Neurological complications and sequalae of COVID-19

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COVID-19

Global Infections: 608 Million
Global Deaths: 6.8 Million

US Infections: 95 Million
US deaths: 1,050,000; 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**

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)

Subacute

Inflammatory Syndromes

Acute disseminated encephalomyelitis

Acute necrotizing hemorrhagic encephalopathy

Limbic encephalitis

Multisystem Inflammatory Syndrome

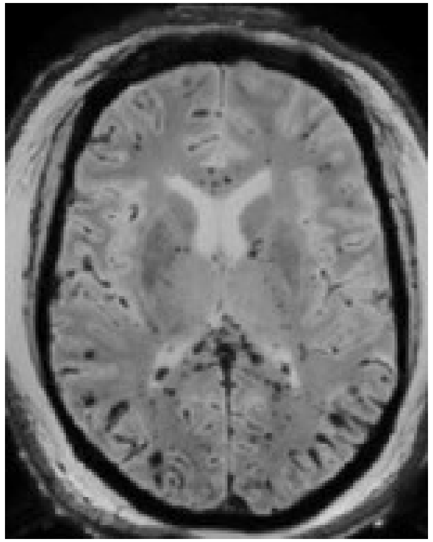
Chronic

Long COVID

VASCULAR INJURY

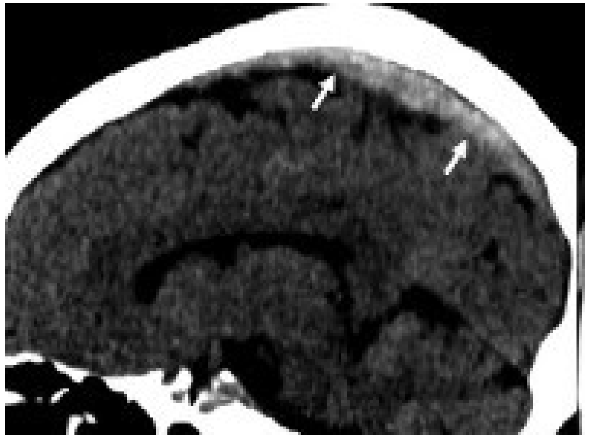
Strokes and vascular disease with COVID-19

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



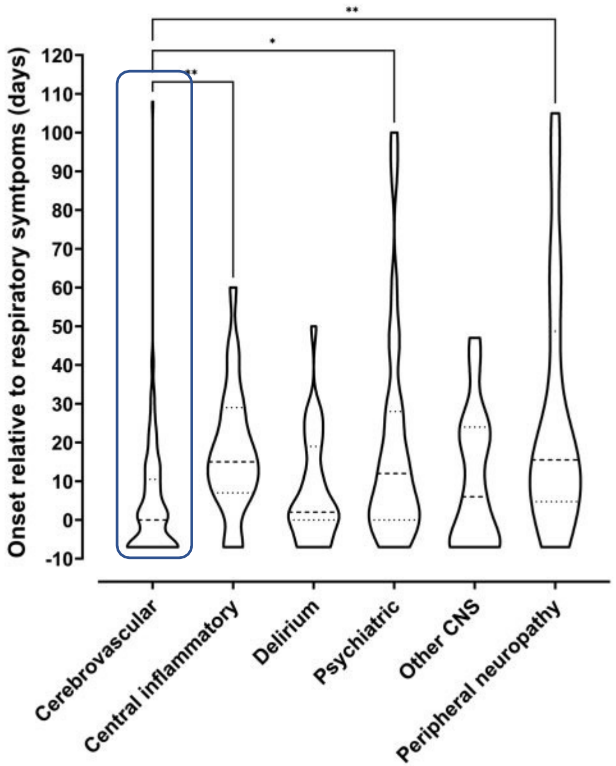
Coolen et al., MedRxiv 2020
DOI:10.1101/2020.10.18.20214221v1

ECHMO (external heart lung machine)



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

CVD can occur prior to development of respiratory symptoms



Amy L. Ross Russel et al., Brain Communications 2021

Autoantibodies can raise the risk of strokes

Zuo et al.:

Looked for antiphospholipid (aPL) antibodies in blood of patients hospitalized with COVID-19.

About half the patients tested positive for these potentially pathogenic autoantibodies

Science Translational Medicine RESEARCH ARTICLES

Cite as: Y. Zuo *et al.*, *Sci. Transl. Med.* 10.1126/scitranslmed.abd3876 (2020).

CORONAVIRUS

Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19

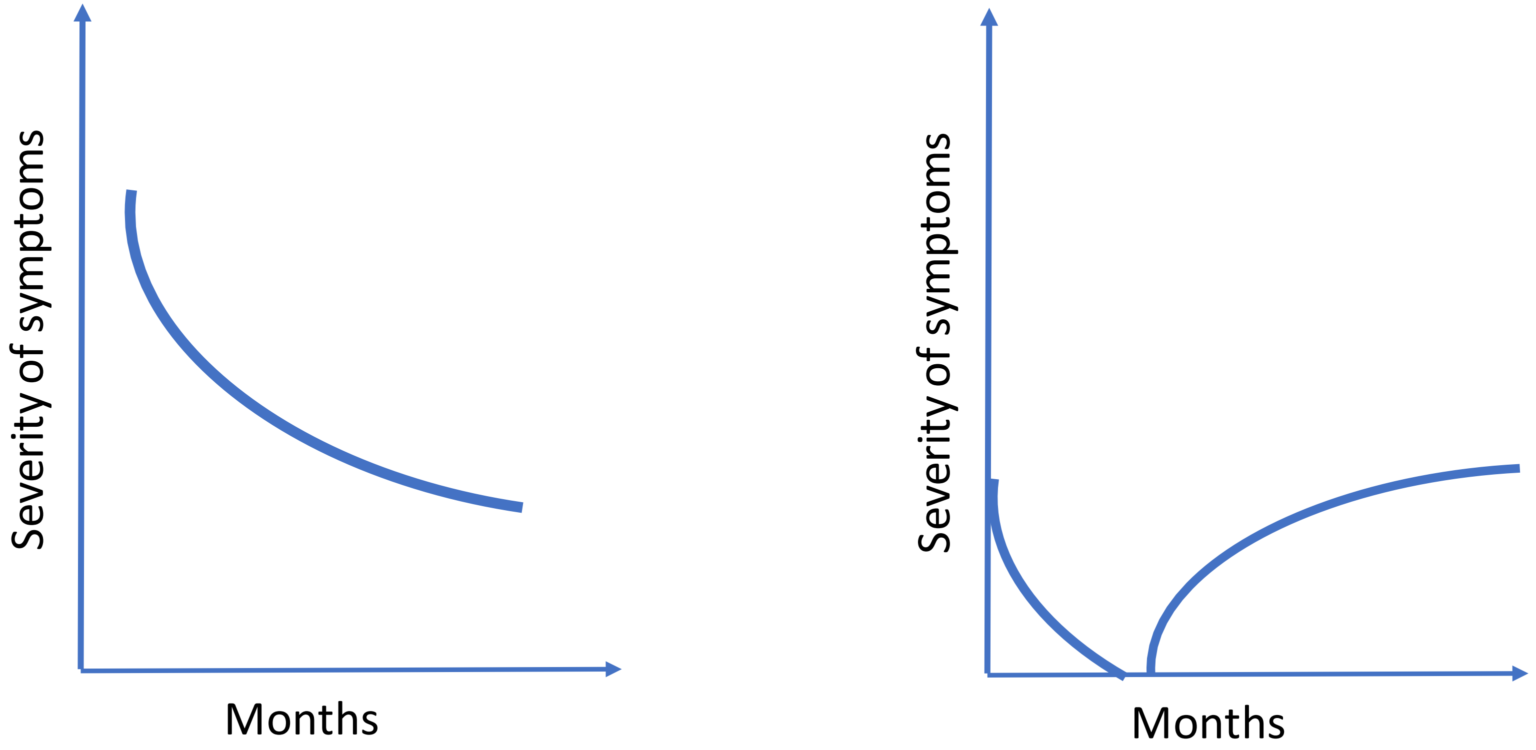
Yu Zuo[1], Shanea K. Estes[1], Ramadan A. Ali[1], Alex A. Gandhi[1], Srilakshmi Yalavarthi[1], Hui Shi[1,2], Gautam Sule[1], Kelsey Gockman[1], Jacqueline A. Madison[1], Melanie Zuo[3], Vinita Yadav[4], Jintao Wang[5], Wrenn Woodard[6], Sean P. Lezak[6], Njira L. Lugogo[7], Stephanie A. Smith[8], James H. Morrissey[8], Yogendra Kanthi[4,5‡], and Jason S. Knight[1‡]

Table 1. Prevalence of antiphospholipid antibodies in serum from COVID-19 patients (n=172)

aPL antibody	Number positive (manufacturer's cut-off)	%	Number positive (titer ≥40 units)	%
aCL IgG	8	4.7%	2	1.2%
aCL IgM	39	23%	13	7.6%
aCL IgA	6	3.5%	1	0.58%
aβ_2GPI IgG	5	2.9%	3	1.7%
aβ_2GPI IgM	9	5.2%	7	4.1%
aβ_2GPI IgA	7	4.1%	3	1.7%
aPS/PT IgG	42	24%	21	12%
aPS/PT IgM	31	18%	21	12%
any positive aPL	89	52%	52	30%

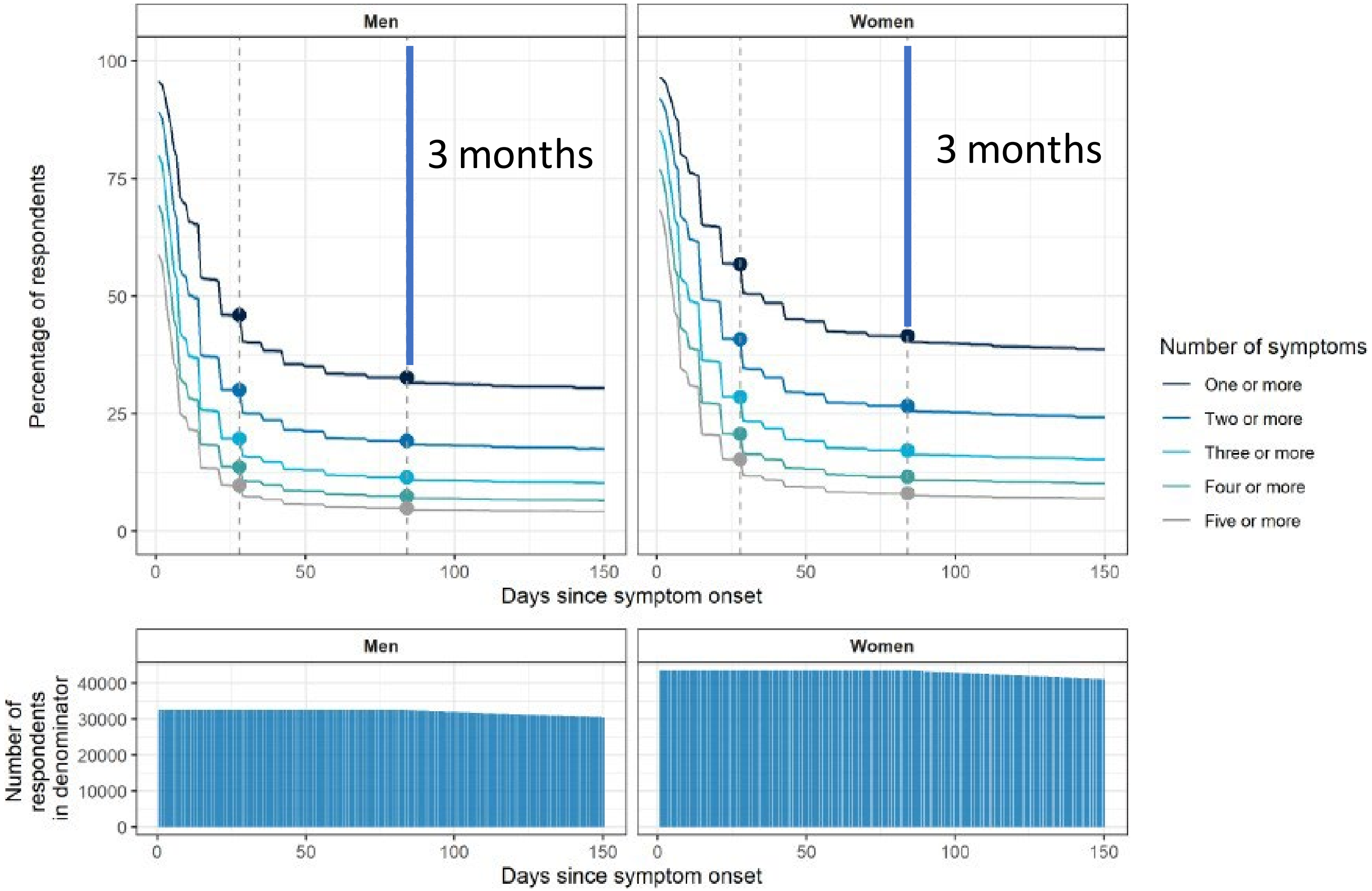
Chronic
Long-COVID

PATTERNS OF LONG-COVID



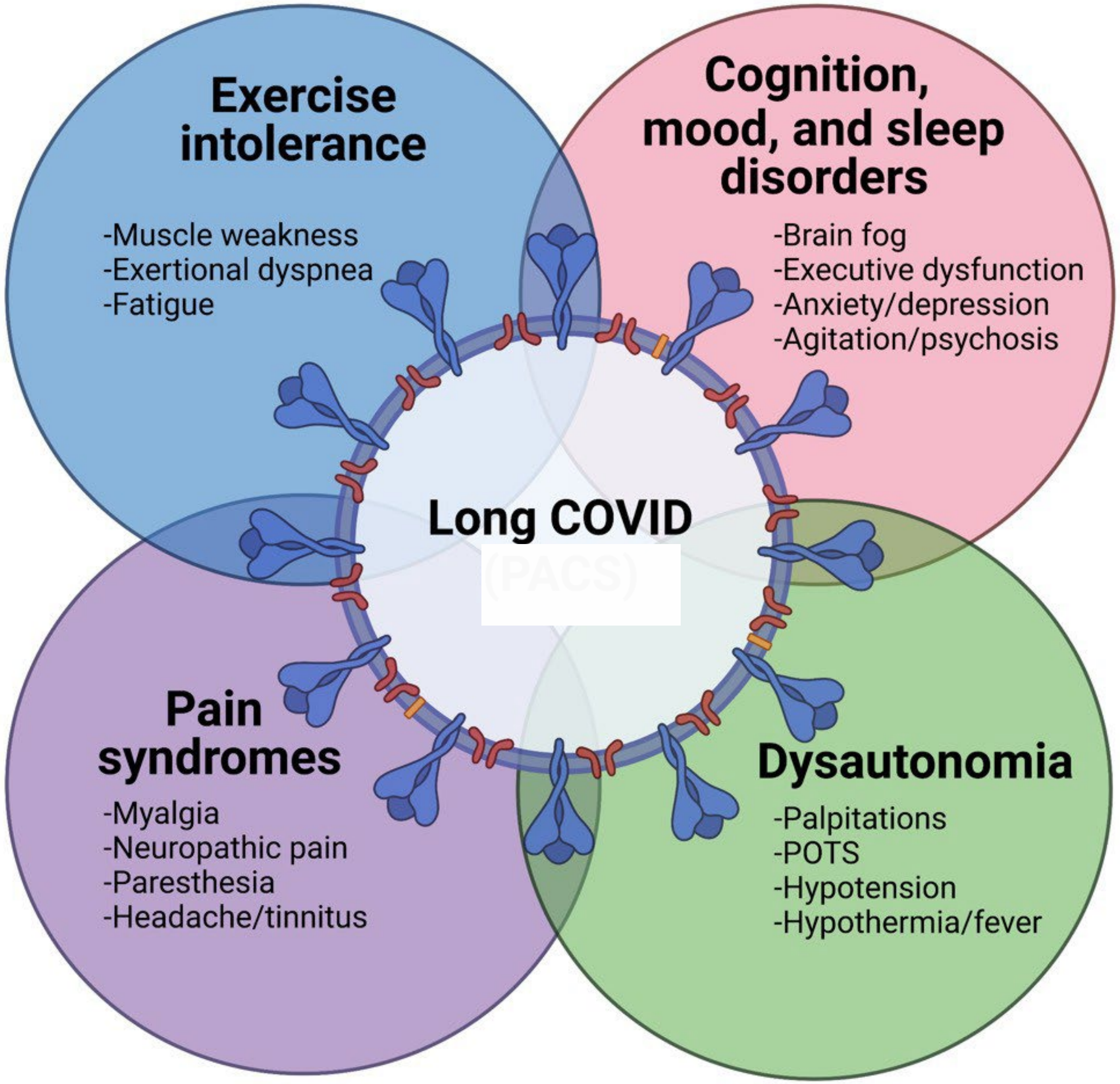
Recovery is unlikely after 3-6 months of persistent symptoms

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



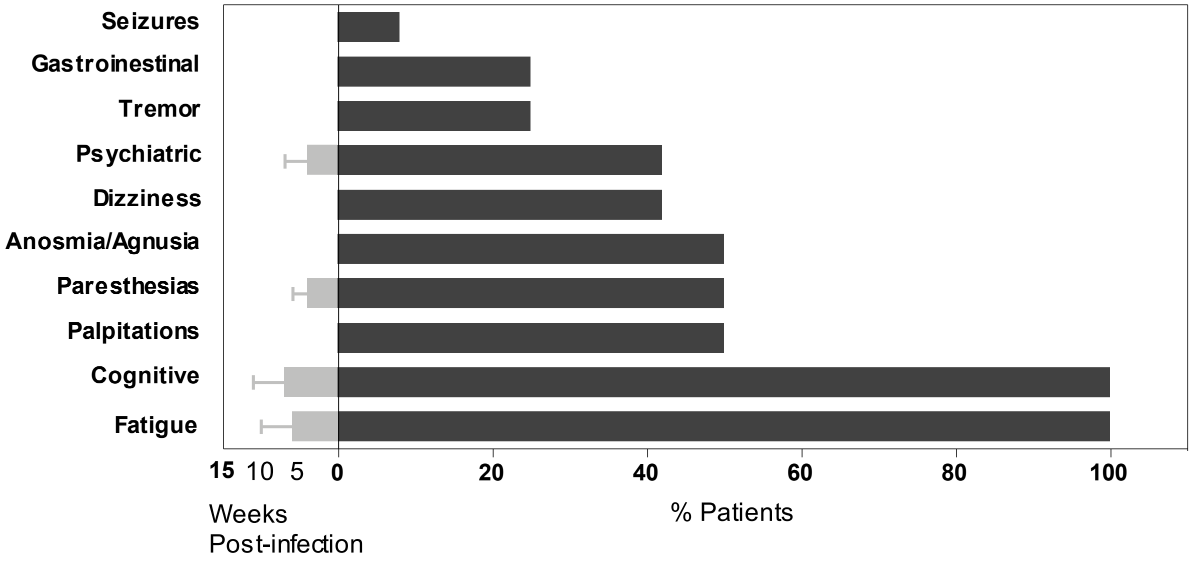
Whitaker et al., 2021
Imperial College London

Post-Intensive Care Syndrome



Balcom, et al., Brain 2021

Neurological Symptoms following Mild COVID



Mina et al., unpublished

JCSM | Journal of Clinical Sleep Medicine May, 2022

SCIENTIFIC INVESTIGATIONS

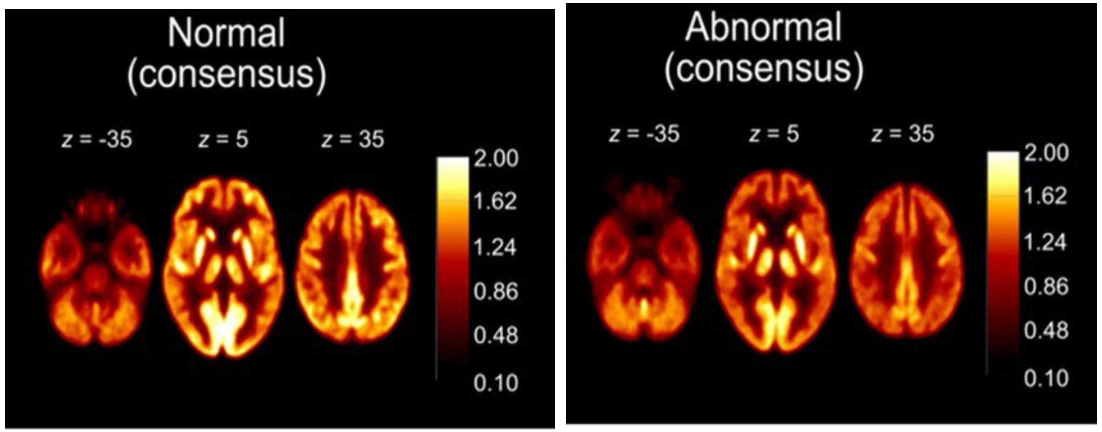
Restless legs syndrome is associated with long-COVID in women

Leonard B. Weinstock, MD, FACG[1]; Jill B. Brook, MA[2]; Arthur S. Walters, MD[3]; Ashleigh Goris, RN, BSN, MPH, CIC, FAPIC[4]; Lawrence B. Afrin, MD[5]; Gerhard J. Molderings, MD[6]

N=136 in each group

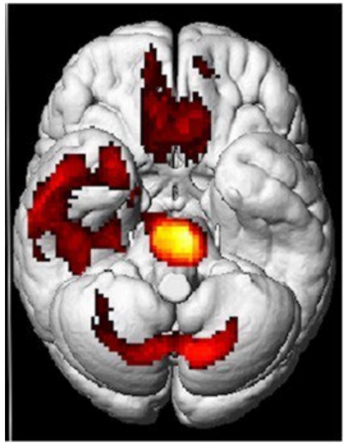
	Controls	Pre-COVID-19 Participants with Long-COVID	Post-COVID-19 Participants with Long-COVID
RLS prevalence, n (%)	6 (6.7%)	7 (5.7%)	18 (14.8%)[c]
RLS Severity Score, mean (SD)[a]	14.0 (4.5)	[d]	18.1 (7.8)
RLS Sleep Impact Score, mean (SD)[a]	5.0 (1.4)	[d]	9.6 (3.8)

^{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

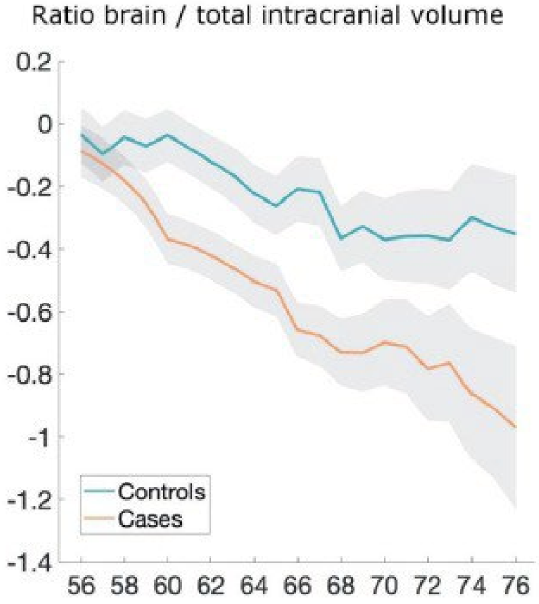


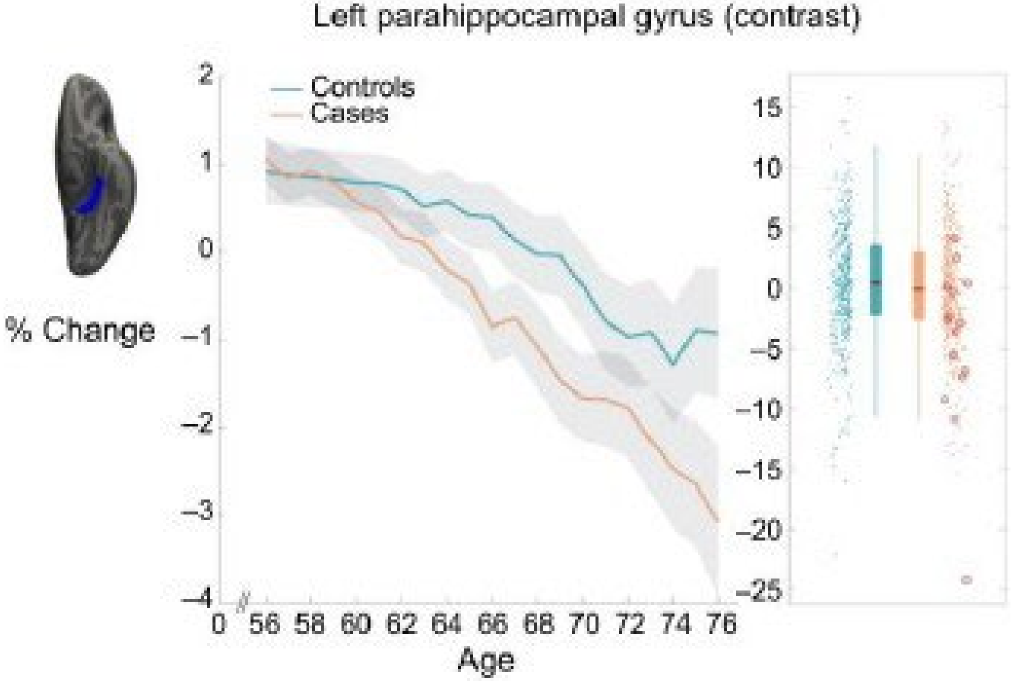
Regions of hypometabolism
(n=44)

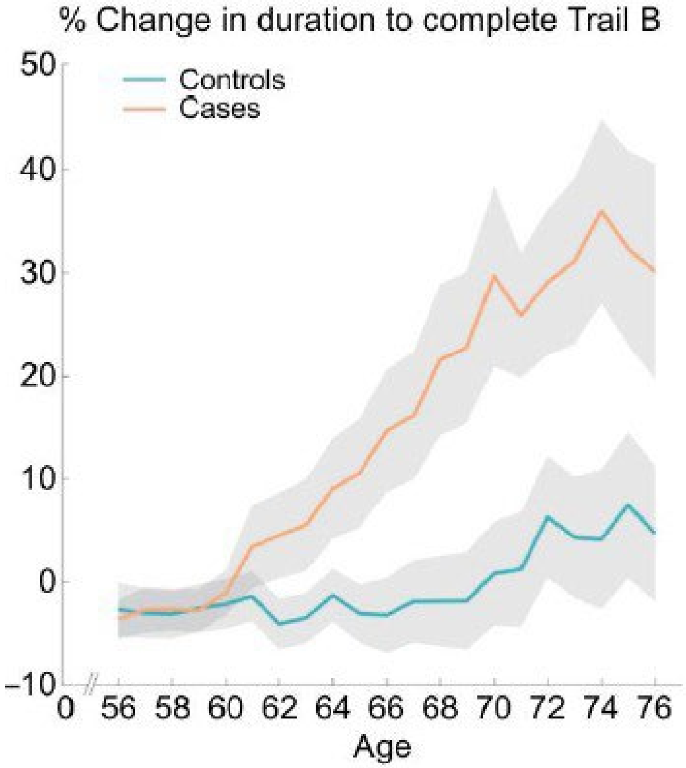
Guedj et al., European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:2823–2833

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

DIRECT VIRAL INFECTION

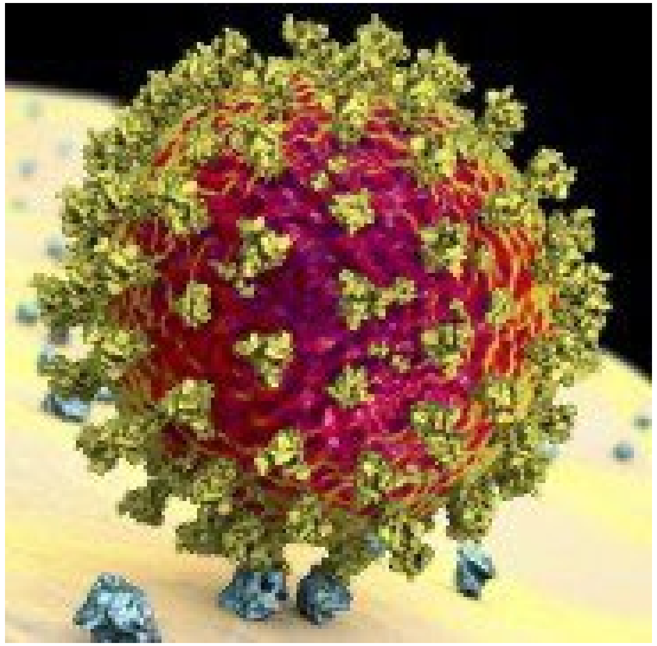
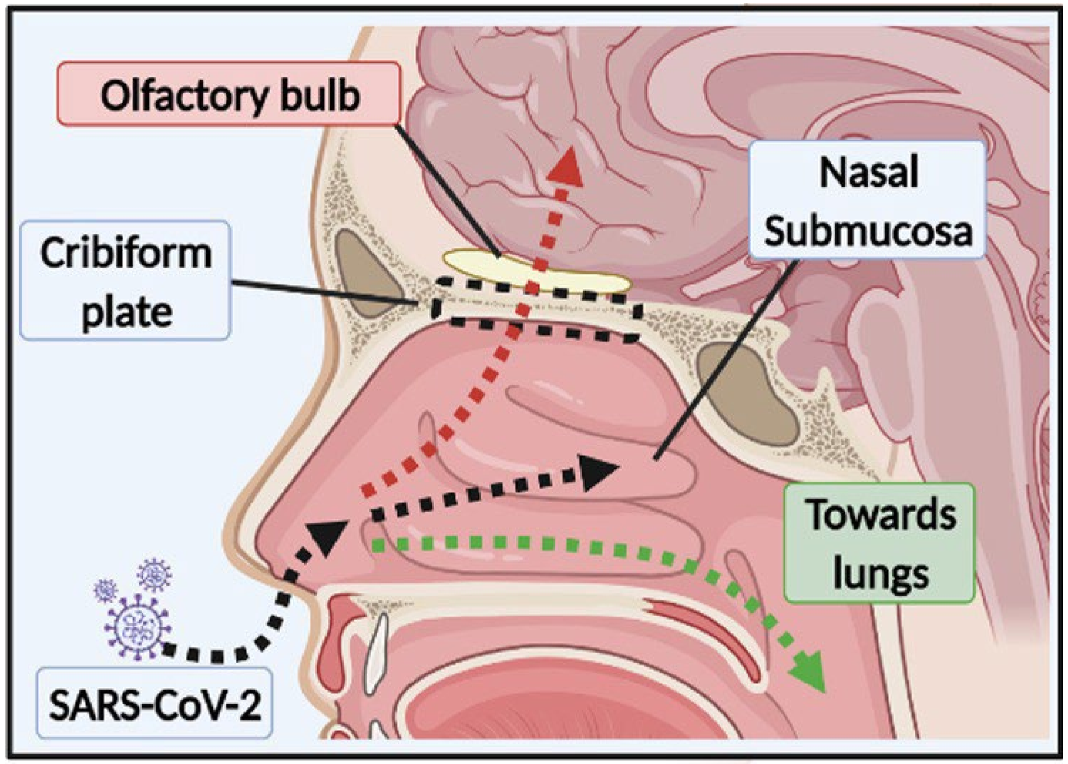
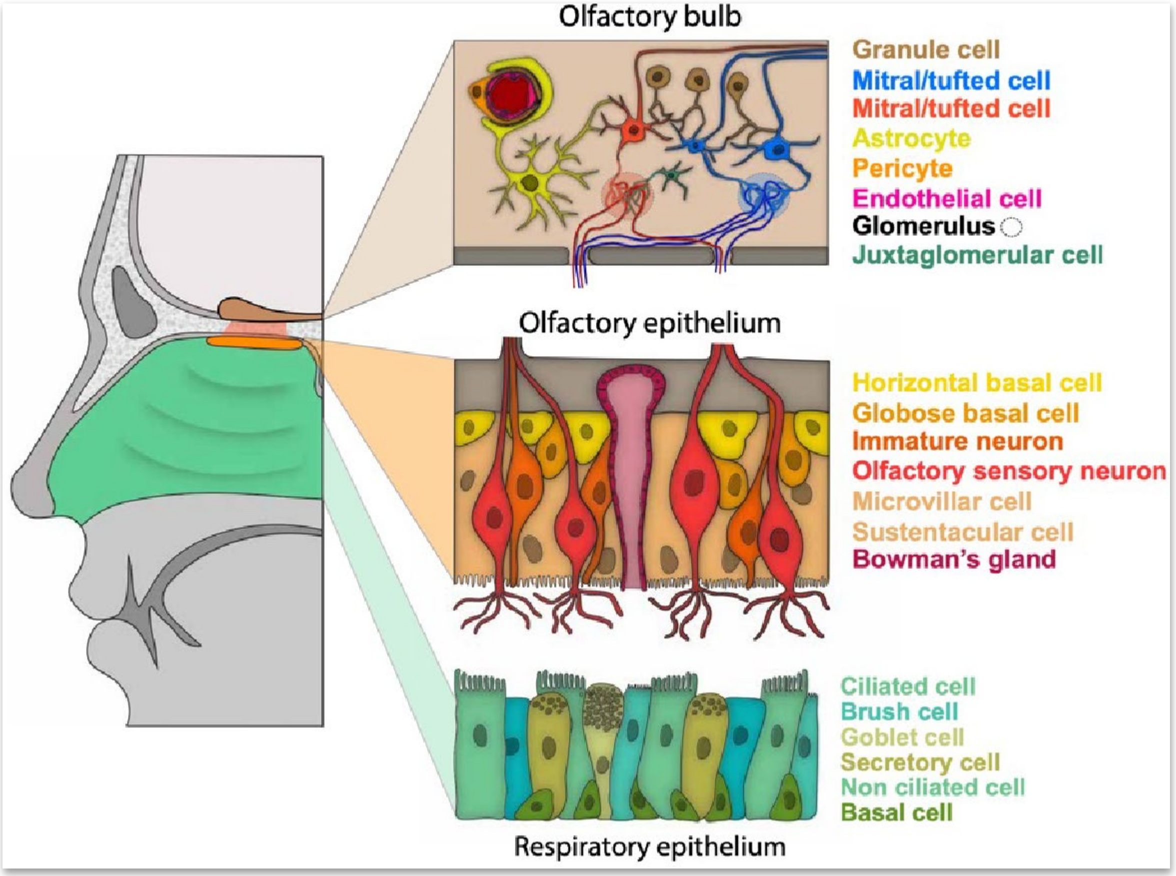


Image credit: KATERYNA KON/SCIENCE PHOTO LIBRARY via Getty Images

Can the virus enter the brain through the olfactory pathways?

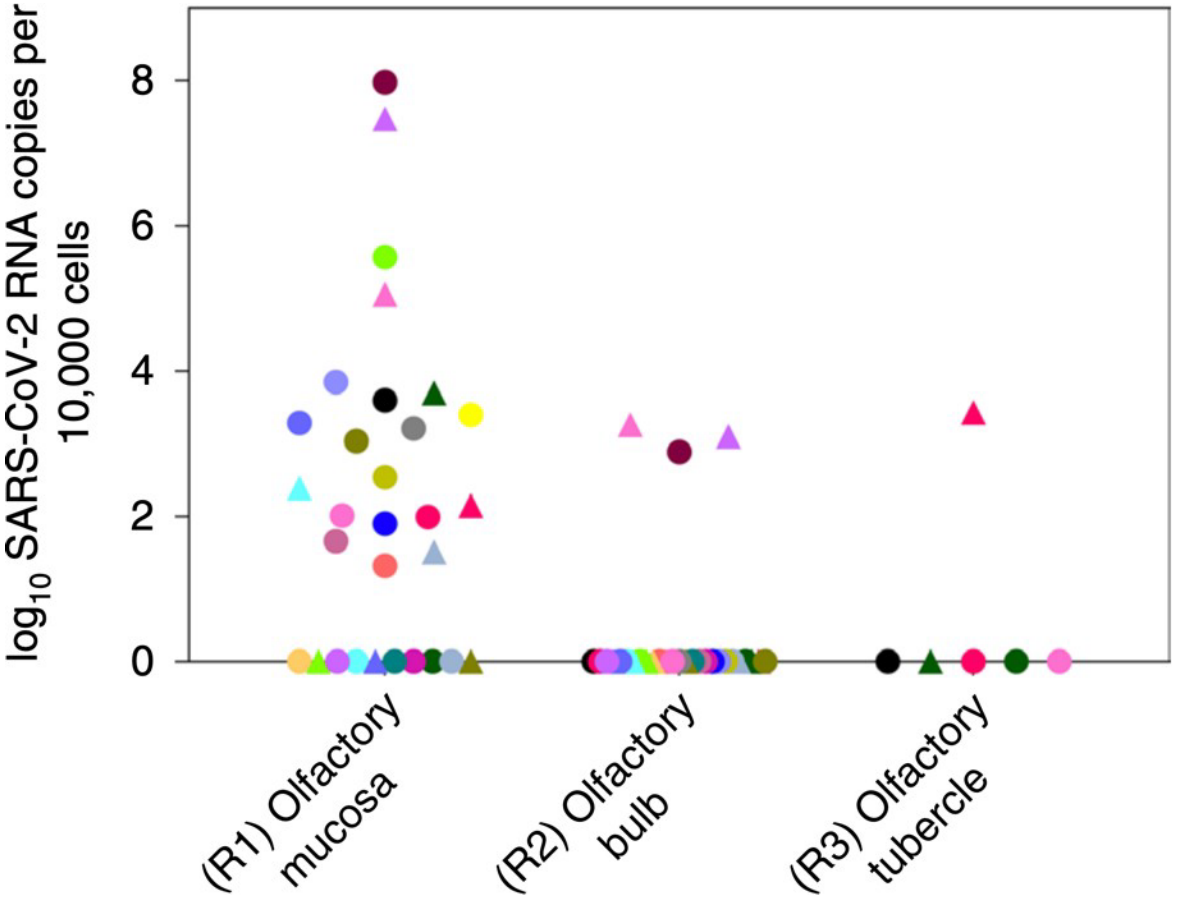


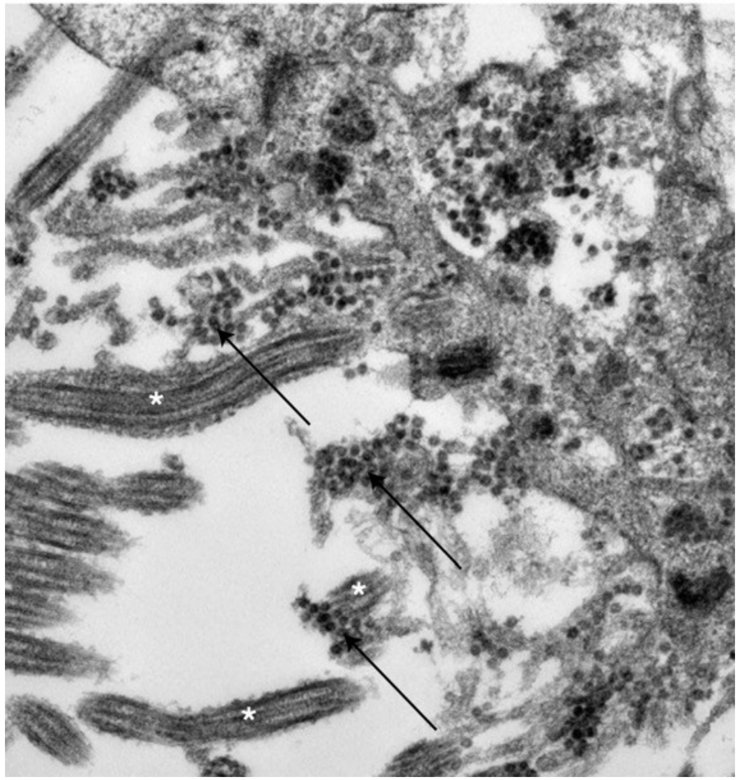


Images: McQuaid et al., 2021 DOI: 10.1186/s12987-021-00267-y; Brann et al., 2020 DOI:10.1126/sciadv.abc5801

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

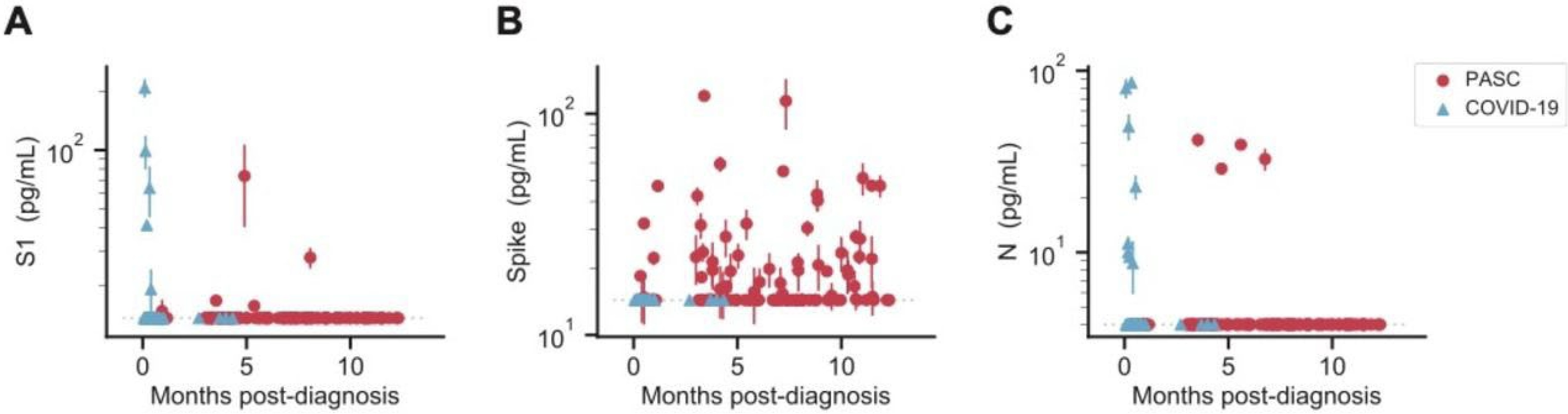
Lee et al., NEJM 2021; Lee et al., Brain 2022

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	0.42 (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)

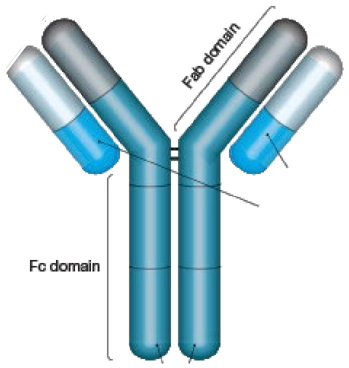
Chertow et al., Research Square 2021

Detection of Spike protein in blood of patients with PASC (Long-COVID)

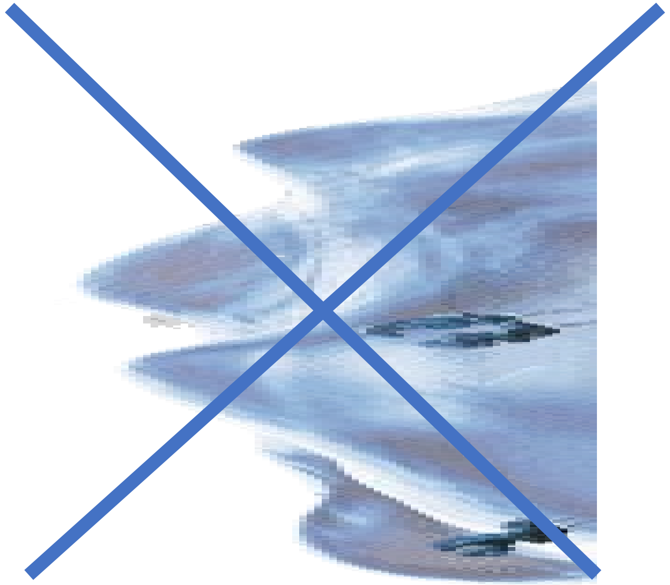


Swank et al., MedRxiv 2022

IMMUNE MEDIATED PATHOGENESIS

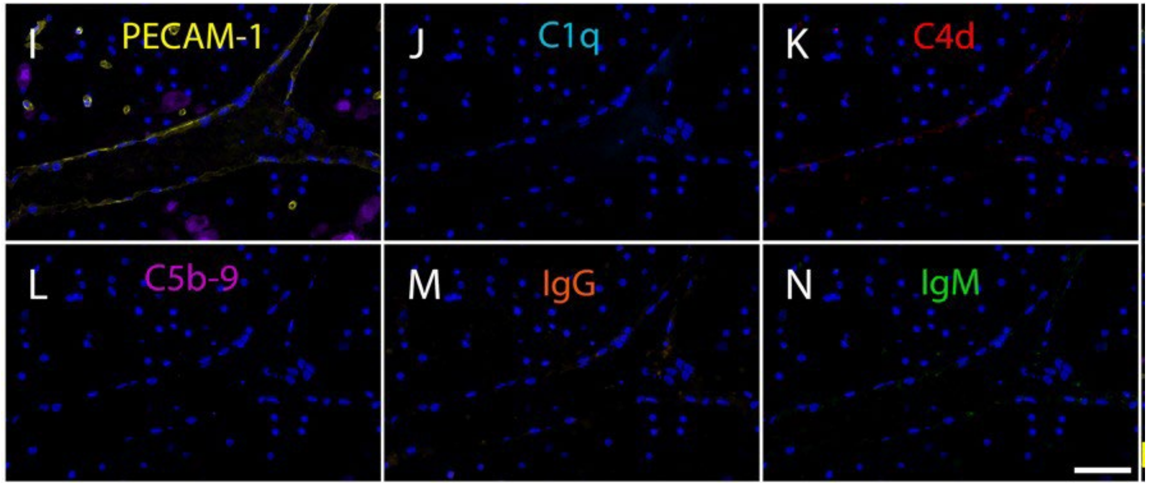


Antibodies

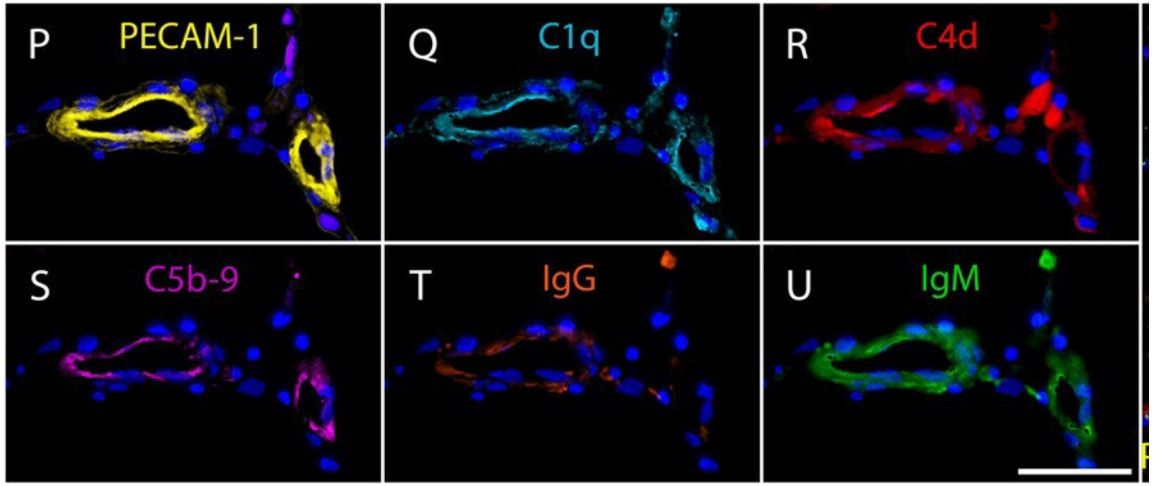


Macrophages

Control



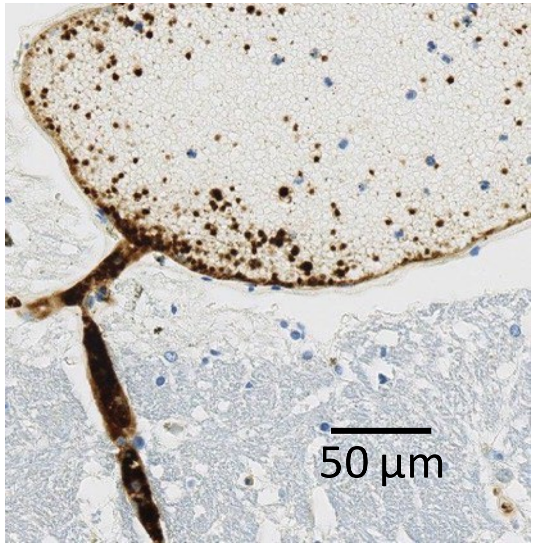
COVID-19



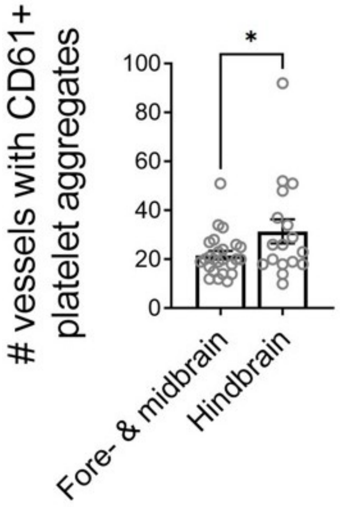
Activation of endothelial cells (PECAM-1)
Deposition of complement
Deposition of IgG and IgM

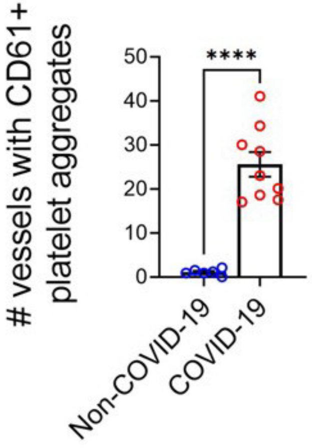
Lee at al., Brain 2022

Platelets are activated and form clots in small blood vessels



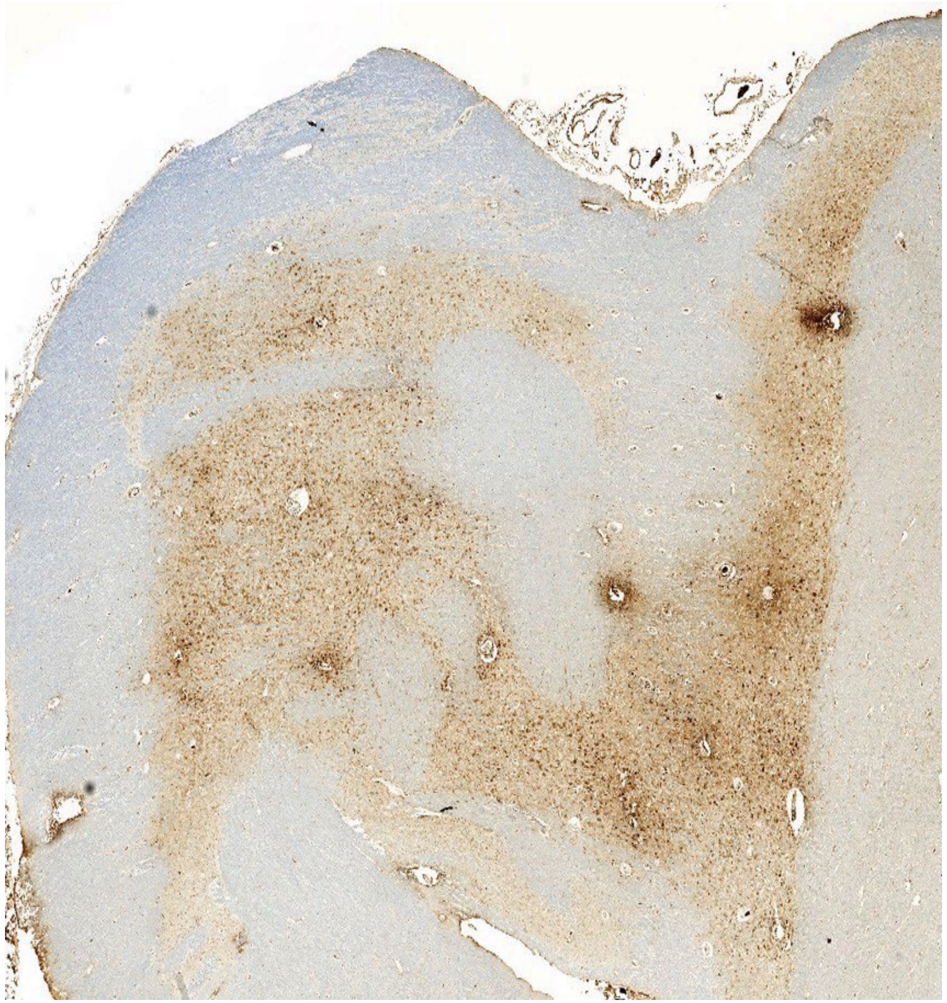
Anti-CD61 (activated platelets)



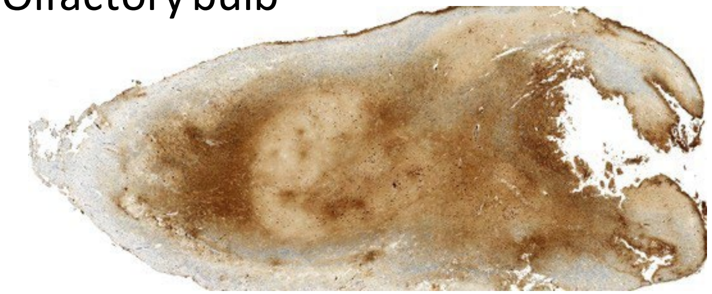


Lee et al., Brain 2022

Perivascular fibrinogen leakage indicates vascular injury

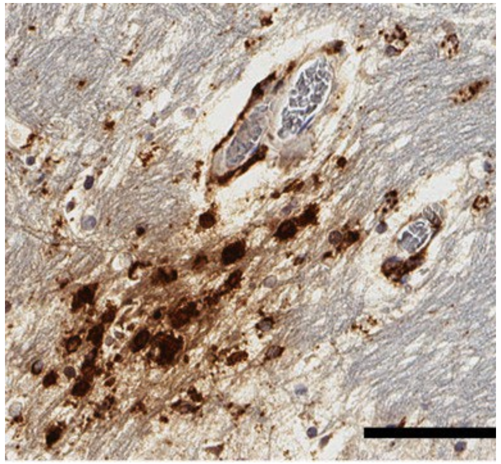


Olfactory bulb

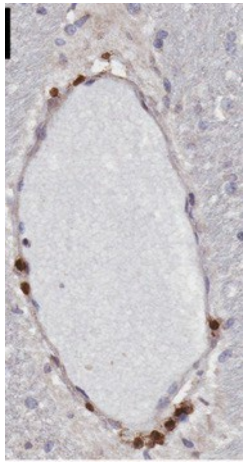


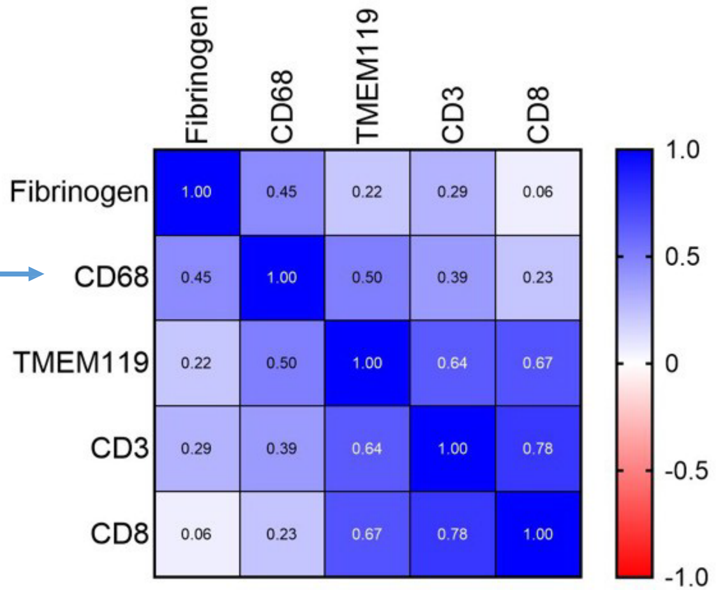
Lee et al., Brain 2022

CD68: Macrophages

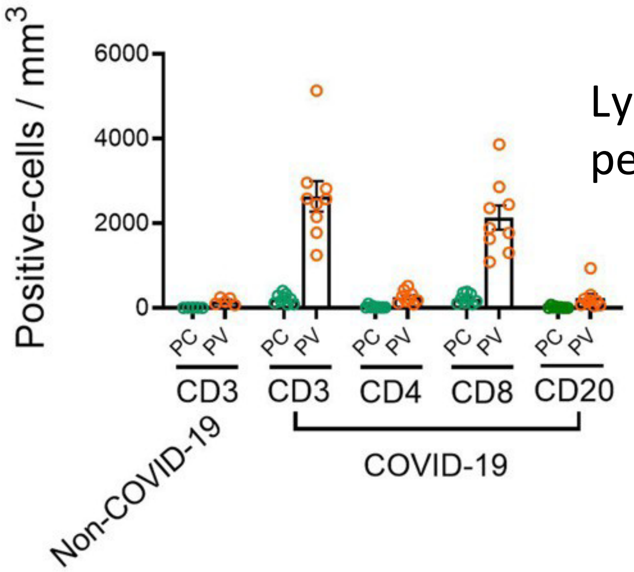


CD3 T cells





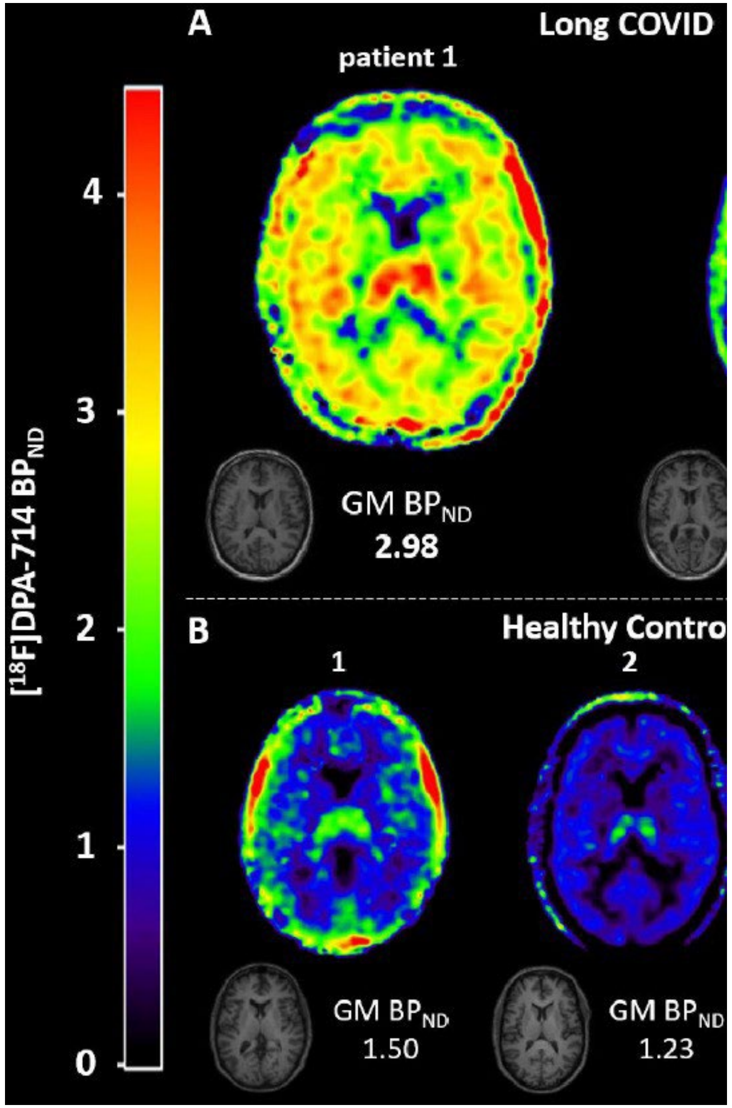
Correlation between leakage of fibrinogen and infiltration of macrophages



Lymphocytes in mainly perivascular (PV) regions

Lee et al., Brain 2022

Diffuse microglial cell activation in Long-COVID



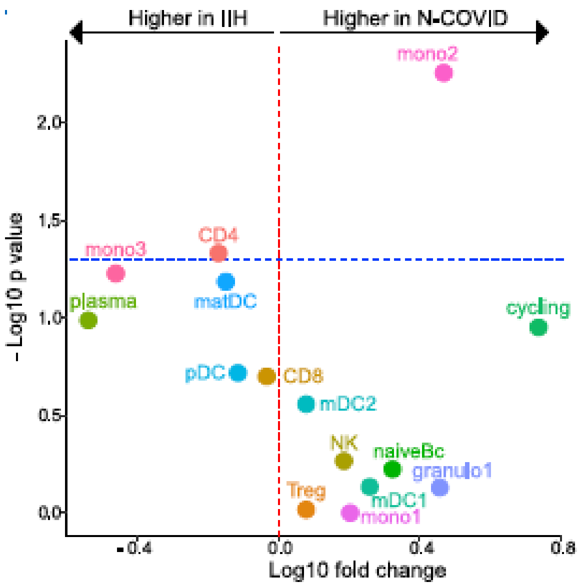
Visser et al., Med Rxiv 2022

CellPress
Immunity
Heming et al., 2021, Immunity *54*, 164–175
January 12, 2021 © 2020 Elsevier Inc.

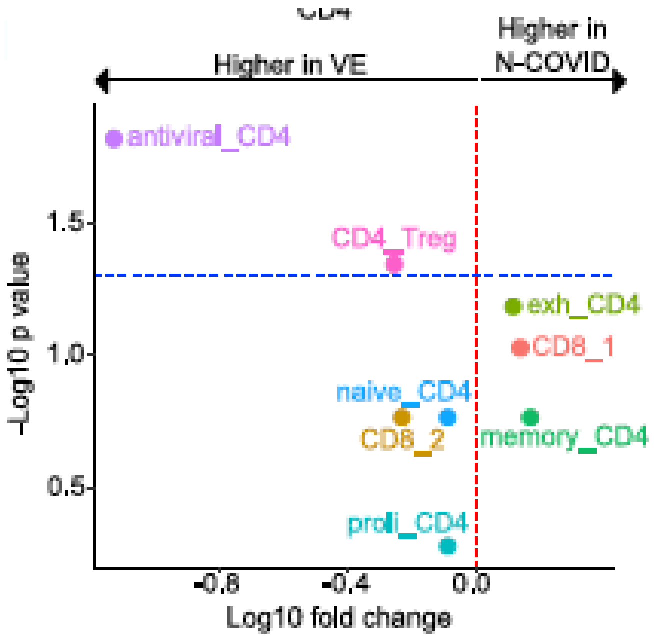
Article

Neurological Manifestations of COVID-19 Feature T Cell Exhaustion and Dedifferentiated Monocytes in Cerebrospinal Fluid

Michael Heming,[1,9] Xiaolin Li,[1,9] Saskia Räuber,[1] Anne K. Mausberg,[2] Anna-Lena Börsch,[1] Maike Hartlehnert,[1] Arpita Singhal,[3] I-Na Lu,[1] Michael Fleischer,[2] Fabian Szepanowski,[2] Oliver Witzke,[4] Thorsten Brenner,[5] Ulf Dittmer,[6] Nir Yosef,[3,7,8] Christoph Kleinschnitz,[2] Heinz Wiendl,[1] Mark Stettner,[2,10,*] and Gerd Meyer zu Hörste[1,10,11,*]



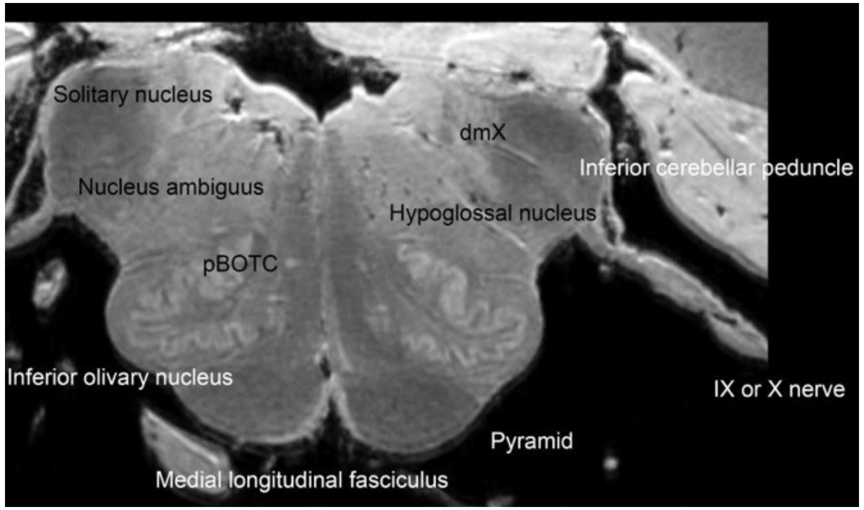
Increased dedifferentiated monocytes

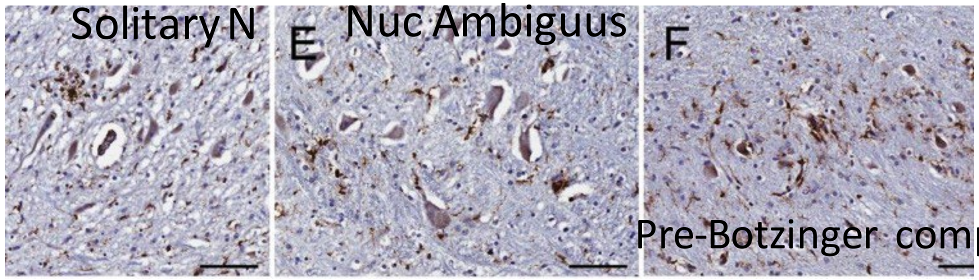


Increased T cell exhaustion

Neuronal Injury in Brainstem

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

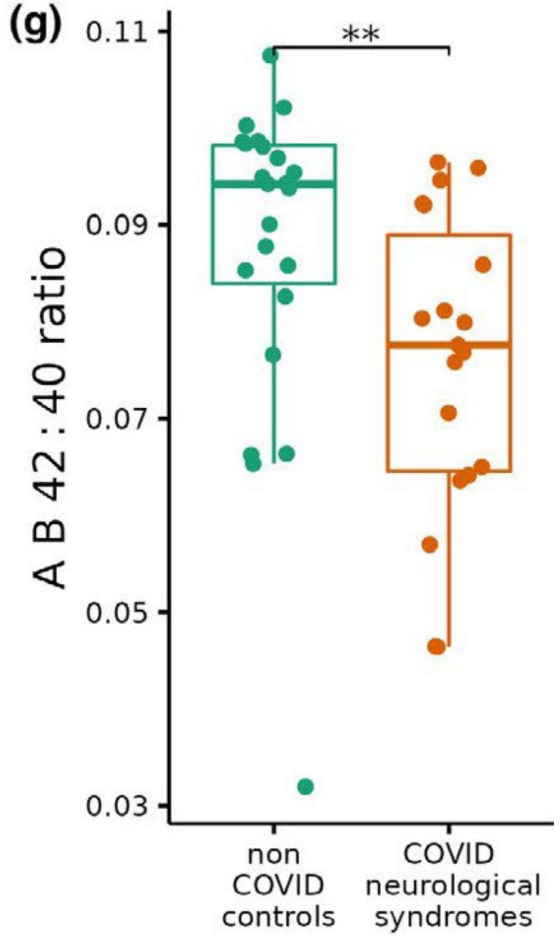


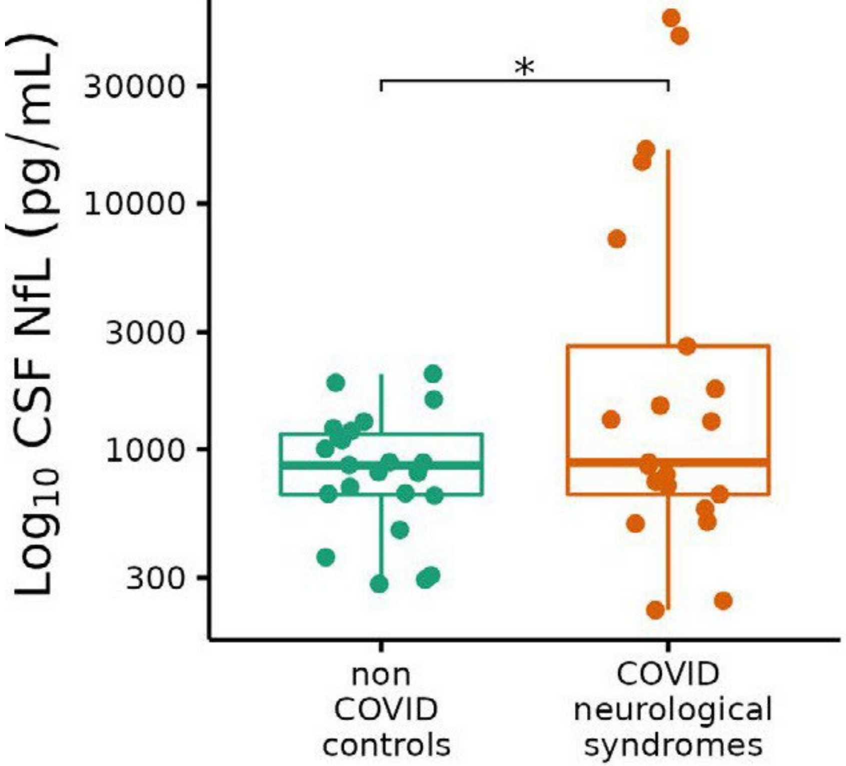


CD68

Neuronophagia

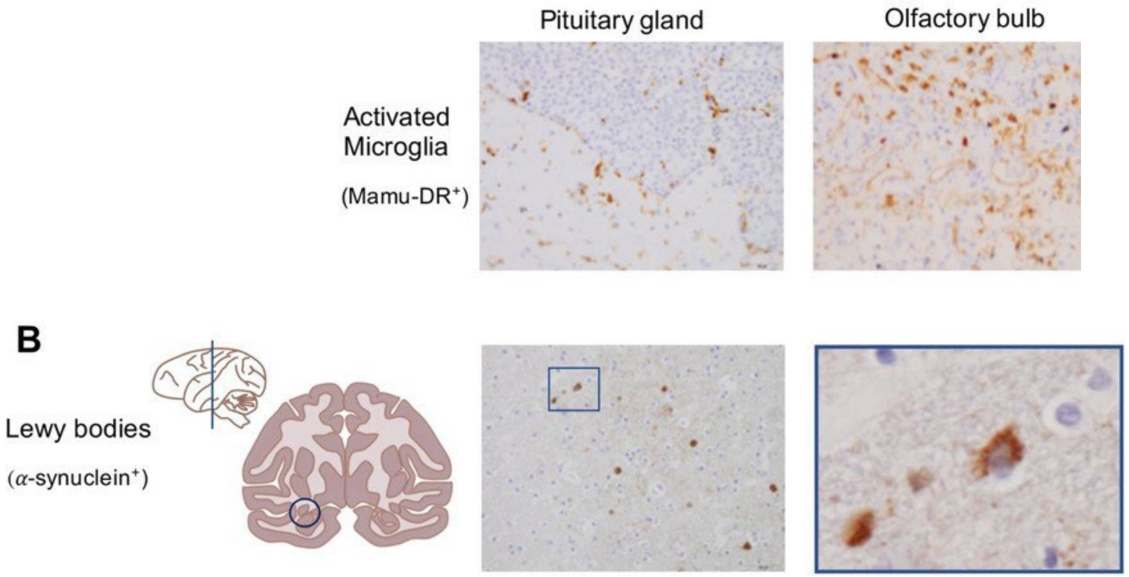
MARKERS OF NEURONAL INJURY





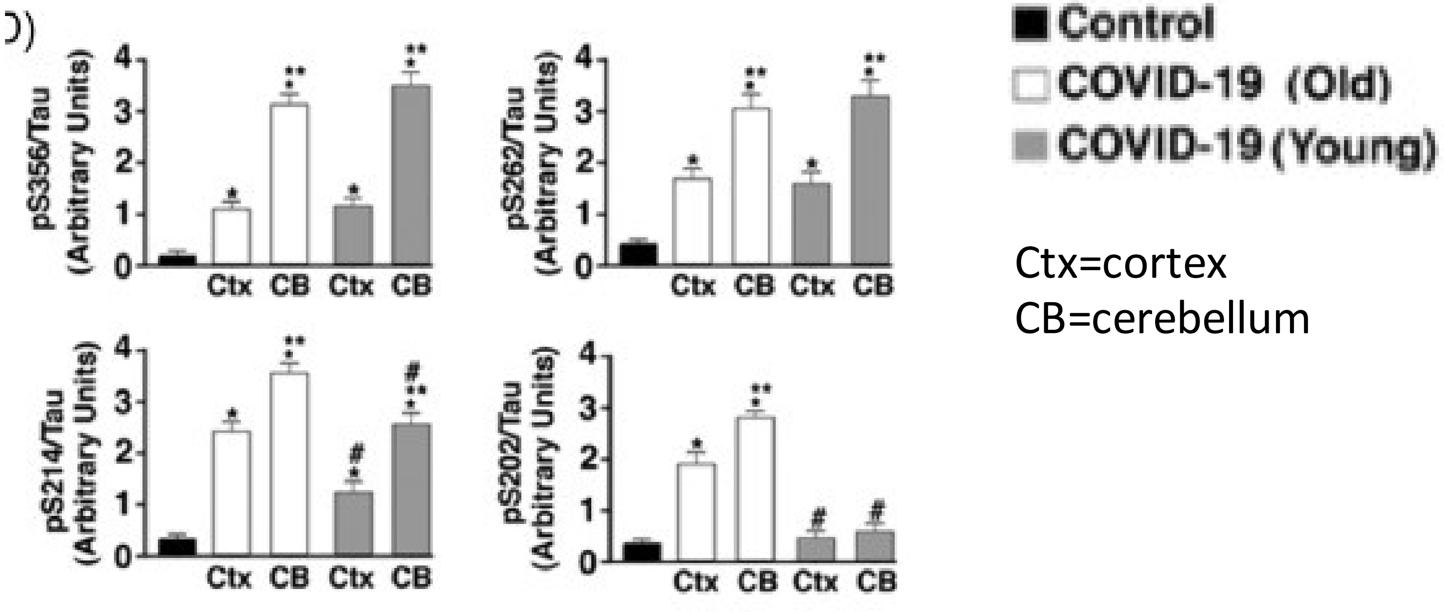
Ziff et al., J Neurochem 2021

SARS-CoV-2 causes brain inflammation and induces Lewy body formation in macaques



Philippens et al.,

Increased pTau in COVID brain



N=5 in each group

Ctx=cortex
CB=cerebellum

Peripheral Neuropathy Evaluations of Patients With Prolonged Long COVID

Anne Louise Oaklander, MD, PhD, Alexander J. Mills, BS, Mary Kelley, DO, Lisa S. Toran, MD, Bryan Smith, MD, Marinos C. Dalakas, MD,* and Avindra Nath, MD*

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Neurol Neuroimmunol Neuroinflamm 2022;9:e1146. doi:10.1212/NXI.0000000000001146

N=17
Mild COVID (n=16)
Age: 43$\pm$3 yrs
Female: 68.8%
Small fiber neuropathy

Treatment:
corticosteroids n=6
IVIG: n=6

Multisystem Involvement in Post-Acute Sequelae of Coronavirus Disease 19

ANN NEUROL 2022;91:367–379

Peter Novak, MD, PhD,[1,2] Shibani S. Mukerji, MD, PhD,[2,3] Haitham S. Alabsi, DO,[2,3] David Systrom, MD,[2,4] Sadie P. Marciano, PA-C,[1] Donna Felsenstein, MD,[2,5] William J. Mullally, MD,[1,2†] and David M. Pilgrim, MD[1,2†]

N=9
Small fiber neuropathy with autonomic dysfunction

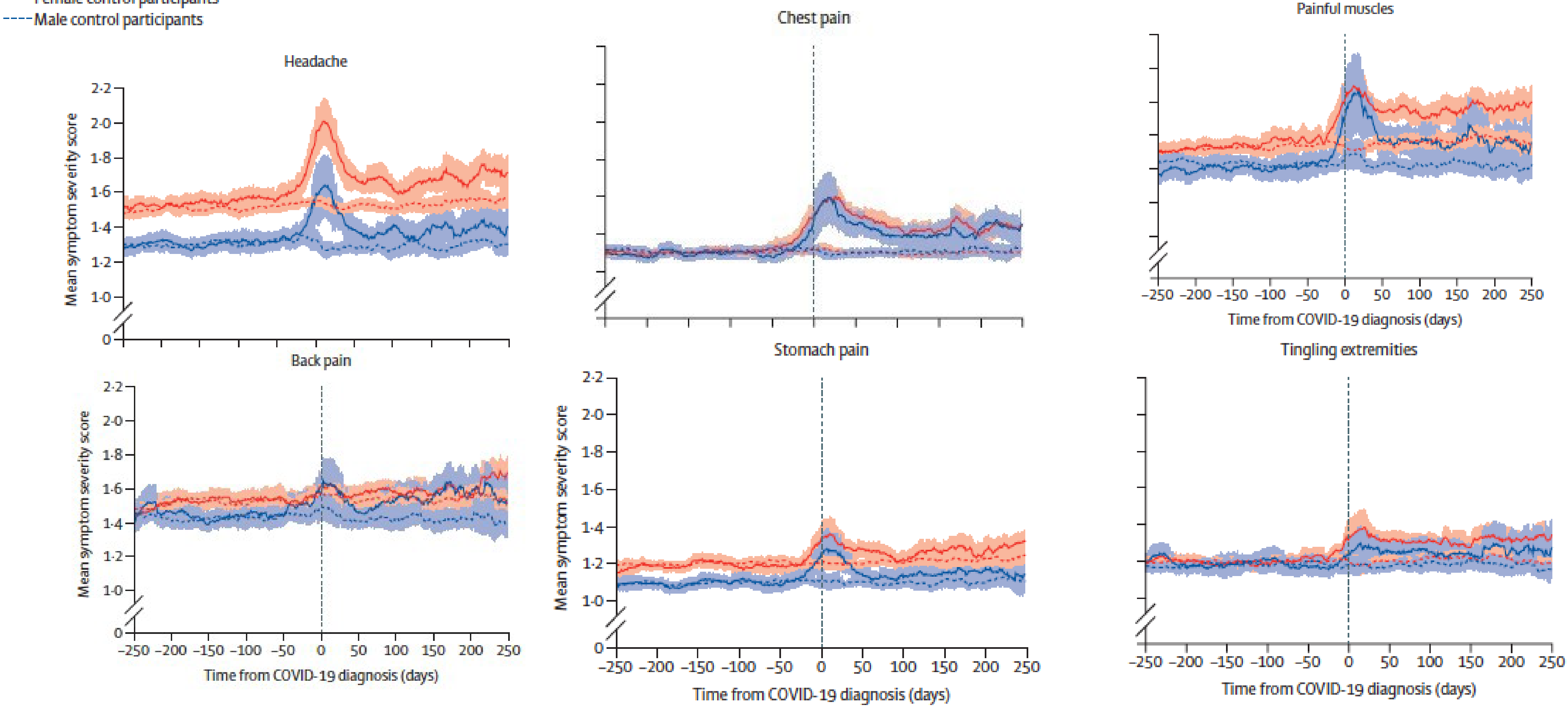
frontiers in Neurology
published: 13 April 2021

COVID-19 Dysautonomia

Brent P. Goodman[1*], Julie A. Khoury[1], Janis E. Blair[2] and Mario F. Grill[1]

N=6

Pain syndromes with Long-COVID



COVID (N=4231)

Controls (N=8462)

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

FUTURE DIRECTIONS

Biomarkers

Neuronal injury

NfL, pNfH, GFAP, SNAP25

Vascular injury

sICAM, VEGF, P-selectin, E-selectin, MMP-3, antibodies to ACE2,

Immune activation

Virological markers

proteins: nucleocapsid, spike

RNA:

antibodies for epitope mapping

Clinical Trials

Immunomodulatory agents

Potential Therapeutic Targets

- Innate immune responses:
  - IVIg; anti-IL-1 and anti-IL-6 antibodies; BTK inhibitors, GM-CSF inhibitors
- Anti-T cell therapies
  - Mycophenolate; azathioprine; methotrexate
- 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
- Endothelial cell damage by immune complexes is the primary pathophysiological process in Neuro-COVID
- Neuroinflammation may accelerate protein aggregation

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)

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