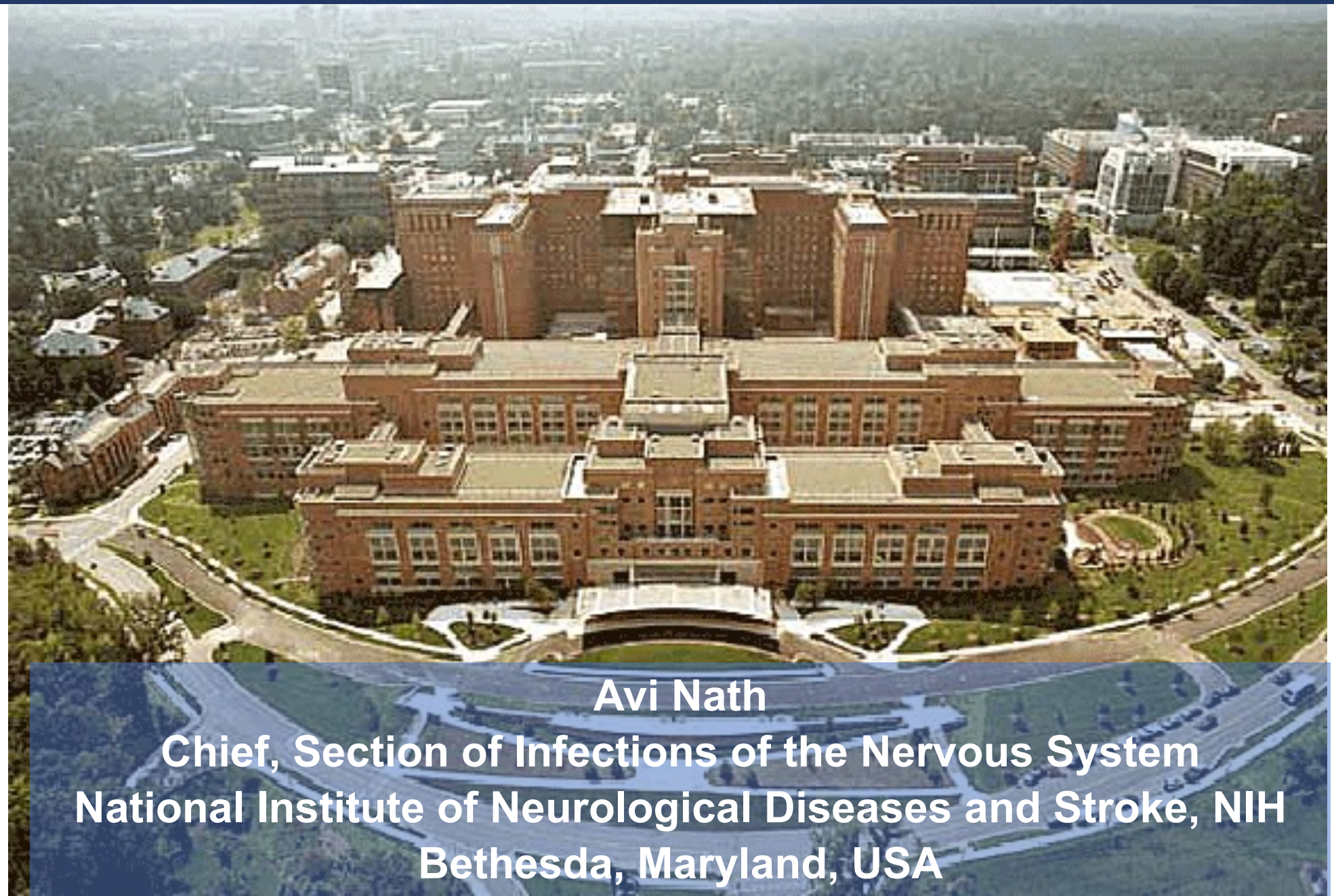
Neurological and Neuromuscular complications of COVID



Avi Nath

Chief, Section of Infections of the Nervous System

National Institute of Neurological Diseases and Stroke, NIH

Bethesda, Maryland, USA

NASEM

March 21, 2022

Acute

Anosmia

Metabolic/hypoxic encephalopathy

Strokes

Viral Encephalitis (rare)

Sudden death (Ondine's curse)

Subacute

Inflammatory Syndromes

Acute disseminated encephalomyelitis

Acute necrotizing hemorrhagic encephalopathy

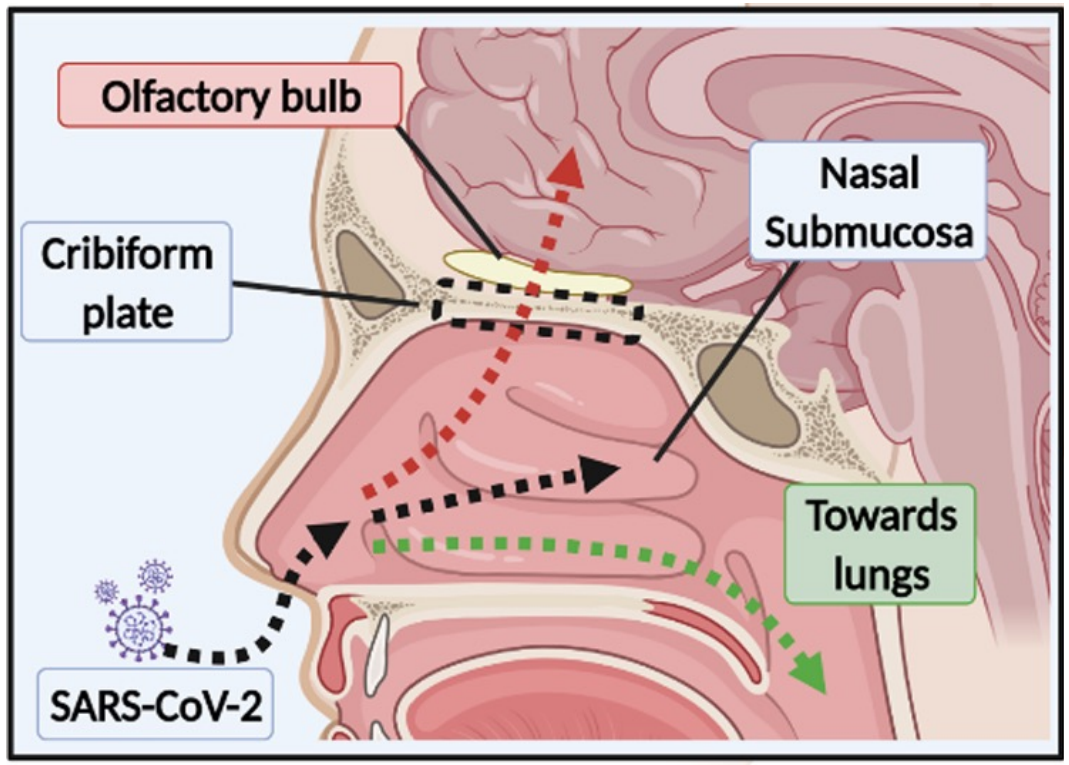
Limbic encephalitis

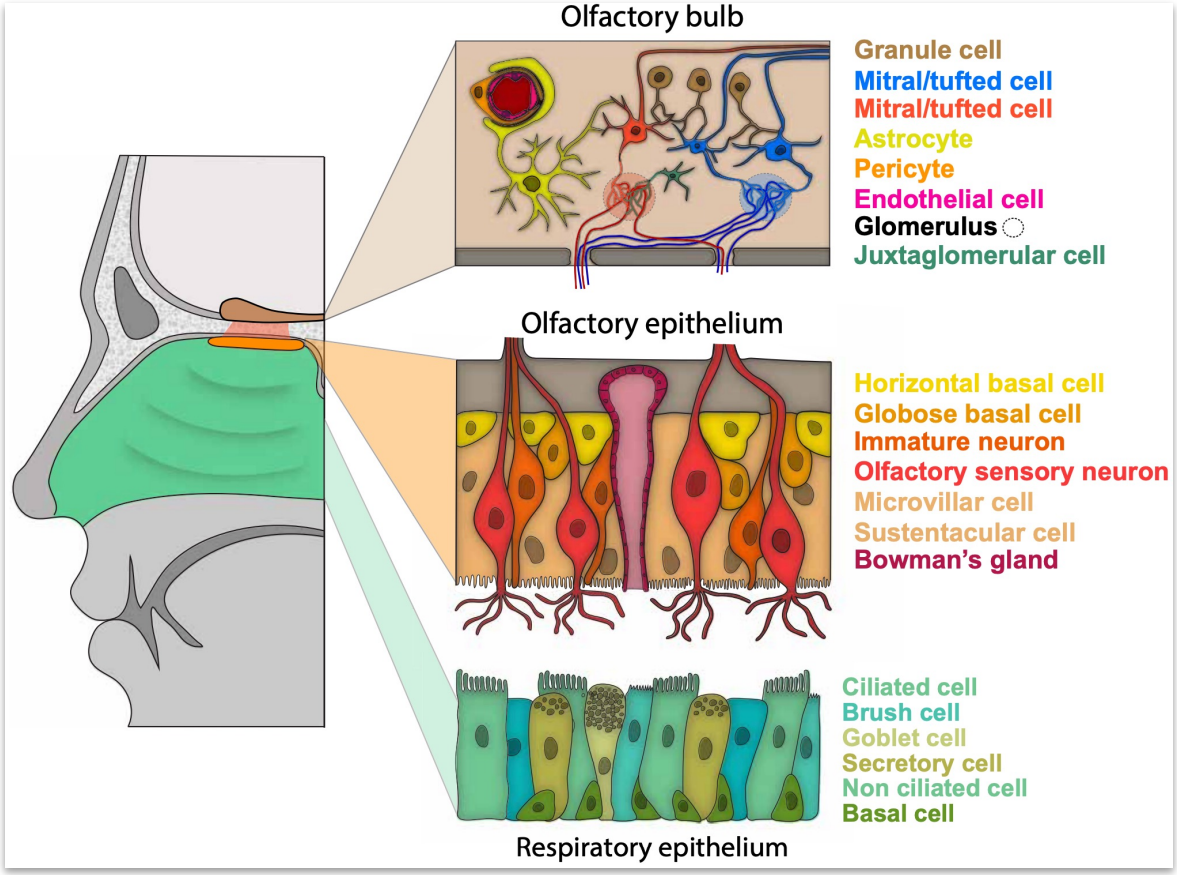
Multisystem Inflammatory Syndrome

Chronic

Long COVID

Can the virus enter the brain through the olfactory pathways?

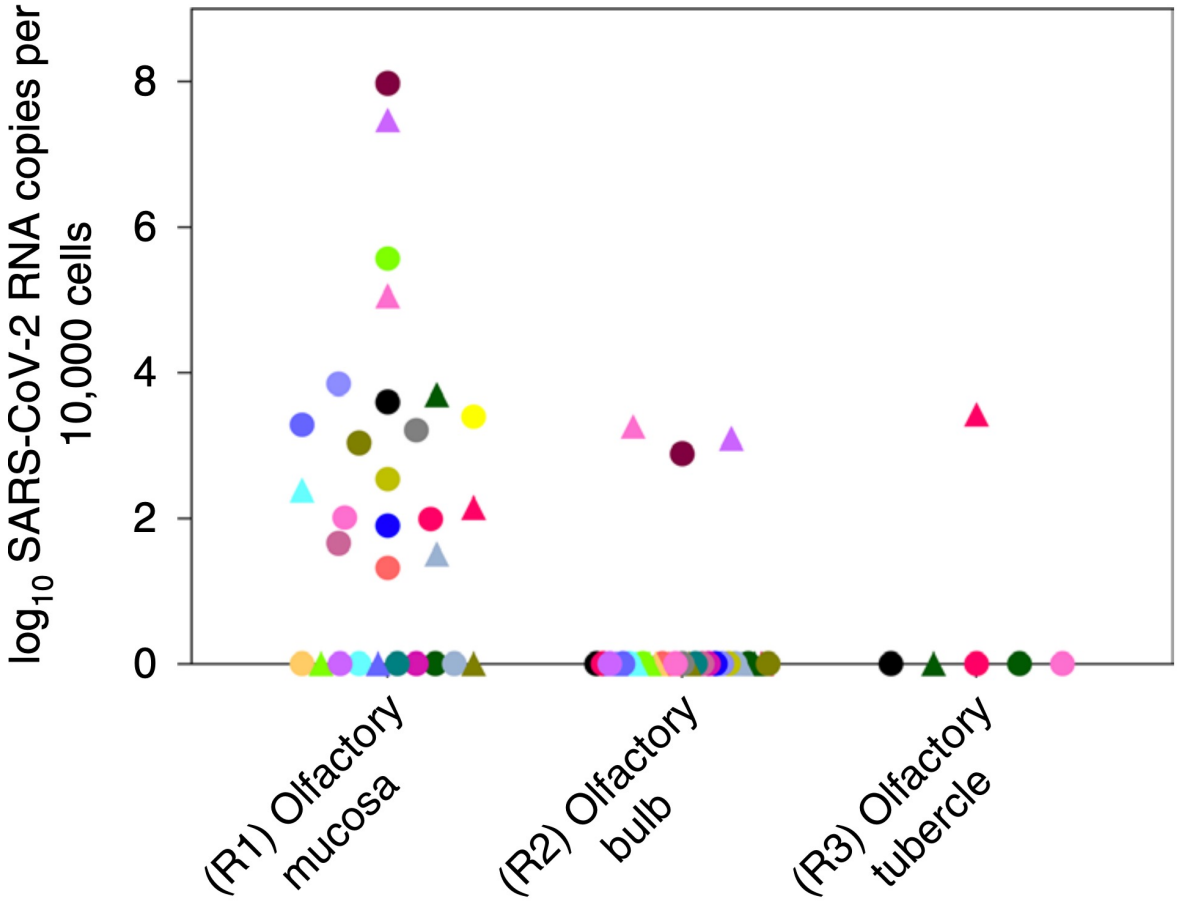


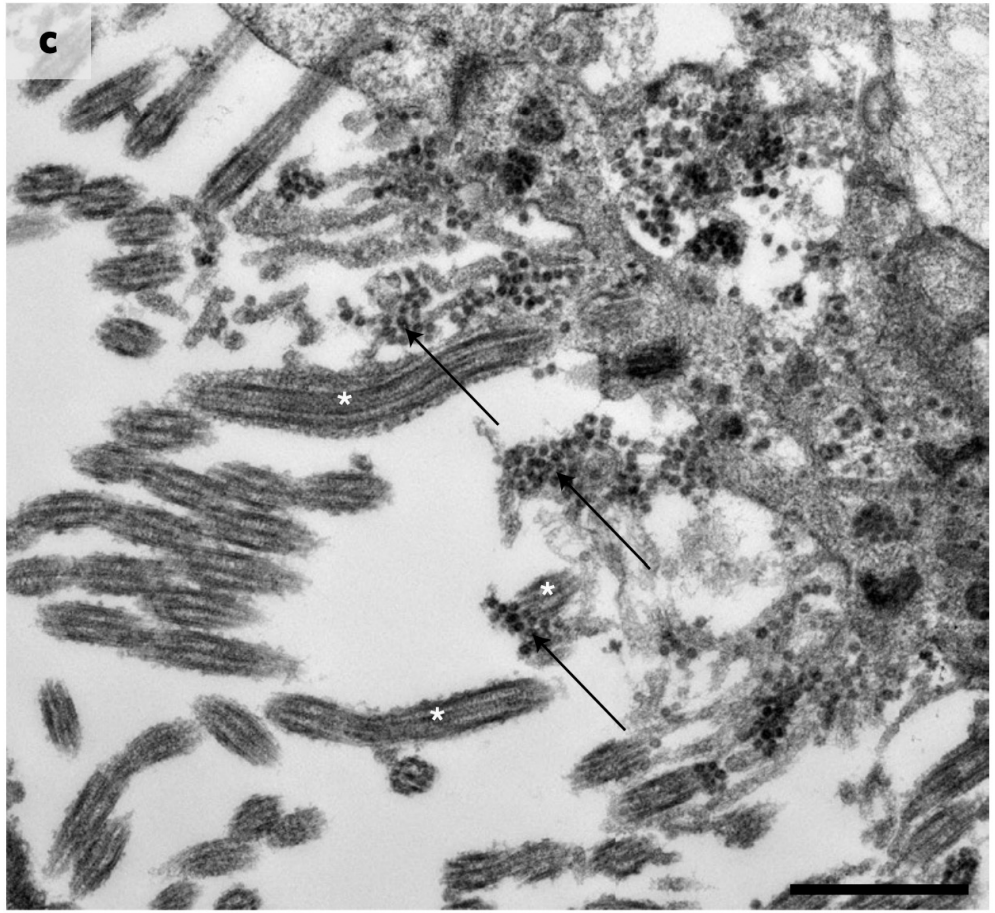


Images: McQuaid et al., 2021 DOI: 10.1186/s12987-021-00267-y; Brann et al., 2020 DOI:10.1126/sciadv.abc5801

There is a route the virus can follow to get from the nose to the brainstem

Robust infection in olfactory mucosa





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

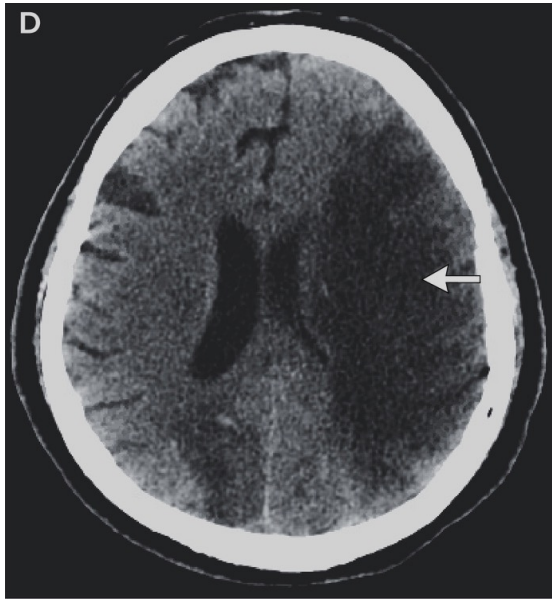
Detection of virus in brain at autopsy

- 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

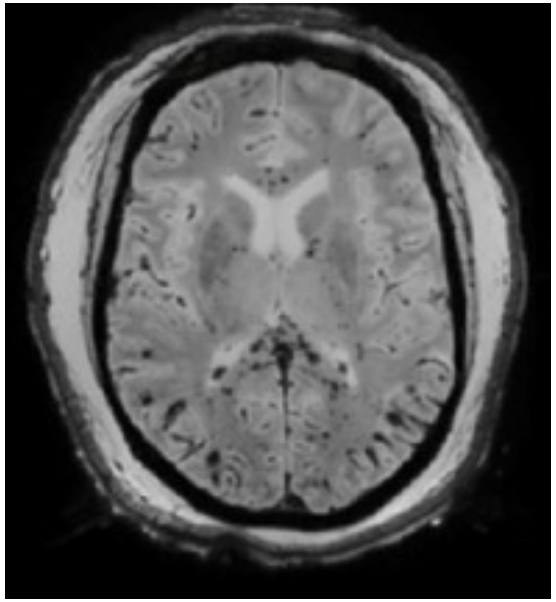
Lee et al., NEJM 2021

VASCULAR INJURY

Strokes and vascular disease with COVID-19



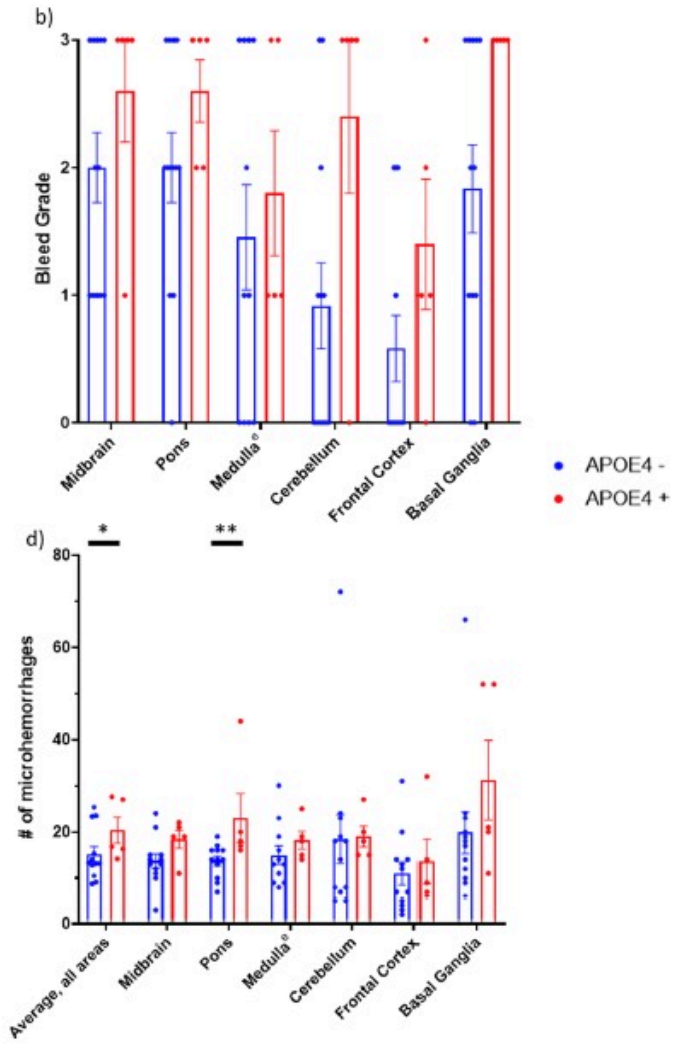
Berlin et al., NEJM 2020
DOI: 10.1056/NEJMcp2009575



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

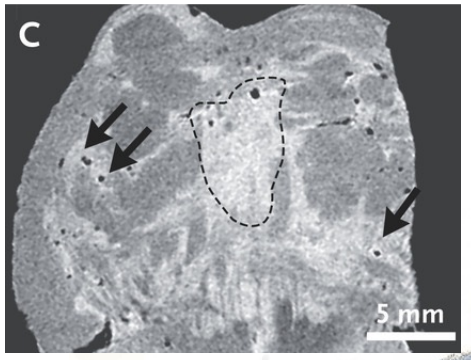
Abdalkader et al., J Stroke and Cerebrovascular Diseases 2021
DOI:10.1016/j.jstrokecerebrovasdis.2021.105733

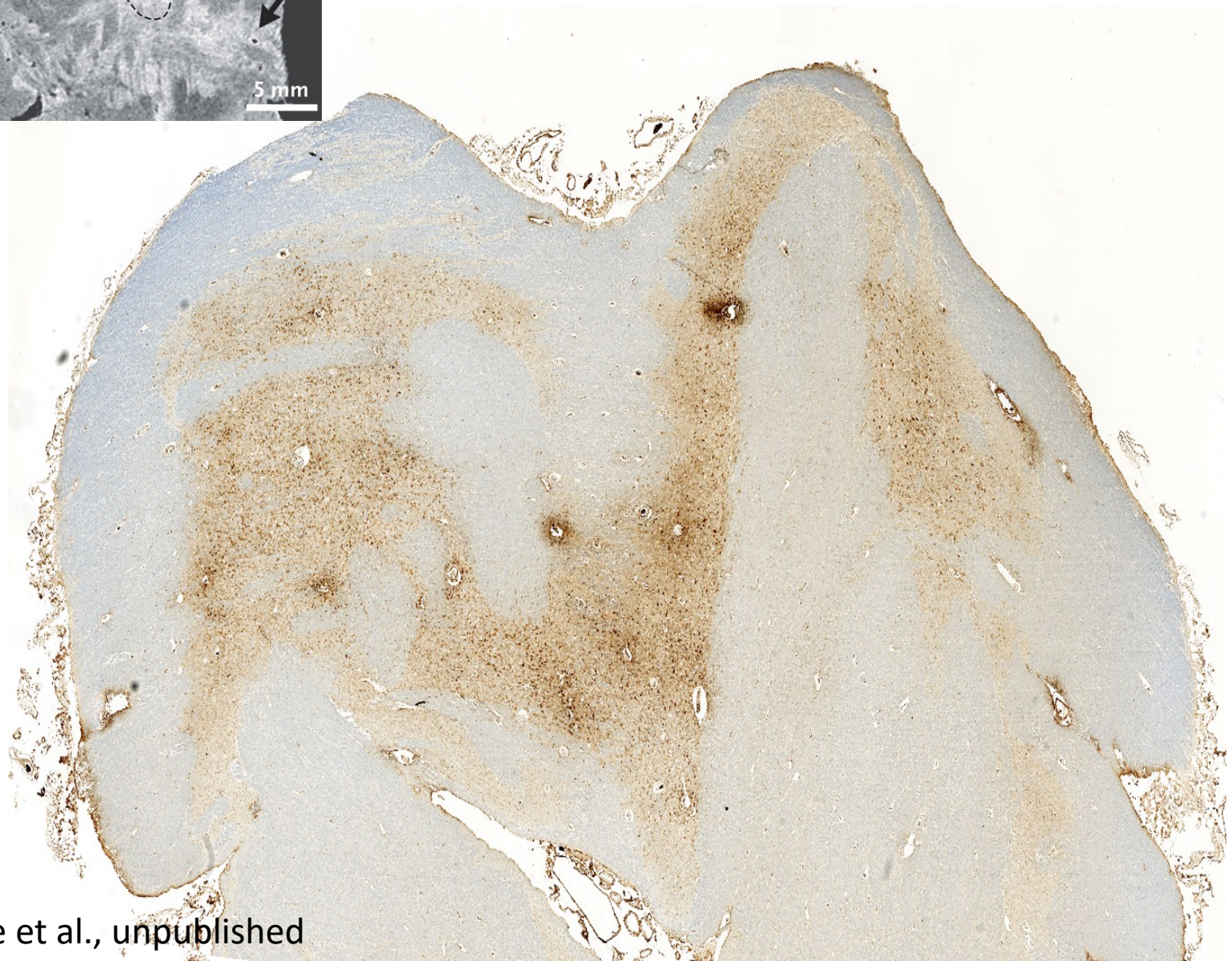
Increased risk for bleeds with APOE4

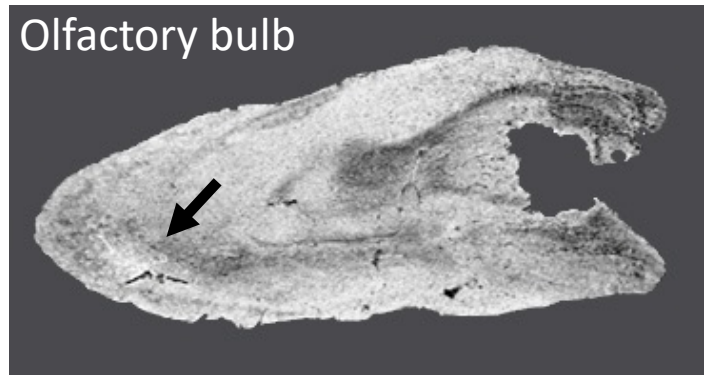


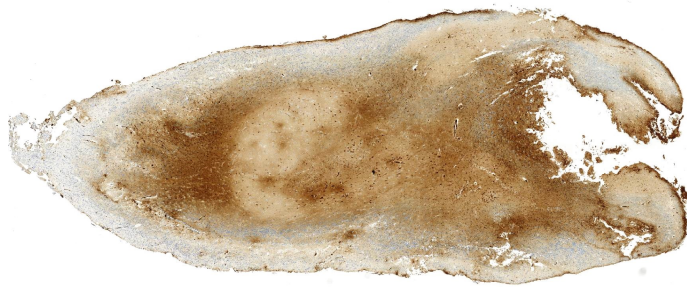
Kurki et al. Acta Neuropath Comm 2021

Perivascular fibrinogen leakage indicates vascular injury



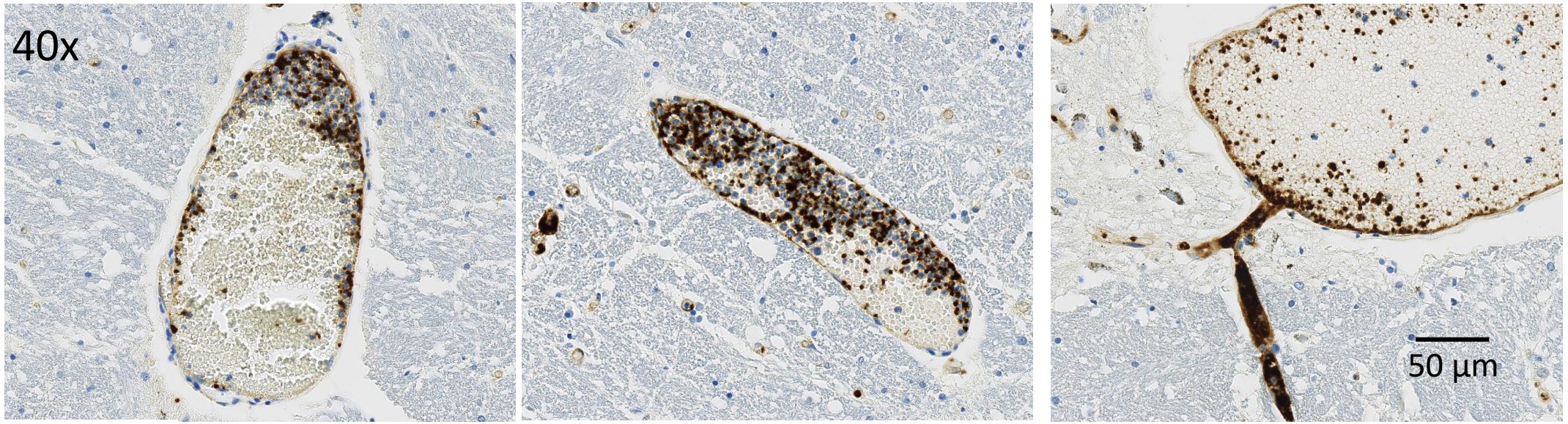


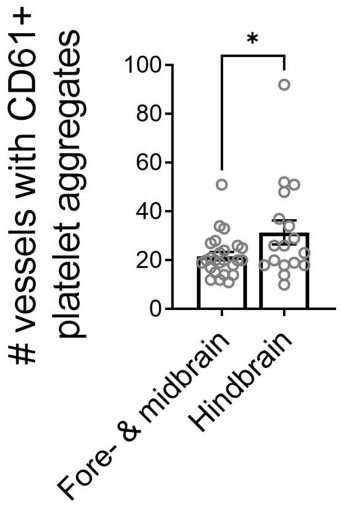


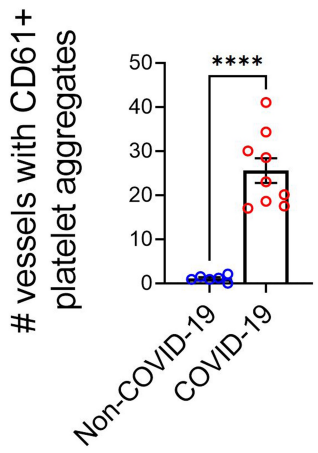


Lee et al., unpublished

Platelets are activated and form clots in small blood vessels







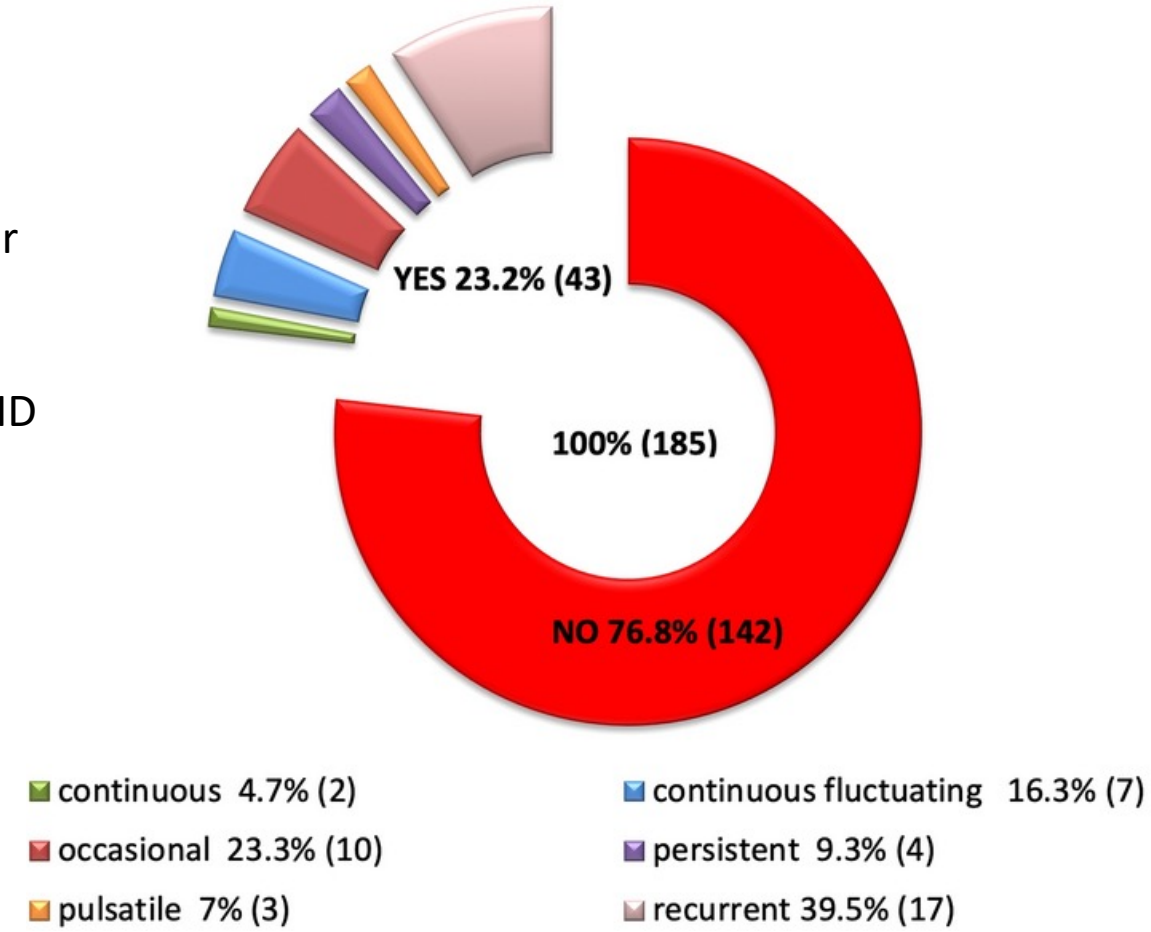
Anti-CD61 (activated platelets)

Lee et al., unpublished

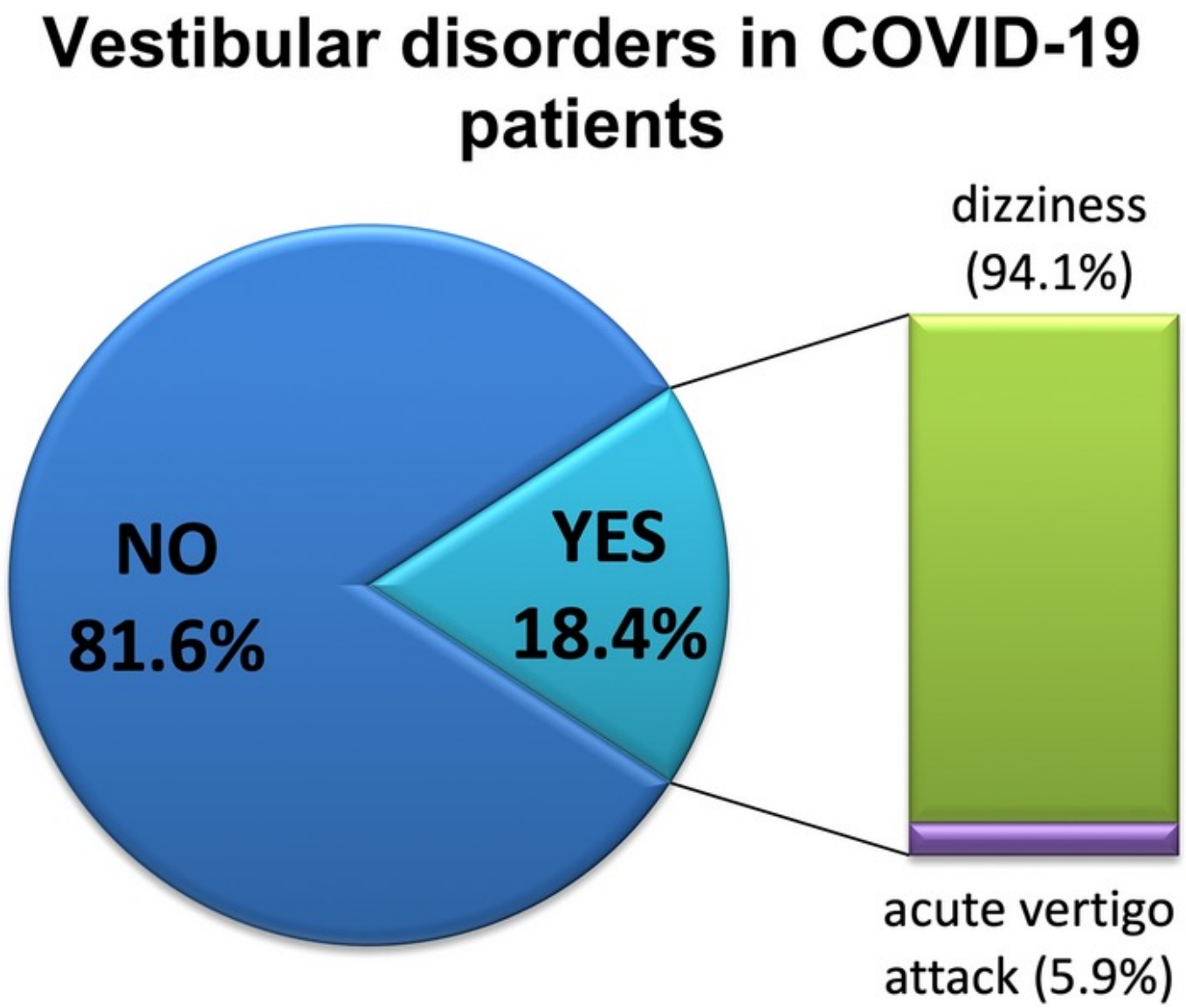
Tinnitus in COVID-19 patients

6.6% of hospitalized patients complain of tinnitus. (Manchester study) Munro et al., 2020

40% tinnitus got worse with COVID Beukes et al., 2020



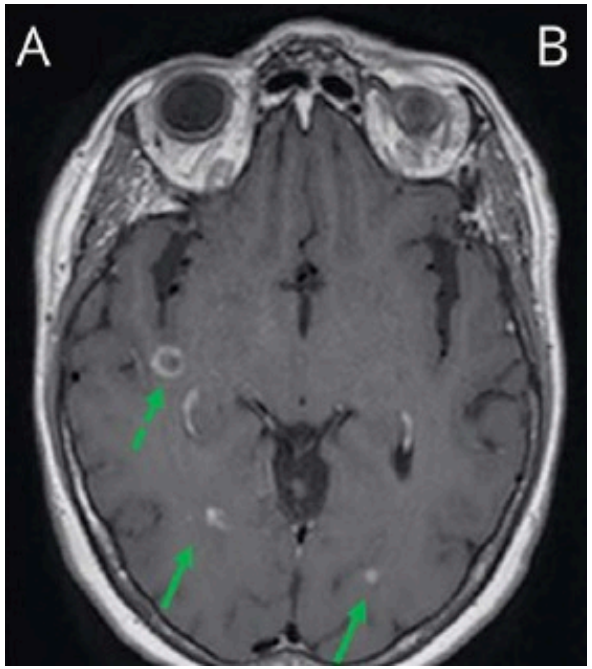
Viola et al., 2020



Viola et al., 2021

Subacute NEURO-INFLAMMATION

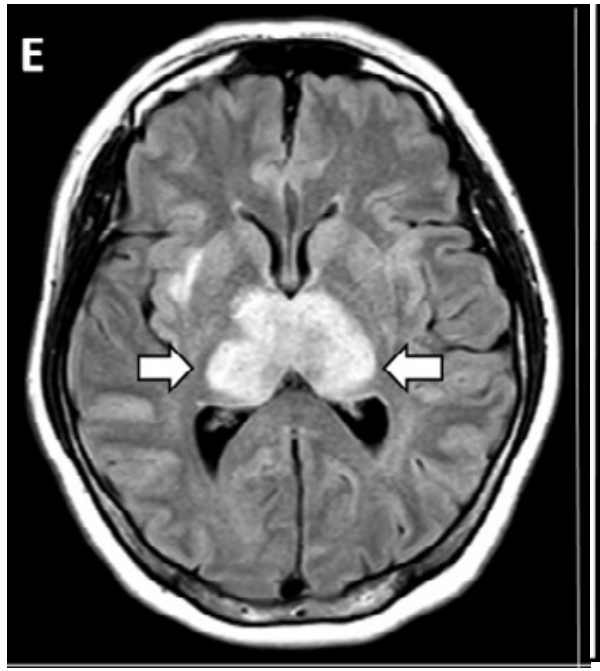
Types of inflammation in the brain

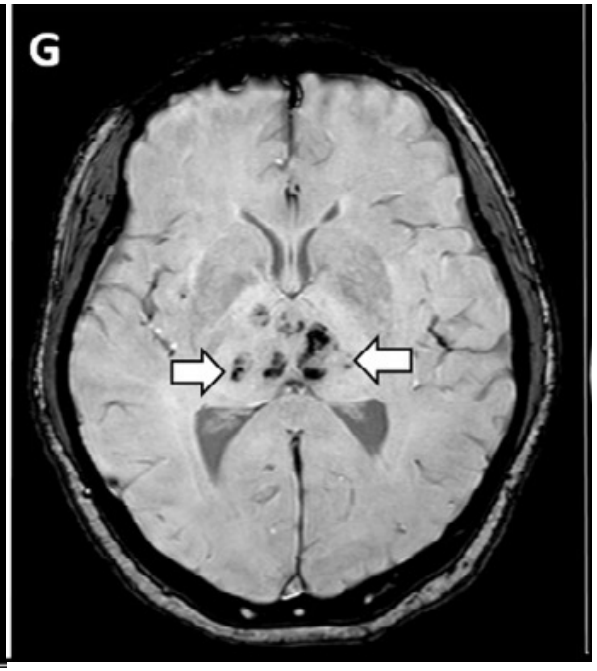


Acute disseminated encephalomyelitis

T-cell mediated

Novi et al., Neurol Neuroimmunol Neuroinflamm 2020





Acute necrotizing hemorrhagic encephalopathy

Cytokine mediated

Poyiadji et al., Radiology 2020

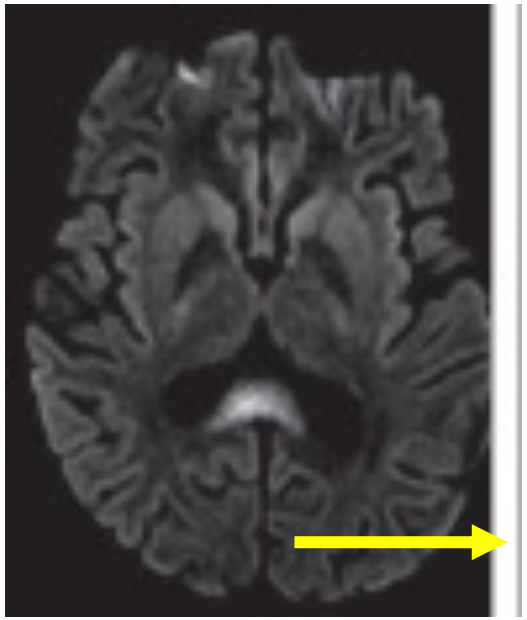
Multi-system Inflammatory Syndrome with COVID-19 (MIS-C) in Children

Fever, dyspnea, rash, vomiting, circulatory failure

2 weeks later
Encephalopathy
Dysarthria
Dysphagia
Generalized flaccid weakness

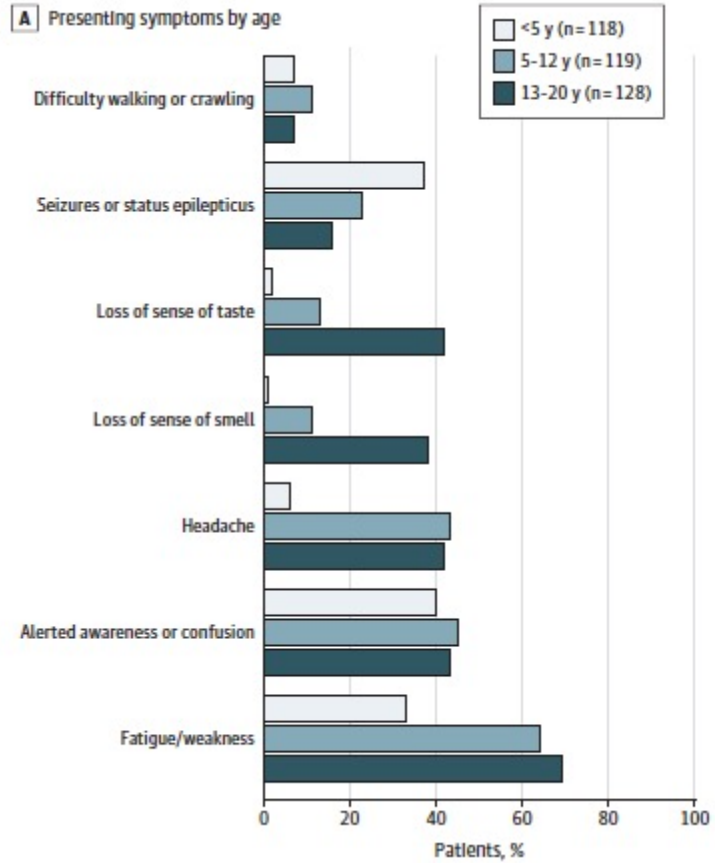
Dexamethasone
IVIG
Partial response

Abdel-Mannan et al., JAMA Neurol 2020



Restricted diffusion on DWI in Splenium of Corpus Callosum

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



N=365 hospitalized children

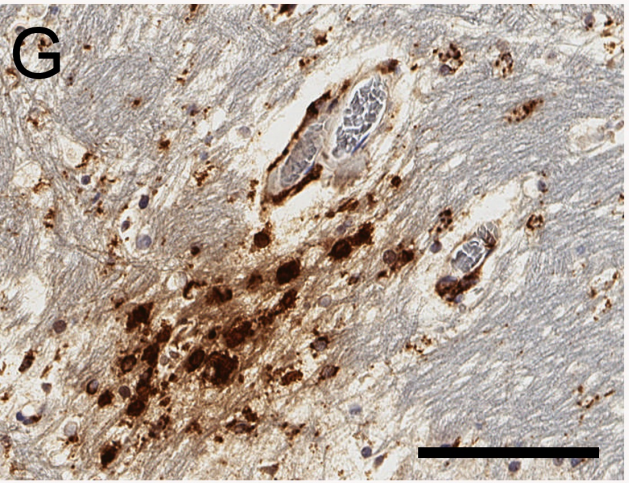
La Rovere et al., JAMA Neurol 2021

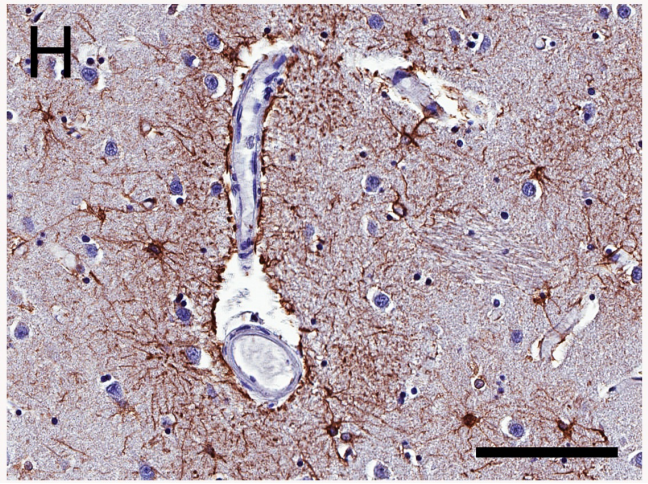
CD68: Macrophages

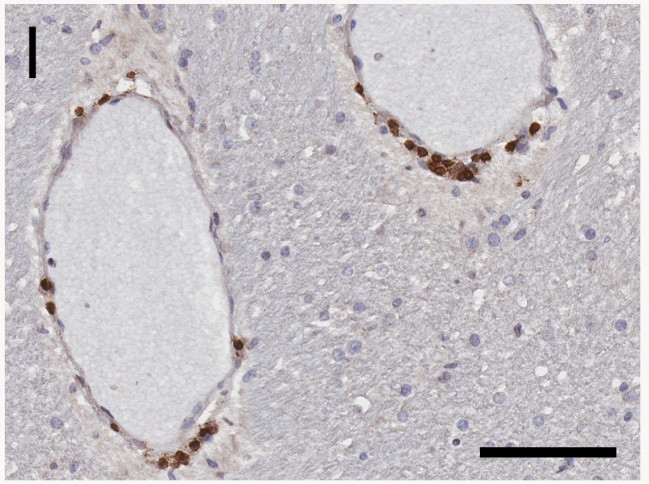
GFAP: Astrocytes

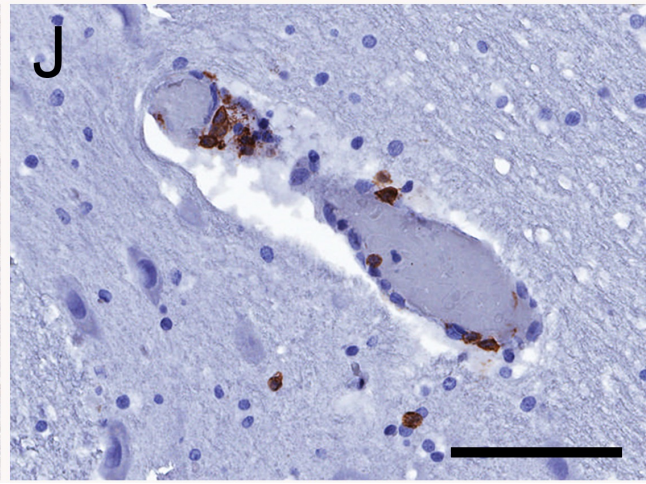
CD3 T cells

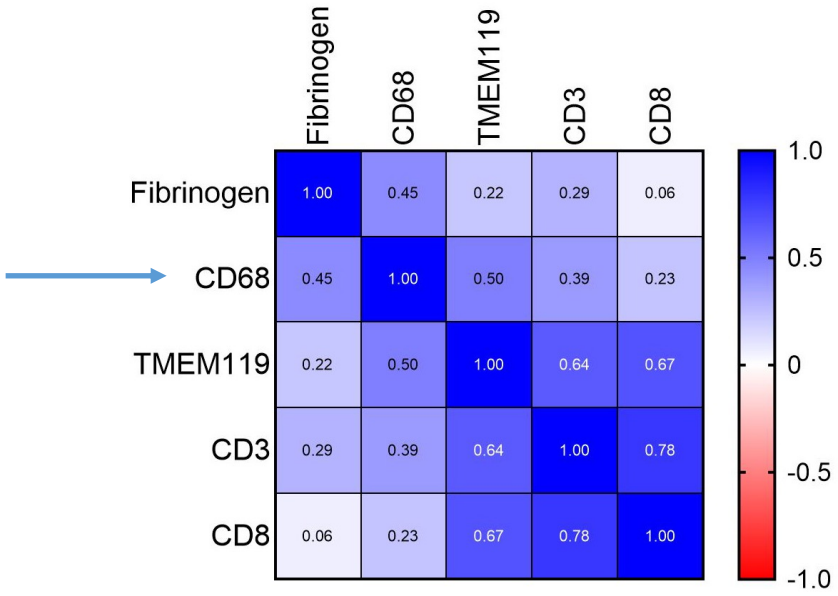
CD8 T cells



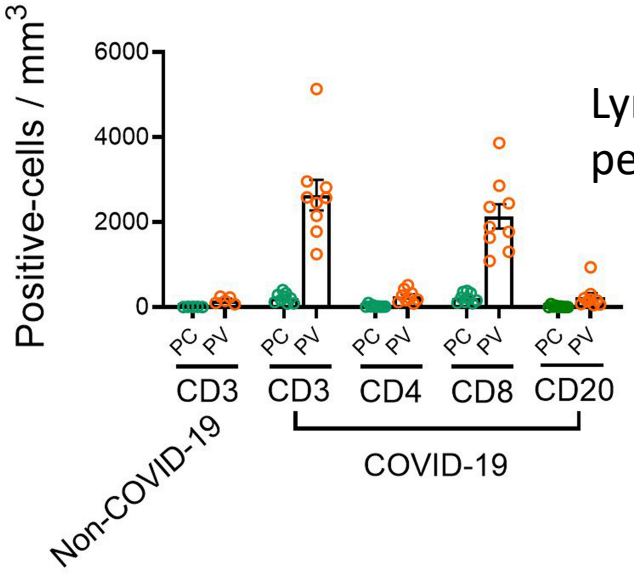








Correlation between leakage of fibrinogen and infiltration of macrophages



Lymphocytes in mainly perivascular (PV) regions

Lee et al., unpublished

Miller Fisher syndrome and polyneuritis cranialis in COVID-19

Consuelo Gutiérrez-Ortiz, MD, PhD, Antonio Méndez-Guerrero, MD, Sara Rodrigo-Rey, MD, Eduardo San Pedro-Murillo, MD, Laura Bermejo-Guerrero, MD, Ricardo Gordo-Mañas, MD, Fernando de Aragón-Gómez, MD, and Julián Benito-León, MD, PhD

Correspondence
Dr. Benito-León
jbenitol67@gmail.com

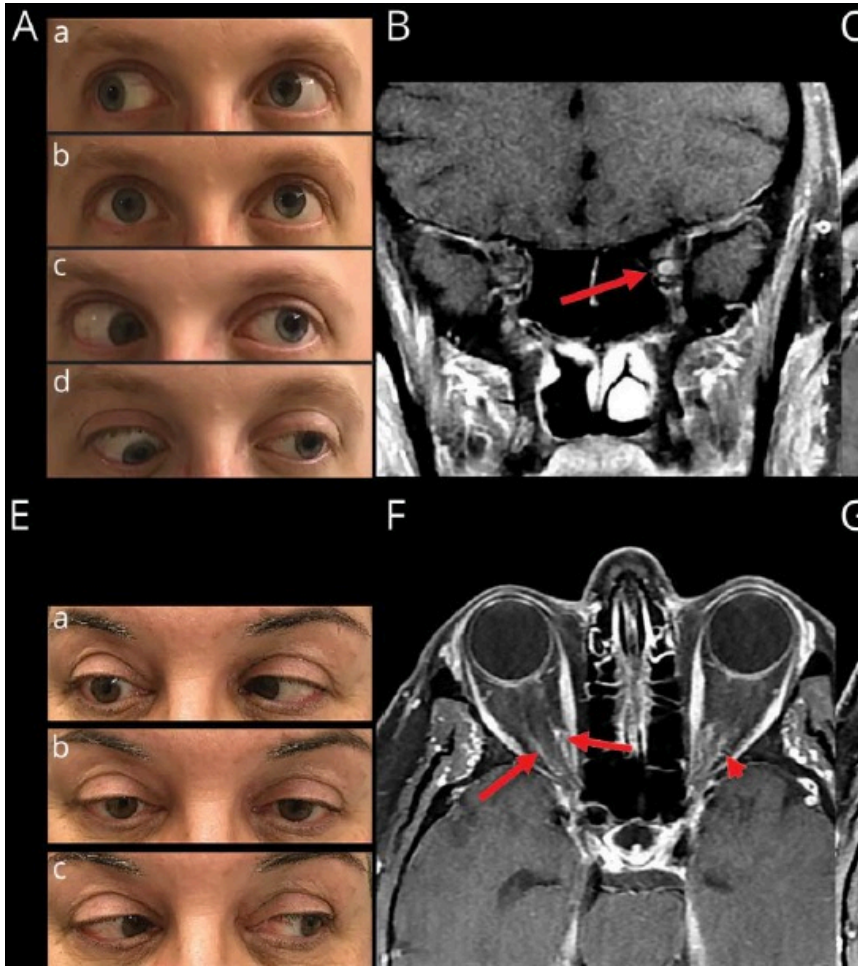
Neurology® 2020;95:e601-e605. doi:10.1212/WNL.0000000000009619

COVID-19 presenting with ophthalmoparesis from cranial nerve palsy

Marc Dinkin, MD, Virginia Gao, MD, PhD, Joshua Kahan, MBBS, PhD, Sarah Bobker, MD, Marialaura Simonetto, MD, Paul Wechsler, MD, Jasmin Harpe, MD, Christine Greer, MD, Gregory Mints, MD, Gayle Salama, MD, Apostolos John Tsiouris, MD, and Dana Leifer, MD

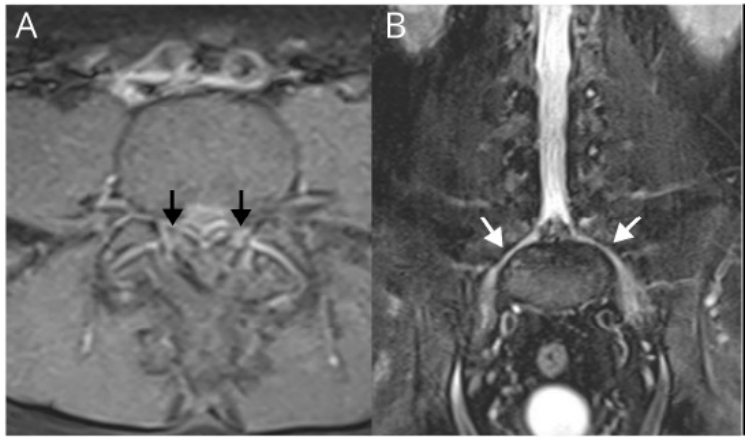
Correspondence
Dr. Dinkin
mjd2004@med.cornell.edu

Neurology® 2020;95:221-223. doi:10.1212/WNL.0000000000009700



Acute Polyradiculitis with COVID-19

Antunes Diaz et al., Neurology Clinical Practice 2020



All responded to IVIG

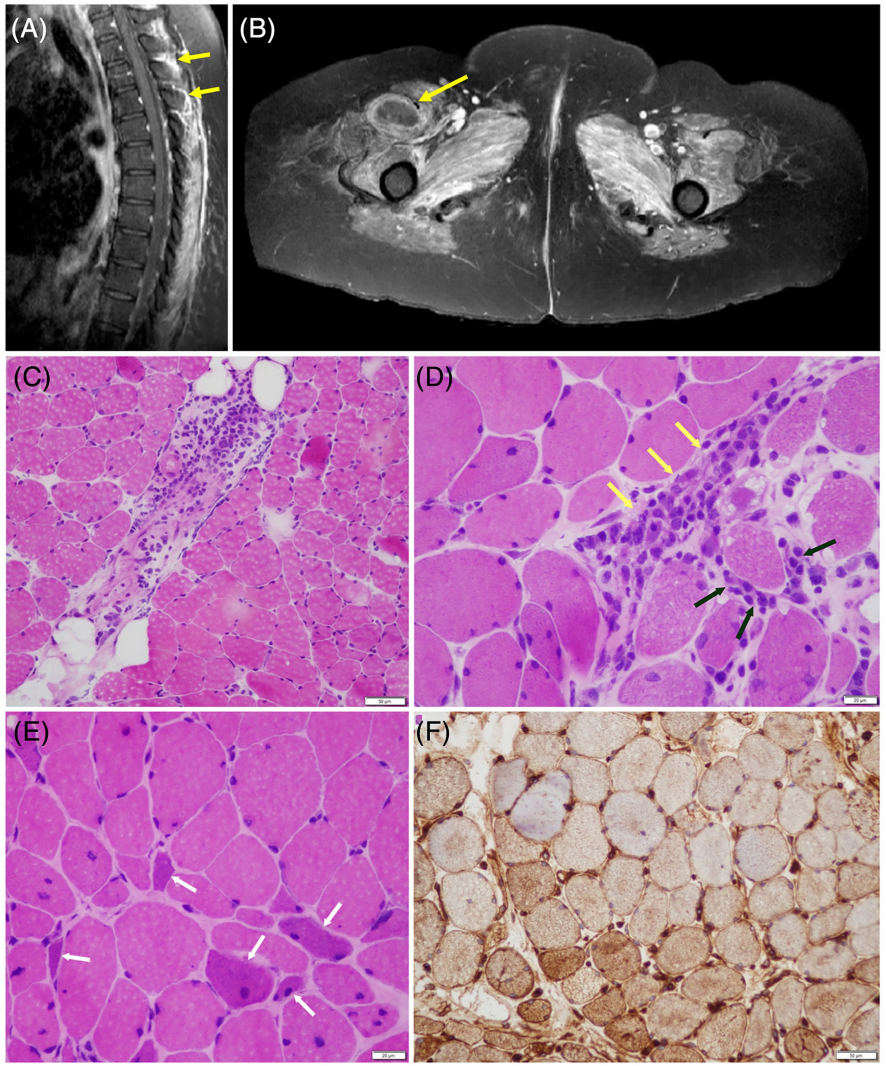
COVID-19–associated myositis with severe proximal and bulbar weakness

58 yr woman
Ptosis, facial weakness, dysarthria, proximal muscle weakness

CPK: 700

Treated with 1g/day of methylprednisolone x 5 days

Improvement in 2 weeks



myonecrosis

Inflammatory infiltrates

Regenerating fibers

HLA

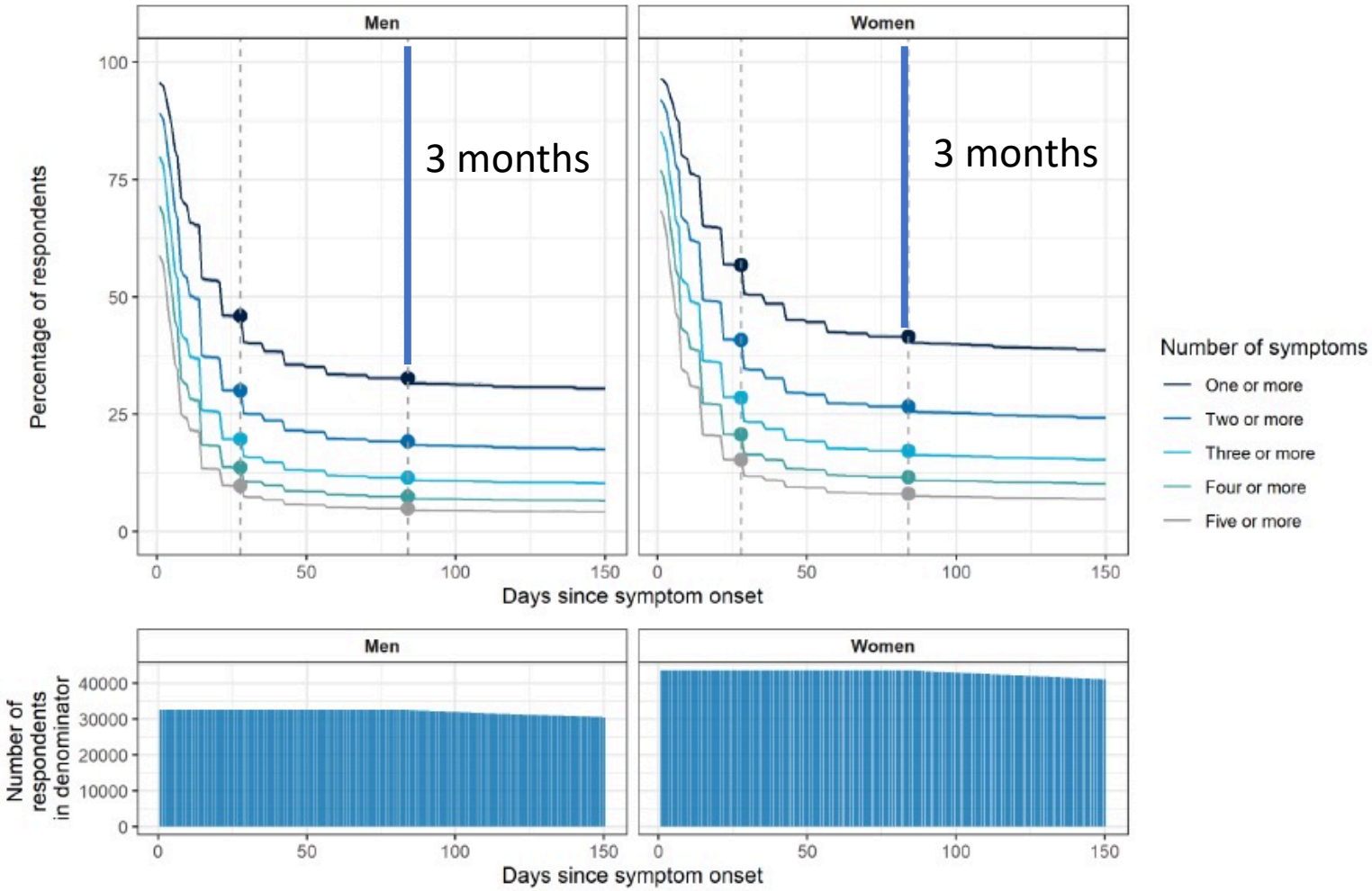
Positive for Ku, anti–SAE 1 IgG, and anti–SS-A

Muscle & Nerve, Volume: 62, Issue: 3, Pages: E57-E60, : 14 June 2020,

Chronic
Long-COVID

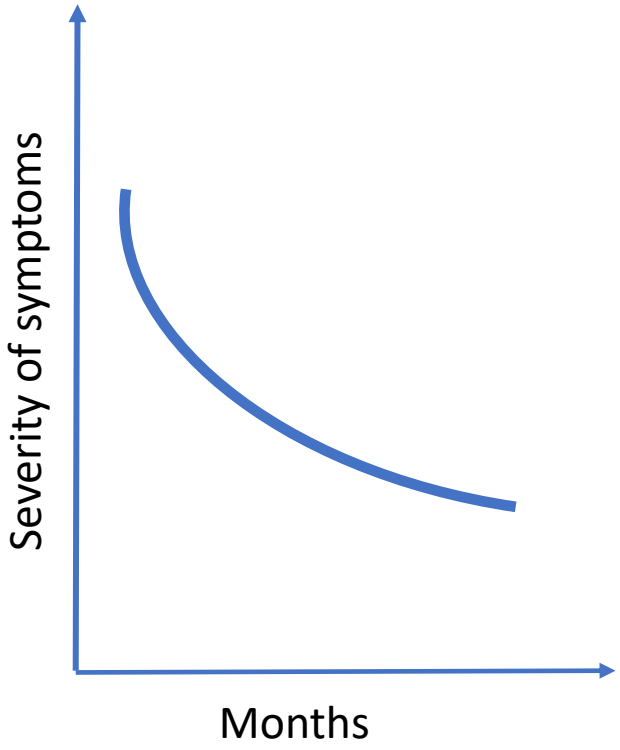
Recovery is unlikely after 3 months of persistent symptoms

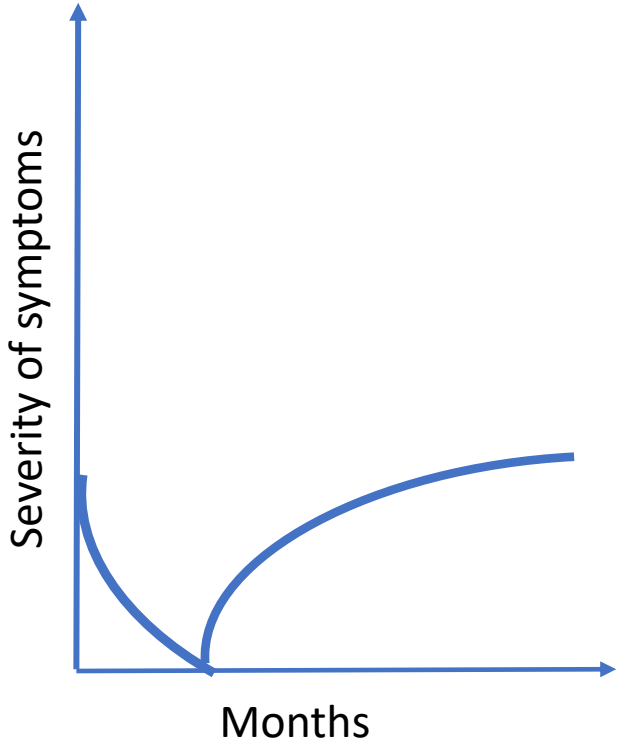
Symptomatic at onset: n=79,155
at 4 wks: n=39,737 (52%)
at 12wks: n=28,713 (38%)



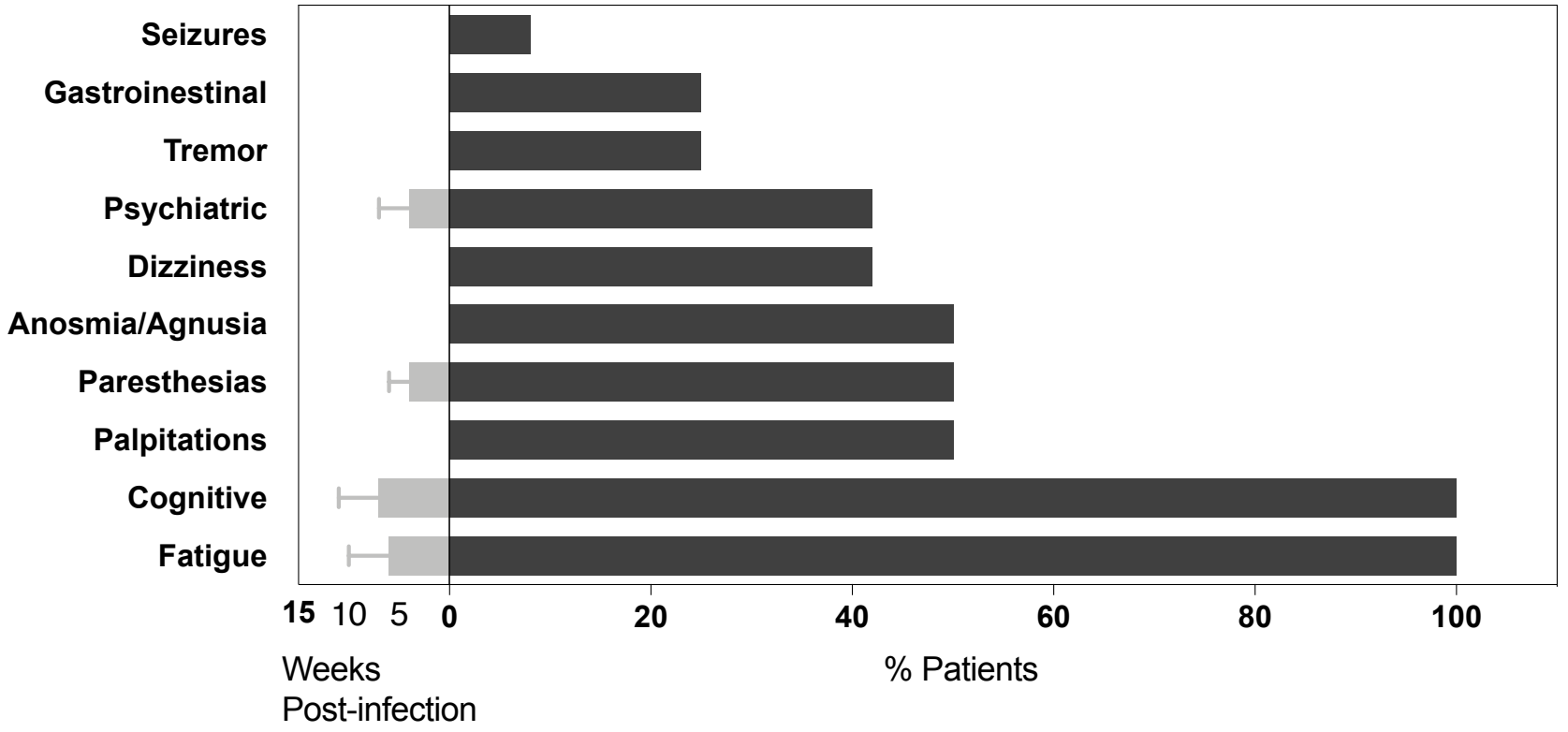
Whitaker et al., 2021
Imperial College London

PATTERNS OF LONG-COVID

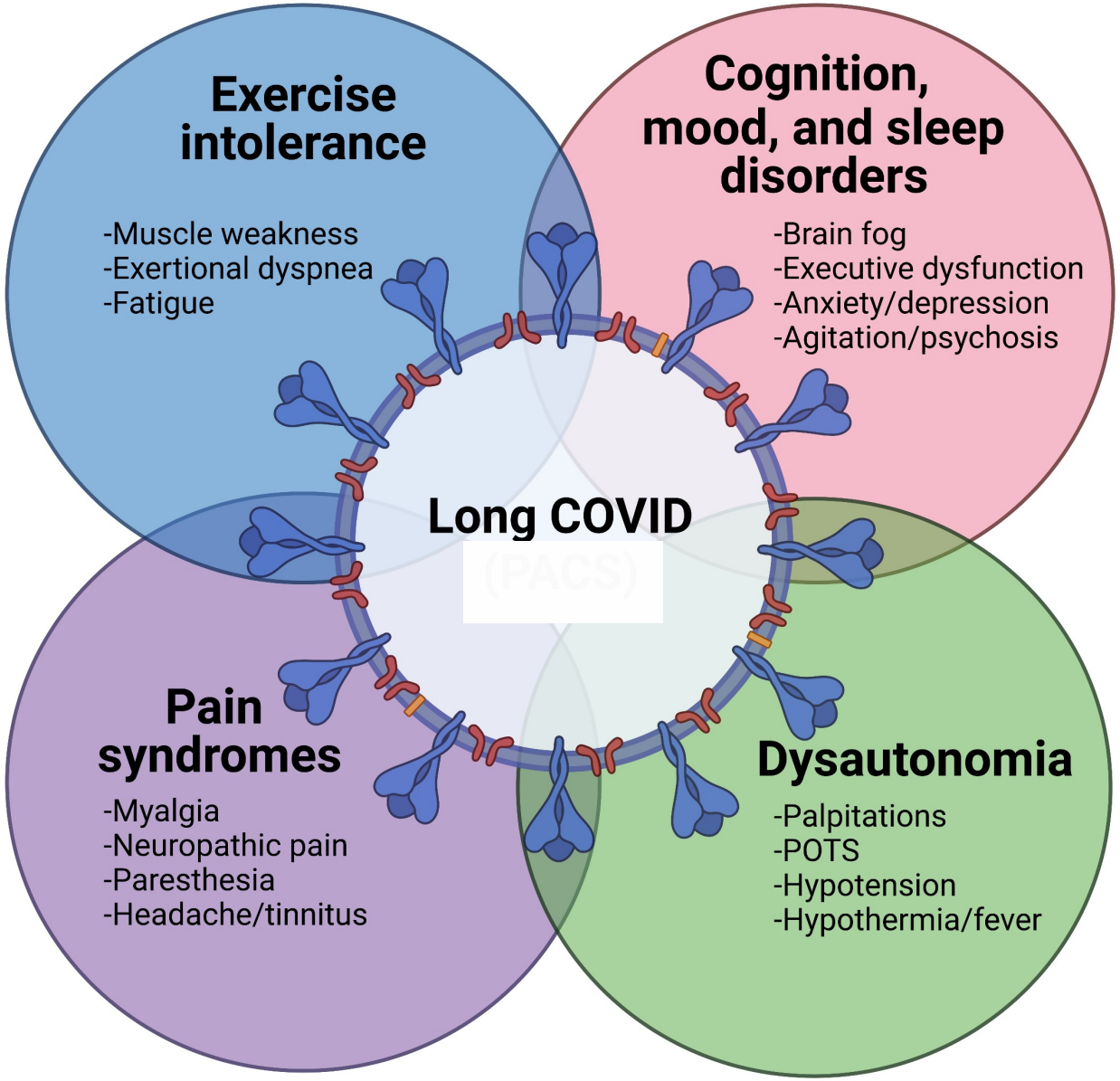




Neurological Symptoms following Mild COVID

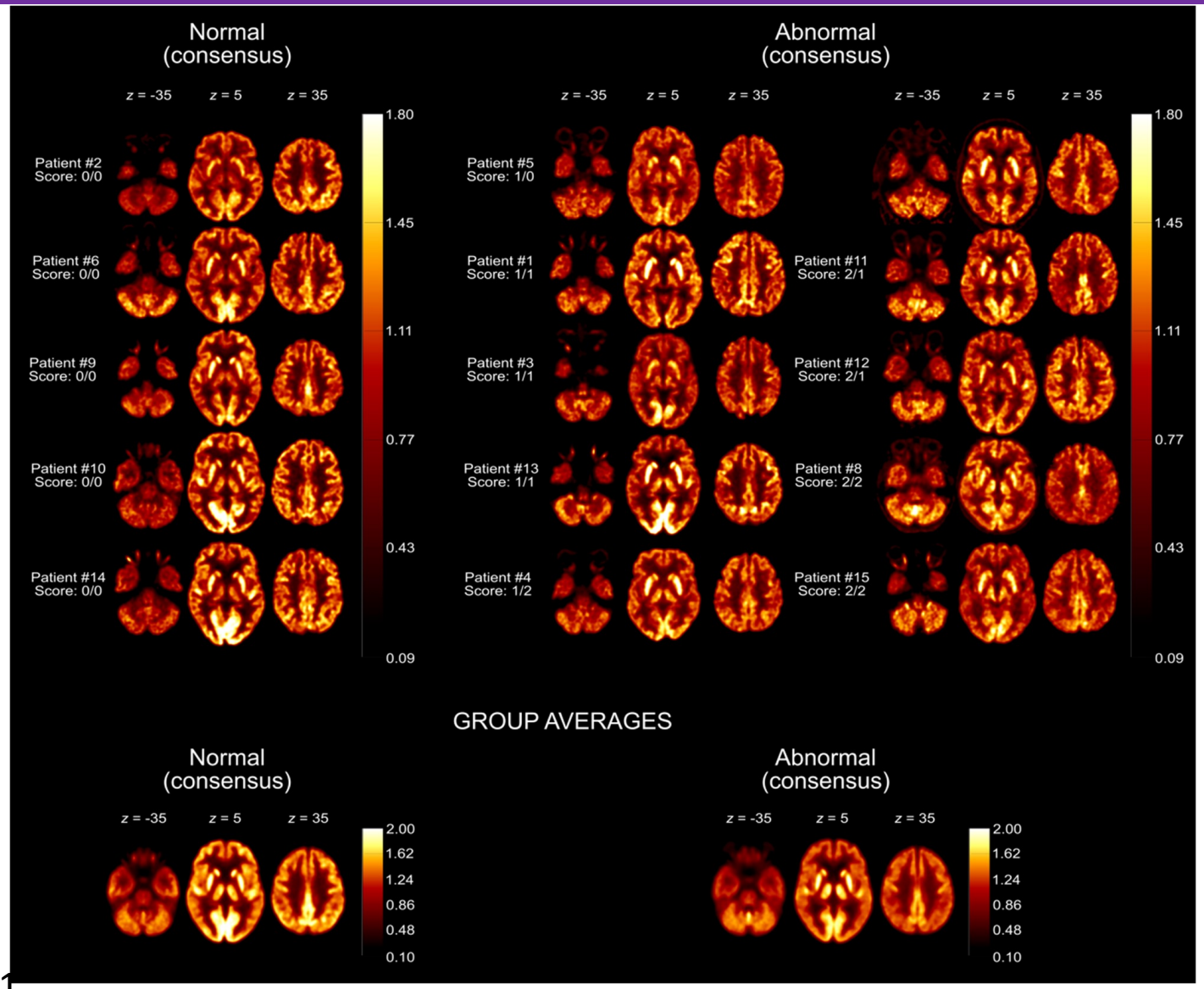


Mina et al., unpublished



Balcom, et al., Brain 2021

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



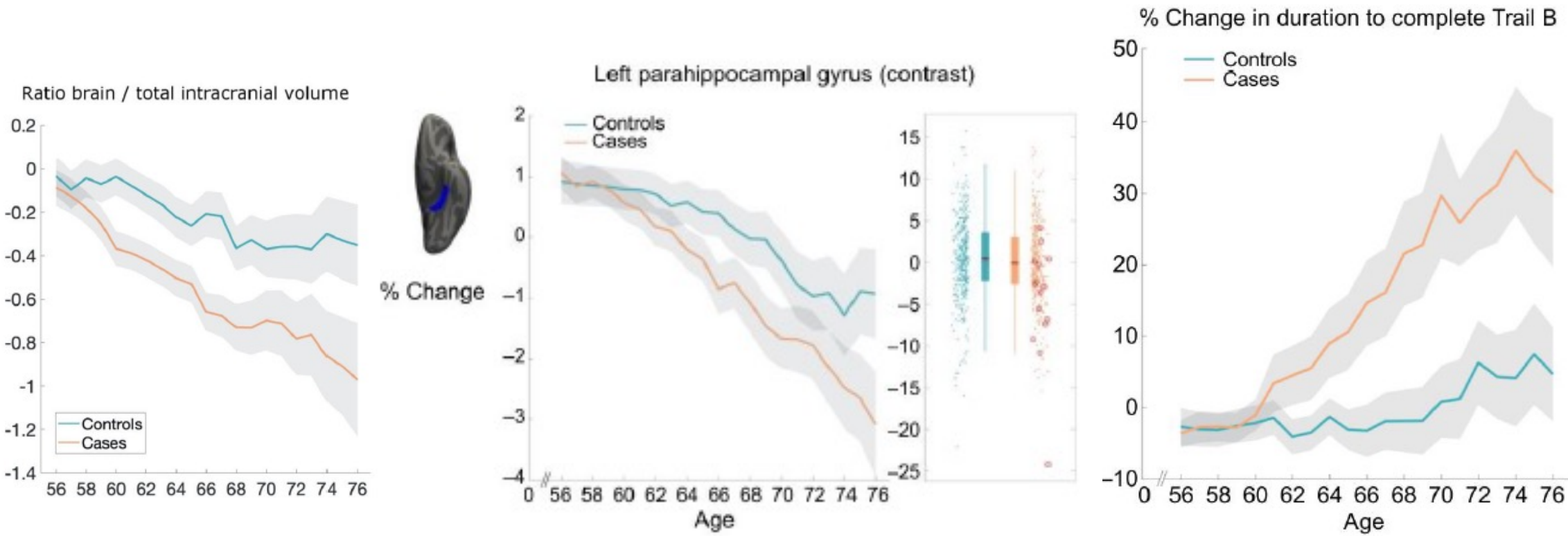
Hosp et al., Brain 2021

nature

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

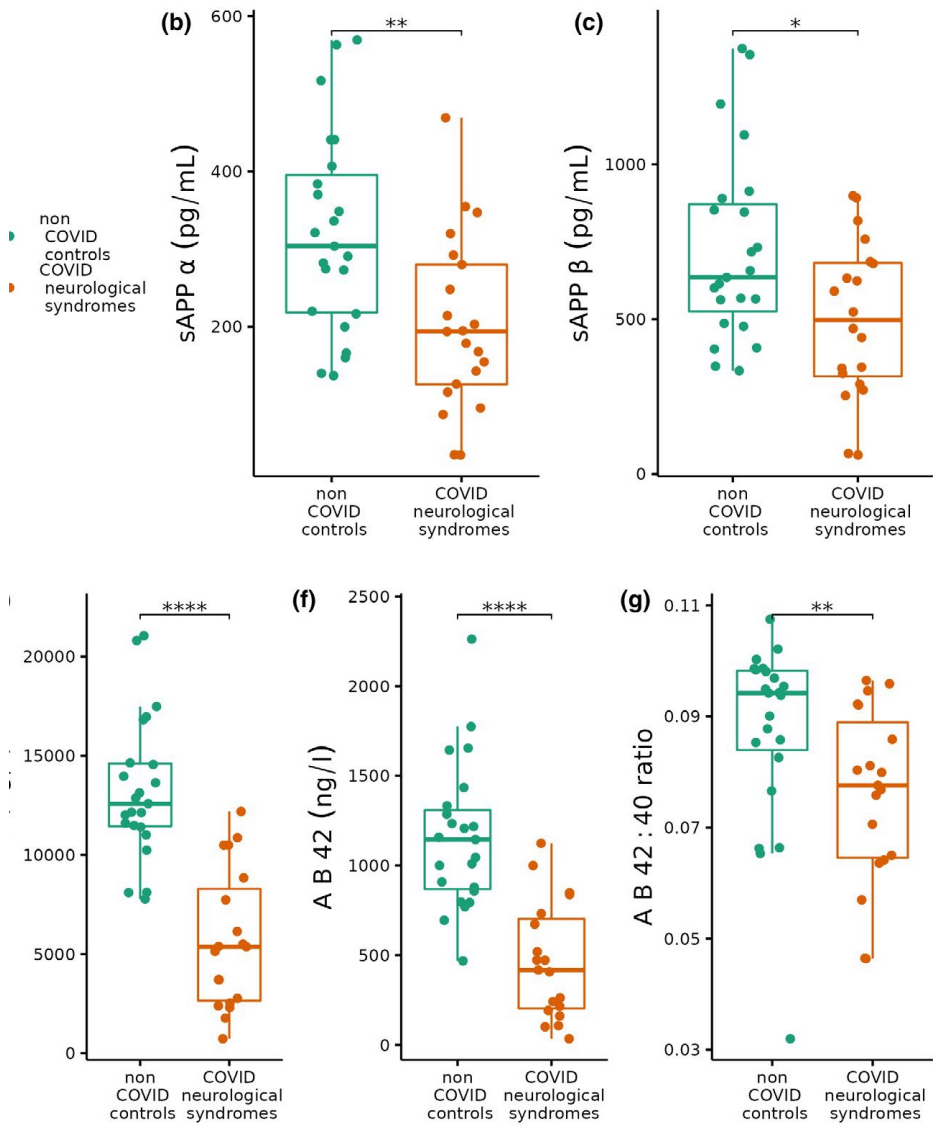
Accelerated Article Preview

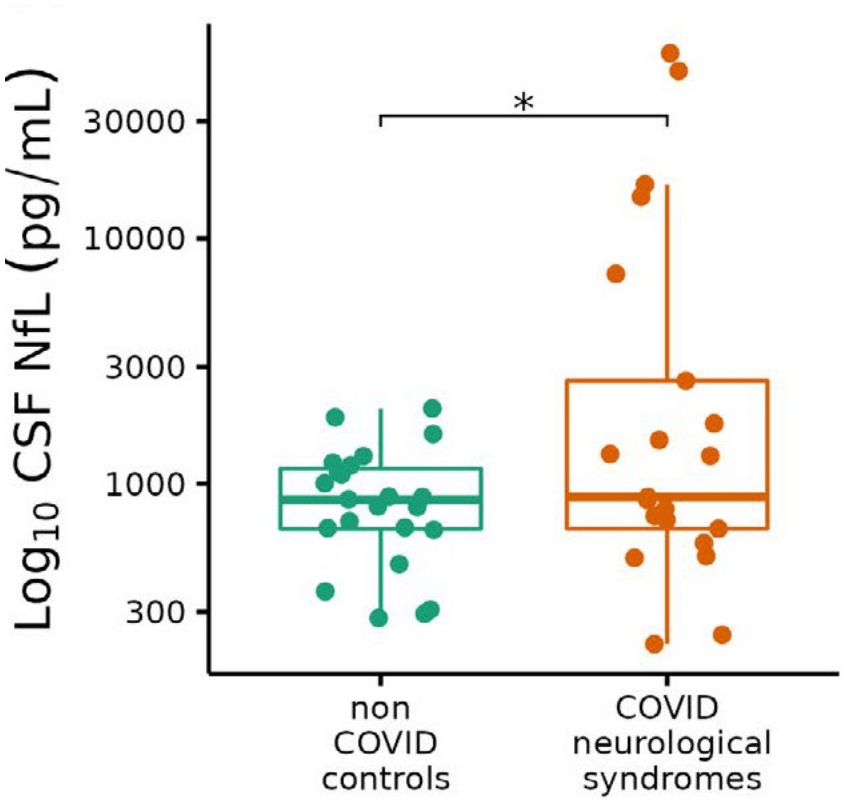
SARS-CoV-2 is associated with changes in brain structure in UK Biobank



COVID cases: 401
Controls: 384

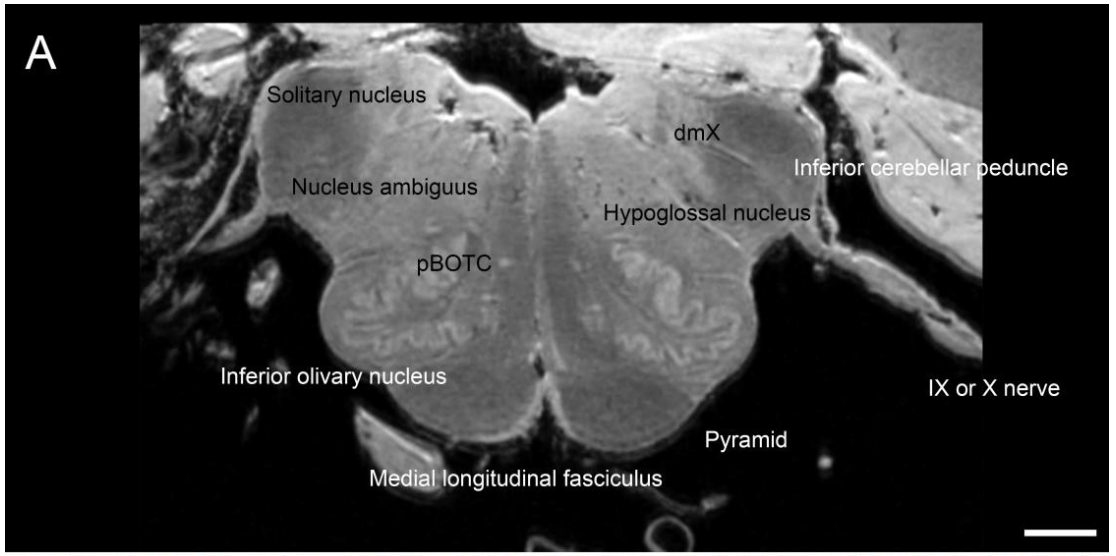
Douaud et al., 2022



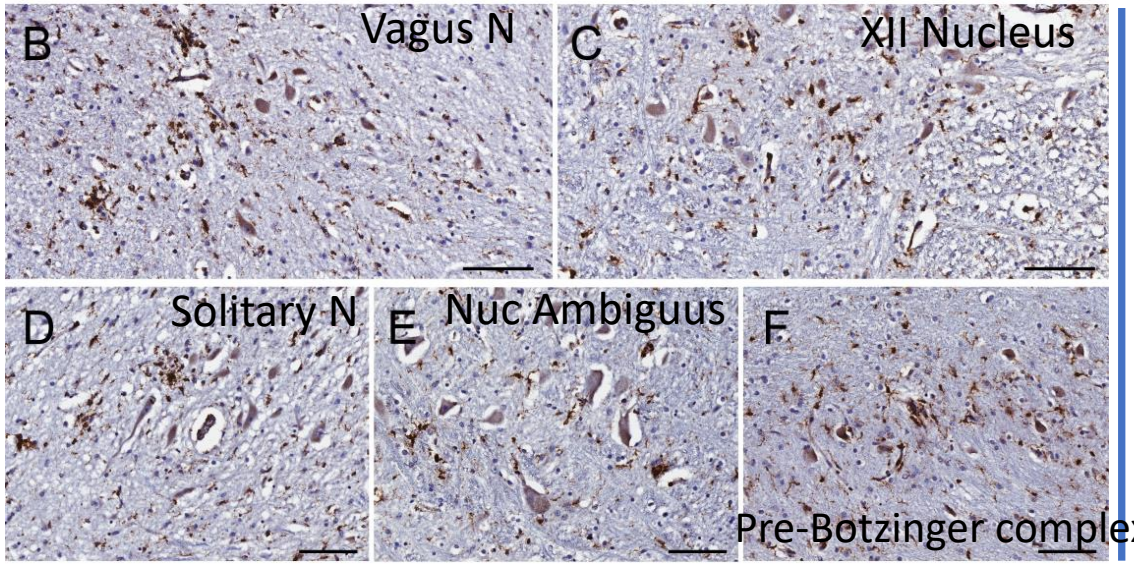


Ziff et al., J Neurochem 2021

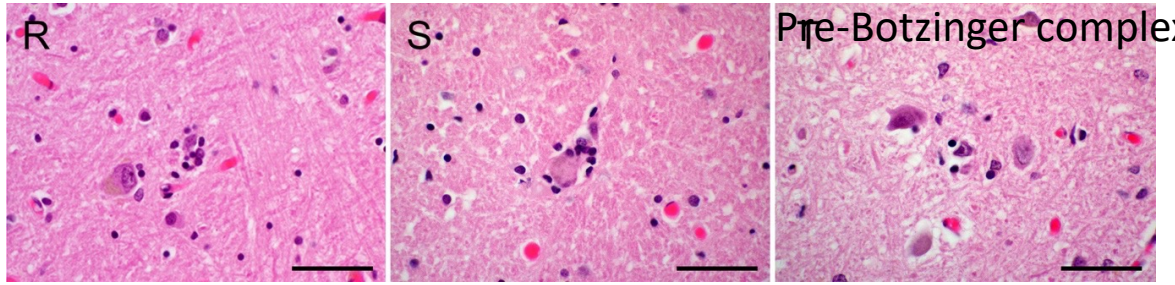
Neuronal Injury in Brainstem



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



CD68



Neuronophagia

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
- Endothelial cell damage by immune complexes is the primary pathophysiological process in Neuro-COVID

Acknowledgements

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