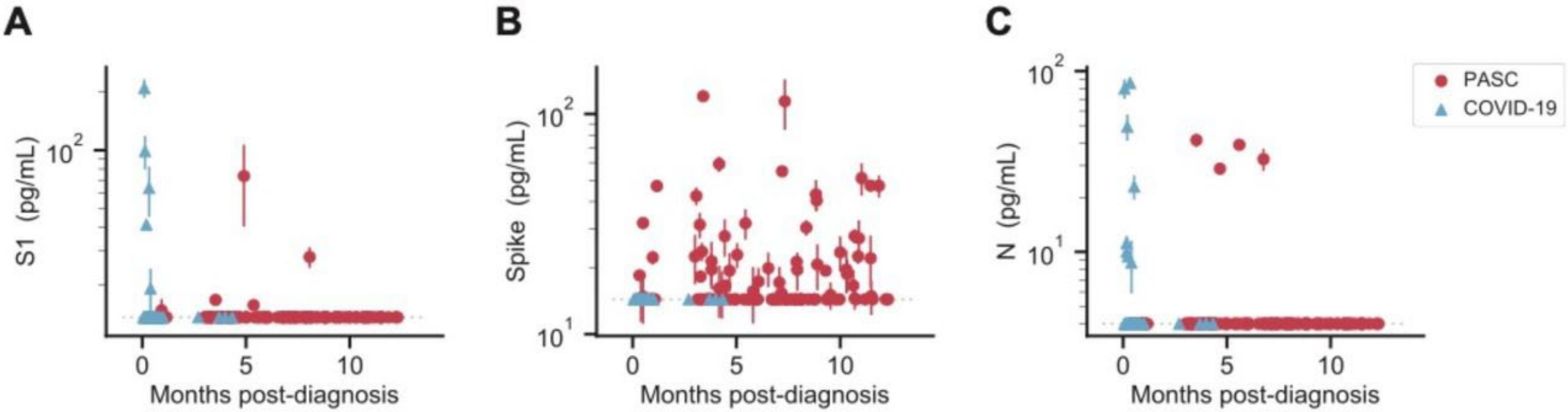




Spike protein: green
Nucleocapsid: Red

Yao Q,----Egan JM. NEJM Evidence 2023

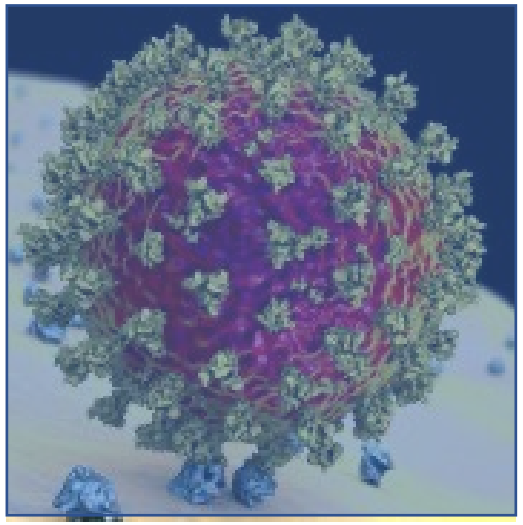
Detection of Spike protein in blood of patients with PASC (Long-COVID): Restricted viral replication



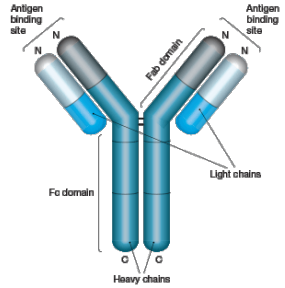
60% positive with PASC

Swank et al., CID 2022

Persistent viral infection



Immune dysregulation



Antibodies

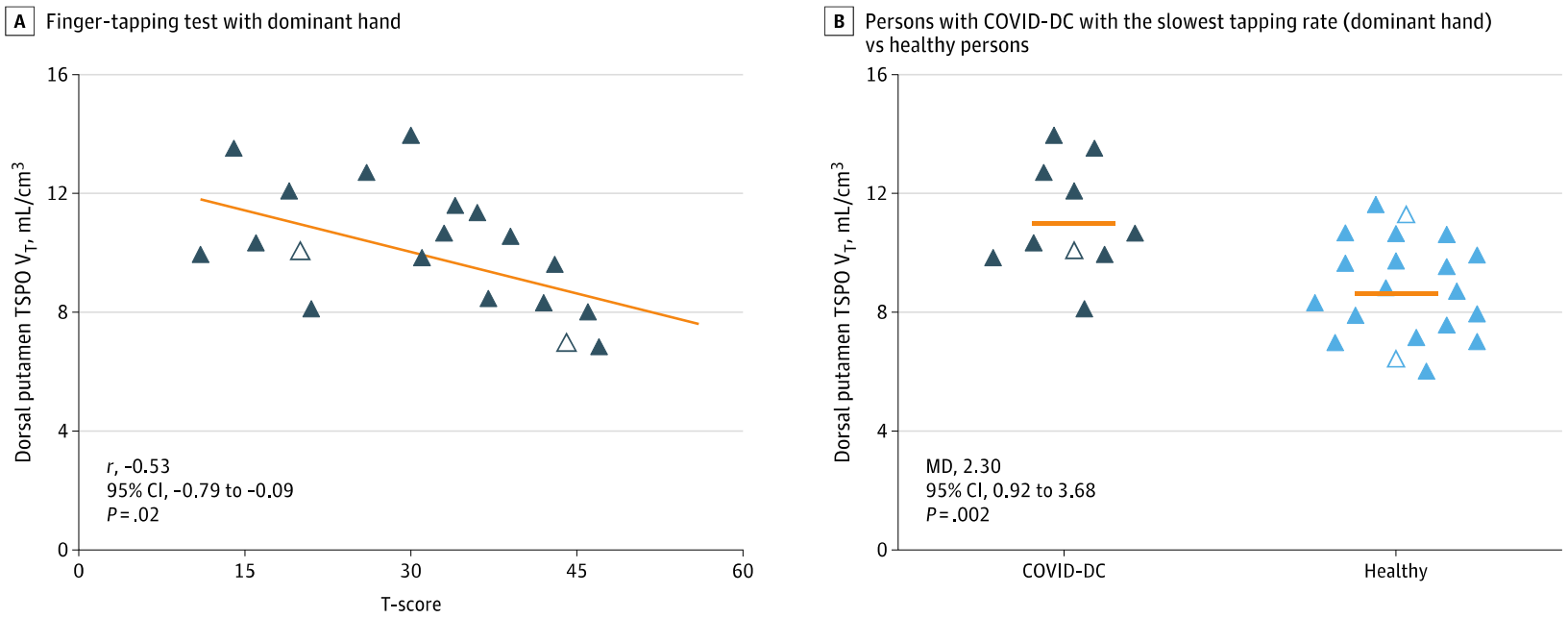
Macrophages

JAMA Psychiatry | Original Investigation

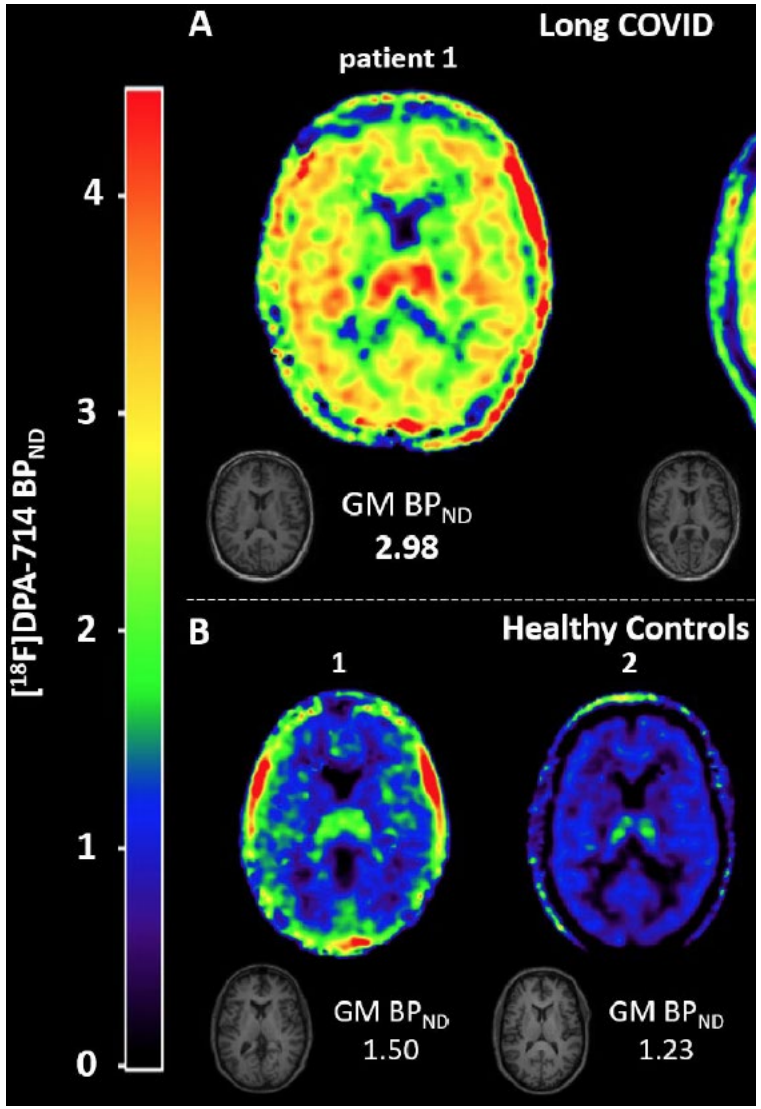
Neuroinflammation After COVID-19 With Persistent Depressive and Cognitive Symptoms

Joeffre Braga, BSc; Mariel Lepra, BSc; Stephen J. Kish, PhD; Pablo. M. Rusjan, PhD; Zahra Nasser; Natasha Verhoeff, BHSc; Neil Vasdev, PhD; Michael Bagby, PhD; Isabelle Boileau, PhD; M. Ishrat Husain, MBBS, MD; Nathan Kolla, MD, PhD; Armando Garcia, BSc; Thomas Chao, PhD; Romina Mizrahi, PhD; Khunsa Faiz, MD; Erica L. Vieira, PhD; Jeffrey H. Meyer, MD, PhD

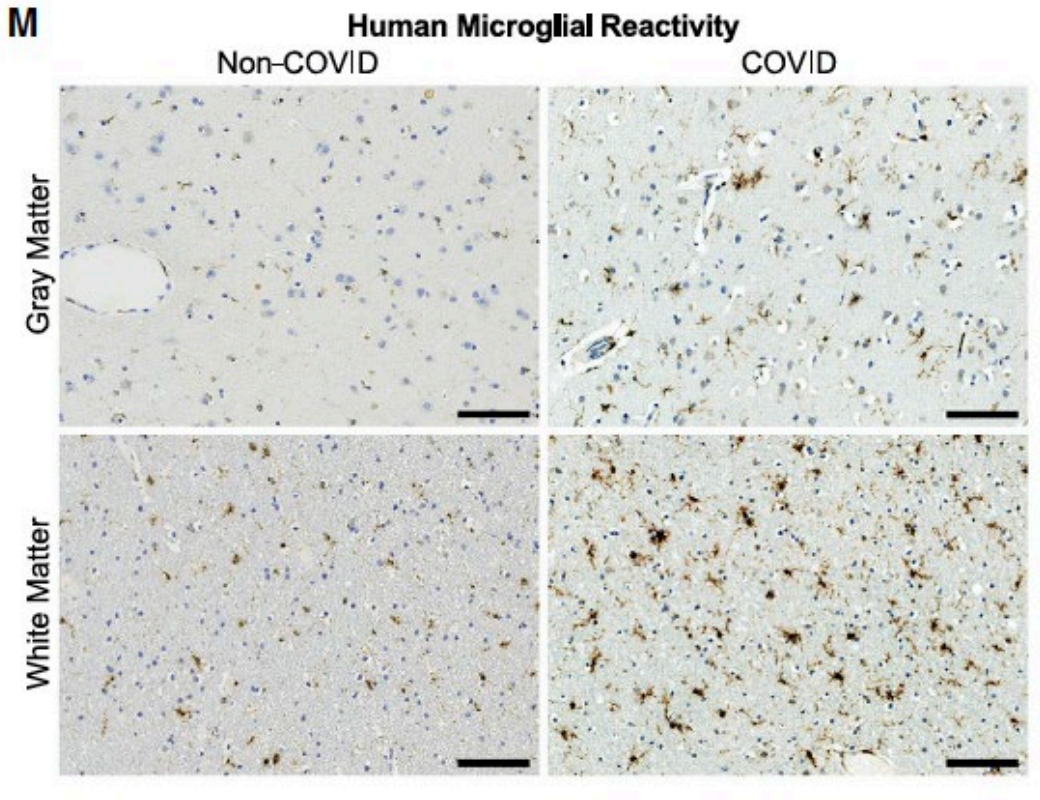
Figure 2. Pearson Correlation Between Translocator Protein Total Distribution Volume (TSPO V_T) in the Dorsal Putamen and Motor Speed

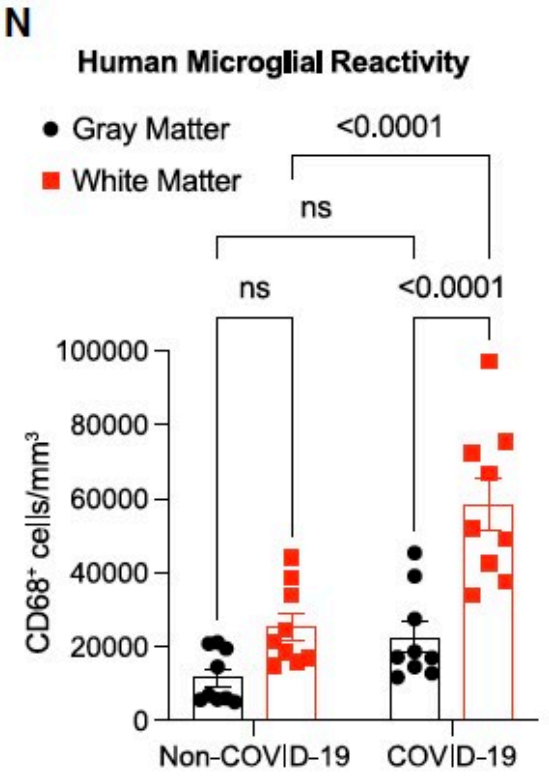


Diffuse microglial cell activation in Long-COVID



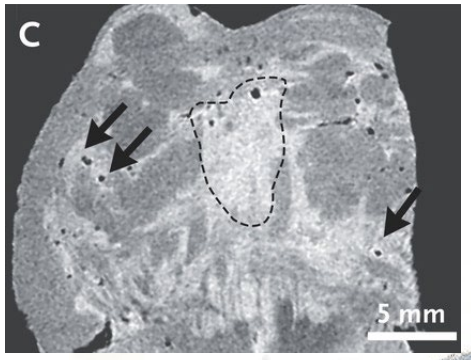
Visser et al., Med Rxiv 2022

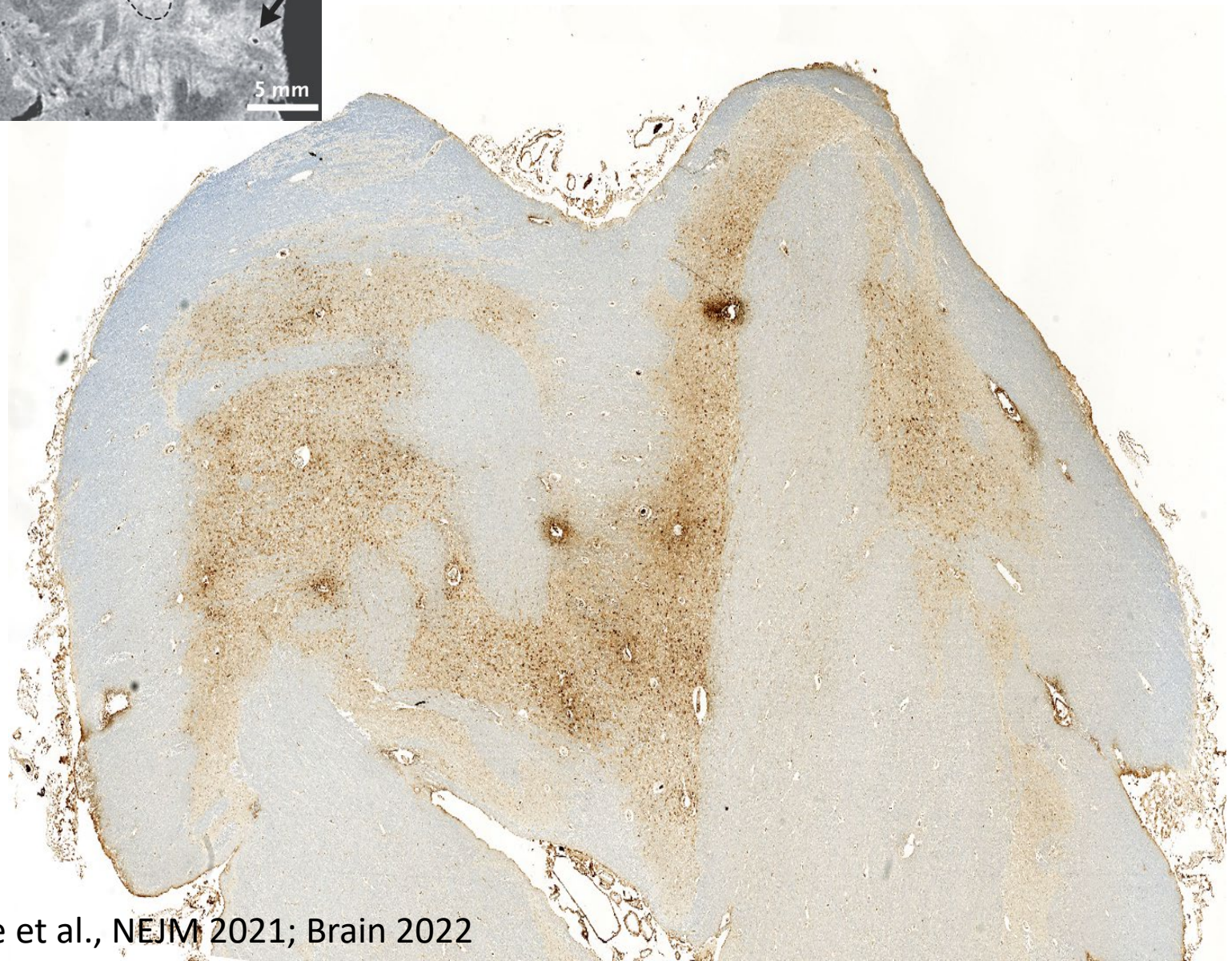


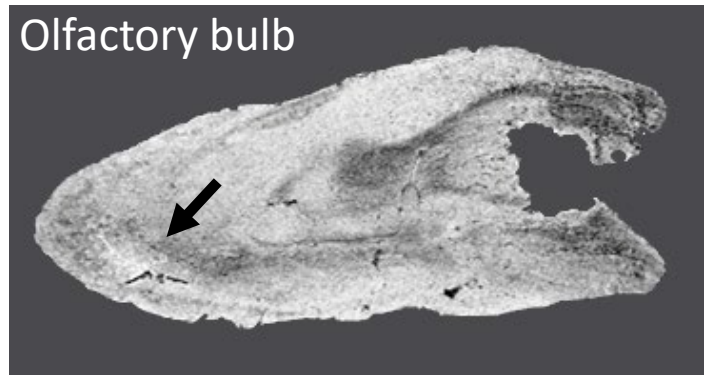


Fernandez-Castaneda et al., Cell, 2022

Perivascular fibrinogen leakage indicates vascular injury

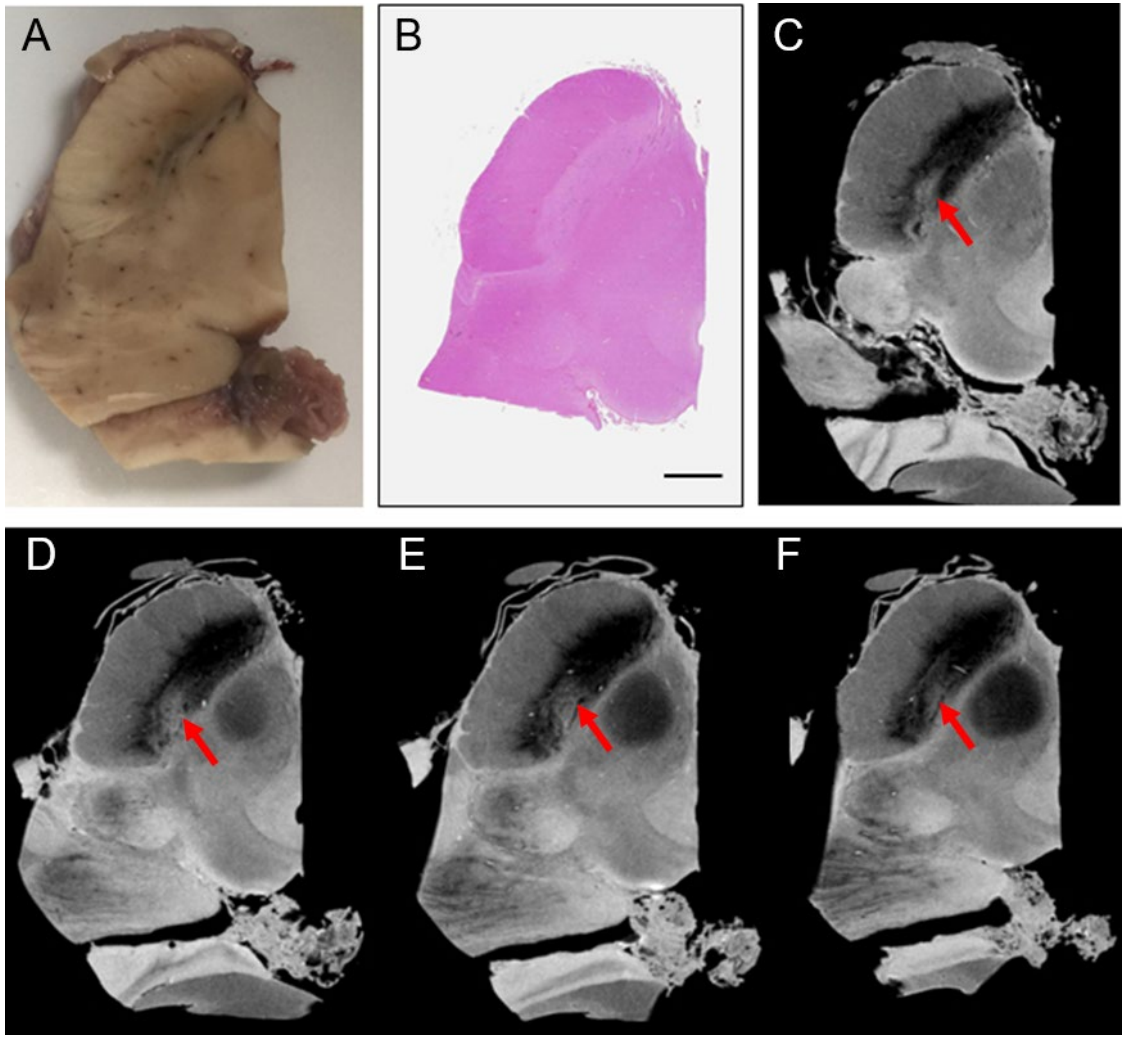


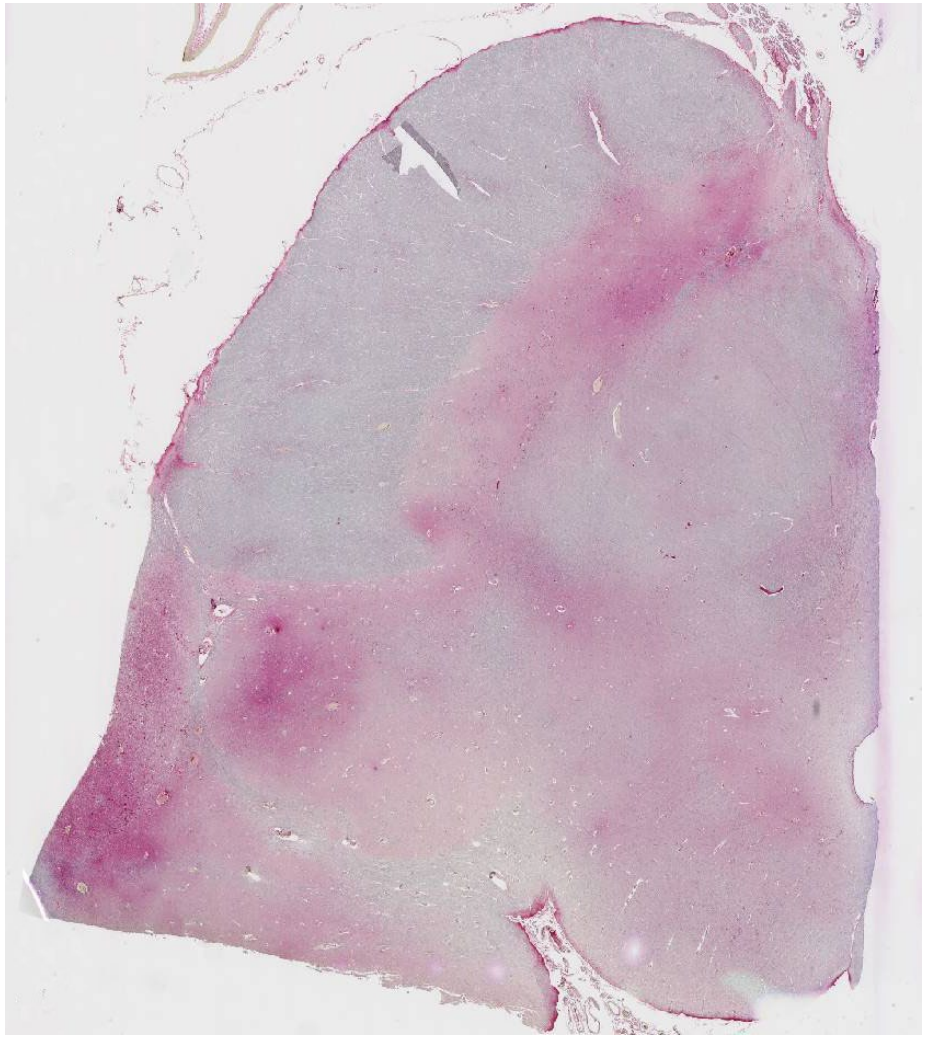




Lee et al., NEJM 2021; Brain 2022

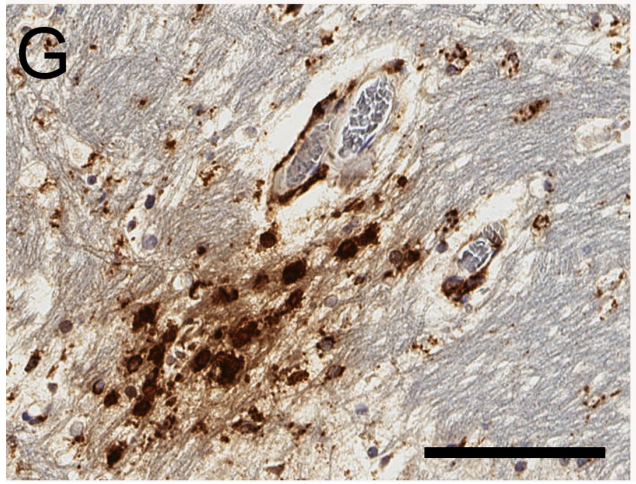
NY4 midbrain





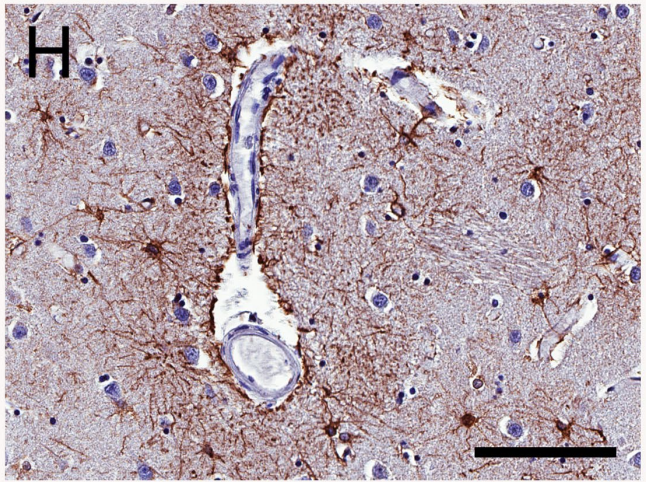
Microvascular disease

CD68: Macrophages



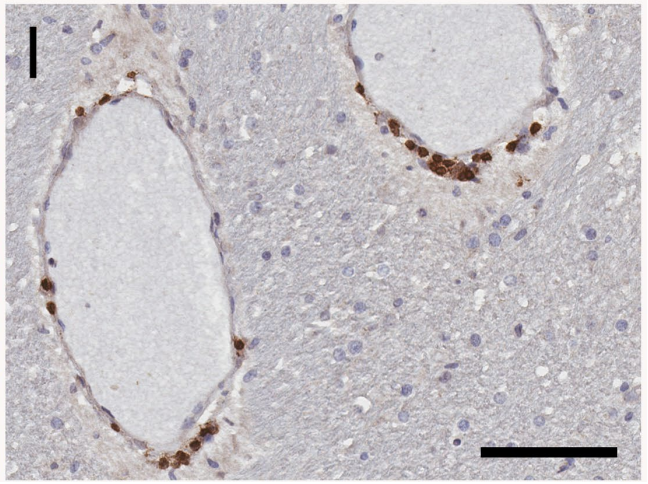
Perivascular activated macrophages

GFAP: Astrocytes



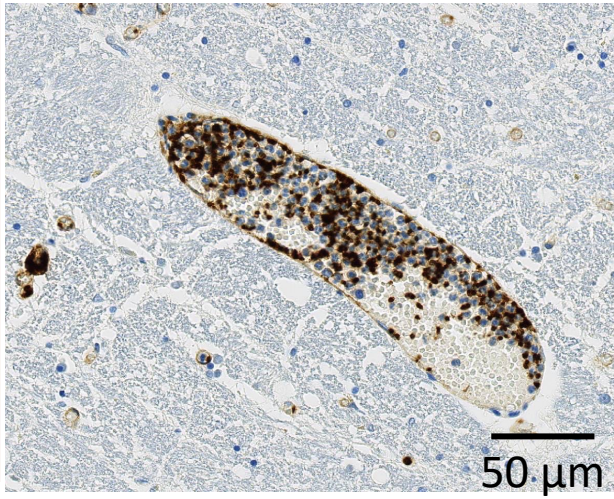
Perivascular activated astrocytes

CD3 T cells



Very few T cells and confined to the blood vessels

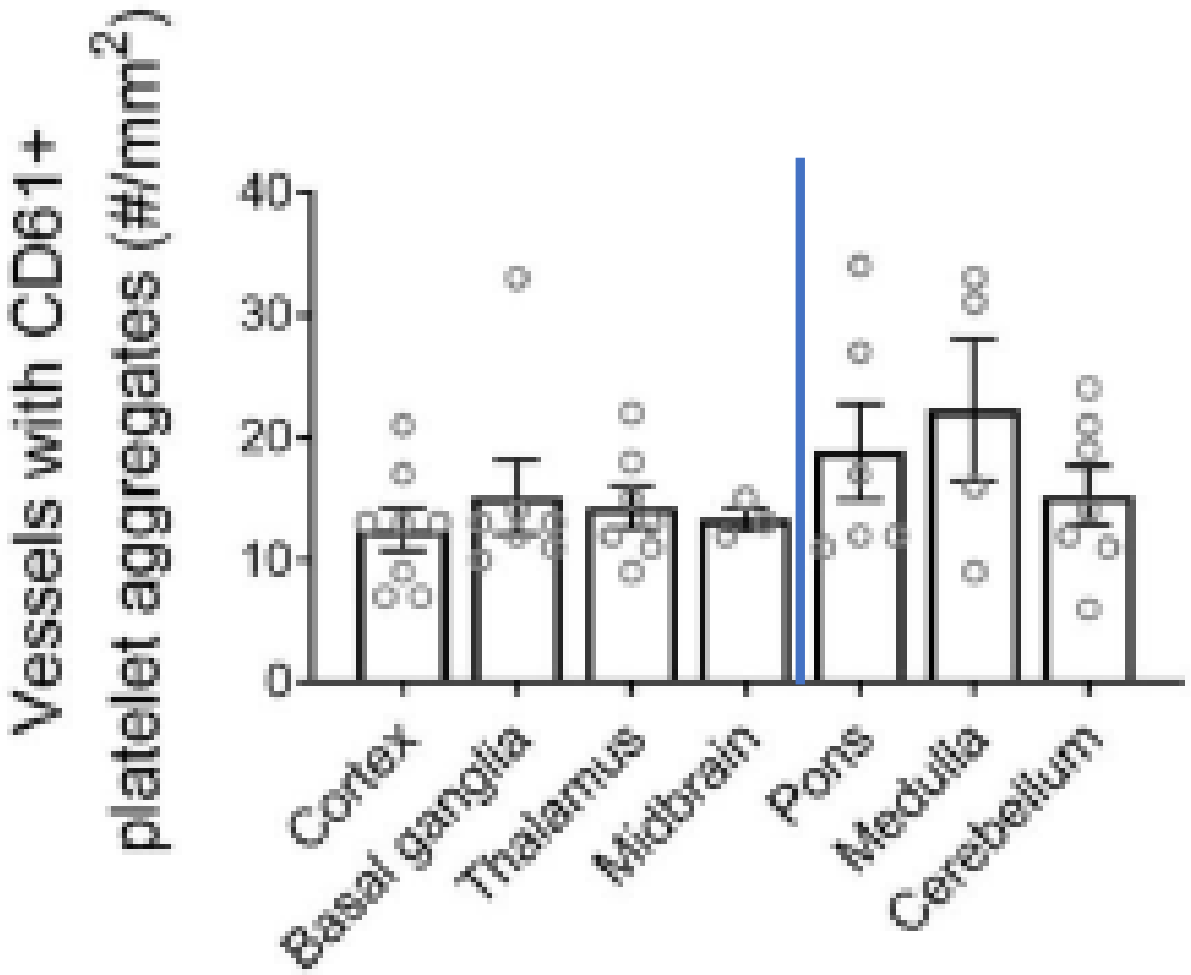
CD61: Activated platelets

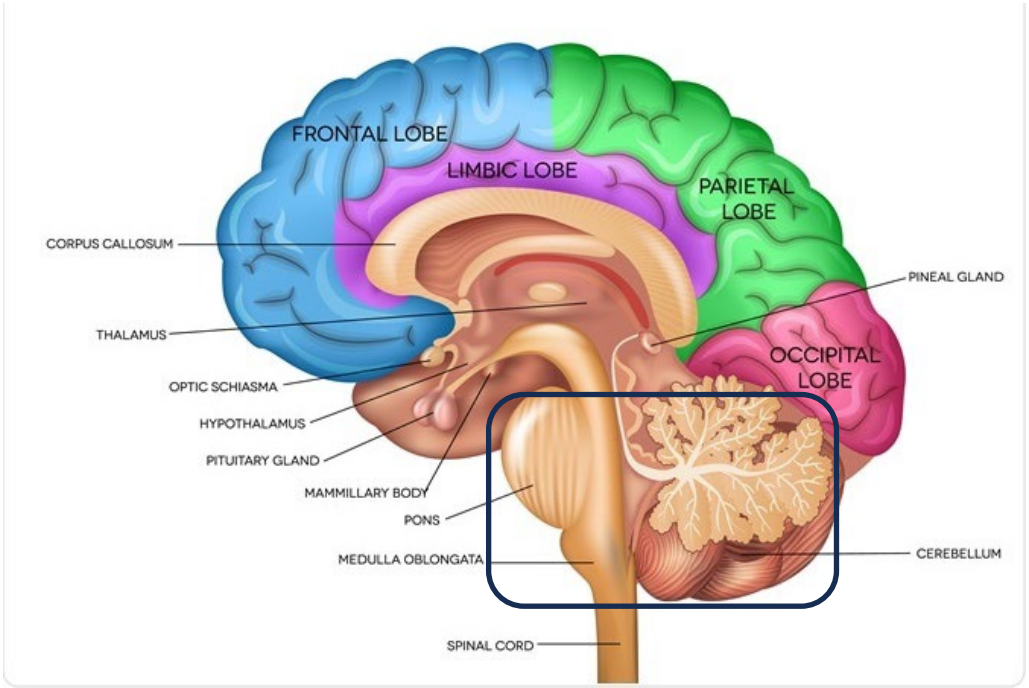


Platelets are sticking to endothelial cells and forming clots

Lee et al. Brain 2022

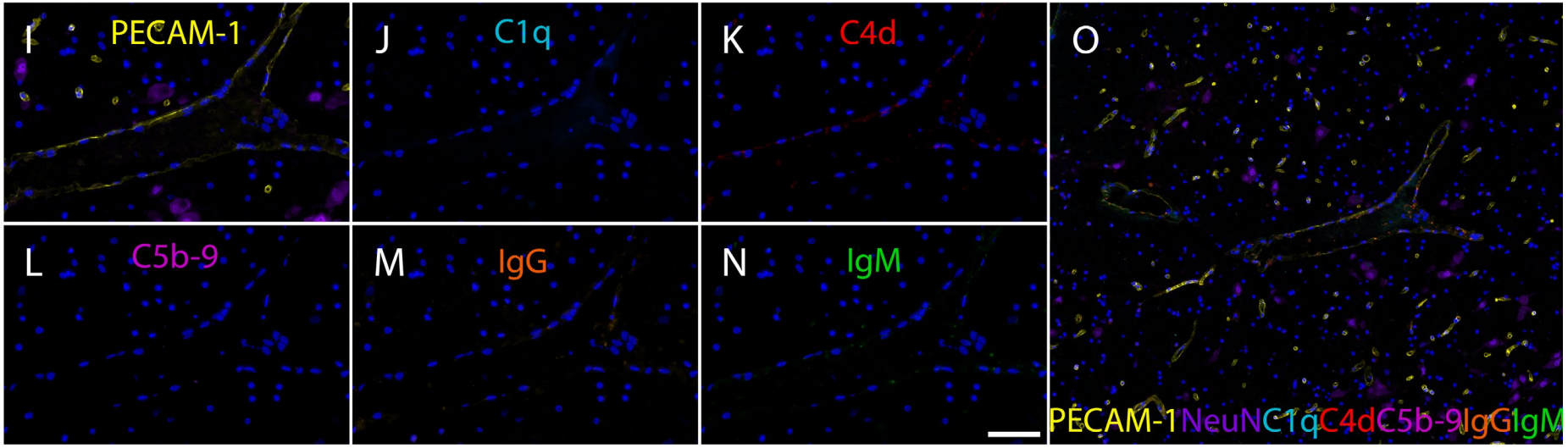
Lee et al., NEJM 2021


Vessels with CD61+
platelet aggregates (#/mm2)
40
30
20
10
0
Cortex
Basal ganglia
Thalamus
Midbrain
Pons
Medulla
Cerebellum

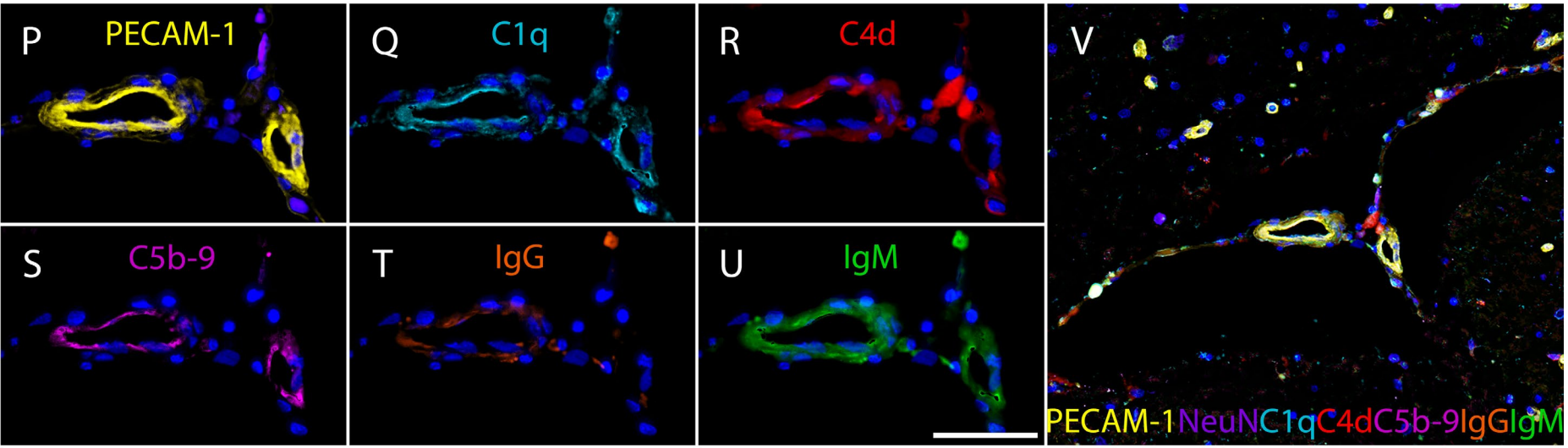

FRONTAL LOBE
LIMBIC LOBE
PARIETAL LOBE
OCCIPITAL LOBE
CORPUS CALLOSUM
PINEAL GLAND
THALAMUS
OPTIC SCHIASMA
HYPOTHALAMUS
PITUITARY GLAND
MAMMILLARY BODY
PONS
MEDULLA OBLONGATA
CEREBELLUM
SPINAL CORD

Antibody mediated complement dependent microvascular disease

Control



COVID-19



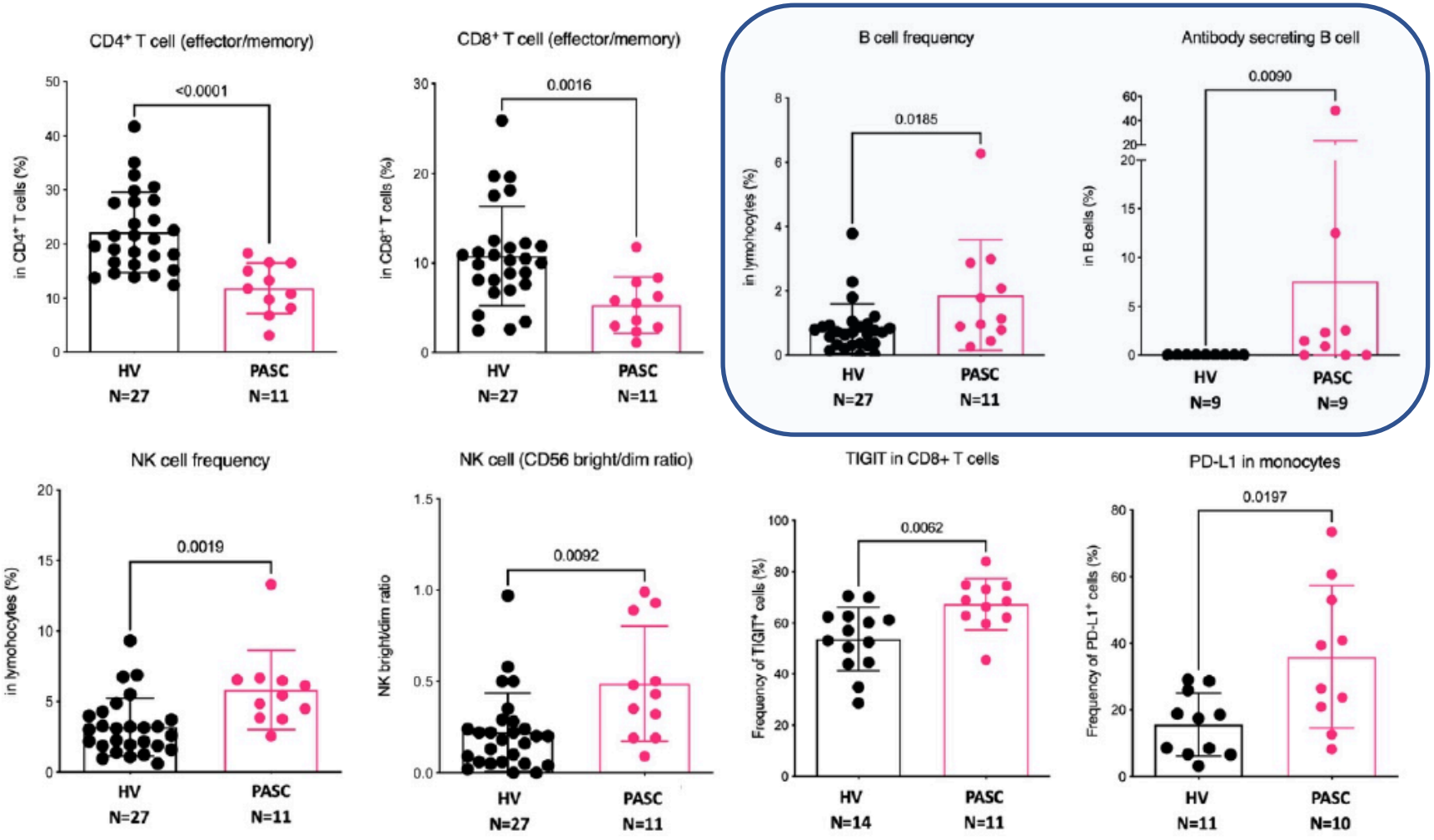
Activation of endothelial cells (PECAM-1)

Deposition of complement

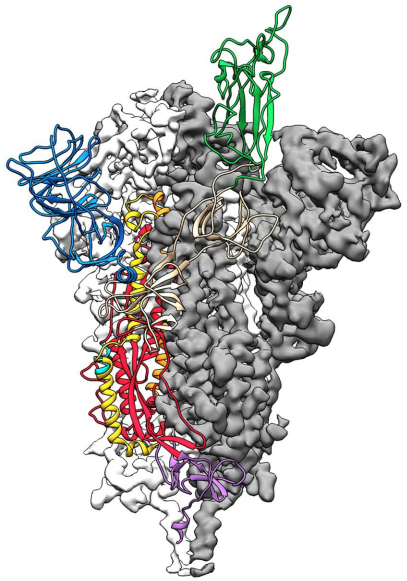
Deposition of IgG and IgM

Lee at al., Brain 2022

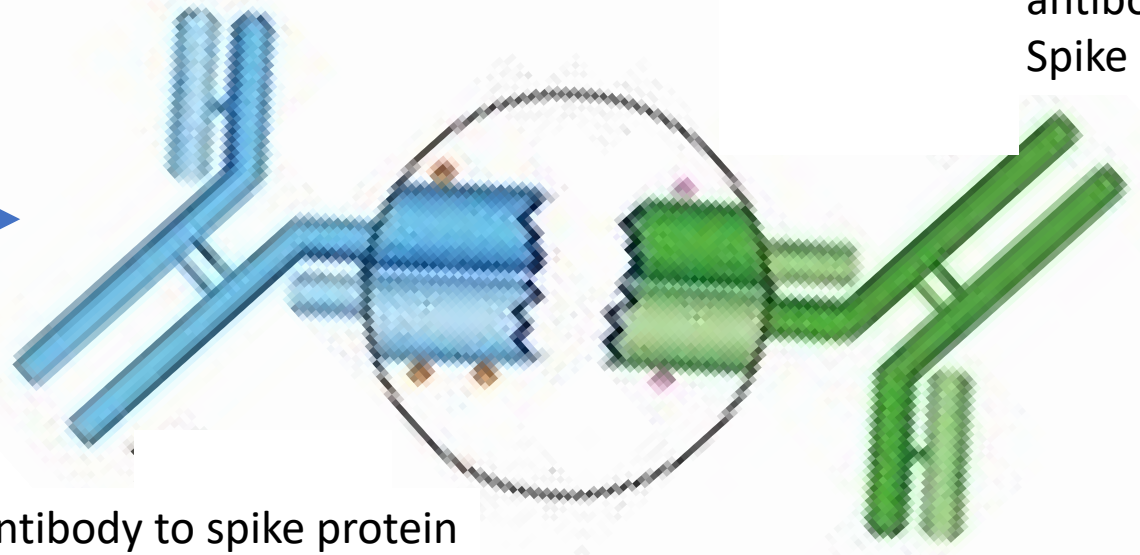
Increased plasma B cells in Long-COVID



Mina et al., 2023

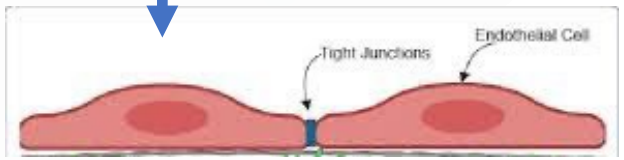


Spike protein



Antibody to spike protein

Anti-idiotypic antibody that mimics Spike protein



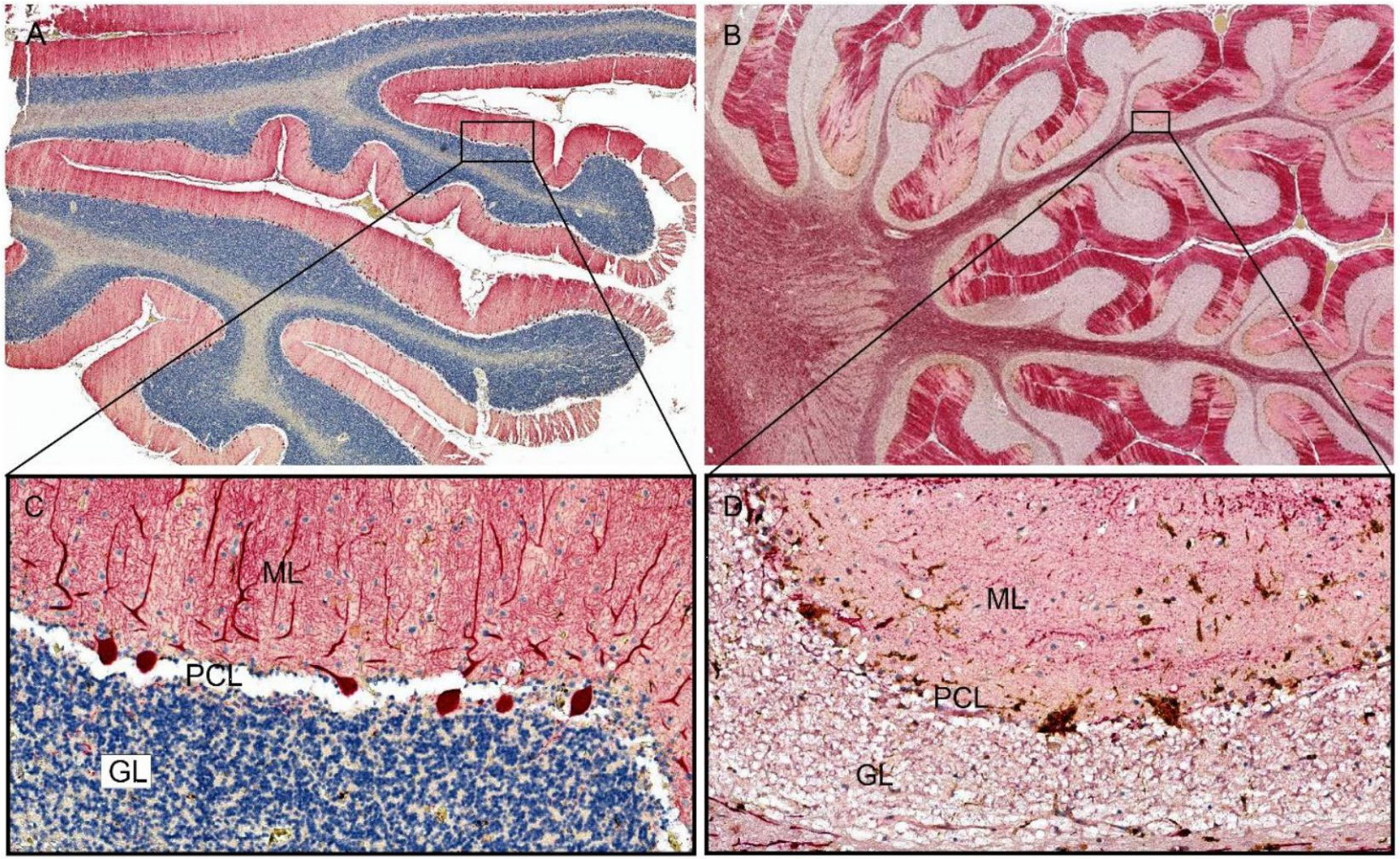
Brain endothelial cells


MGH
1811
MASSACHUSETTS
GENERAL HOSPITAL
RESEARCH INSTITUTE

Loss of Purkinje cells in cerebellum

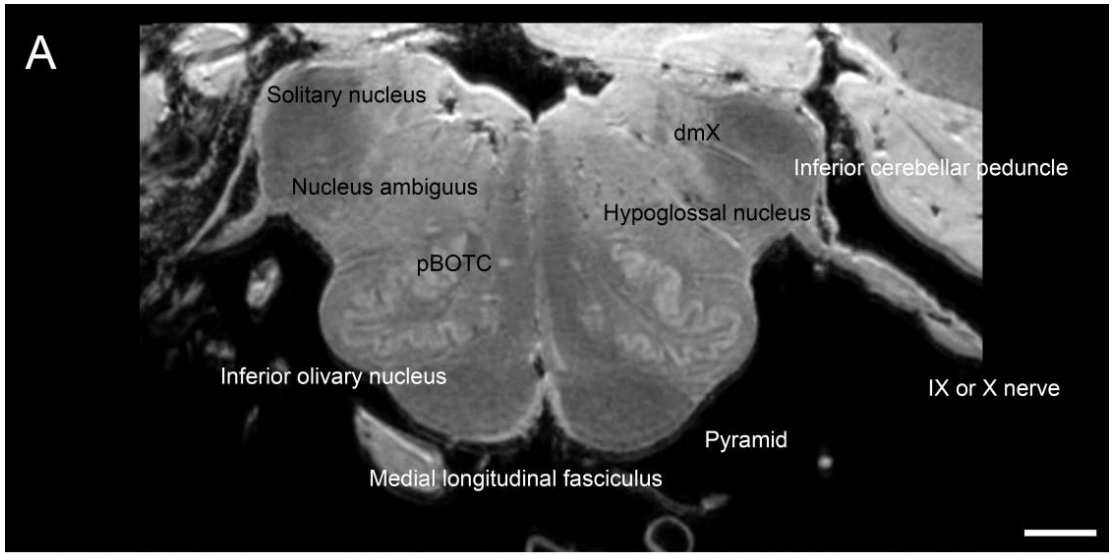
Control cerebellum

COVID-19

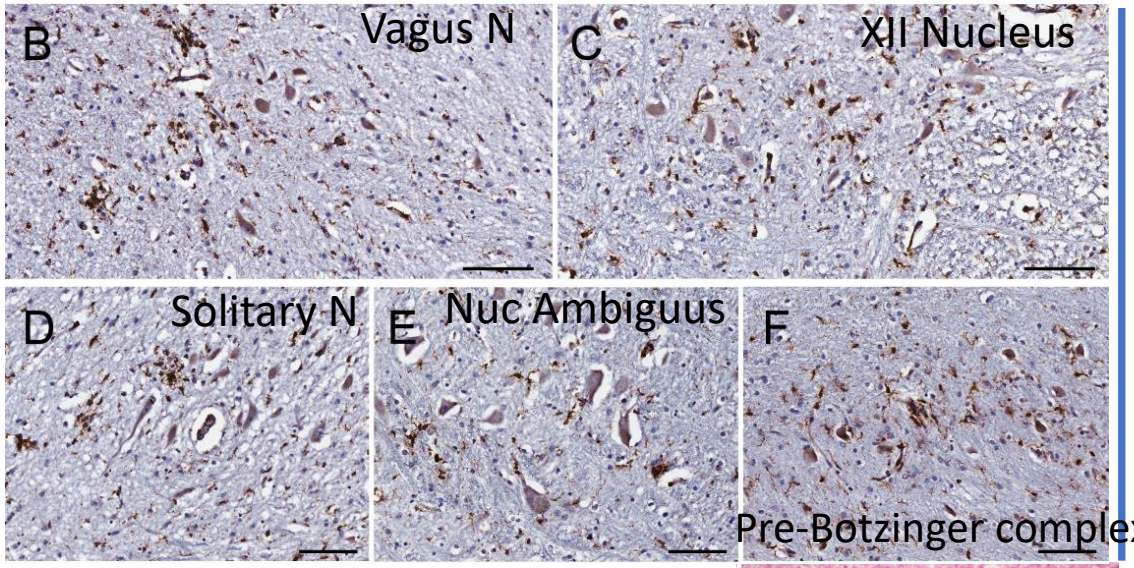


Lee et al., Brain 2022

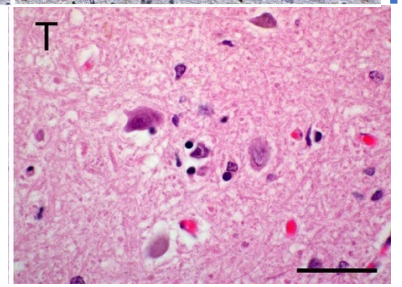
Neuronal Injury in Brainstem



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



CD68

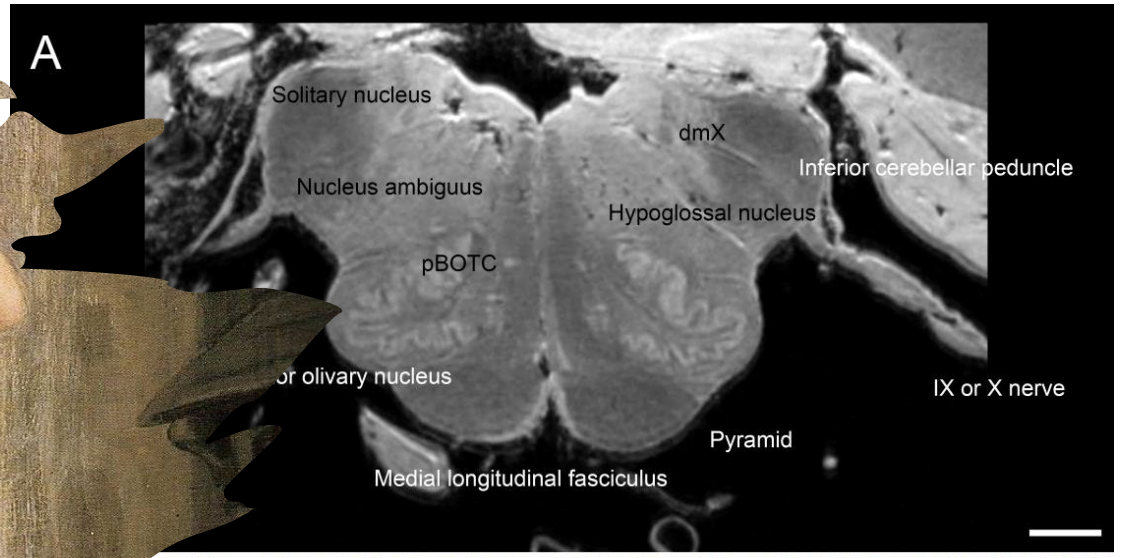


Pre-Botzinger complex

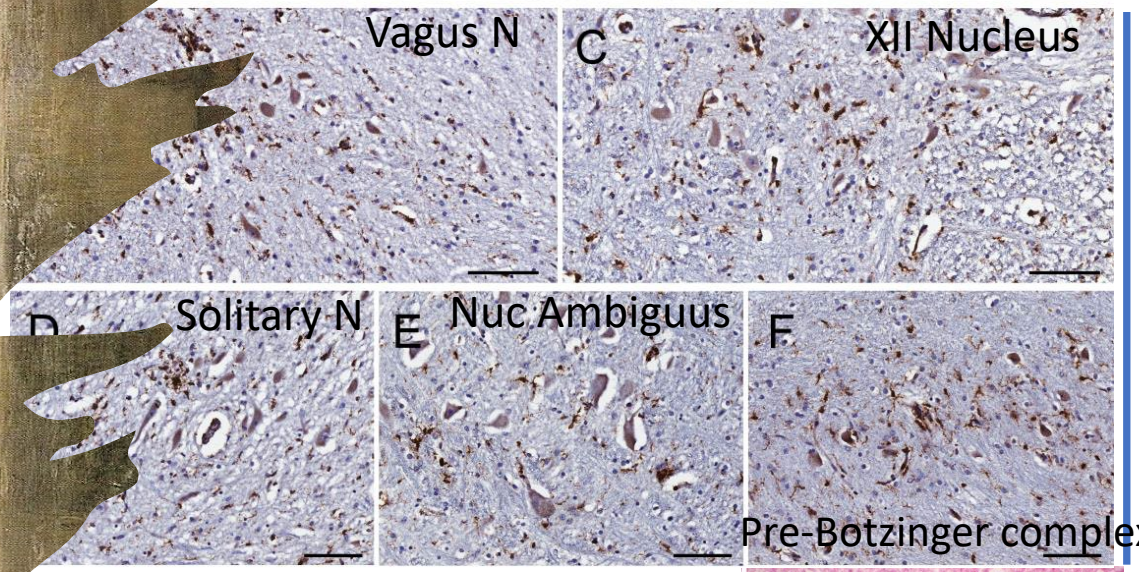
Neuronophagia

Lee et al., NEJM 2021

Ondine's Curse

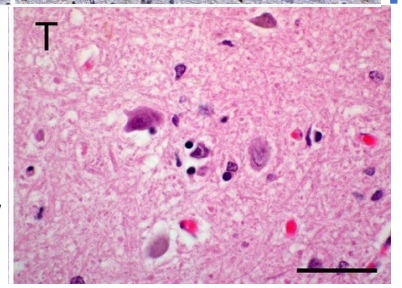


Post-mortem MRI
(11.4T scanner)
100 micron sections



CD68

Pre-Botzinger complex



Pre-Botzinger complex

Neuronophagia

https://en.wikipedia.org/wiki/Central_hypoventilation_syndrome

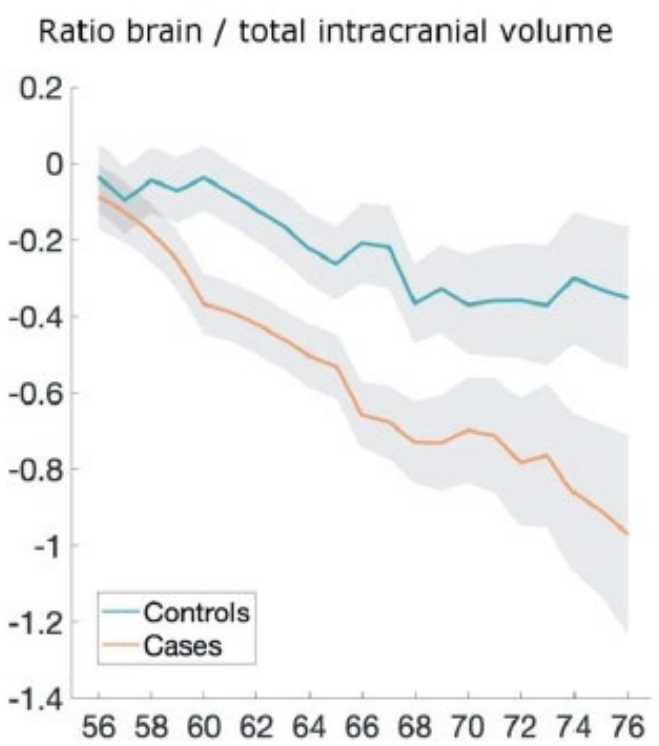
Can SARS-CoV-2 infection accelerate Brain atrophy and Alzheimier's Disease pathology?

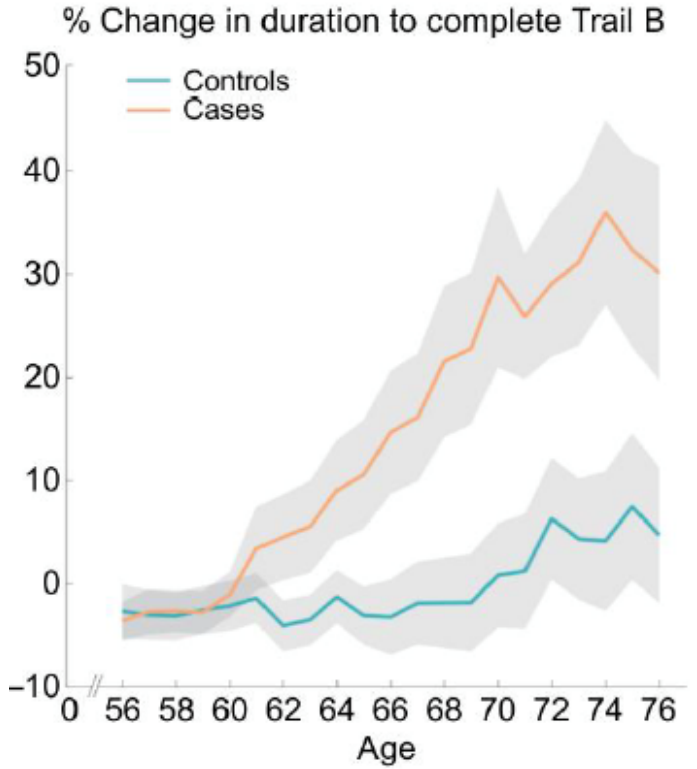
nature

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

Journal of Alzheimer's Disease 89 (2022) 411–414
DOI 10.3233/JAD-220717
IOS Press

Short Communication

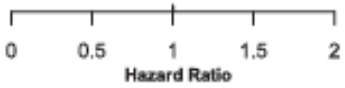
Association of COVID-19 with New-Onset Alzheimer's Disease

Lindsey Wang[a], Pamela B. Davis[b], Nora D. Volkow[c], Nathan A. Berger[a], David C. Kaelber[d] and Rong Xu[e,*]

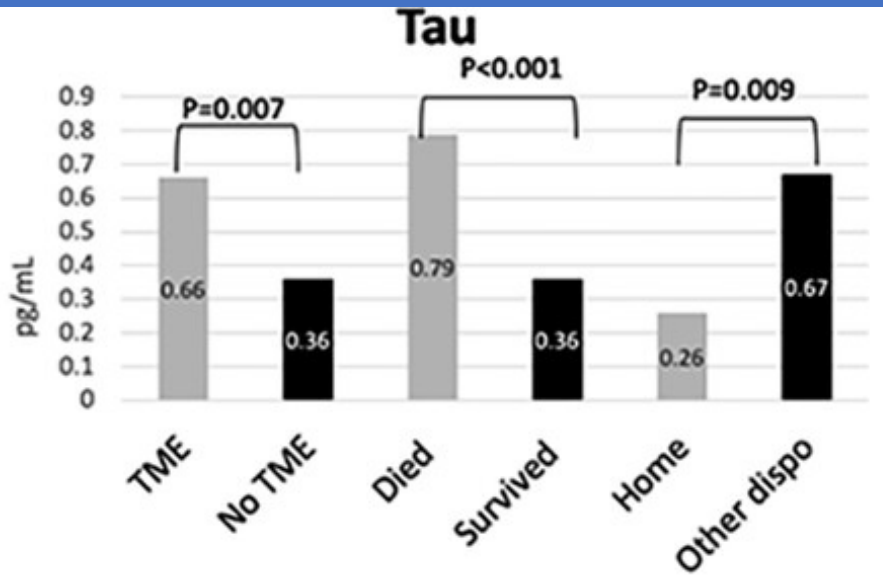
- Reviewed 95 million health records in US
- 6.2 Million >65 yrs with medical encounters 2/2020-5/2021

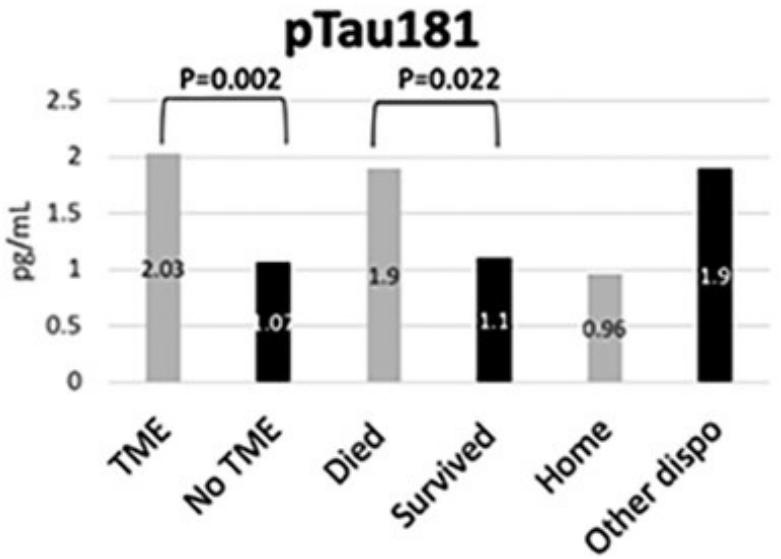
Comparison of 360−day risk for new diagnosis Alzheimer's disease (matched COVID−19 vs non−COVID−19 cohorts)

Population	Matched Cohort (COVID−19)	Matched Cohort (non−COVID−19)	HR (95% CI)
Overall (>=65)	0.68% (2,716/399,916)	0.47% (1,910/403,672)	1.69 (1.53−1.72)
65−74	0.20% (416/213,508)	0.13% (359/213,814)	1.59 (1.37−1.85)
75−84	0.87% (1,111/127,298)	0.59% (752/128,534)	1.69 (1.54−1.85)
>=85	2.01% (1,189/59,110)	1.33% (812/61,032)	1.89 (1.73−2.07)
Women	0.80% (1,696/213,138)	0.48% (1,042/215,383)	1.82 (1.69−1.97)
Men	0.55% (1,020/186,698)	0.42% (785/188,026)	1.50 (1.37−1.65)
Black	0.77% (306/39,925)	0.53% (212/40,206)	1.62 (1.36−1.93)
White	0.70% (2,094/301,366)	0.49% (1,475/303,865)	1.61 (1.51−1.72)
Hispanic	0.47% (128/27,229)	0.41% (112/27,265)	1.25 (0.97−1.61)

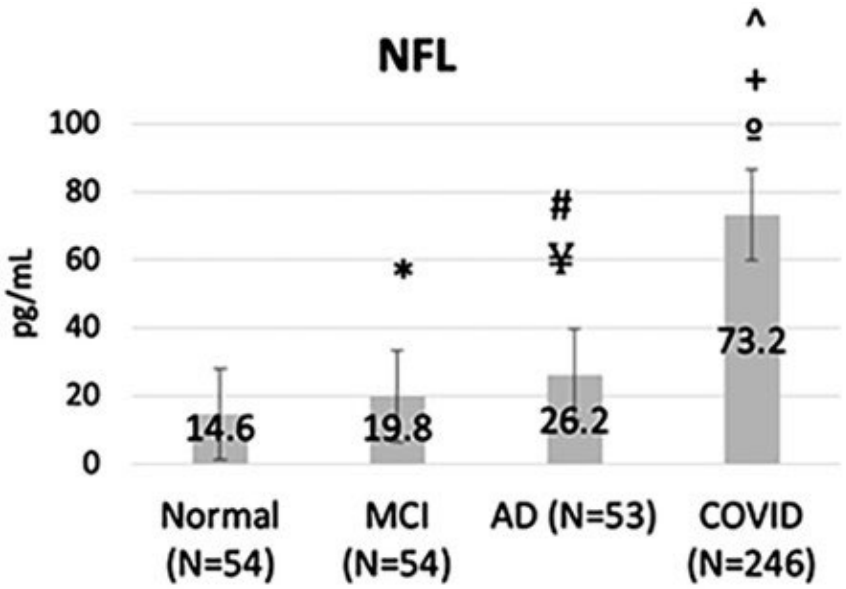


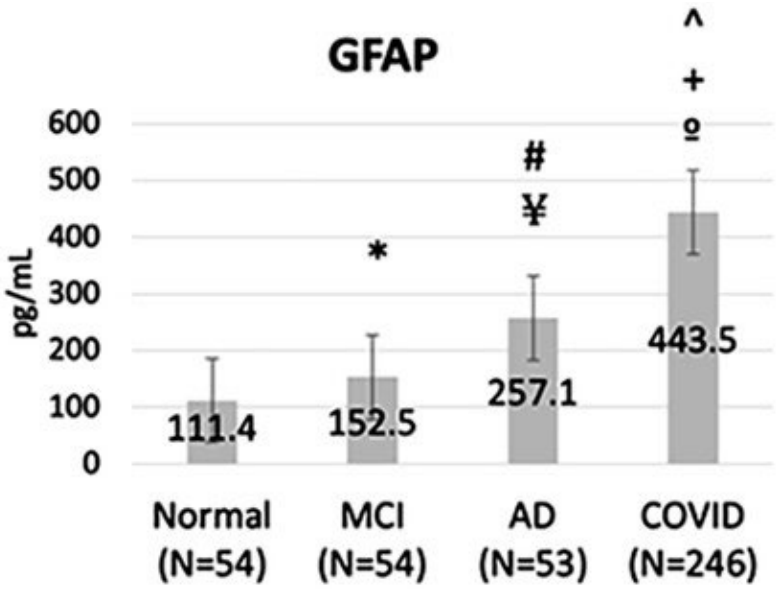
Hospitalized patients with COVID





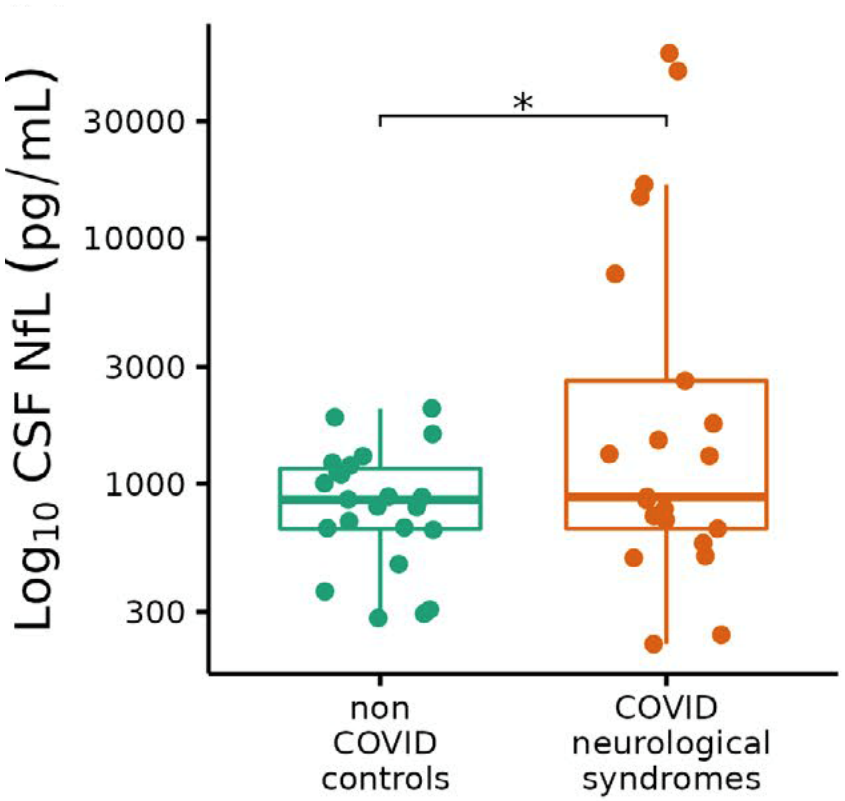
TME=toxic metabolic encephalopathy

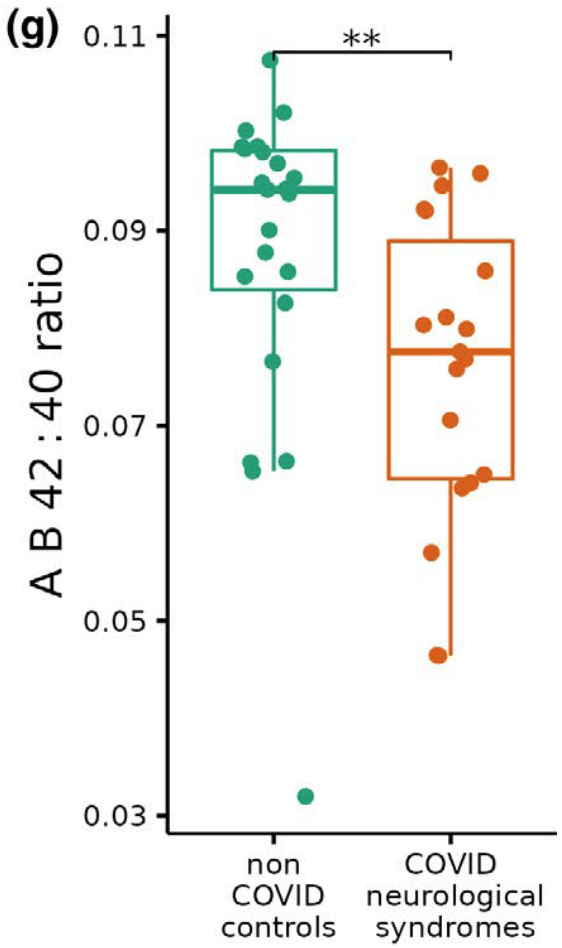


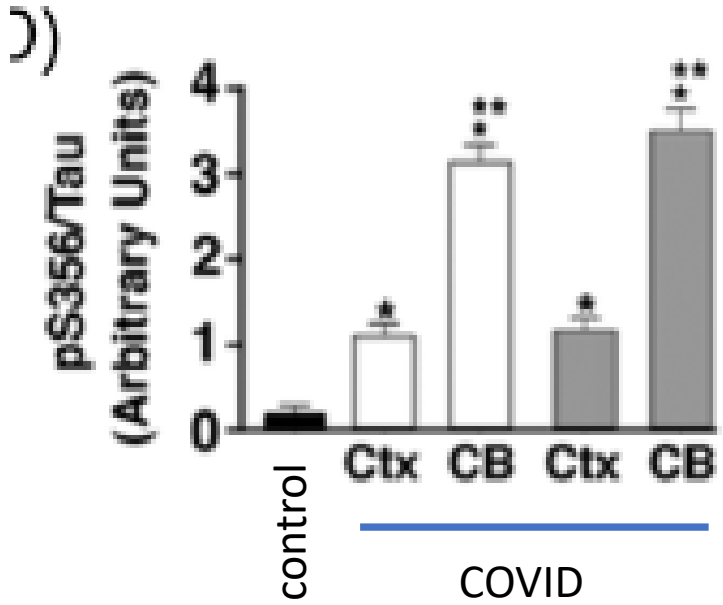


Fonterra et al., J Alz Dem 2022

MARKERS OF NEURONAL INJURY and ALZHEIMER's DISEASE

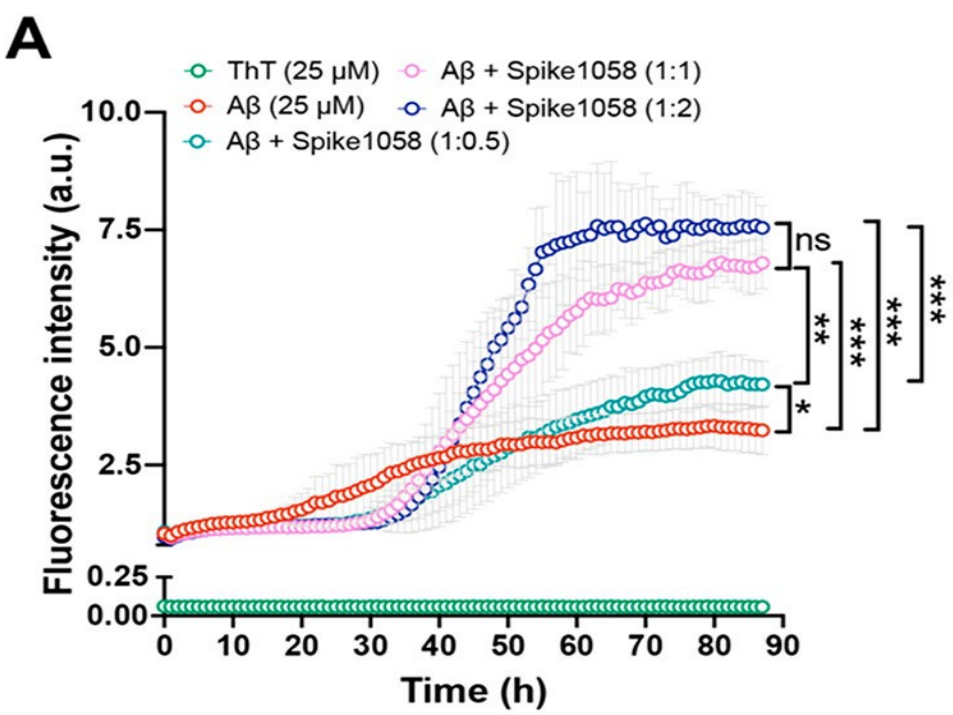


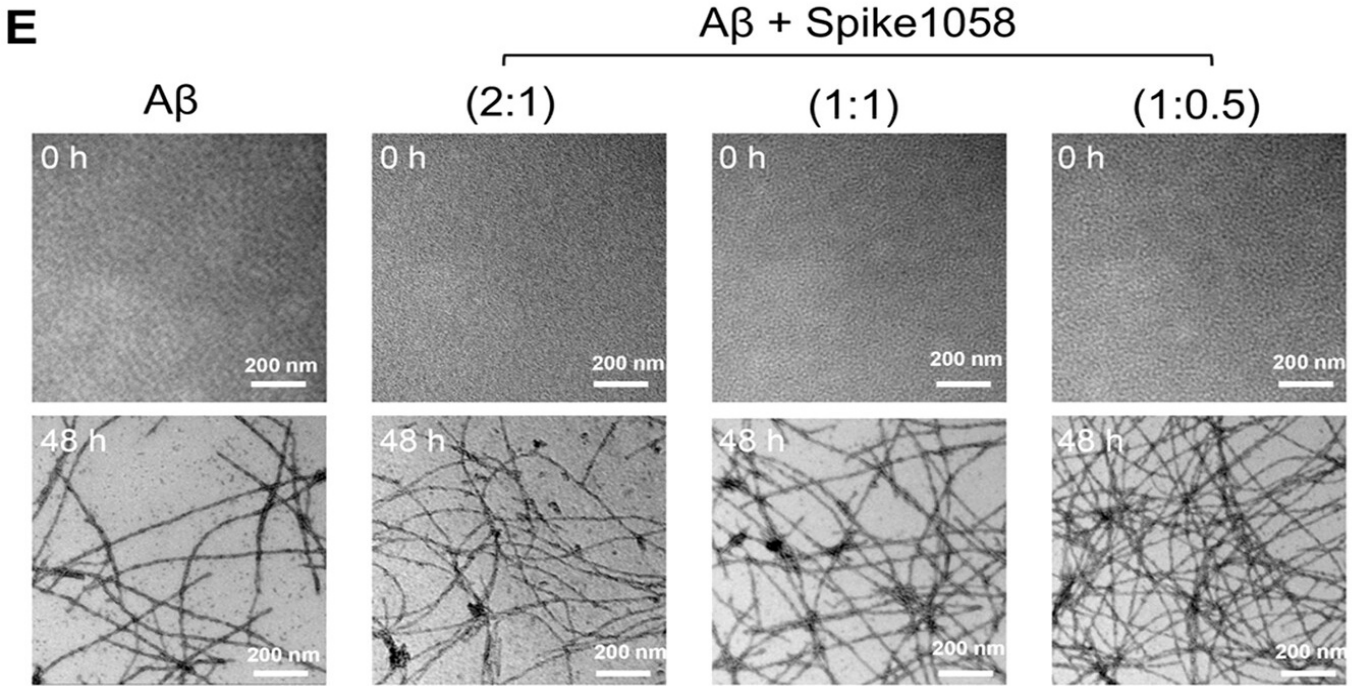




Ziff et al., J Neurochem 2021

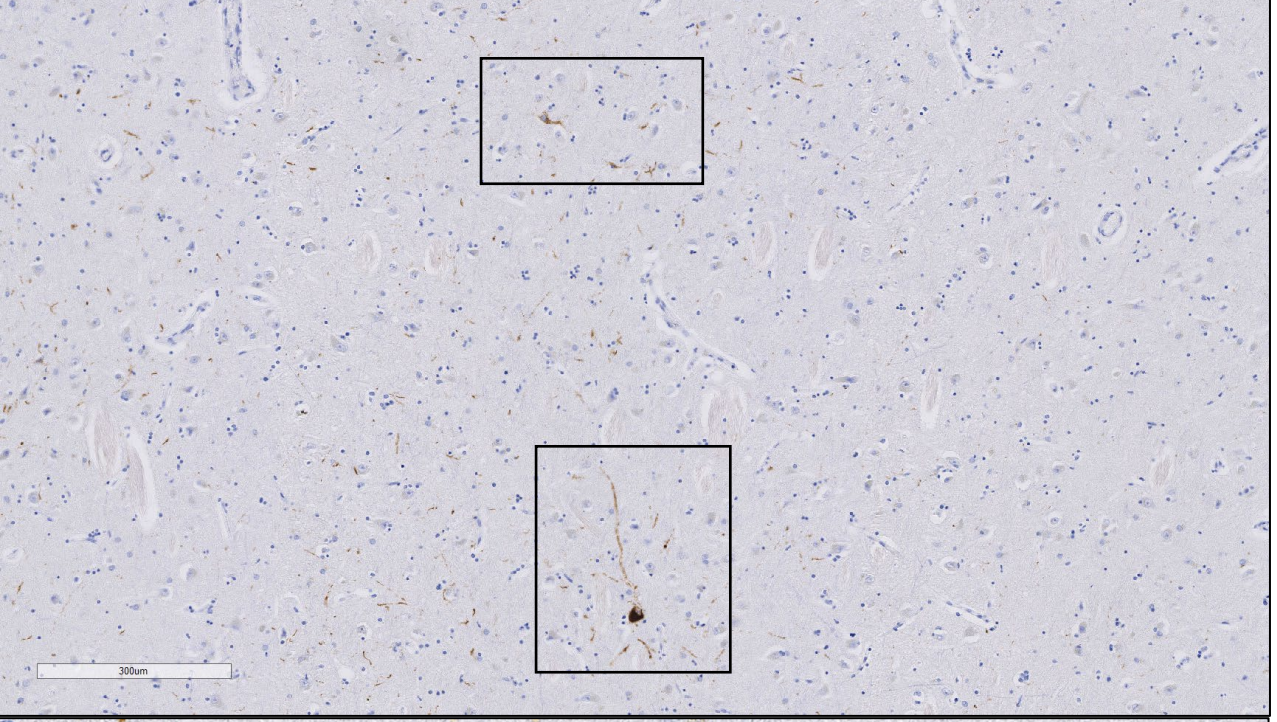
Acceleration of Amyloid fibril formation with Spike protein fragment

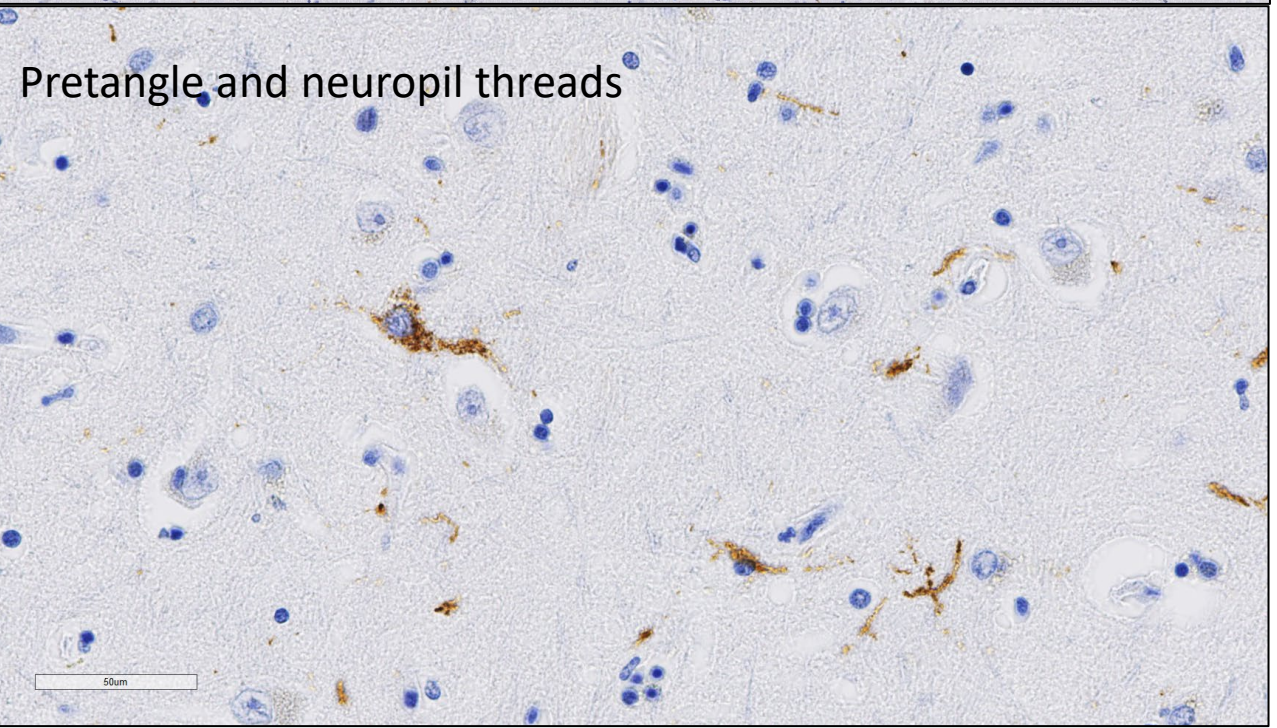


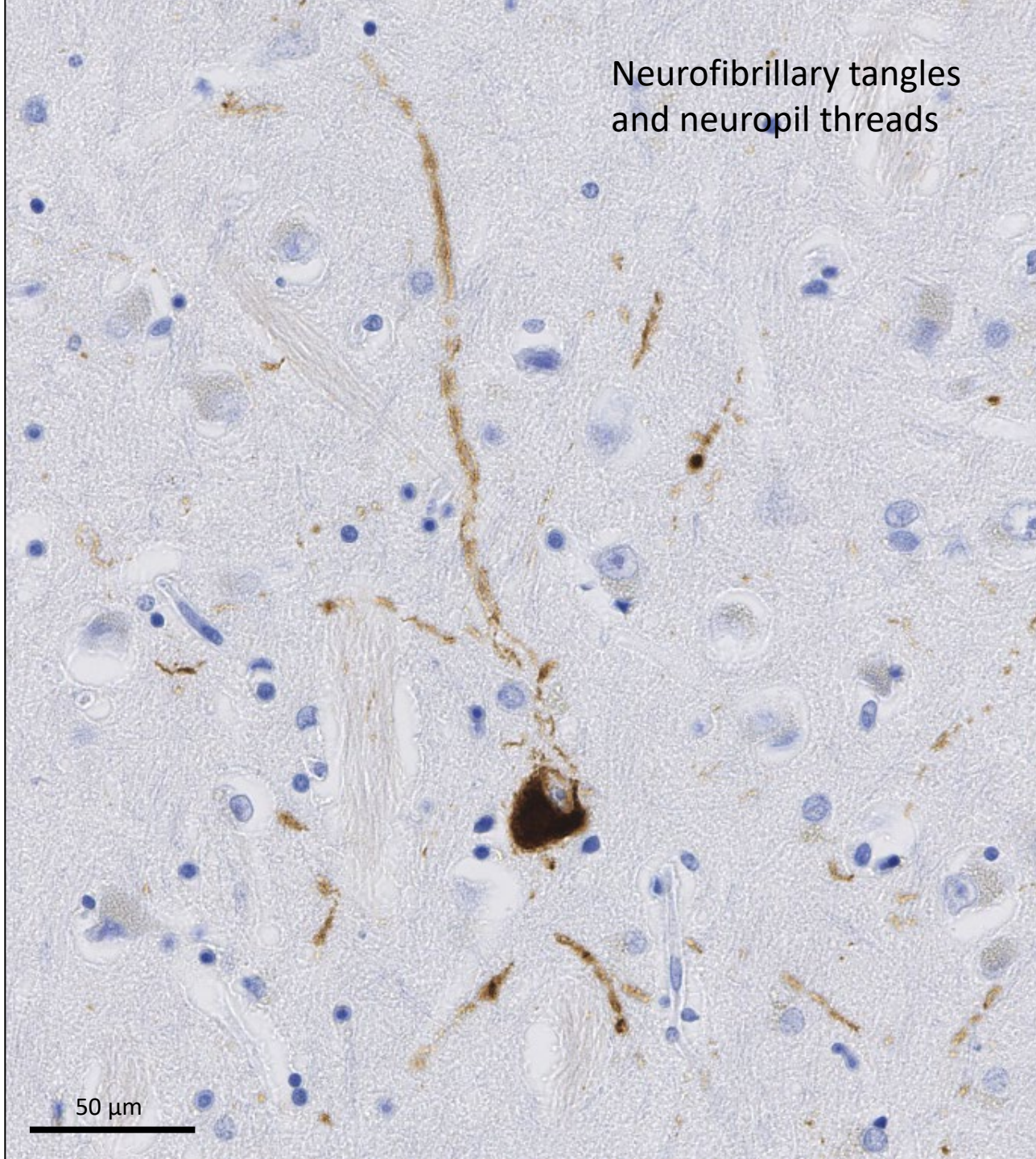


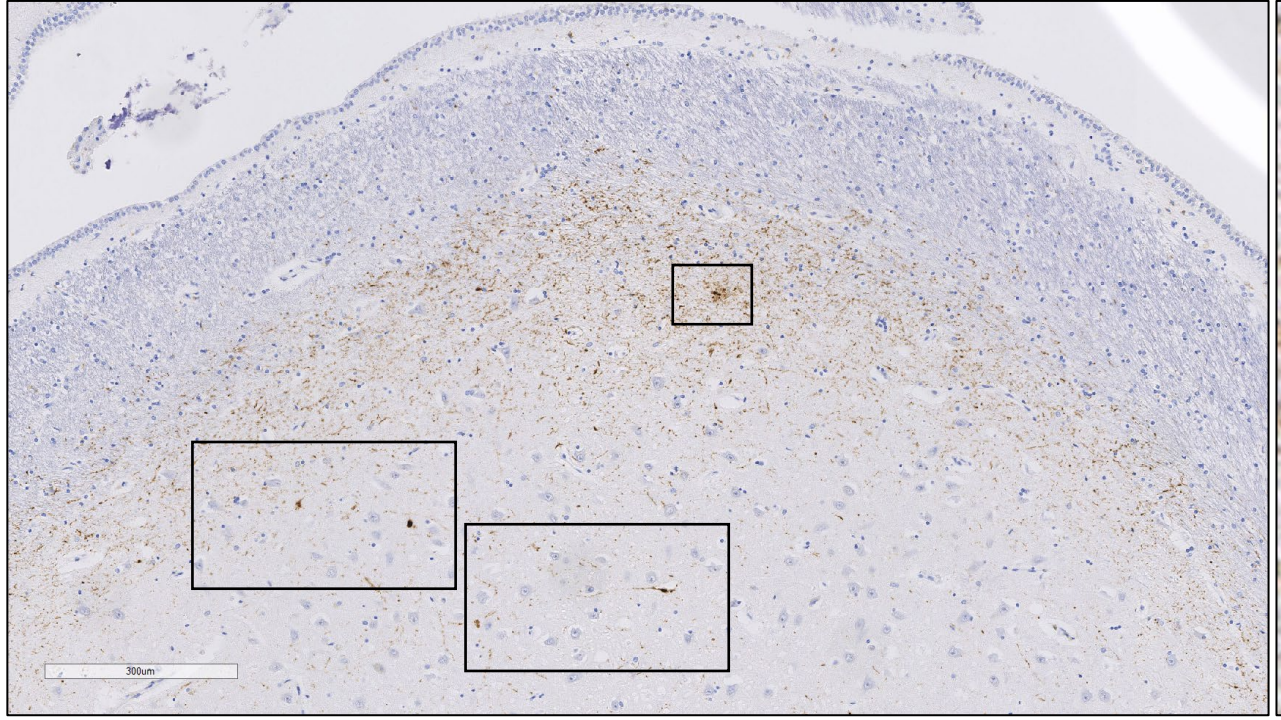
Spike 1058-68: HGVFLHVTYV

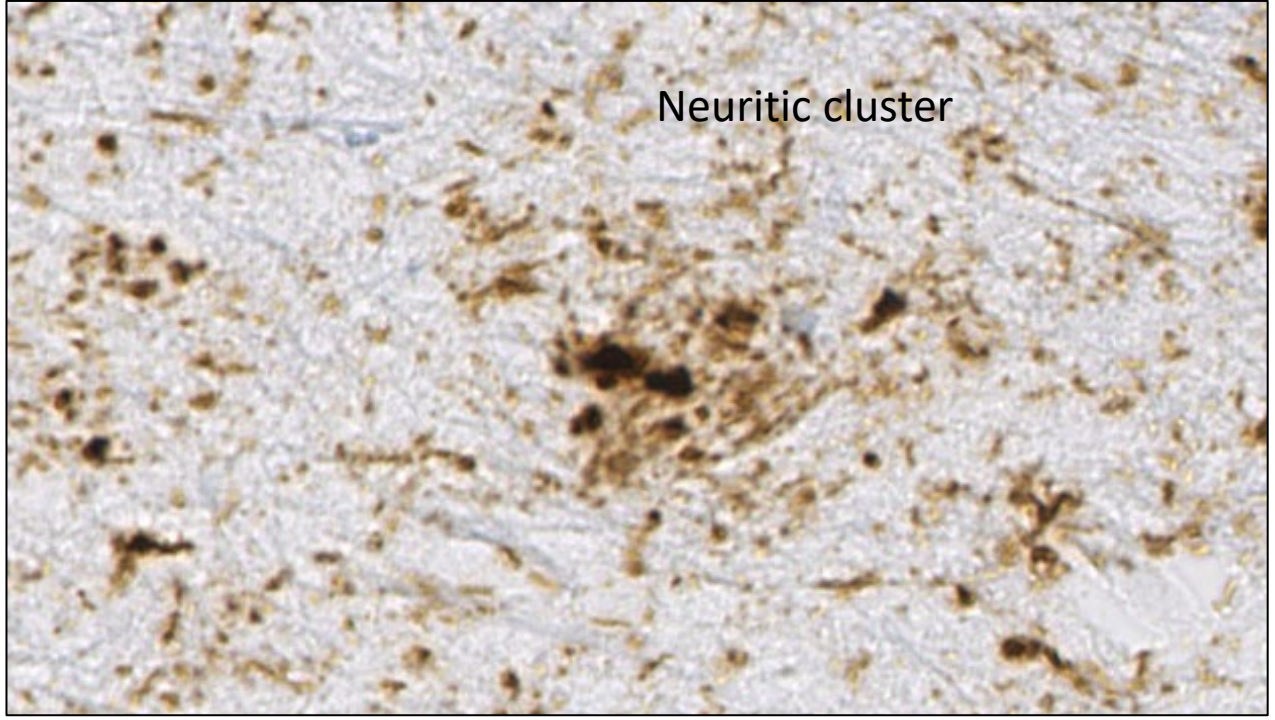
Cao et al., ACS Appl Mater Interfaces 2023

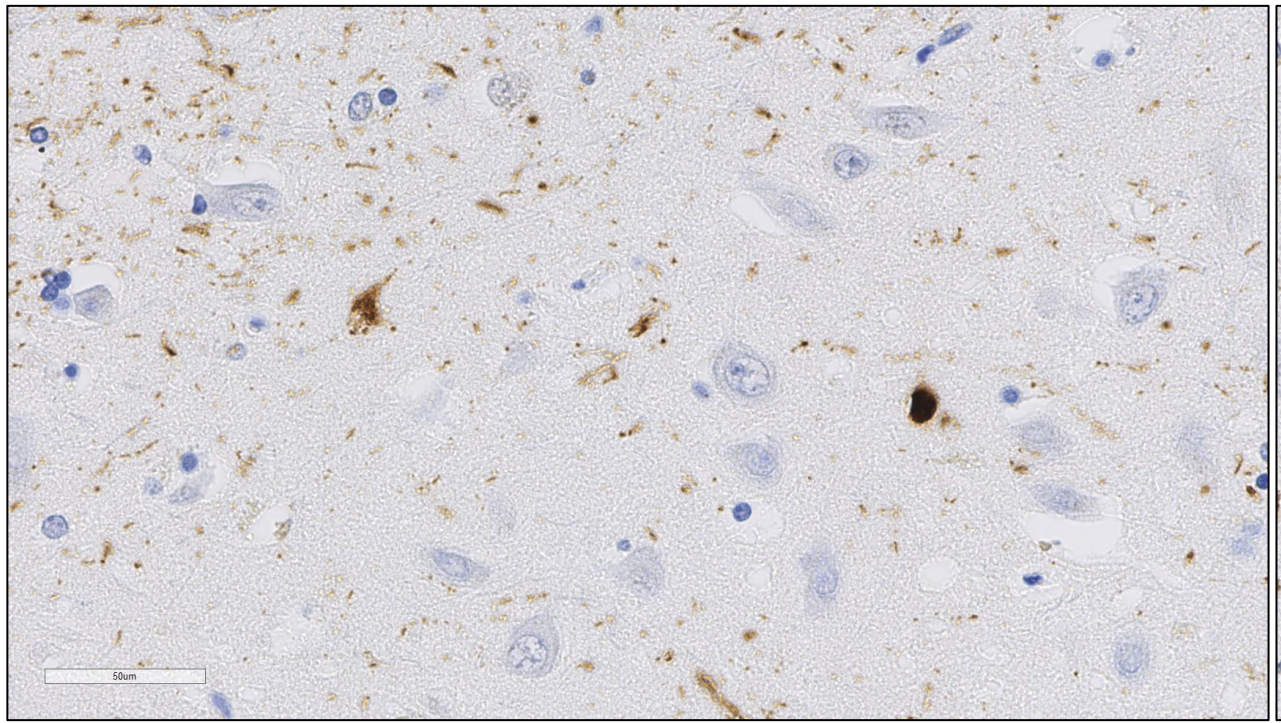

300um


Pretangle and neuropil threads
50um


Neurofibrillary tangles
and neuropil threads
50 µm


300um


Neuritic cluster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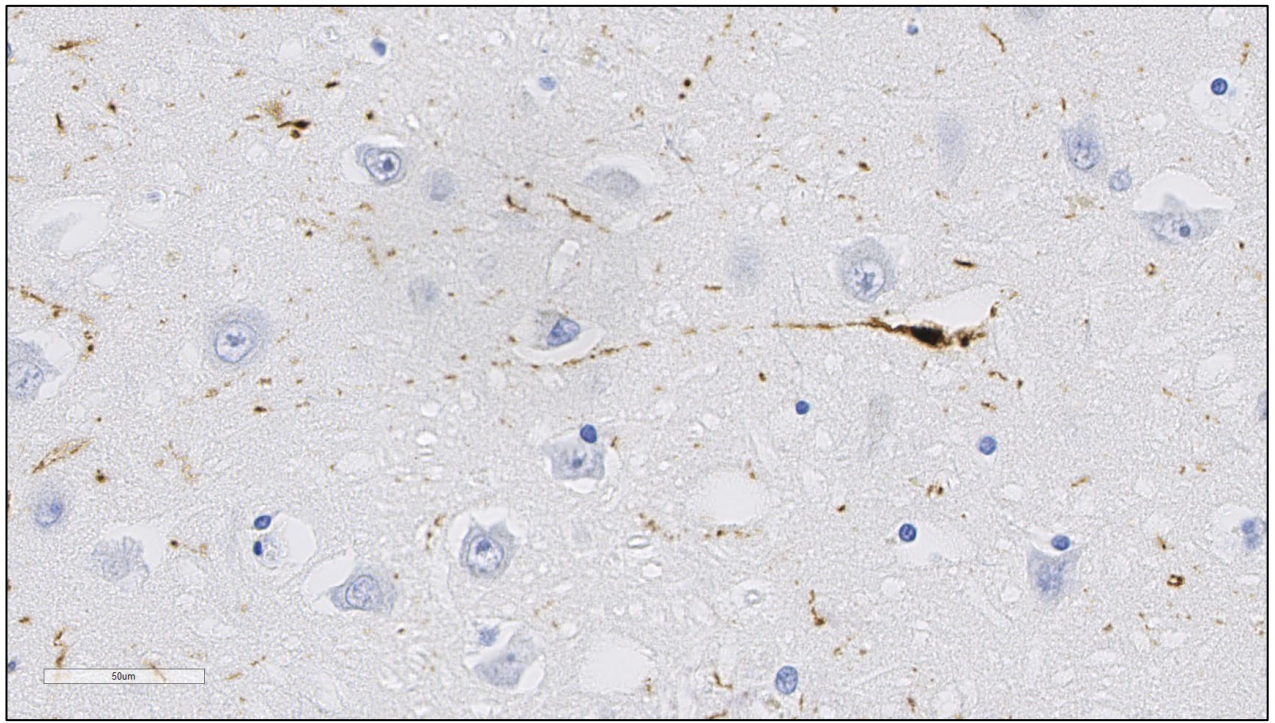

50um

Symptomatic therapy
(assuming that other underlying causes have been excluded)

- Brain fog: Cognitive therapy
- Dysautonomia: Mineralocorticoids, compression stocking, IV fluids
- Sleep disruption: Sleep studies and treat accordingly
- Mood disorders: anxietolytic, anti-depressive agents
- Pain: Gabapentin; Nortryptiline
- Tinnitus: Hearing aids
- Fatigue: Pacing
- Functional disorders

Immunomodulatory therapy (Need Clinical Trials)

- **Non-specific immunomodulatory agents**
- Corticosteroids
- Intravenous Immunoglobulin
- Plasmapheresis

- **Innate immune system**
- IL-1, IL-6 and TNF-alpha antagonists
- JAK-STAT inhibitors
- BTX inhibitors

- **Reversal of immune exhaustion**
- Checkpoint inhibitors

Feb 2023

Prevention with Vaccination

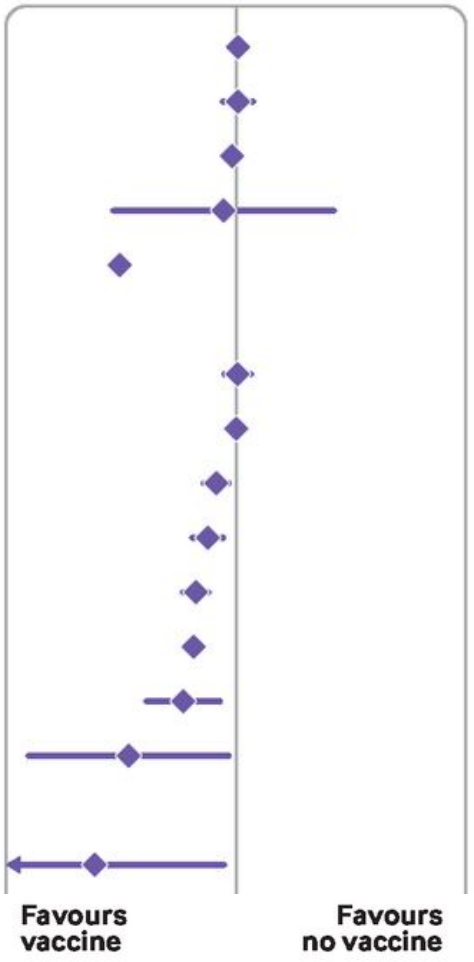
bmjmedicine

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)



Clinical Protocols on Neuro-COVID at NIH

- Natural History Study
- Viral Reservoir Study (in development)
- Clinical Trial (placebo vs IVIG)

Conclusions

- Direct invasion of the brain by SARS-CoV-2 is rare and may 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)*

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Amanda Weibold Ladifatou Fouanta, Anita Jones

Govind Nair, Alan Koretsky, Helen Murray (MRI)

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