Long COVID: The Pandemic Upon The Pandemic

We are Facing a Tsunami of Impacts on Health

Long COVID and Post VAX injuries are launching a Tsunami upon US

- We are facing a catastrophic health crisis
- The neurological impacts of Long COVID are vast and profound
- Long COVID is a mass disabling event
- Health care systems will be crushed under the burden of this huge surge in chronically ill patients
- Centers of Excellence for Recovery are urgently needed

- The Challenge of Neurodegenerative Diseases The Harvard Discovery Center 2019

Will We See a Rise in Neurodegenerative Disease ? Yes

- Neurodegenerative illnesses are often characterized by protein aggregates, such as tau and beta-amyloid (Aβ) peptides in Alzheimer's disease (AD) and α-synuclein (αS) in PD, which form amyloid deposits ALS & CJD has been reported after COVID and COVID vaccine SARS-CoV-2 spike protein interactions with amyloidogenic proteins
- Prion spreading and exosomes
- Viral reactivation
- Microvascular disease
- Decrease in Innate immunity and immune dysregulation
- Autoantibodies have been implicated in NDD
- High levels of neuroinflammation
- AC2 plays a regulatory role in NDD
- Advanced senescence by spike protein
- Mitochondrial damage
- Potential for integration of the spike protein gene into human DNA
- A study , June 2022 showed that the risk of neurodegenerative was increased among COVID-19 positive outpatients compared to other viruses Frequency of Neurological Disease After COVID-19, Influenza A/B and Bacterial Pneumonia Front Neurol June 2022

What are the Symptoms of PASC

- 7 out of 10 have cognitive issues
- MC symptoms include fatigue, shortness of breath, brain fog, headache, body pain
- A study at the University College London (UCL) identified 200 symptoms affecting 10 organ systems
- Not related to severity of COVID
- Long COVID symptoms can also occur in patients who have an adverse reaction to one of the COVID vaccinations
- This is a multisystem disease

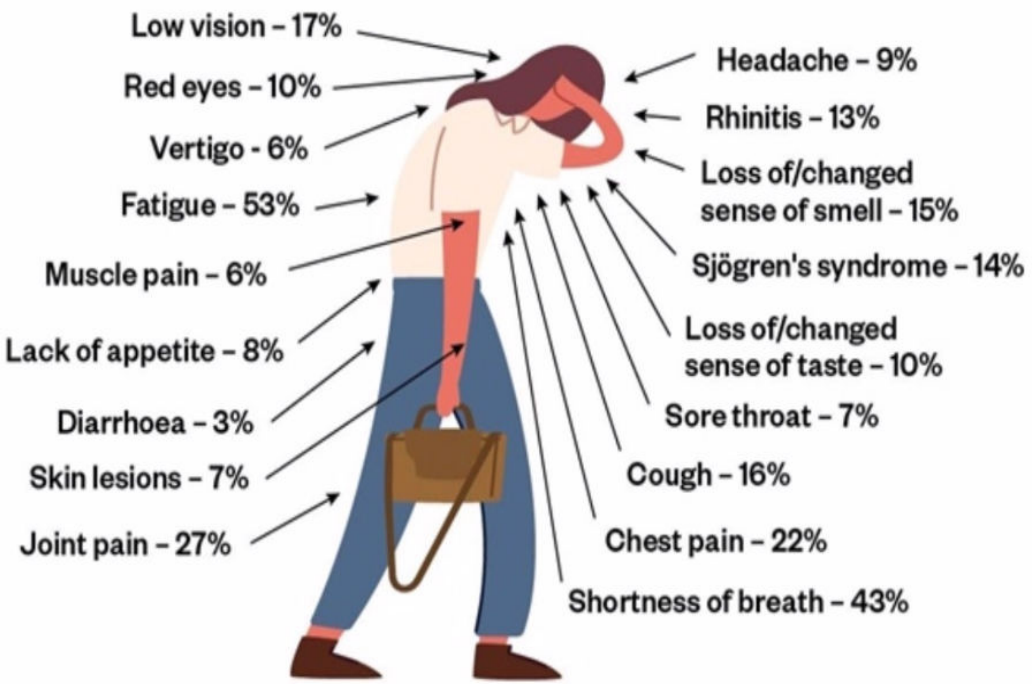
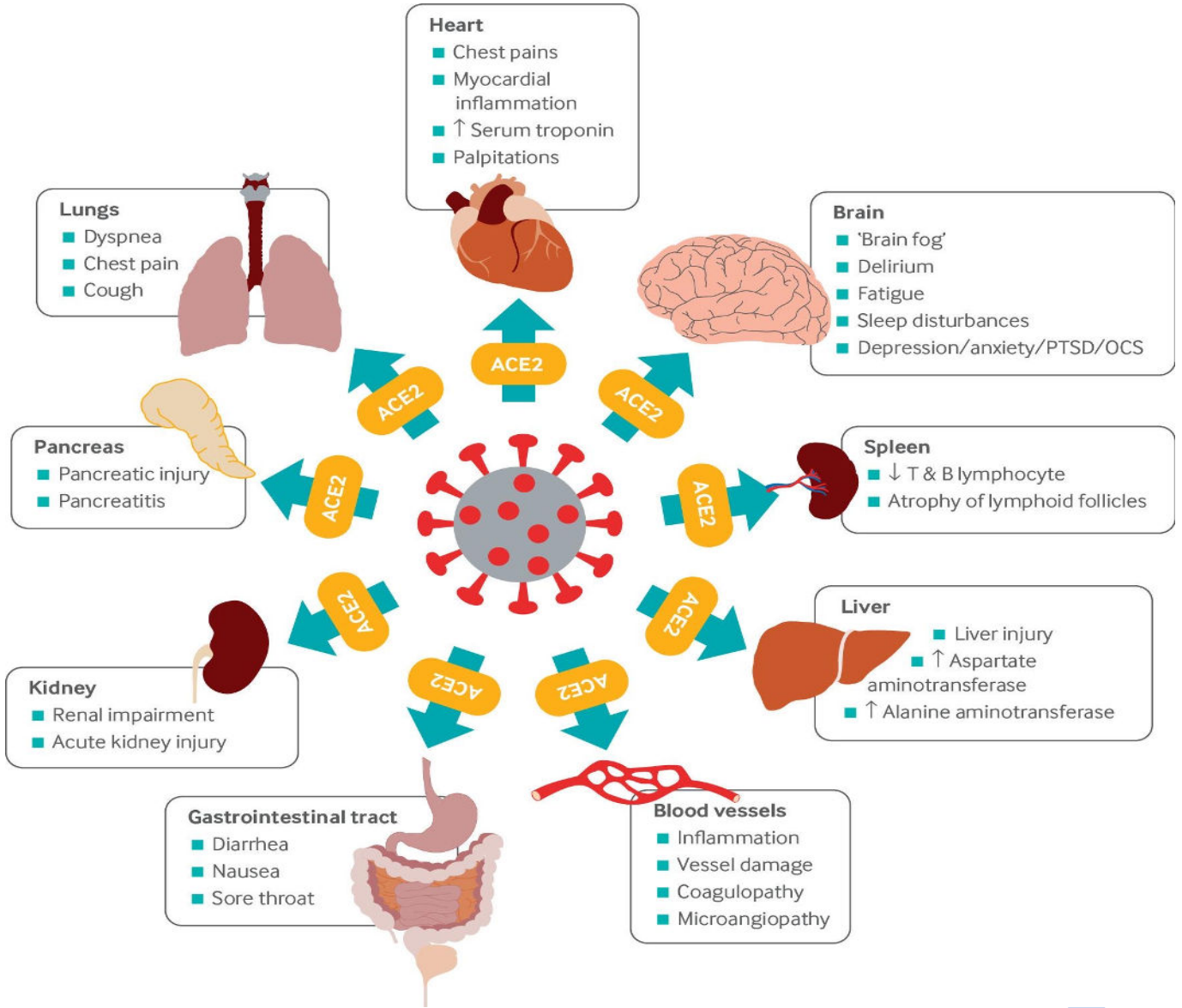


Figure: Long COVID symptoms
Source: JAMA 2020;324(6):603-605

COVCOG 2: Cognitive and Memory Deficits in Long COVID: A Second Publication From the COVID and Cognition Study Guo,et al Frontiers Aging Neuroscience March 2022)

Outcomes of SARS-CoV-2 Reinfection Hiyad A et al Preprint June 2022 Wash U School of Medicine


Heart
Chest pains
Myocardial inflammation
↑ Serum troponin
Palpitations
Lungs
Dyspnea
Chest pain
Cough
Brain
'Brain fog'
Delirium
Fatigue
Sleep disturbances
Depression/anxiety/PTSD/OCS
Pancreas
Pancreatic injury
Pancreatitis
Spleen
↓ T & B lymphocyte
Atrophy of lymphoid follicles
Kidney
Renal impairment
Acute kidney injury
Liver
Liver injury
↑ Aspartate aminotransferase
↑ Alanine aminotransferase
Gastrointestinal tract
Diarrhea
Nausea
Sore throat
Blood vessels
Inflammation
Vessel damage
Coagulopathy
Microangiopathy
ACE2

More COVID More Mortality, More PASC More Risk to the Brain

- In *Outcomes of SARS COV 2 Reinfection*, it was shown that the risk of getting Long COVID increased in a graded fashion according to the **number of infections**
- One or two or more vaccines : **NO change of outcome**
- Reinfection contributes additional risks of all-cause mortality, hospitalization, and adverse health outcomes

Outcomes of SARS-CoV-2 Reinfection Hiyad A et al Preprint June 2022 Wash U School of Medicine

Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers JAMA July 2022

Long COVID after breakthrough SARS-CoV-2 infection Nature Medicine May 2022

Long-COVID Symptoms Affect 1 in 8, Study Suggests

An Urgent Problem with Mounting Human Toll

- A study published in The Lancet August 2022 had **76,400 adults** in the Netherlands fill out an online questionnaire on 23 common long COVID symptoms
- **They calculated a prevalence 12.7% with long COVID**
- In the 2021 Taquet study, (236 379 patients) post COVID-19, showed 33-62% had a neurological or psychiatric diagnosis in the following 6 months

- Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study Ballering A et al Lancet August 6, 2022
- Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19 Taquet, M Plos Medicine September 28, 2021

Long Long Long COVID: A Neurological Health Crisis

- Researchers at the University of Oxford studied health records from more than 89 million people around the world matched over a million s/p COVID to controls with other respiratory illness
- Those who had a SARS-CoV-2 infection were at an increased risk for several neurological and psychiatric disorders, including cognitive deficits, anxiety, mood disorders, neuromuscular issues, strokes, dementia, and seizures
- **4.5 percent of older people developed dementia in the two years after infection,** compared with 3.3 percent of the control group

- Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients Tauget M et al The Lancet psychiatry August 17, 2022

tanislawczyk sits with her daughter Olivia, 3, while receiving a saline infusion at her Walkersville, e. (Matt Roth for The Washington Post)

HEALTH CARE

'Left to rot': The lonely plight of long Covid sufferers

Some studies suggest long Covid could affect as much as 30 percent of people who are infected.

NEXSTAR MEDIA WIRE

Long COVID: With as many as 4M out of work, how can they come back?

NEWS

Alzheimer's and Long Covid, could they be related?

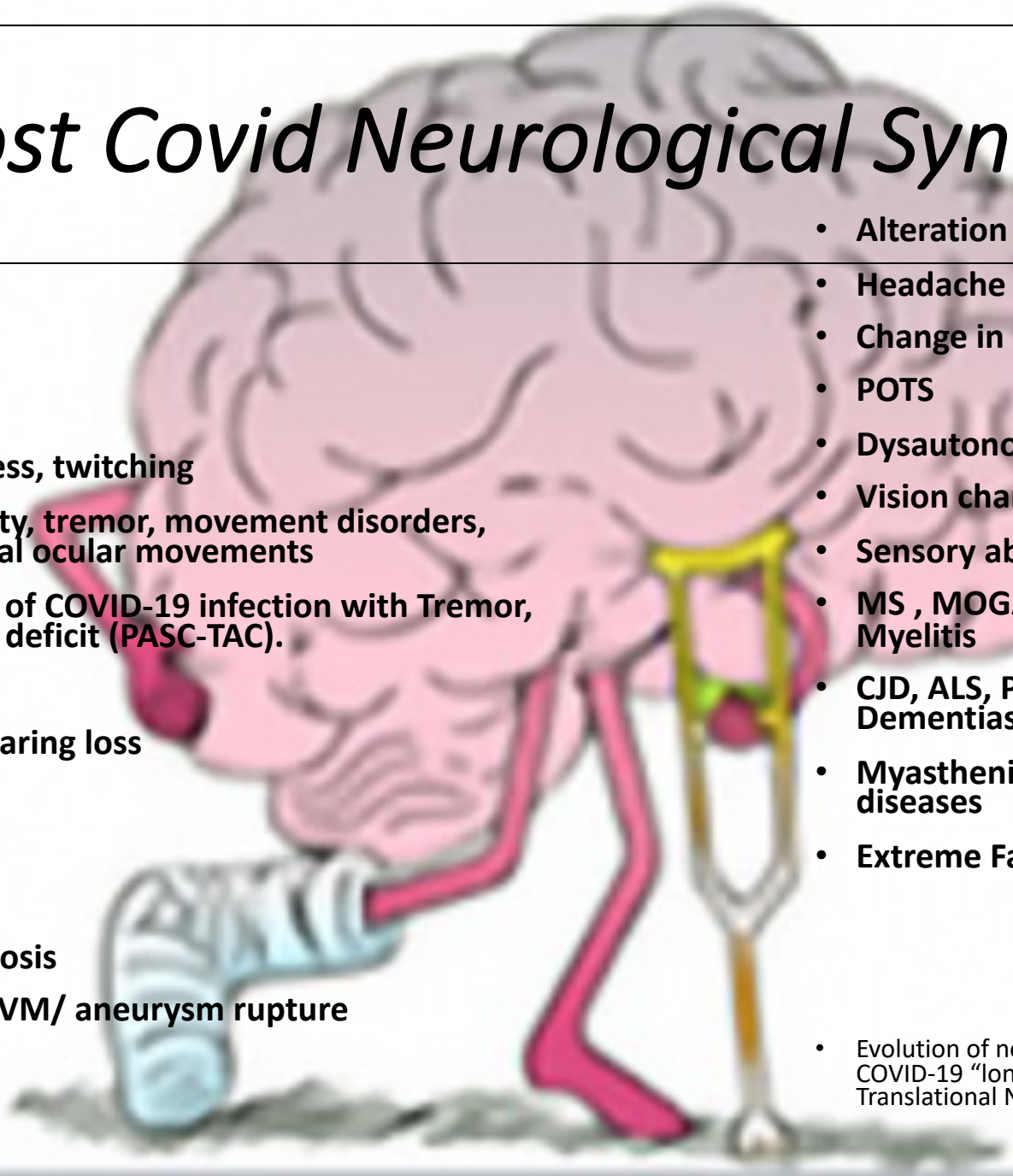
by: Brooklynn Norris, Stuart Price
Posted: Aug 13, 2022 / 02:23 PM CDT
Updated: Aug 13, 2022 / 02:23 PM CDT

Long Covid clinic wait times blow out to five months as Australia's health experts call for national approach

THE POST'S VIEW

Opinion | 'Long covid' may haunt 1 in 8 people – or more – for years to come

PCNS: Post Covid Neurological Syndrome



- **Cognitive issues**
- **Neuropathy**
- **AIDP or CDIP**
- **Muscle pain, weakness, twitching**
- **Coordination difficulty, tremor, movement disorders, tics, chorea, abnormal ocular movements**
- **Post-Acute Sequelae of COVID-19 infection with Tremor, Ataxia and Cognitive deficit (PASC-TAC).**
- **Tinnitus**
- **Dizziness, sudden hearing loss**
- **Sleep impairment**
- **Seizures**
- **CVA**
- **Cortical Vein thrombosis**
- **Intracranial bleed/ AVM/ aneurysm rupture**
- **Encephalitis**

- **Alteration of mood**
- **Headache**
- **Change in taste and or smell**
- **POTS**
- **Dysautonomia**
- **Vision changes**
- **Sensory abnormalities**
- **MS , MOGAD, Optic Neuritis, Transverse Myelitis**
- **CJD, ALS, PKD, Alzheimer's and other Dementias**
- **Myasthenia Gravis and other muscle diseases**
- **Extreme Fatigue**

- Evolution of neurologic symptoms in non-hospitalized COVID-19 "long haulers." Ali S et al Annals of Clinical and Translational Neurology June 202

The Mystery Of Long Covid

Multiple Mechanisms to Consider

- Cytokine Storm
- Roque antibodies
- Molecular mimicry
- Alteration of the Immune system
- Increased Oxidative Stress
- Vascular inflammation and damage
- Advanced senescence
- Spike protein
- Mitochondrial damage
- Exosomes
- Gut Microbiome
- Mast Cell Activation
- Damage to DNA
- Viral reactivation
- Alteration of Neurotransmitters
- Amyloid and Prions
- Neurotoxin

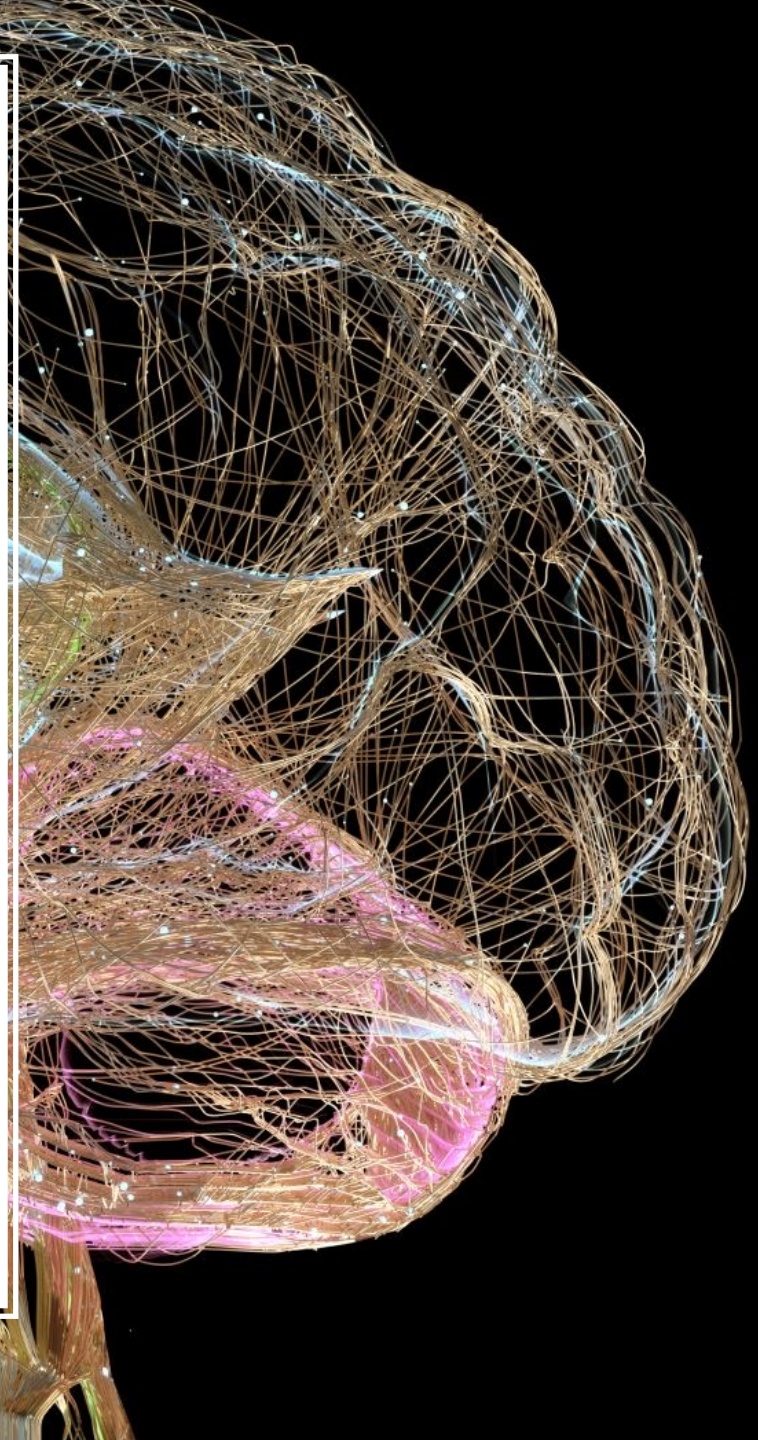
Viral fragments but No Virus

- Early in the pandemic, researchers speculated that the virus might cause damage by somehow entering the brain and infecting neurons, the cells responsible for transmitting and processing information.
- The virus has difficulty getting past the blood–brain barrier
- On the other hand, Spike protein easily crosses the BBB

How COVID-19 can damage the brain Nature Sept 2020

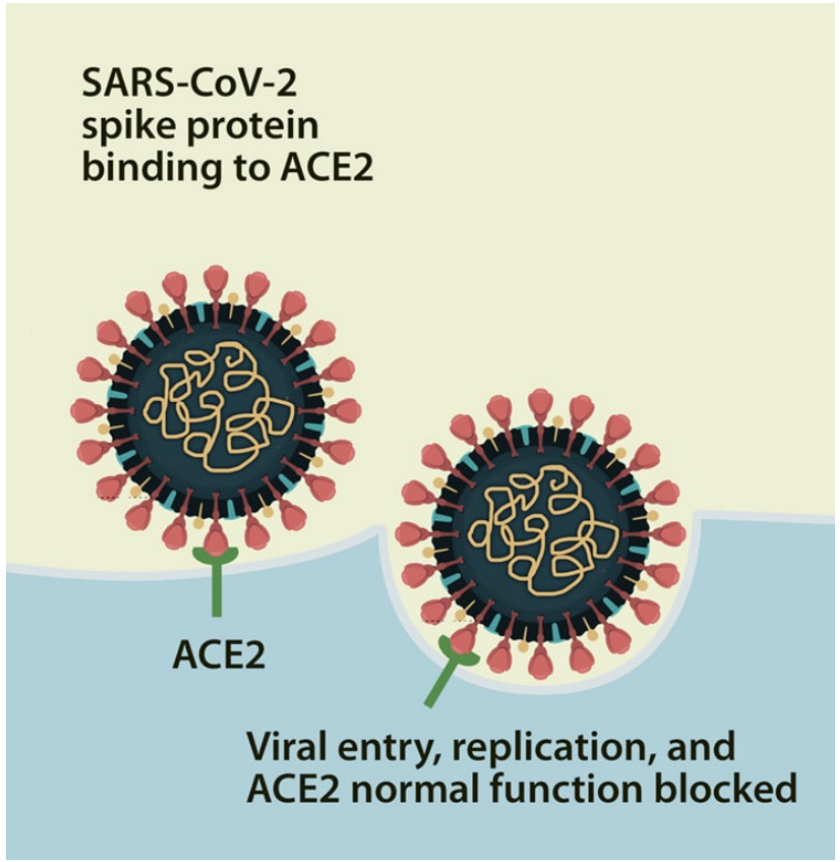
NIH study uncovers blood vessel damage and inflammation in COVID-19 patients' brains but no infection Dec 2020

Microvascular Injury in the Brains of Patients with COVID-19. New England Journal of Medicine, 12-2020



Spike protein: A Biomarker for PASC

- High levels of vascular inflammation / activation of platelets
- High Inflammation dances with increased risk of clotting/bleeding
- Autoantibodies form against S1
- Sometimes mRNA lingers too
- Any ACE 2 receptor is a target for lingering spike protein
- Spike protein alone is toxic and can cross the BBB
- Spike protein lingers after infection and after the vaccines



SARS-CoV-2 spike protein S1 induces fibrinogen resistant to fibrinolysis: Implications for microclot formation in COVID-19 Lize M. Grobbelaar, et al Bioscience Report 2021

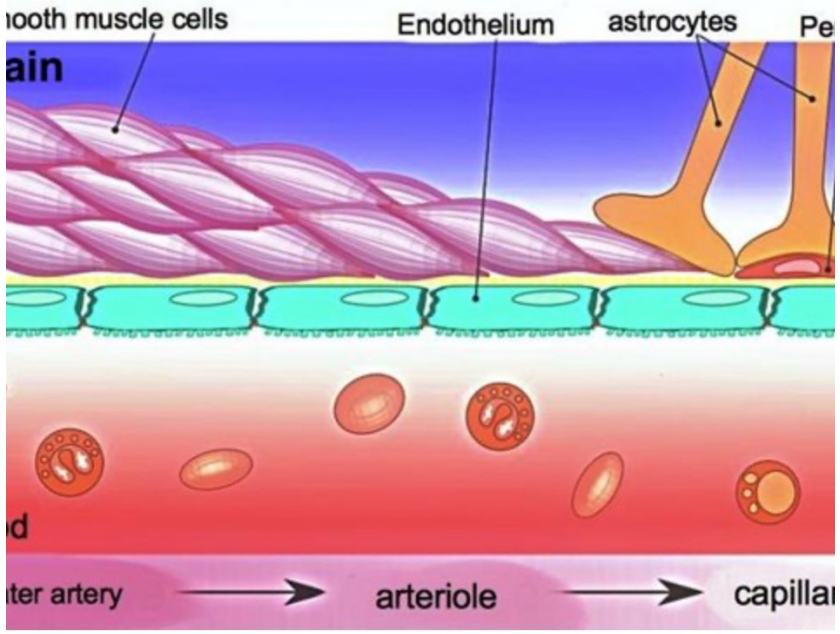
SARS-CoV-2 spike protein alone may cause lung damage Experimental Biology 2021

Rhea E et al S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice. Nature Neuroscience, 2020

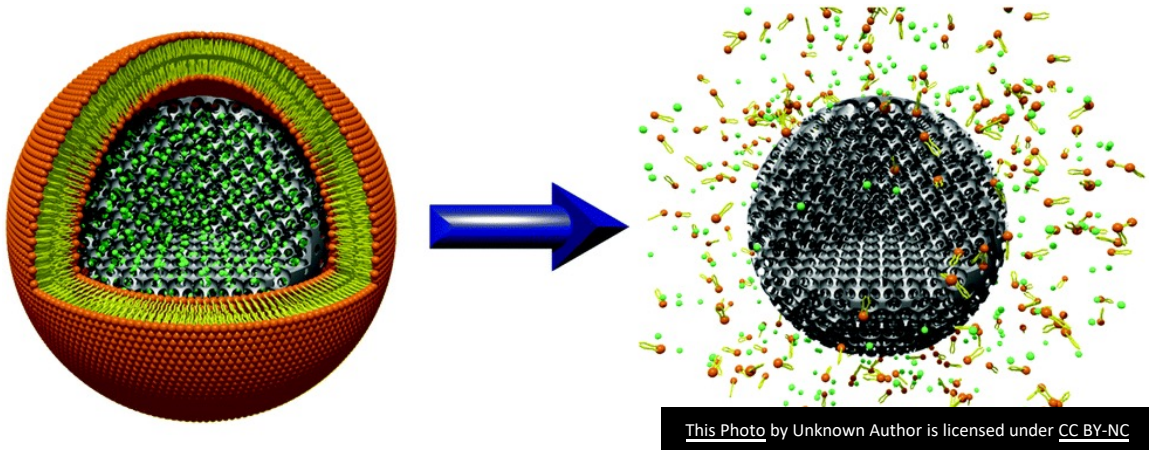
Spike Protein Damages the BBB

- Spike-induced degradation of endothelial junctional proteins affects endothelial barrier function and is the likely cause of vascular damage observed in COVID-19 affected individuals
- 2 studies have shown S1 disrupts the BBB
- S1 promote inflammatory responses on the endothelial cells that form the blood-brain barrier.

- SARS-CoV-2 Spike Protein Disrupts Blood-Brain Barrier Integrity via RhoA Activation DeOre B et al J Neuroimmune Pharma Dec 2021
- The S1 protein of SARS-CoV-2 crosses the blood–brain barrier in mice Rhea Elizaabeth et al Nature Neuroscience DEC 2020
- SARS-CoV-2 Spike Protein Induces Degradation of Junctional Proteins That Maintain Endothelial Barrier Integrity Raghaven, S et al Front. Cardiovasc. Med., 11 June 2021



n of a microvessel in the brain lined by the blood-brain barrier. The
arrier is a multicellular, compound structure composed of endothel
es and astrocytes in direct contact with brain tissue.
https://commons.wikimedia.org/wiki/File:Blood_vessels_brain_eng



COVID Vaccines: Lipid Nanoparticles the RNA Shield

- Theoretically, the lipid nanoparticles (LNPs) in which the mRNA is encapsulated should have a very restricted biodistribution, targeting the draining axillary lymph nodes There are raised concerns that the lipid nanoparticles (LNPs) can diffuse quickly to the CNS through the olfactory bulb or blood
- Studies have recovered COVID-19 mRNA from the cerebrospinal fluid of vaccinees, suggesting it can cross the blood-brain barrier (BBB)
- Are they safe?
- There is some evidence that exposure to nanoparticles could cause adverse brain effects and increase risk of neurodegenerative disease

Lipid Nanoparticles: A Novel Approach for Brain Targeting Shankar R et al Pharm Nanotechnol 2016

Drug delivery and nanoparticles:applications and hazards. Int J Nanomedicine De Jong H et al 2008

Nanoparticles for gene delivery: therapeutic and toxic effects Choi Y et al Molecular & Cellular Toxicology volume 10, pages 1–8 (2014)

VAERS COVID Vaccine Adverse Event Reports

Reports from the Vaccine Adverse Events Reporting System. Our default data reflects all VAERS data including the "nondomestic" reports.

All VAERS COVID Reports | US/Territories/Unknown

1,385,398 Reports Through August 12, 2022

30,347 DEATHS	**173,449** HOSPITALIZATIONS	**133,938** URGENT CARE
203,191 DOCTOR OFFICE VISITS	**9,915** ANAPHYLAXIS	**15,853** BELL'S PALSY

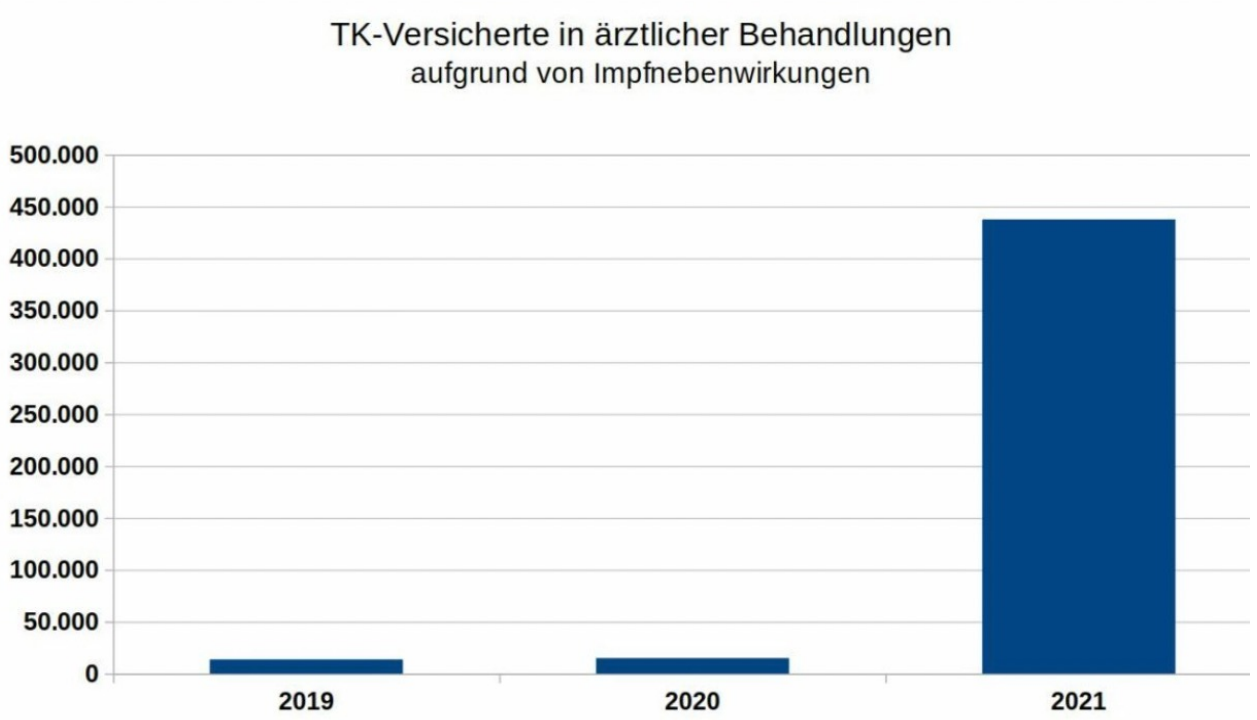
4,941 Miscarriages	**16,278** Heart Attacks	**51,566** Myocarditis/ Pericarditis	**56,734** Permanently Disabled
8,891 Thrombocytopenia/ Low Platelet	**33,583** Life Threatening	**44,417** Severe Allergic Reaction	**14,518** Shingles

How Common are Vaccine injuries? Findings from Germany

Germany's Largest Health Insurer Reveals 1 in 25 Clients Underwent Medical Treatment in 2021 for Covid 'Vaccine' Side Effects

Amy Mek August 3, 2022 12 comments 4 min read

Based on the figures from Techniker Krankenkasse, as many as 1 in 500 covid vaccine injections are expected to cause serious side effects.



Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults Doshi P et al Vaccine August 2022

- An independent analysis of the Pfizer and Moderna clinical trial data
- mRNA vaccines were associated with an excess risk of serious adverse events in 12.5 per 10,000 vaccinated
- 16 % were at higher risk of serious side effects then the control group
- Safe and Effective??

Covid-19 vaccinations and all-cause mortality -a long-term differential analysis among municipalities Redert A et al July 2022

- The relation between covid-19 vaccinations and all-cause-mortality in N=340 Dutch municipalities (17.3M people, ~99% of population), during the entire pandemic period were analyzed
- There was NO mortality-reducing effect of vaccination after vaccination and booster campaigns.
- They did find a 4-sigma-significant **mortality-enhancing effect** during the two periods of high unexplained excess mortality

Spike Protein Lingering

- Dr Bruce Patterson found S1 in a subset of monocytes up to 15 months in Long COVID and vaccine injured
- S1 was found in Exosomes up to 4 months (Bansal et al)
- A Japanese bio-distribution study for the Pfizer vaccine found that, in the 48 hours post-vaccination, vaccine particles had travelled to various tissues throughout the body and did not stay at the injection site, with high concentrations found at the liver, bone marrow, and ovaries

- Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning Patterson et al Front Immunology 2021
- Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer–BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines Bansai et al The Journal of Immunology
- SARS-CoV-2 S1 Protein Persistence in SARS-CoV-2 Negative Post-Vaccination Individuals with Long COVID/ PASC-Like Symptoms Patterson et al Research Square July 2022

Long COVID: 'Viral reservoir' of spike protein may explain long-term symptoms

Spike Protein is Lingering: What are the Long-Term Risks? Why is S1 not leaving the body?

- A study published in June 2022 by Swank et al, found **SARS-CoV-2 spike antigen** the blood of a **majority of PASC patients up to 12 months** post-diagnosis
- One study found vaccine-encoded spike protein of the COVID-19 virus expressed in the vesicular keratinocytes and endothelial cells in the dermis in a patient with zoster
- Another found S1 in thrombi (De Michelle 2022)

Evidence of SARS-CoV-2 spike protein on retrieved thrombi from COVID-19 patients De Michelle M et al Journal of Hematology & Oncology August 2022

Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae Swank Z et al pre-print June 2022

Persistent varicella zoster virus infection following mRNA COVID-19 vaccination was associated with the presence of encoded spike protein in the lesion Yamamoto M Cutaneous Immunology August 2022

Lingering Remnants: Why? Are S1 and mRNA indestructible?

- A study in preprint, August 2022 by Craddock et al showed **spike protein and/or viral RNA fragments persist in the recovered COVID-19 patients with PASC**
- In some, at higher levels compared to acute COVID-19 patients
- mRNA has been found in muscle tissue, lymph nodes and CSF
- During these time frames mRNA likely retains its ability to induce spike protein
- The mRNA stabilization comes from substituting methyl-pseudouridine for all the uridine nucleotides

Persistent Circulation of Soluble/EV-linked Spike Protein and Viral RNA in Individuals with Post-Acute Sequelae of COVID-19 Craddock V et al Lancet Preprint August 2022

Clinical and Molecular Characterization of a Rare Case of BNT162b2 mRNA COVID-19 Vaccine-Associated Myositis, July 2022

Therapeutic Advances in Infectious Disease October 2021 Viszlayova D et al October 2021

Why Does Long COVID Happen?

- Spike protein and other viral fragments
- Higher viral load promotes higher risk
- Those that harbor EBV (others?)
- Those who have autoimmune antibodies circulating (antibodies to type 1 interferon)
- Those who had neurological symptoms with COVID
- Older age and those with underlying health problems like diabetes, heart disease, obesity , low IgG panels
- Female
- Alteration of the gut microbiome

Risk factors for long COVID: analyses of 10 longitudinal studies and electronic health records in the UK
Thompson E et al preprint 2021

https://covid19.nih.gov/news-and-stories/study-looks-risk-factors-long-covid

Long Covid After Breakthrough SARS COV 2 Nature Medicine Al-Aly A et al May 2022

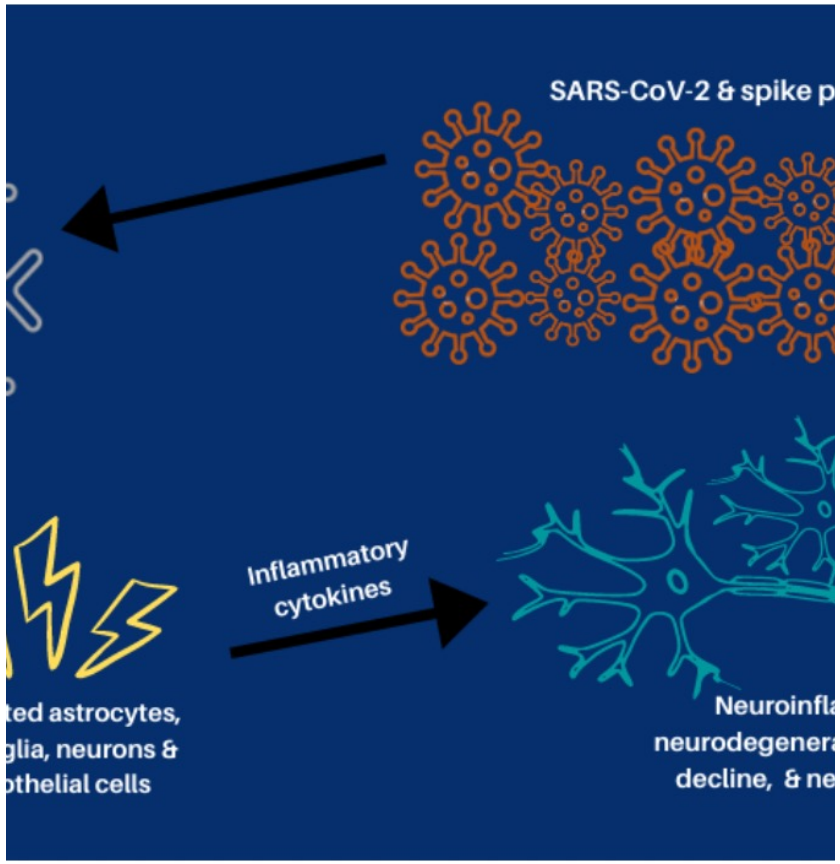
The Five Horsemen of Injury
A Looming Apocalypse

(

- The Book of Revelations in the New Testament lists the Four Horsemen of the Apocalypse (conquest, war, famine and death)
- The fifth Horsemen is Us

Viral fragments are driving Immune Dysregulation in Long COVID

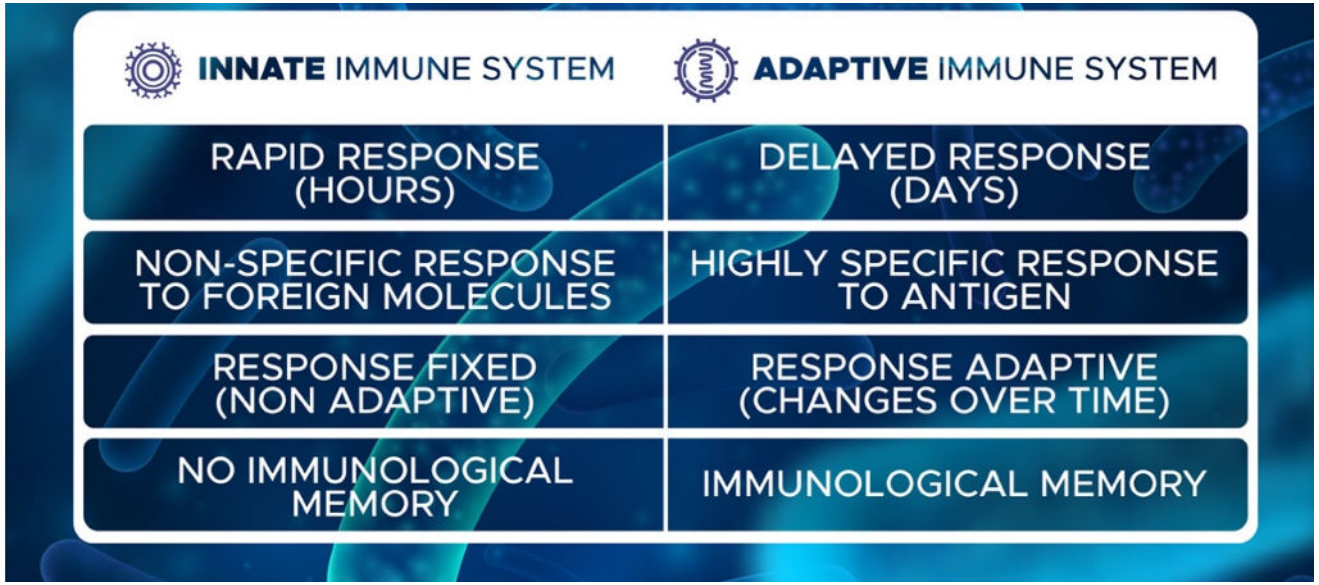
- Studies in long Covid show evidence of sustained inflammation and activation of the immune response for many months
- In this study, ***Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection*** Nature Immunology Jan 2022, they found sustained inflammation even in mild to moderate COVID 19 with **no residual virus** but likely due to **retained 'antigen' and or autoimmunity**



Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) up to 15 Months Post-Infection Patterson et al Front Immun Jan 2021

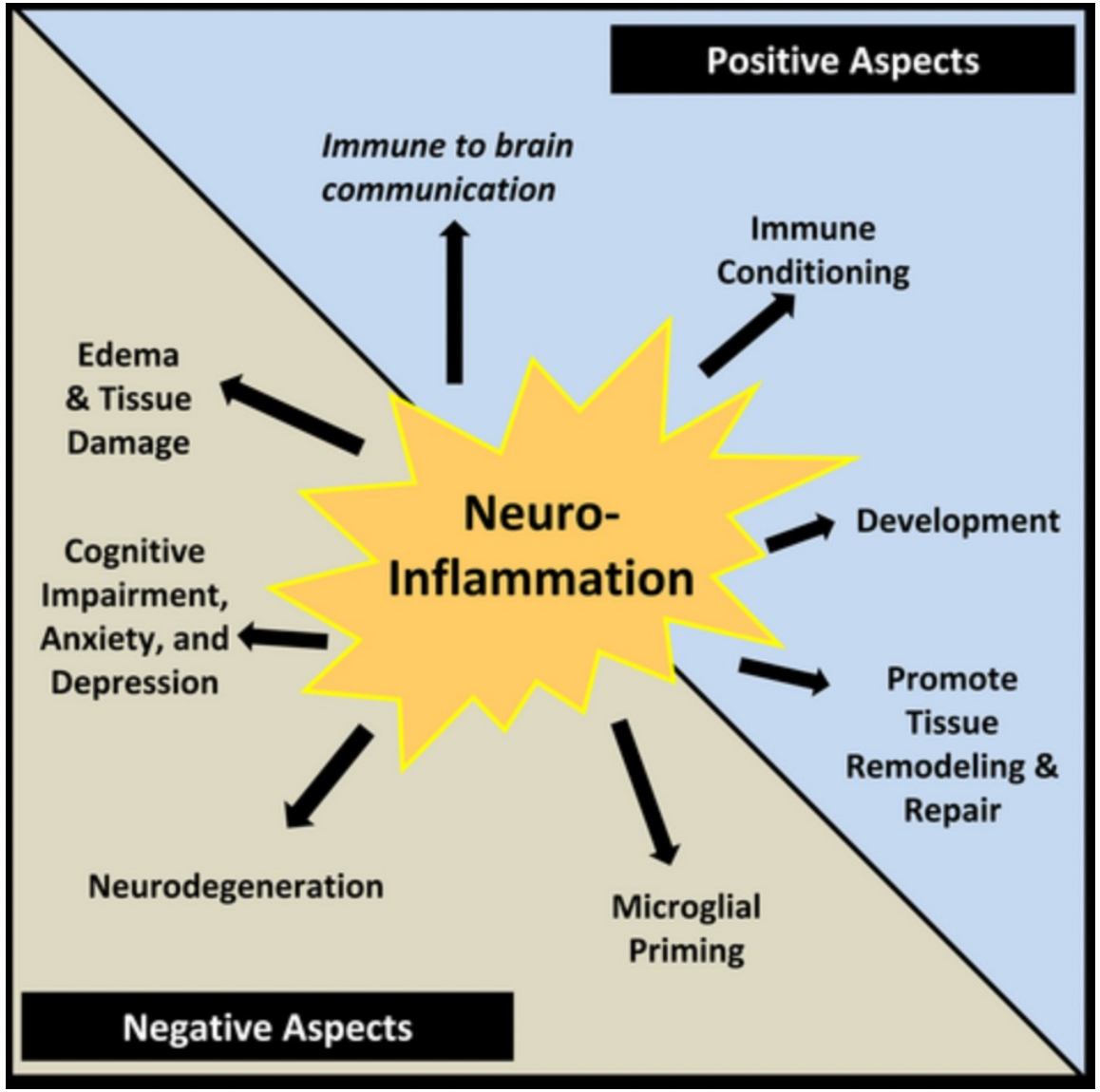
The BNT162b2 mRNA vaccine against SARS-CoV-2 reprograms both adaptive and innate immune responses Fohse F et al Med Rx IV preprint 2021

- The vaccine is altering the innate immune response.
- Innate immune cells had reduced response to toll-like receptor 4 (TLR4), TLR7 and TLR8 – all ligands that play an important role in the immune response to viral infection & tumor surveillance
- This Netherland study showed that these toll-like receptors are down regulated post injection
- We are seeing viral reactivation and cancers post VX rollout



Neuroinflammation: The Devil's in the Details

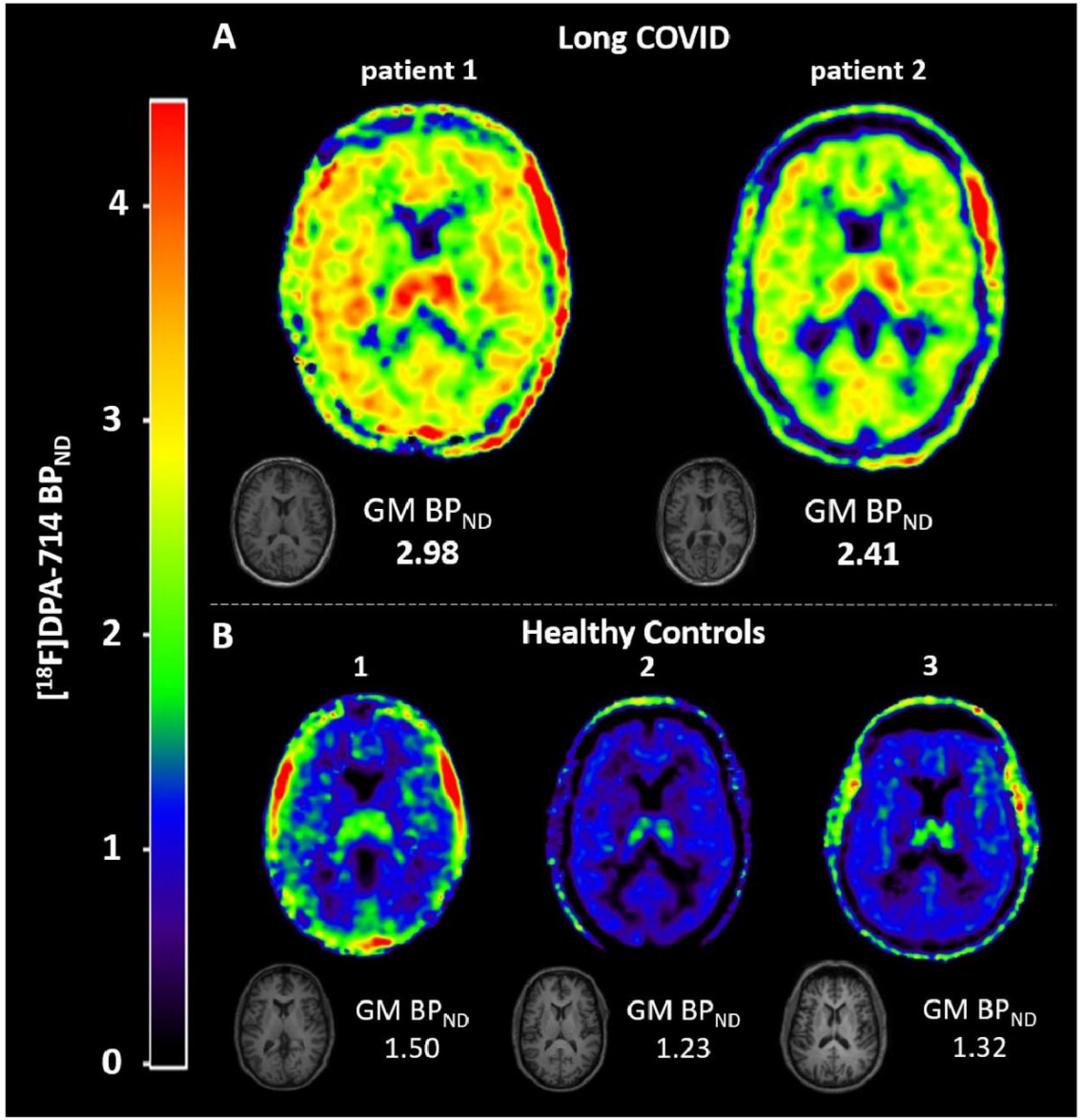
- Chronic neuroinflammation is the downfall of the brain
- Neuroinflammation is defined as an inflammatory response within the brain or spinal cord
- Profound neuroinflammation Is associated with Long COVID pathophysiology



- Neuroinflammation: the devil is in the details Disabato D et al J of Neurochemistry 2016
- Long COVID is associated with extensive in-vivo neuroinflammation on [18F]DPA-714 PET Pre-print June 2022
- COVID-19 induces neuroinflammation and loss of hippocampal neurogenesis Klein R Research Square 2021

Profound Neuroinflammation on PET

- A brain positron emission tomography (PET) scan is an imaging test of the brain. It uses a radioactive substance called a tracer to look for disease or injury in the brain
- Multiple studies now show FDG PET hypometabolism could constitute a cerebral biomarker of long COVID



- Long COVID is associated with extensive in-vivo neuroinflammation on [18F]DPA-714 PET medRxiv preprint 2022
- Visual interpretation of brain hypometabolism related to neurological long COVID: a French multicentric experience Eur J Nucl Med March 2022

NeuroQuant® TBI

Triage Brain Atrophy Report

Patient Information

Patient: [redacted]
Patient ID: PPI44658
Sex: M
Age: 61
Referring Physician: GAZDA, SUZANNE

Report Information

Scan Date: 2022-03-11
Scan Accession: 10066292
Report Date: 2022-03-11
Software Version: 3.1.0

Site Information

Paesanos Parkway Imaging
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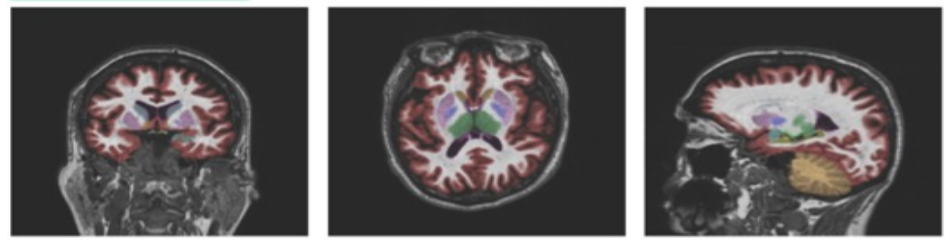
Brain Structure Visualization



Brain Structure Volumes

Brain Structure	Volume (cm^3)	Normative Percentile
Intracranial Volume	1796	-
Whole Brain	1423	78
Forebrain Parenchyma	1241	78

Brain Structure	Normative Percentiles		
	Left	Right	Total
Cerebral White Matter	15	22	18
Cortical Gray Matter	97	98	98
Ventricle	15	38	25
Cerebral WM Hypointensities*	51	83	78
Subcortical Structures			
— Cerebe ar White Matter	53	66	60
— Cerebe ar Gray Matter	38	49	43
— Brainstem	-	-	83
— Tha amus	40	63	52
— Ventra Diencepha on	87	41	69
Basal Ganglia			
— Putamen	58	63	61
— Caudate	33	36	35
— Nuc eus Accumbens	72	45	60
— Pa idum	68	67	68
Cingulate	94	90	93
— Anterior Cingu ate	73	84	82
— Posterior Cingu ate	58	38	48
— Isthmus Cingu ate	97	94	97

*White matter hypointensities are abnorma y ow signa intensity regions within the white matter as observed on a T1-weighted MRI scan.

Color Code Key:
Pink: A tissue is be ow the 5th percenti e OR a ventric e that is above the 95th percenti e OR WM hypointensity that is above the 50th percenti e.
Blue: A tissue is above the 95th percenti e OR a ventric e is be ow the 5th percenti e

Brain Structure	Normative Percentiles		
	Left	Right	Total
Frontal Lobe	85	86	85
— Superior Fronta	54	62	58
— Midd e Fronta	91	79	89
— Inferior Fronta	94	69	88
— Latera Orbitofronta	30	67	46
— Media Orbitofronta	57	66	64
— Paracentra	99	97	99
— Primary Motor	34	71	54
Parietal Lobe	93	94	95
— Primary Sensory	74	62	70
— Media Parieta	97	99	99
— Superior Parieta	63	81	75
— Inferior Parieta	97	93	98
— Supramargina	39	51	43
Occipital Lobe	99	99	99
— Media Occipita	99	99	99
— Latera Occipita	96	99	99
Temporal Lobe	76	54	66
— Transverse Tempora + Superior Tempora	81	96	92
— Posterior Superior Tempora Su cus	50	37	40
— Midd e Tempora	10	1	2
— Inferior Tempora	66	11	34
— Fusiform	99	97	99
— Parahippocampa	96	97	98
— Entorhina Cortex	76	56	69
— Tempora Po e	53	21	33
— Amygda a	71	50	63
— Hippocampus	70	88	81

COVID-19:

IS LONG COVID A NEW AUTOIMMUNE DISEASE?

CARINA STORRS, PHD

JUNE 16, 2022

A pathologist weighs in on the latest research involving the link between autoimmunity and Long COVID

Autoimmune problems post COVID and post vaccine

- Guillain-Barré syndrome
- MS/ Optic neuritis/MOGAD/Transverse myelitis
- Autoimmune encephalitis
- Neuropathy
- Myasthenia Gravis
- Polymyositis
- Temporal arteritis
- Bechet's disease
- Myocarditis
- Inflammatory myopathies
- Crohn's / IBD

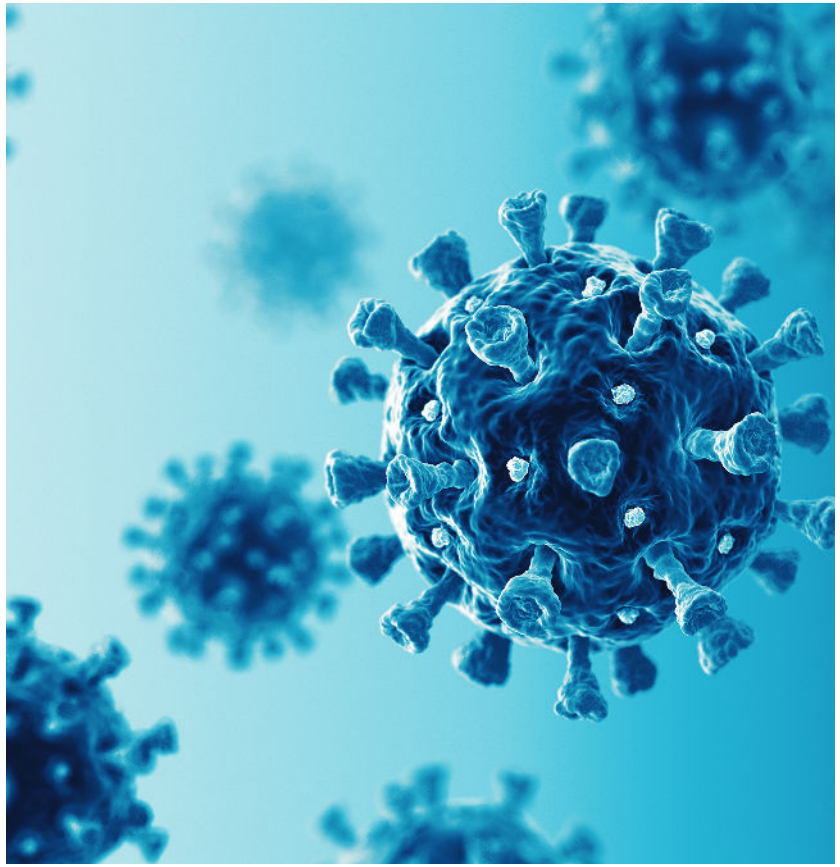
- RA/ Lupus/ Vasculitis/ Sjogrens
- Kawasaki vasculitis
- ANCA vasculitis
- ITP
- Hashimoto's/ Graves disease
- Diabetes
- Cold agglutinin disease
- Autoimmune hemolytic anemia
- Autoimmune Hepatitis
- Psoriasis
- Type I Hypersensitivity reactions
- Immune Complex Glomerulonephritis

- Autoimmune post-COVID vaccine syndromes: does the spectrum of autoimmune/inflammatory syndrome expand? Jara,L et al Clin Rheumatol. 2022; 41(5): 1603–1609.
- New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination Yano M April 2022 Internal Medicine
- COVID-19 vaccine and autoimmunity. A new case of autoimmune hepatitis and review of the literature Dominquez L et al Journal of Translational Autoimmunity 2022

Molecular Mimicry

- Molecular mimicry is one of the leading mechanisms by which infectious or chemical agents may induce autoimmunity. It occurs when similarities between foreign and self-peptides favor an activation of autoreactive T or B cells by a foreign-derived antigen in a susceptible individual
- Molecular mimicry plays a role in vaccine injuries (the H1N1 and Swine Flu vaccines)

Autoinflammatory and autoimmune conditions at the crossroad of COVID-19 Rodriquez Y, Autoimmun. 2020 Nov; 114:



Molecular Mimicry: The Betty Effect

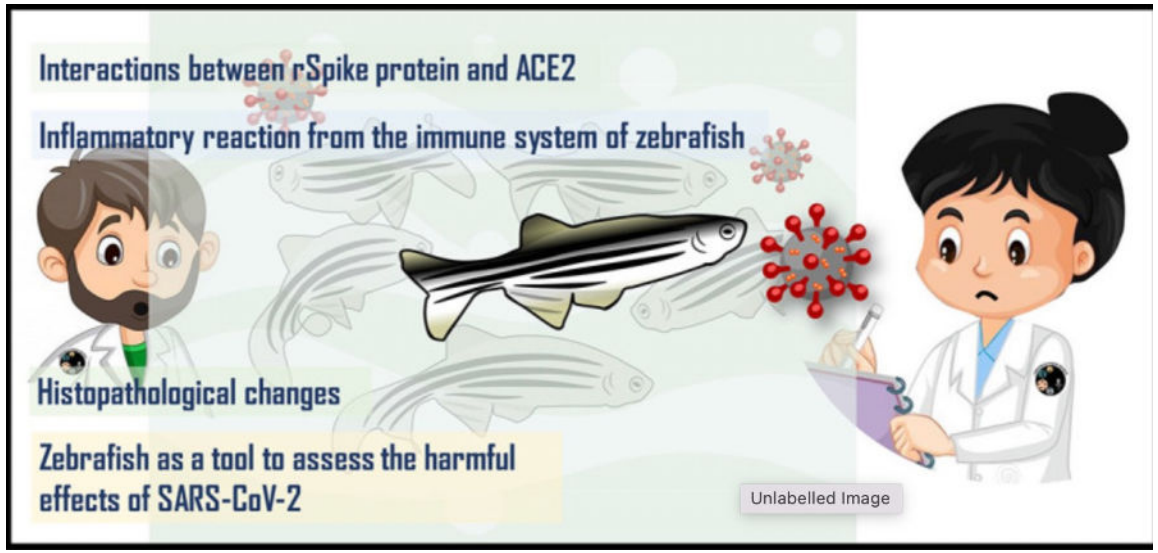
- There is a high degree of structural homology between spike protein and the human proteome which may cause a cross-reaction after COVID and with vaccine-induced immune responses
- Molecular mimicry may explain multi-organ damage in COVID and in Long Haulers and vaccine injured
- A study by Vorjdani et al showed 28 out of 55 human tissues cross reacting with viral fragments
- The Churlow paper, showed 14 peptides shared by S-protein and autoantigens of thyroid, pituitary, adrenal cortex and pancreas

Reaction of Human Monoclonal Antibodies to SARS-CoV-2 Proteins With Tissue Antigens: Implications for Autoimmune Diseases Vorjdani A et al Frontiers of Immunology Jan 2021

Molecular Mimicry between SARS-CoV-2 and Human Endocrinocytes: A Prerequisite of Post-COVID Endocrine Autoimmunity Churlow L, et al Preprint August 2022

Toxicity of spike fragments SARS-CoV-2 S protein for zebrafish: A tool to study its hazardous for human health? Sci Total Environ May 2022

- Zebra fish and humans share high genetic morphology
- Zebra fish when injected with spike protein showed high mortality and adverse effects via molecular mimicry on liver, kidney, ovary and brain tissues.
- Spike protein is Toxic to the Body and Brain
- Will our wastewater be contaminated?



Wastewater samples could help to detect new SARS-CoV-2 variants early. (Arnold Jerocki/Getty)

Chemo Brain and Long COVID Brain: Mechanisms are Strikingly Similar

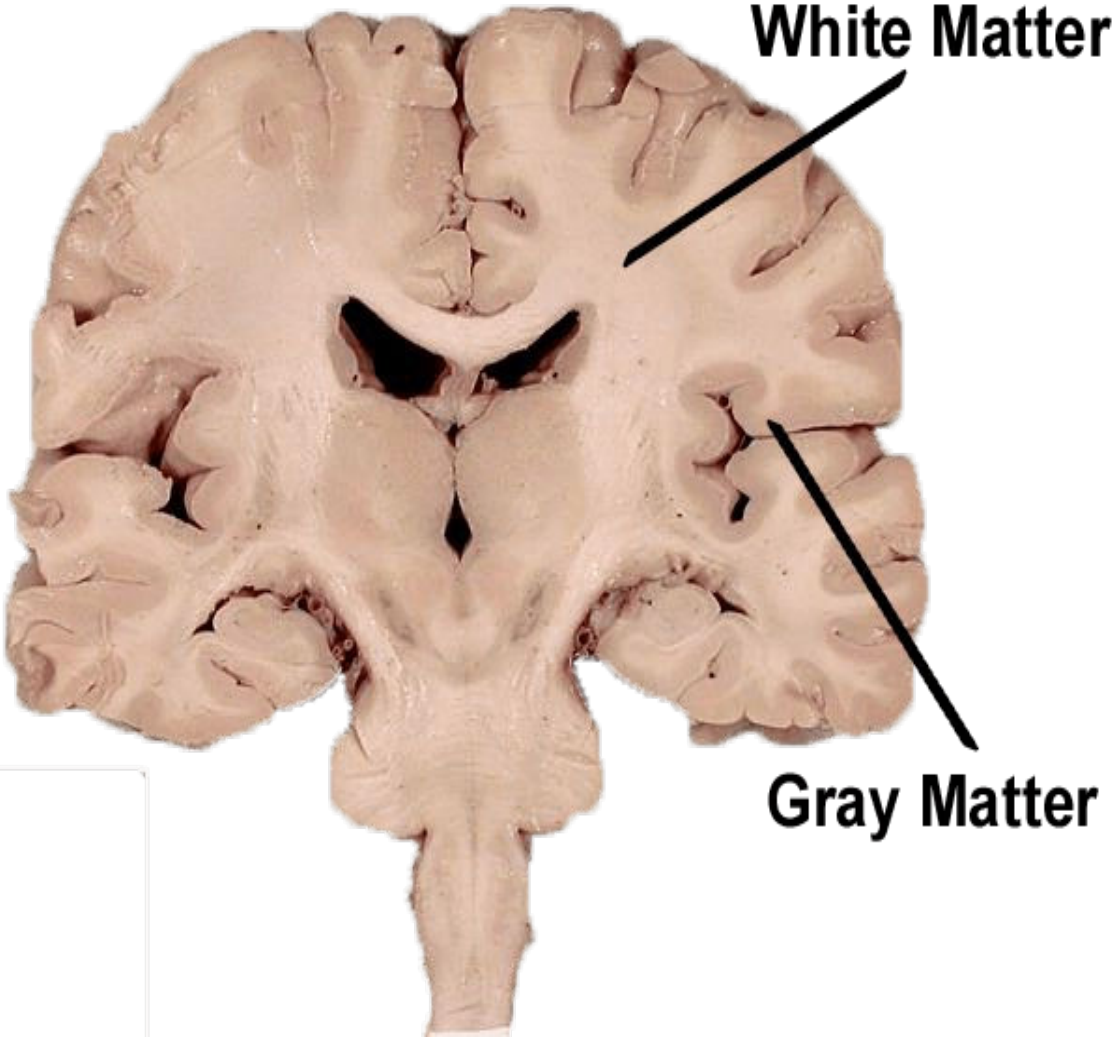
- Dr Michelle Monje's team at Stanford has spent two decades studying cognitive impairment after cancer and found chemotherapy damages myelin , impairs the function of the brain's white matter and damages the hippocampus (the atlas of the mind)
- In their new work they report: Long COVID causes the same findings
- Dr Monje says she sees Long COVID as a "**neurological health crisis"**

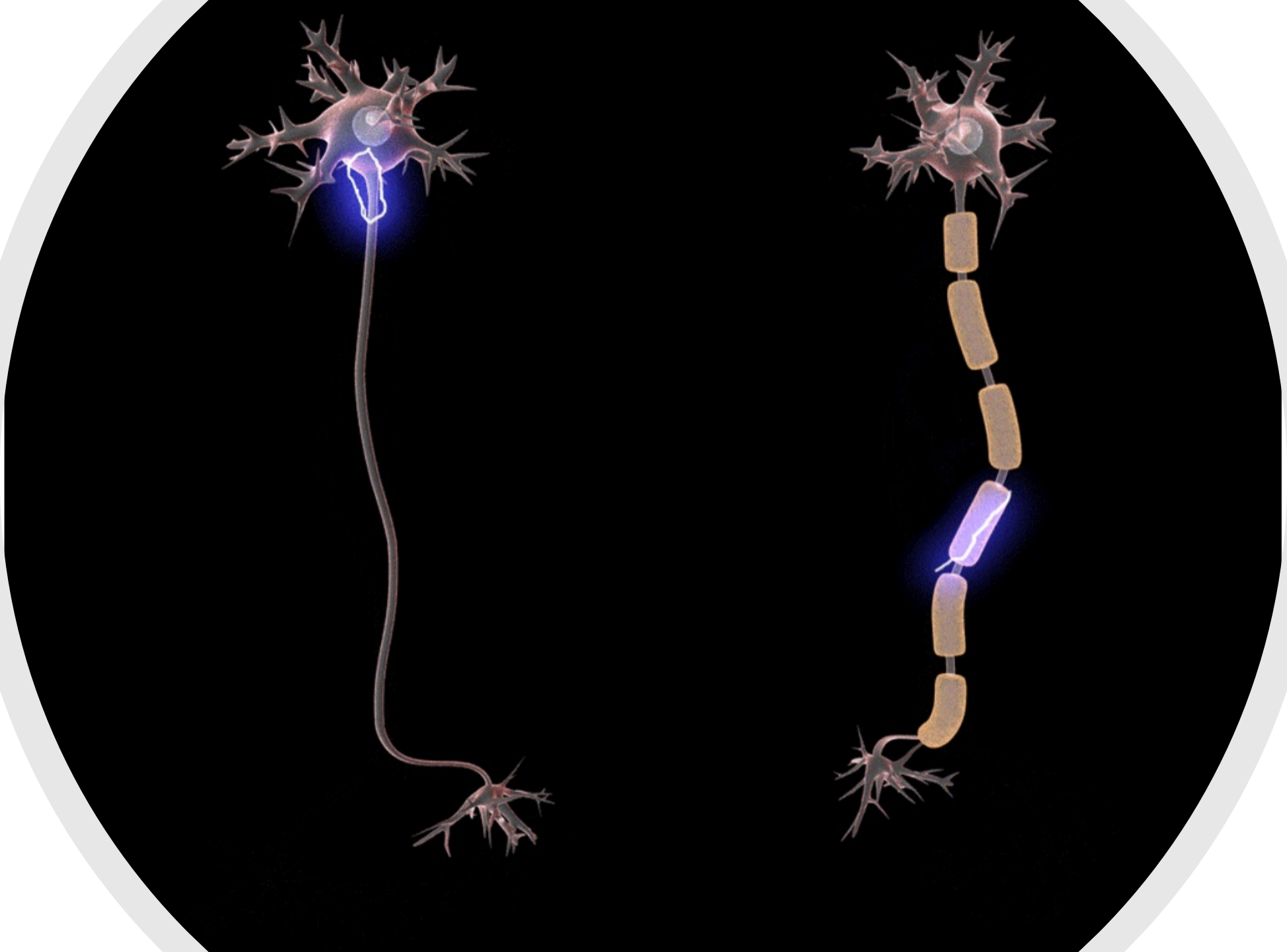
Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemo- therapy-related cognitive impairment. Cell 176 2019

Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation Monje M et al Cell July 2022

White Matter: The Brain's Superhighway

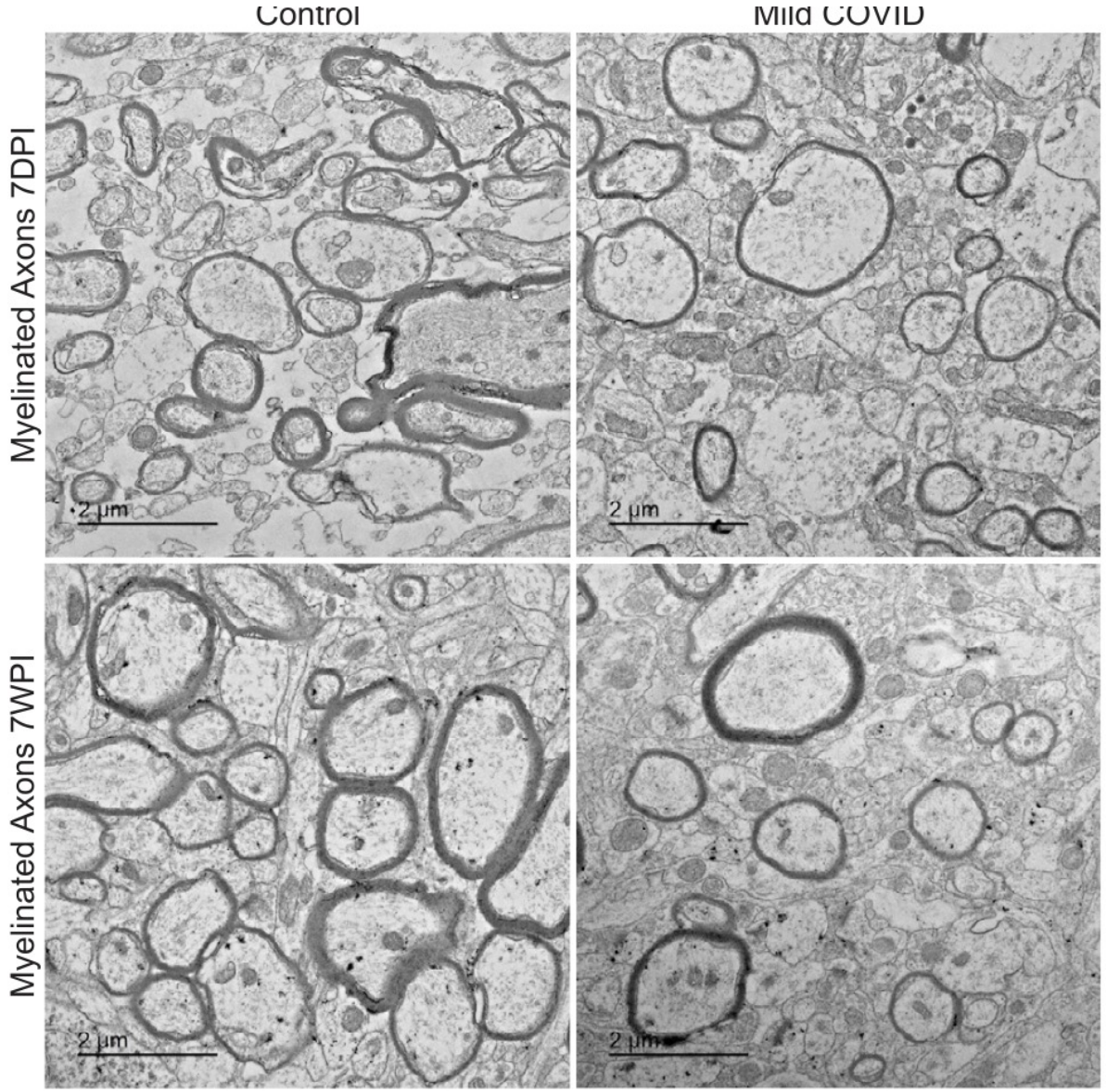
- Long Covid causes intense neuroinflammation
- Damage to oligodendrocytes (cells that make myelin) resulting in damage to the subcortical white matter
- When myelin is damaged nerve impulses slow or even stop
- The Hippocampus is damaged. "The Atlas of the Mind"





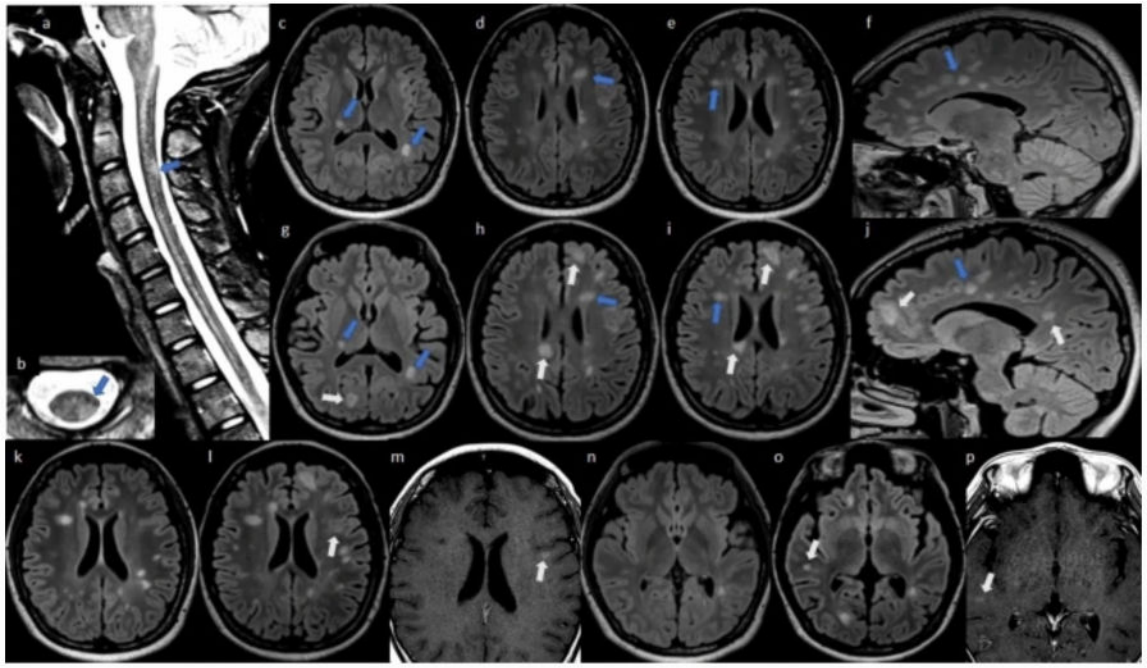
(EM) images at the level of the cingulum of the corpus callosum in cross-section for (G and H). Myelinated axons evident as electron-dense myelin sheaths encircling axons, viewed in X-section

Myelin modulates the speed of neural impulse conduction and provides metabolic support to axons and exhibits adaptive plasticity; even small changes in myelination can exert profound effects on neural circuit dynamics and consequently on cognitive function



COVID-19 mRNA vaccination leading to CNS inflammation: a case series

- 7 cases
- 4 had a h/o of MS but had been stable for years
- 3 were new onset
- Within one to 21 days of either the first (n = 2) or second (n = 5) vaccine dose, these patients developed neurologic symptoms and MRI findings consistent with active CNS demyelination of the optic nerve, brain, and/or spinal cord. Symptoms included visual loss, dysmetria, gait instability, paresthesias, sphincter disturbance, and limb weakness



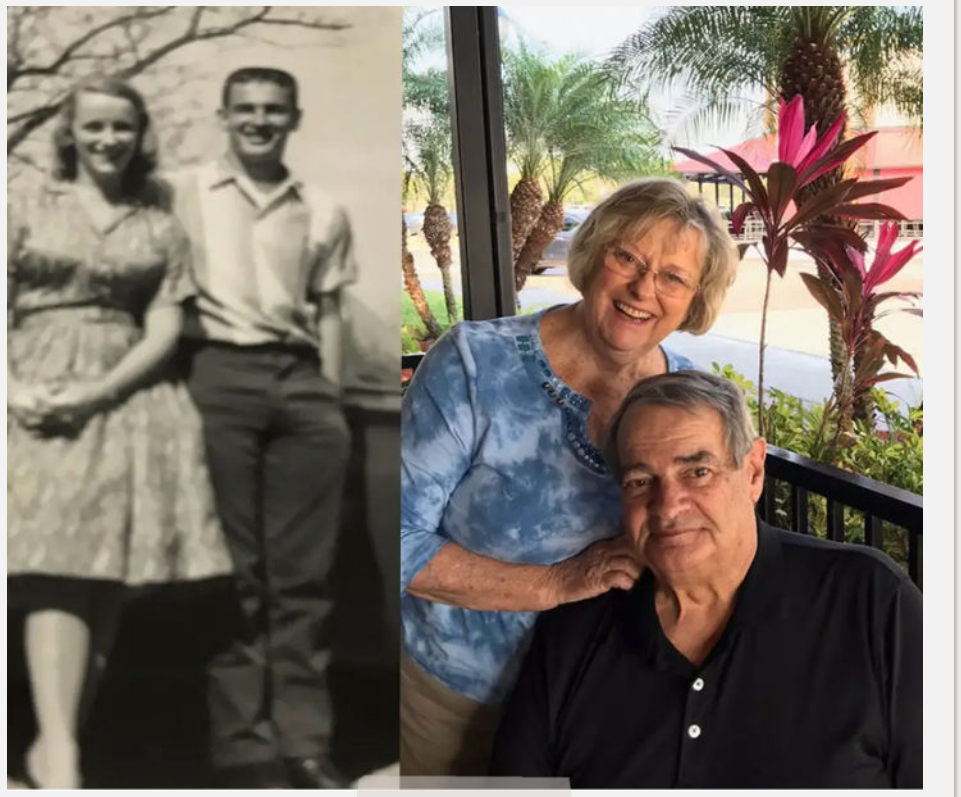
- COVID-19 mRNA vaccination leading to CNS inflammation: a case series Khayat Khoei M et al Journal of Neurology volume 269, pages 1093–1106 (2022)

SARS-CoV-2 spike S1 subunit induces neuroinflammatory, microglial and behavioral sickness responses: Evidence of PAMP-like properties Frank M et al Brain Behavior Immun Feb 2022

- Direct exposure of microglia to S1 resulted in high levels of inflammatory cytokines and microglial cell activation
- Their findings suggest that Spike protein independently acts as a pathogen to induce a neuroinflammatory process
- S1 easily crosses the BBB and is carried by exosomes

Exosomes and PASC: What are They Carrying to Distant places?

- Exosomes are found in every bodily fluid and in the power of our breath
- Exosomes are tiny vesicles secreted from cells that participate in intercellular communication & waste management.
- Did you ever wonder why a couple married X 50 years looks more like brother and sister vs their features long ago?
- Or why some people look like their dog?
- There is shared genetic expression through the power of our breath
- Exosomes in PASC may be a problem



Bioactive DNA from extracellular vesicles and particles Malkin E et al Cell Death and Disease 2020

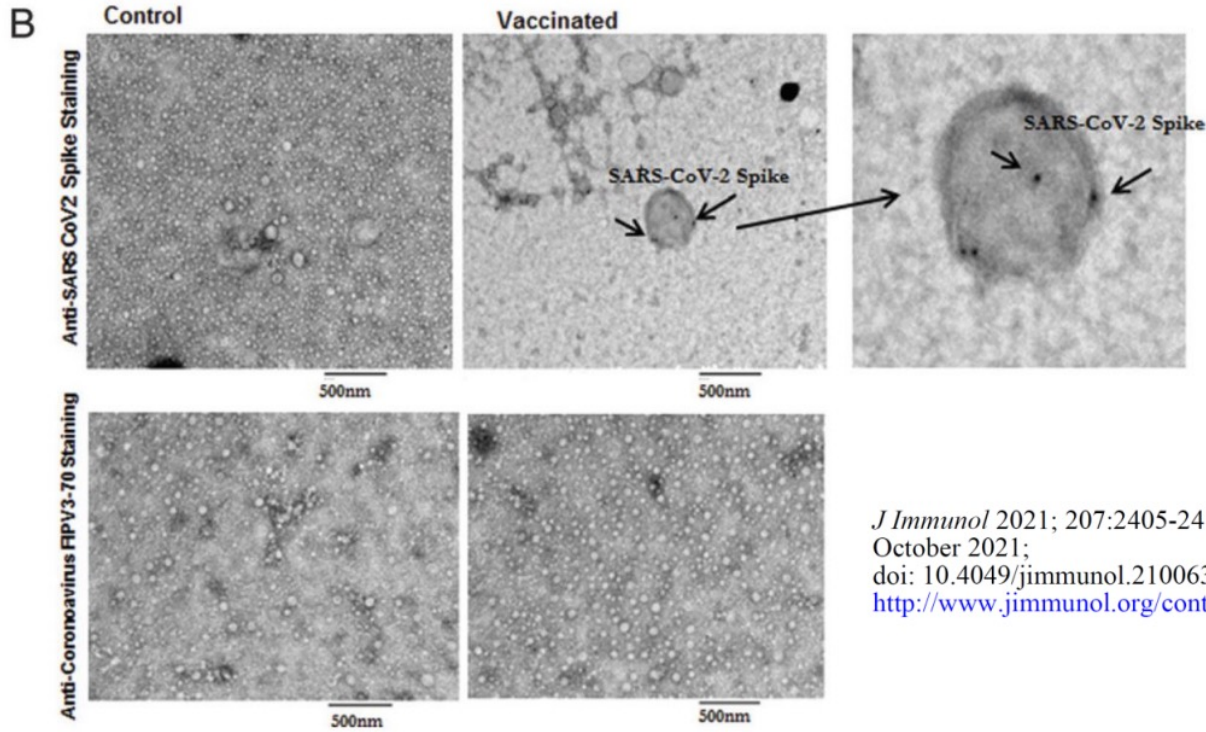
Isolation, characterization and detection of breath-derived extracellular vesicles Dobhi G et al Scientific Reports (2020)

Cutting Edge

The Journal of Immunology

Cutting Edge: Circulating Exosomes with COVID Spike Protein Are Induced by BNT162b2 (Pfizer–BioNTech) Vaccination prior to Development of Antibodies: A Novel Mechanism for Immune Activation by mRNA Vaccines

Sandhya Bansal,* Sudhir Perincheri,† Timothy Fleming,* Christin Poulson,* Brian Tiffany,* Ross M. Bremner,* and Thalachallour Mohanakumar*



J Immunol 2021; 207:2405-2410; Prepublished online 15 October 2021;
doi: 10.4049/jimmunol.2100637
http://www.jimmunol.org/content/207/10/2405

FIGURE 1. (**A**) Representative NanoSight image for exosomes from vaccinated individuals with mean and median sizes (black thin line in the graph indicates the three measurements of the same sample, and red line is the average of all three lines). (**B**) Transmission electron microscopy images of SARS-CoV-2 spike Ag on exosomes from control exosomes from control and vaccinated individuals. Arrows indicate SARS-CoV-2 spike-positive exosomes. Right side, third image is the zoomed image of positive exosome from vaccinated sample (original magnification x 50,000). We have used anti-coronavirus FIPV3-70 Ab as negative control for both the samples.

Neural Derived Exosomes and Mitochondrial damage in 46 Long Haulers

- High levels of two SARS-CoV-2 viral proteins– the nucleocapsid protein and the spike protein were found in the neural derived exosomes
- Mitochondria were damaged (numerous SARS-CoV-2 proteins interact with host mitochondrial proteins)
- Mitochondrial damage occurs in neurodegenerative disease
- Exosomes are pathogenic agents and biomarkers in Alzheimer's
- Exosomes can spread toxic proteins through prion activity and promote neurodegenerative disease

Figure 1

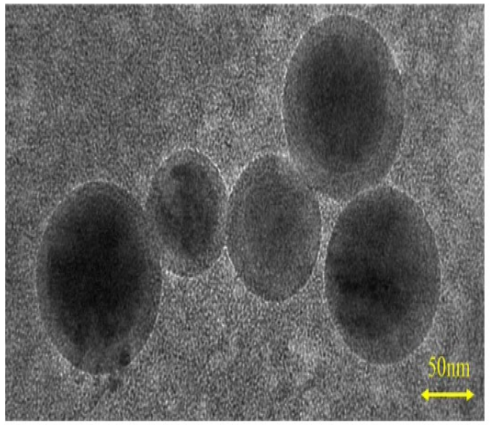


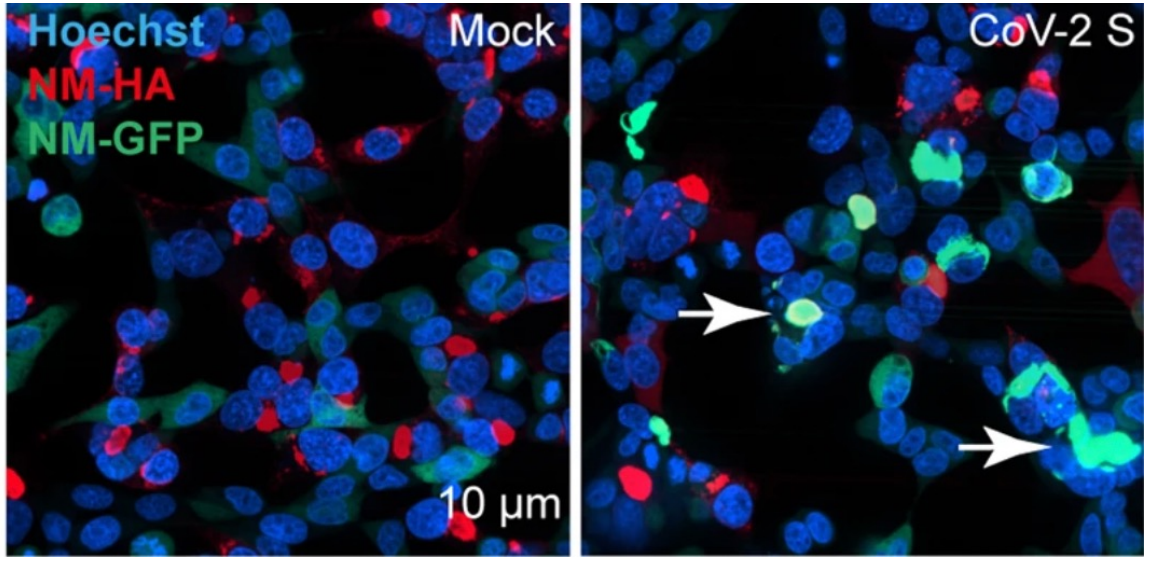
FIGURE 1. Identification of neuron-derived exosomes. Image showing the double-layer membrane structure of exosomes, with a scale bar of 50 nm.

SARS-CoV-2 and Mitochondrial Proteins in Neural-Derived Exosomes of COVID-19 Annals of Neurology March 2022

Discovery Of Novel Markers of Cognitive Decline Using Neural Derived Exosomes Zhong J et al Frontiers in Aging Neuroscience August 2021 (credit photo)

Spike Protein Propagating the Spreading of Tau Through Exosomes from the German Center for Neurodegenerative disease 2021

- Two viral glycoproteins—**VSV-G and the SARS-CoV2 S1 spike**—dramatically boost the form & transfer prions and misfolded tau between cells via secretion of exosomes or direct cell to cell contact (see photo of donor cell culture: green blobs are prions forming after S1)
- **These mis-folded proteins self-propagate through the brain**
- They remind us “the spike protein itself can go rogue and cross the blood-brain barrier”



Highly efficient intercellular spreading of protein misfolding mediated by viral ligand-receptor interactions. Liu S Nat Commun. 2021 Oct 19;12(1):5739.

Propagation of Tau via Extracellular Vesicles Front Neurosci 2019

Evidence for Aerosol Transfer of SARS-CoV2-specific Humoral Immunity Kedl R, et al MedRx preprint April 2022

- They found droplet/**aerosolized antibody transfer** occurs between individuals, much like droplet/aerosolized virus particles can be exchanged by the same route
- * SARS-CoV-2-specific IgG in children living in vaccinated house holds vs the complete deficit of SARS-CoV-2-specific antibody in those in nonvaccinated homes

  * Does this suggest benefit of parental vaccination in reducing the risk of infection in the unvaccinated children in the same home?

  * Or is this evidence of shedding of spike protein in exosomes?

Indirect protection of children from SARS-CoV-2 infection through parental vaccination. Hayek A et al Science 2022

NEWS

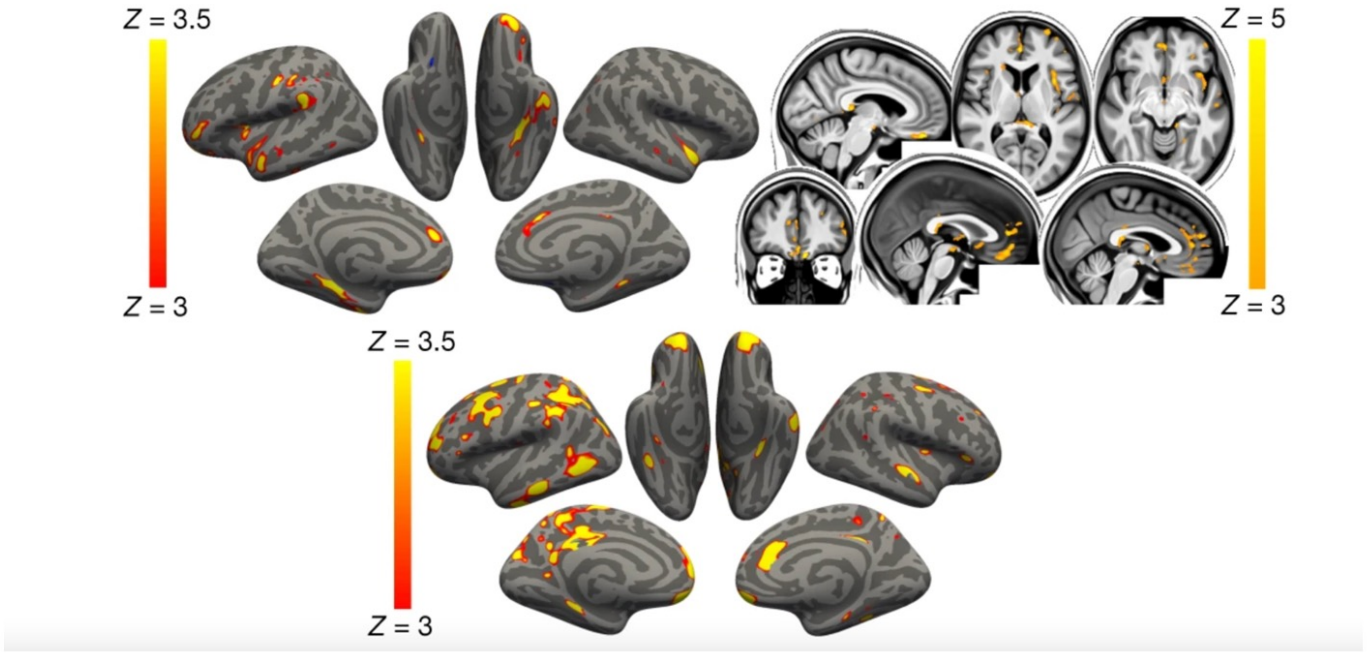
Alzheimer's and Long Covid, could they be related?

by: Brooklynn Norris, Stuart Price

Posted: Aug 13, 2022 / 02:23 PM CDT
Updated: Aug 13, 2022 / 02:23 PM CDT

UK Biobank study Grey matter Damage

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



Top, the main analysis shows that the strongest, localized reductions in grey matter thickness in the 401 infected participants compared with the 384 controls are bilaterally in the parahippocampal gyrus, anterior cingulate cortex and temporal pole, as well as in the left orbitofrontal cortex, insula and supramarginal gyrus.

- COVID patients showed a greater loss of grey matter in the lateral orbitofrontal cortex, temporal pole, para-hippocampal gyrus, anterior cingulate & and the olfactory nucleus
- More generalized brain atrophy post COVID was found
- Post COVID also showed on average larger cognitive decline between the two timepoints
- Because adults typically lose about 0.2 percent of their brain volume in regions related to memory every year, these findings translates to mental decline equivalent to **10 years of aging.**
- **Approximately 3% of patients with pneumonia associated with SARS-CoV-2 infection developed new-onset dementia, over a median period of 182 days !!!!! (Qureshi R et al 2022)**

Brain imaging before and after COVID-19 in UK Biobank Soojin, G et al Bmj Yale October 2021

- *“You know, if we don’t do something about Alzheimer’s in America, every single, solitary hospital bed that exists in America — as the nurses can tell you — every single one will be occupied in the next 15 years with an Alzheimer’s patient — Every one.” President Biden June 2021*

Hundreds of Children Diagnosed With ‘Childhood Dementia’ – Doctors Baffled

Fact checked

August 17, 2022 Baxter Dmitry News, US 20 Comments

Childhood dementia: It's time to face it

Join the FACE it awareness campaign.

What to know about 'childhood Alzheimer's'

Causes | Symptoms | Treatment | Risk factors | Outlook | Summary

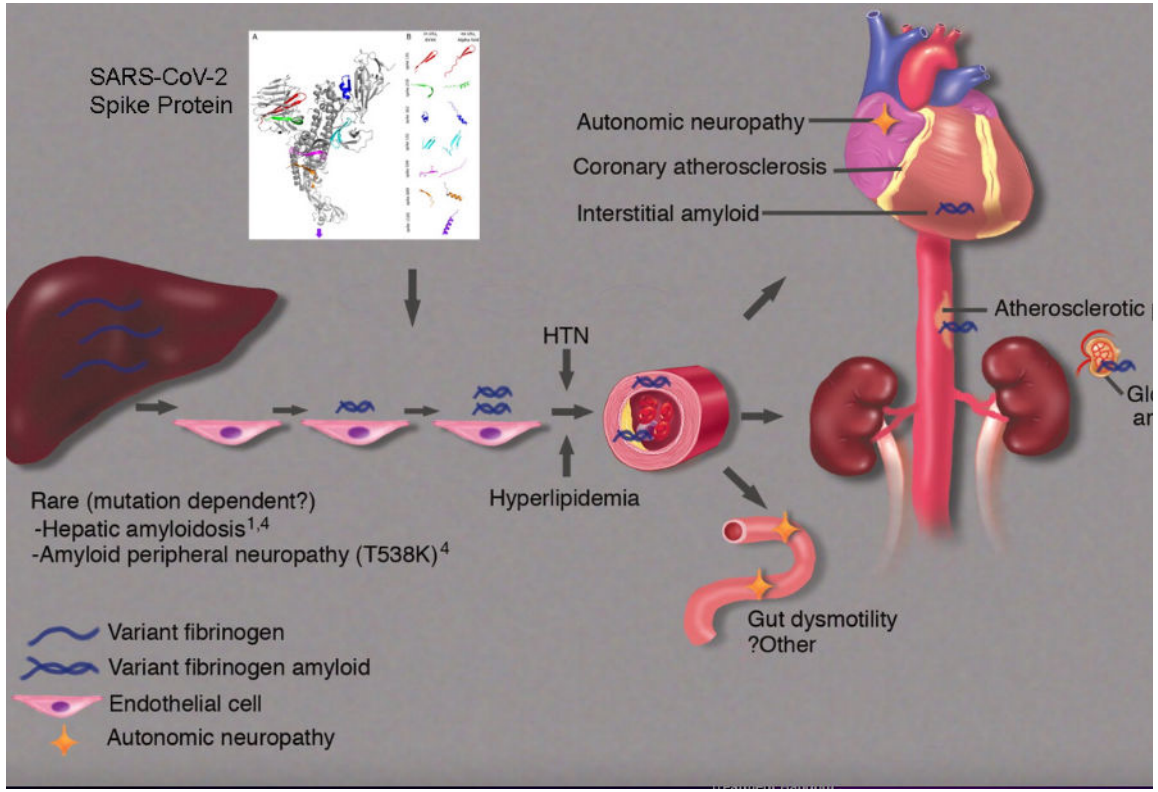
Jerusalem Post > Health & Wellness

Could an Alzheimer's drug help children with autism?

What is Amyloid?

- **Amyloid** is an abnormal protein that is produced in your bone marrow and can be deposited in any tissue or organ including the brain , heart , liver, pancreas, blood vessels)
- Amyloid has been found in micro-clots in LC
- Amyloid and tau are 2 proteins central to the pathology of Alzheimer's disease.
- They act as prions that spread through tissue like an infection by forcing normal proteins to adopt the same misfolded shape

- Aβ and tau prion-like activities decline with longevity in the Alzheimer's disease human brain Condello C et al Science Translational Medicine Vol 11 2021



Alzheimer's Disease and SARS COV 2: shared pathological mechanisms

- Spike protein binds to ACE 2
- AC2 is neuroprotective
- Decreased ACE2 activity is associated with increased activity in TGF-beta which fuels amyloid production & hyperphosphorylation of tau which results are associated with NDG
- Biomarkers of neurodegeneration in the CSF are increased in COVID-19 patients (amyloid, tau)
- Exosomes are carrying viral fragments (ORF 6 , 10, mRNA, spike protein) which can fuel protein misfolding
- Excess amyloid formation causes micro-clotting with resistant fibrin- amyloid clots

Highly efficient intercellular spreading of protein misfolding mediated by viral ligand-receptor interactions. Liu S Nat Commun. 2021 Oct 19;12(1):5739.

Can SARS-CoV-2 Infection Exacerbate Alzheimer's Disease? An Overview of Shared Risk Factors and Pathogenetic Mechanisms Villa, C et al J. Pers. Med. 2022

A central role for amyloid fibrin microclots in long COVID/PASC: origins and therapeutic implications Leo. D et a; Biochemical Journal Feb 2022

Neurotoxic amyloidogenic peptides in the proteome of SARS COV 2: Will Summon Neurodegenerative Disease

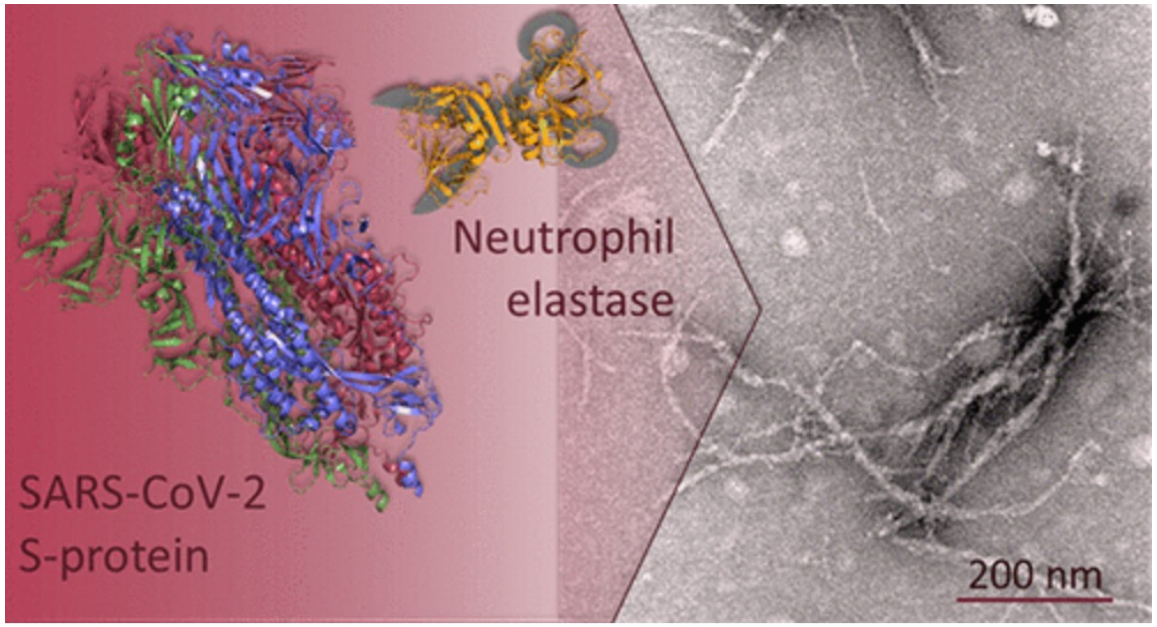
- In this study, by Charmley et al, they found two highly amyloidogenic proteins of SARS COV 2 in the ORF 6 and 10
- **This pathology could be implicated in neuro Long COVID and could represent future risk of neurodegenerative disease**
- Amyloid can prompt other proteins to misfold in the brain via prion mechanisms

Study: Neurotoxic Amyloidogenic Peptides Identified in the Proteome of SARS-COV2: Potential Implications for Neurological Symptoms in COVID-19. Image Credit: Kateryna Kon / Shutterstock.com

Neurotoxic amyloidogenic peptides in the proteome of SARS COV 2: Potential for neurological symptoms in COVID 19, Nature Communications Charnley M et al March 2022

Misfolding of Brain Proteins Triggering Neurodegenerative Diseases Westaway D : Biology, Health and Medicine Dec 2021

Presence of a SARS-COV-2 protein enhances Amyloid Formation of Serum Amyloid A J Phys Chem B 2021



Amyloidogenesis of SARS-CoV-2 Spike Protein Nystrom S et al May 2022 Journal of American Chemical Society

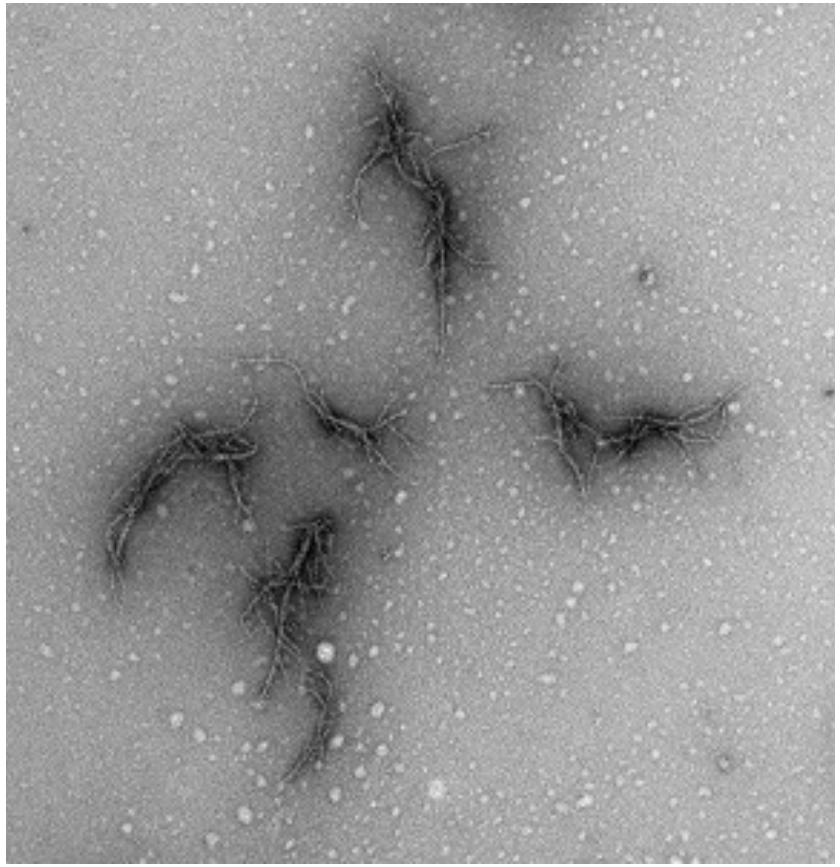
- Combining the **S-protein** with protease neutrophil elastase **formed amyloid-like fibrils** which potentially can cause neurological symptoms and disturbed blood coagulation in patients with COVID-19

- Neutrophil elastase is an enzyme released by WBC's and overproduced during high levels of inflammation

- The research suggests that the immune system's interaction with spike protein may be leading to the production of these misfolded proteins

Picture of amyloid from the SARS-CoV-2 virus' spike protein, seen using an electron microscope

- *"We have never seen such perfect, but scary, fibrils as these ones from the amyloid-producing SARS-CoV-2 spike protein"*

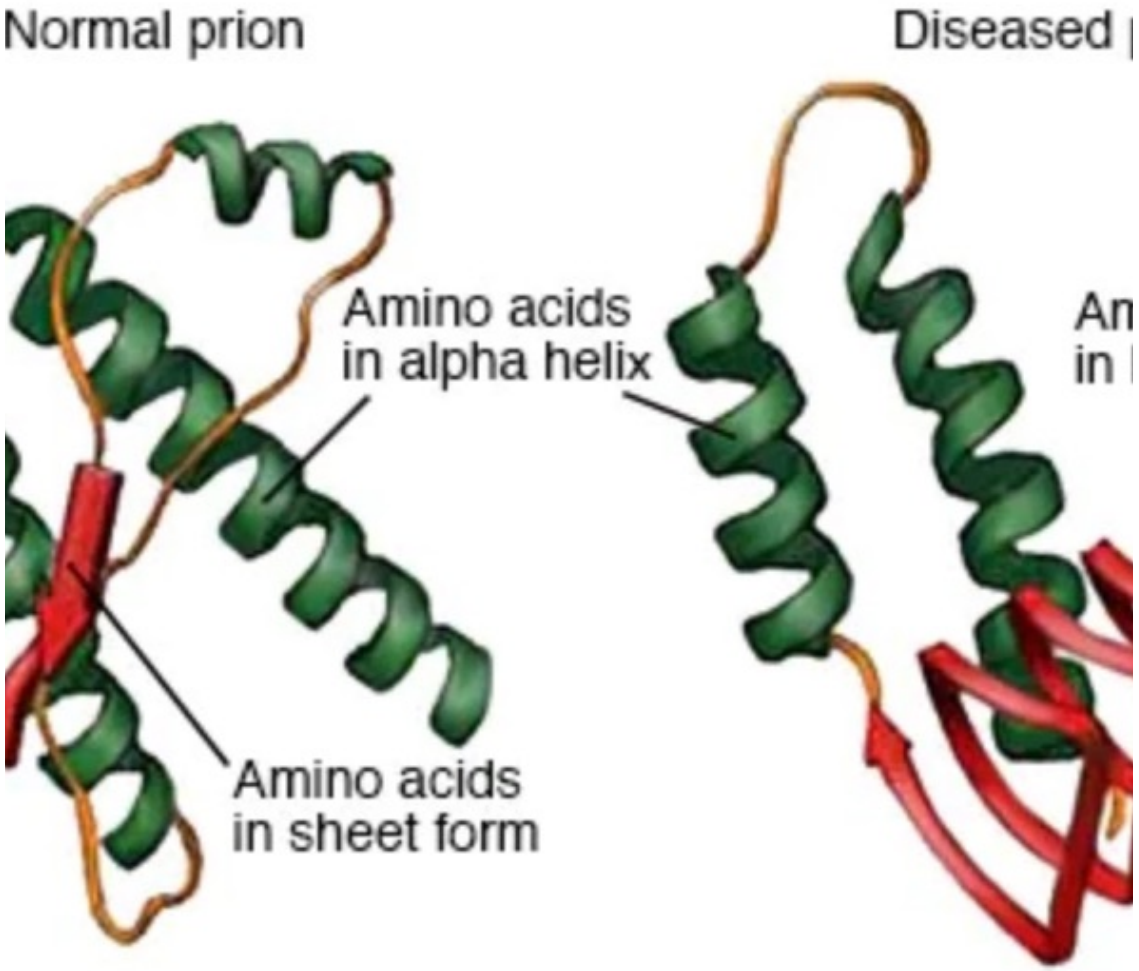


Amyloidogenesis of SARS-CoV-2 Spike Protein Nystrom S et al May 2022 Journal of American Chemical Society

Worse Than the Disease? Reviewing Some Possible Unintended Consequences of the mRNA Vaccines Against COVID-19 S Seneff 2021

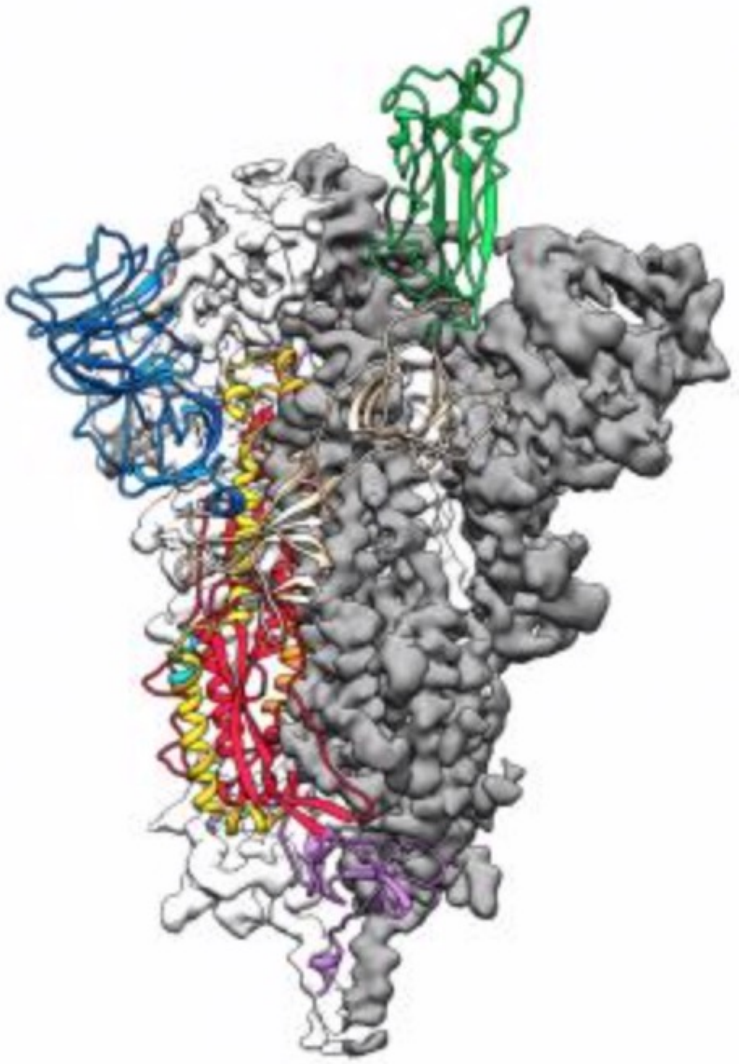
What Are Prions?

- A prion is a type of protein that can cause disease by triggering normally healthy proteins in the brain to fold abnormally
- Only prion proteins can mis-fold to produce prions and, again, these prions are special in that they are resistant to proteolysis



Prion Activation

- SARS-CoV-2 is the only coronavirus with a prion-like domain found in the receptor-binding domain of the S1 region of the spike protein.
- Prions have important functional roles in viral adhesion and entry

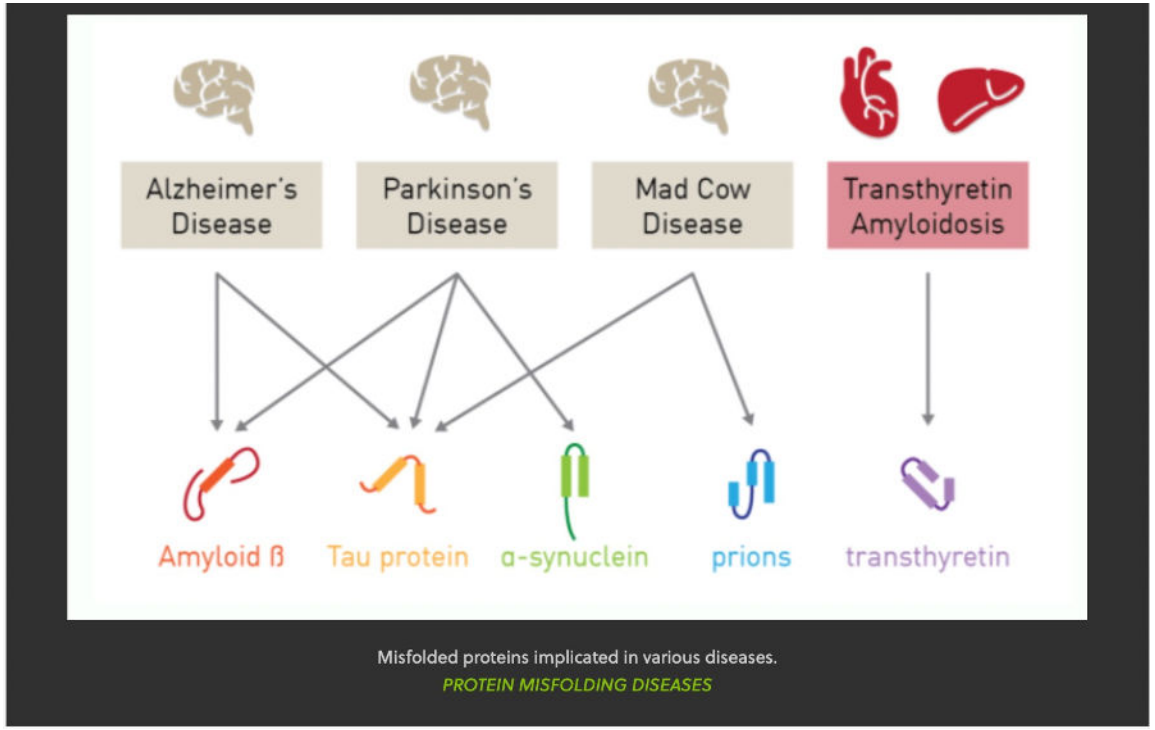


SARS-CoV-2 Prion-Like Domains in Spike Proteins Enable Higher Affinity to ACE2 Tetz George et al, Human Microbiology Institute March 2020

Visual credit UT Austin McLellan Lab

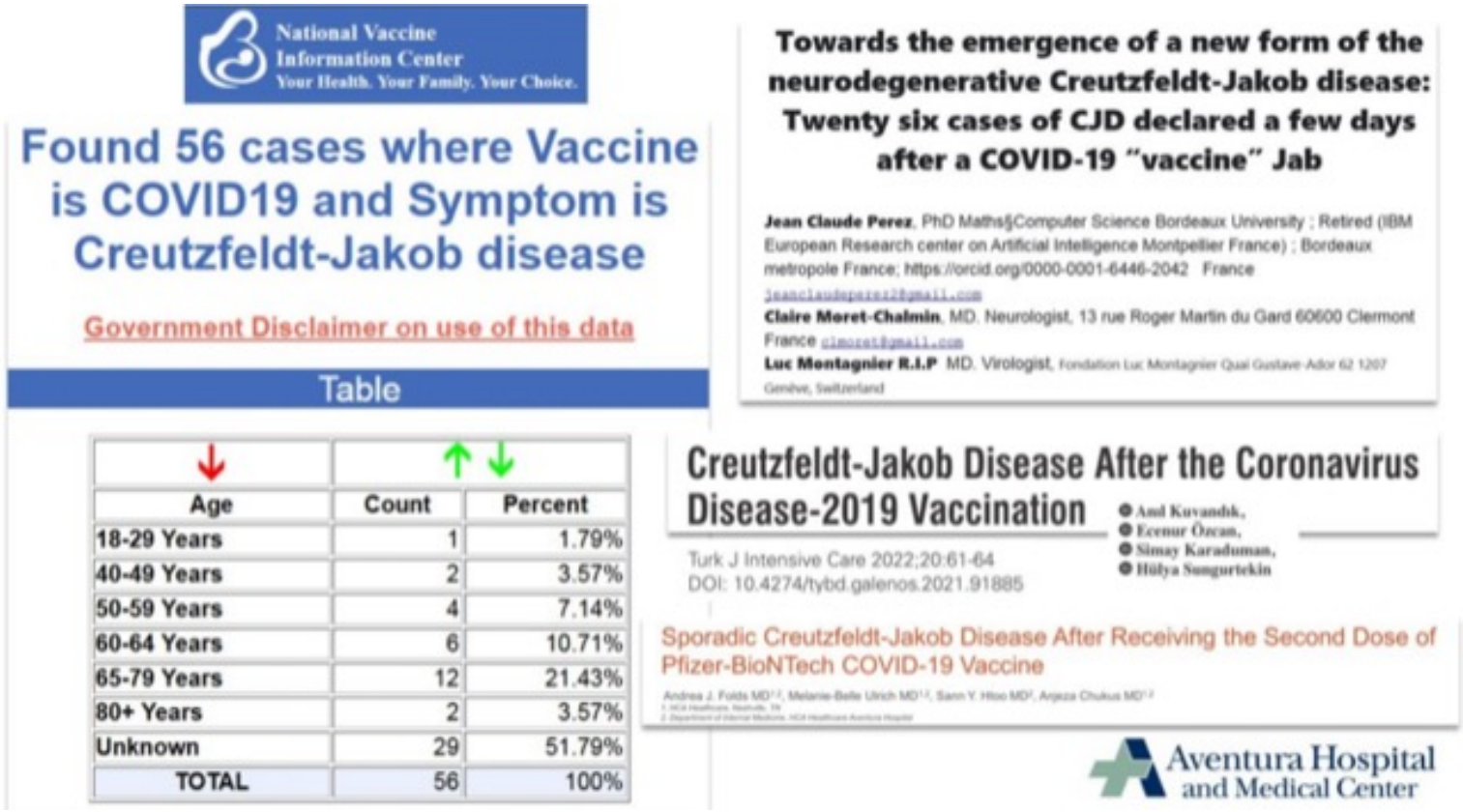
What Happens When Protein Folding Goes Wrong in the Brain? Prion Disease

- In neurodegenerative diseases, a small group of proteins can be incorrectly folded and then cluster together and then propagate their own formation by taking new, normally folded proteins and disrupting their structure to be misfolded
- These are collectively referred to as prion diseases
- Many neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, Lewy Body Dementia, ALS and even MS are thought to be a result of prion-like activity.
- Prions travel from cell to cell and self-propagate



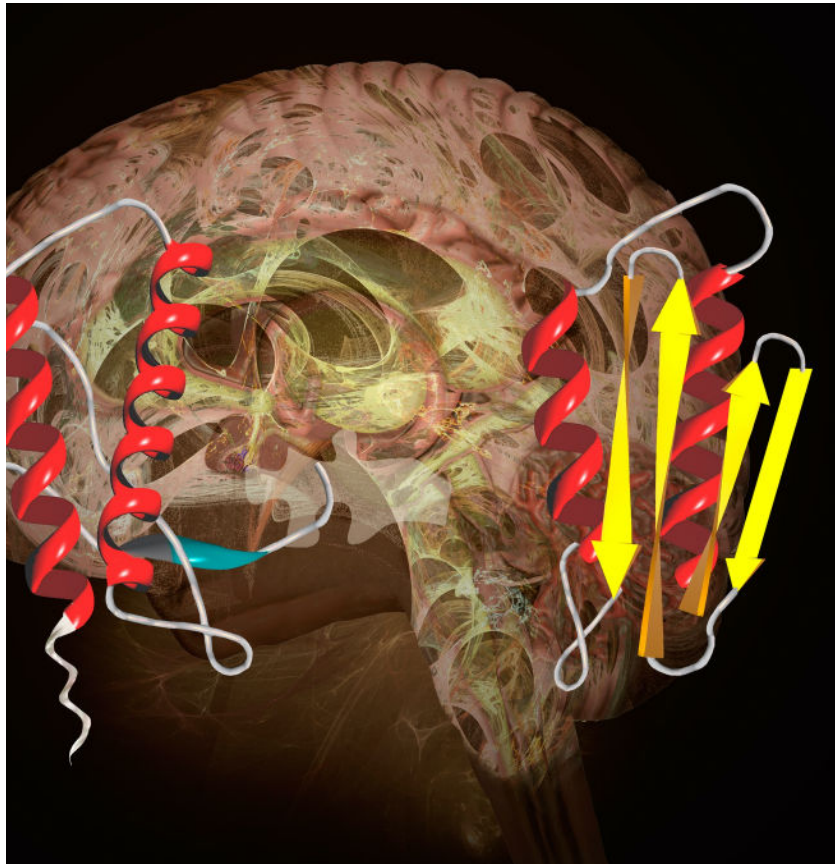
- Misfolding of Brain Proteins Triggering Neurodegenerative Diseases Westaway D : Biology, Health and Medicine Dec 2021
- Is MS a Transmissible Protein Misfolding Disorder? ACTRIMS 2018 Tsutsui S University of Calgary

CJD is a fatal prion disease that can be very difficult to diagnose with vague initial symptoms (memory, personality change, vision issues, balance) Usually death within 2 years although some have slow progression and subclinical disease for years



Towards the emergence of a new form of the neurodegenerative Creutzfeldt-Jakob disease: Twenty -six cases of CJD declared a few days after a COVID-19 "vaccine" Montagnier L et al Research Gate Preprint June 2022

- A preprint French study show the emergence of a new type/ very aggressive and progressive form of sporadic CJD post vaccination
- They conducted two complementary methods of prion analysis and found prions in all post vaccine , all variants except the Omicron variant
- 26 CJD cases post COVID-19 vaccines were studied
- These cases were very rapid in onset and aggressive (symptoms appearing within 11.38 days of being vaccinated and death within 4-5 months with 8 patients succumbing to 'sudden death'



- COVID-19 RNA Based Vaccines and the Risk of Prion Disease Classen B Microbiology & Infectious Disease 2021
- SARS-CoV-2 Spike Protein in the Pathogenesis of Prion-like Diseases Seneff S et al Athorea August 2022

Movement Disorders

- One study showed showed that patients after COVID and after vaccines, had profound vibrations and tremors
- After COVID or the vaccine some have new onset or worsening PKD or new movement disorders

Internal Tremors and Vibration Symptoms Among People with Post-Acute Sequelae of SARS-CoV-2: A narrative review of patient reports Preprint 2021

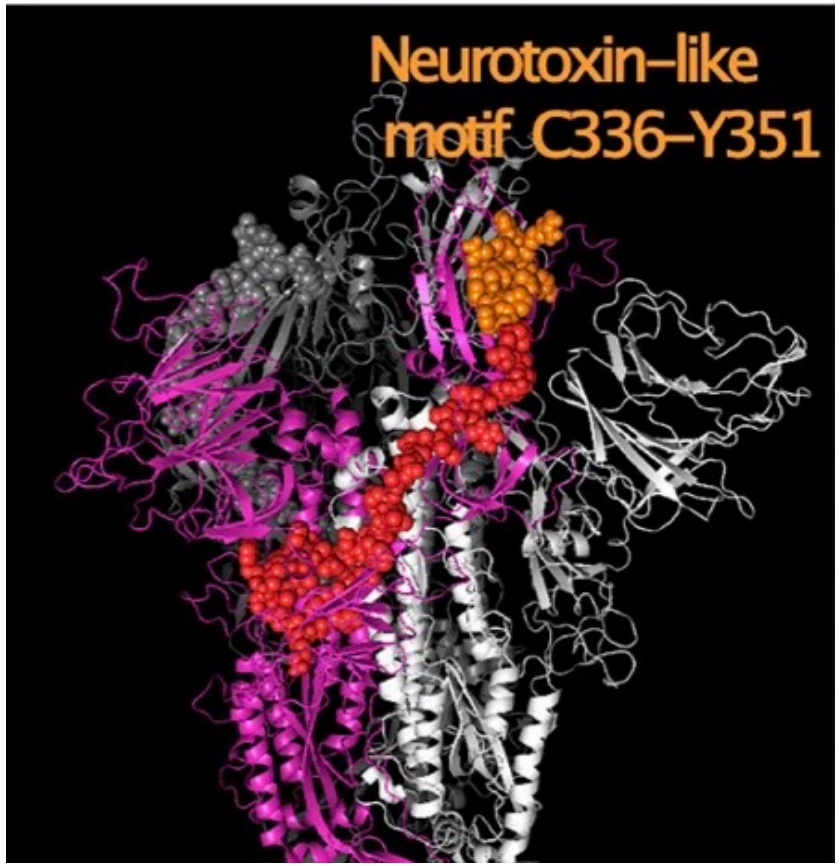
SARS-CoV-2 Proteins Interact with Alpha Synuclein and Induce Lewy Body-like Pathology In Vitro Wu Z et al Int J Mol Sci. 2022 Mar; 23 .

Cloud generated from Survivor Corps Facebook comments in response to poll related to vibrations, , and neuropathic pain

Post Vax Movement Disorder

The Fourth Horseman: A Neurotoxin

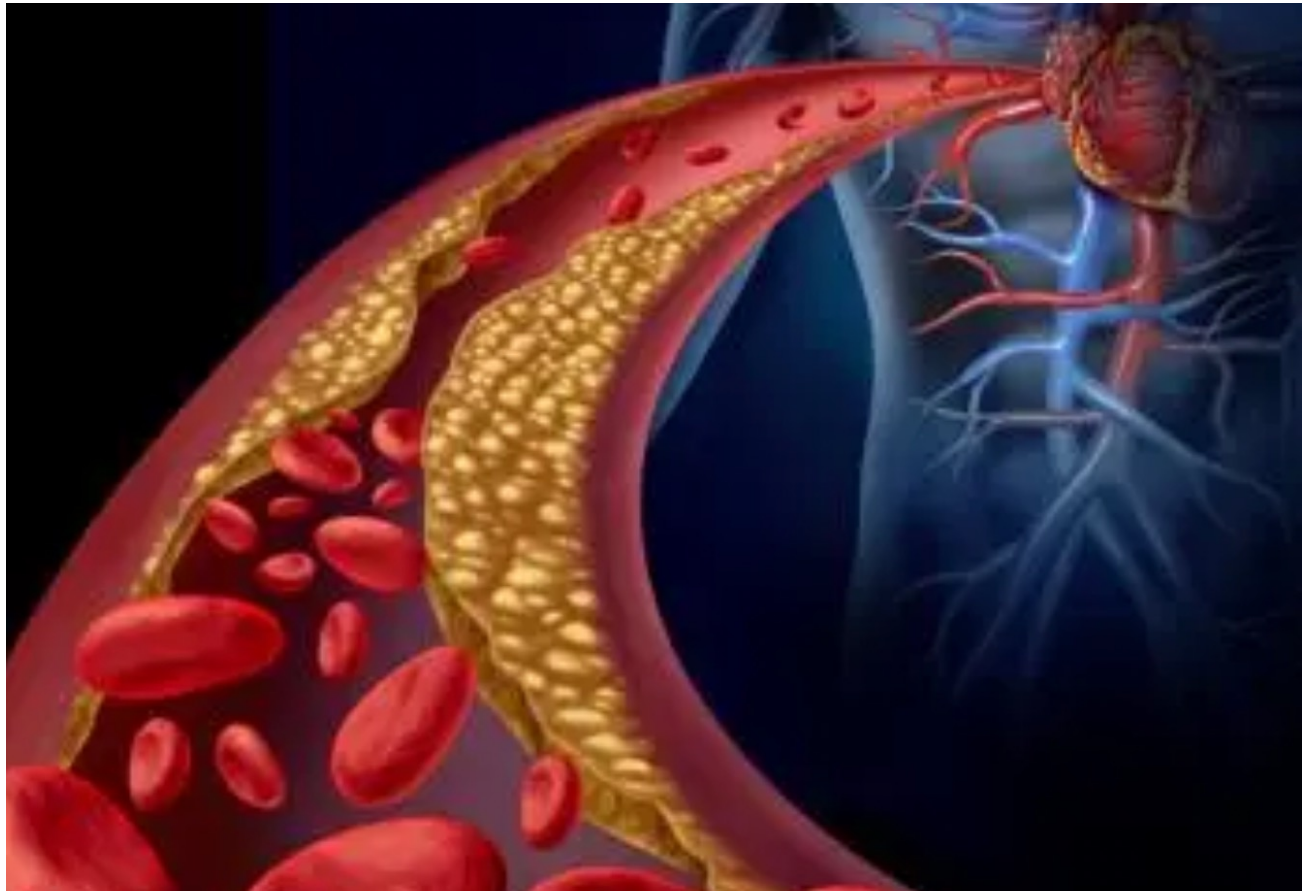
- In the spike protein motif, a viral super antigen complex and neurotoxin were found
- The neurotoxin is homologous to alpha-neurotoxin motifs from snake venom**.**
- Will spike protein have direct neurotoxic activity and contribute to the neurological symptoms?
- The authors propose that with intense antiviral immune response, SARS-CoV-2 (spike) persistence and repeated viral exposure this all may lead to a maladapted immune responses that cross-react with autoantigens leading to autoimmune disease



- Multisystem Inflammatory Syndrome in Children and Long COVID: The SARS-CoV-2 Viral Superantigen Hypothesis Frontiers of Immunology July 2022

Vascular disease and neurodegeneration: advancing together The Fifth Horseman

- Vascular risk factors and vascular disease enhance the risk of neurodegenerative disease and is linked to higher amyloid (JAMA 2017) with or without APOE 4
- Vascular disease fuels other NDG diseases
- Vascular inflammation and micro-clotting are key mechanisms in Long COVID



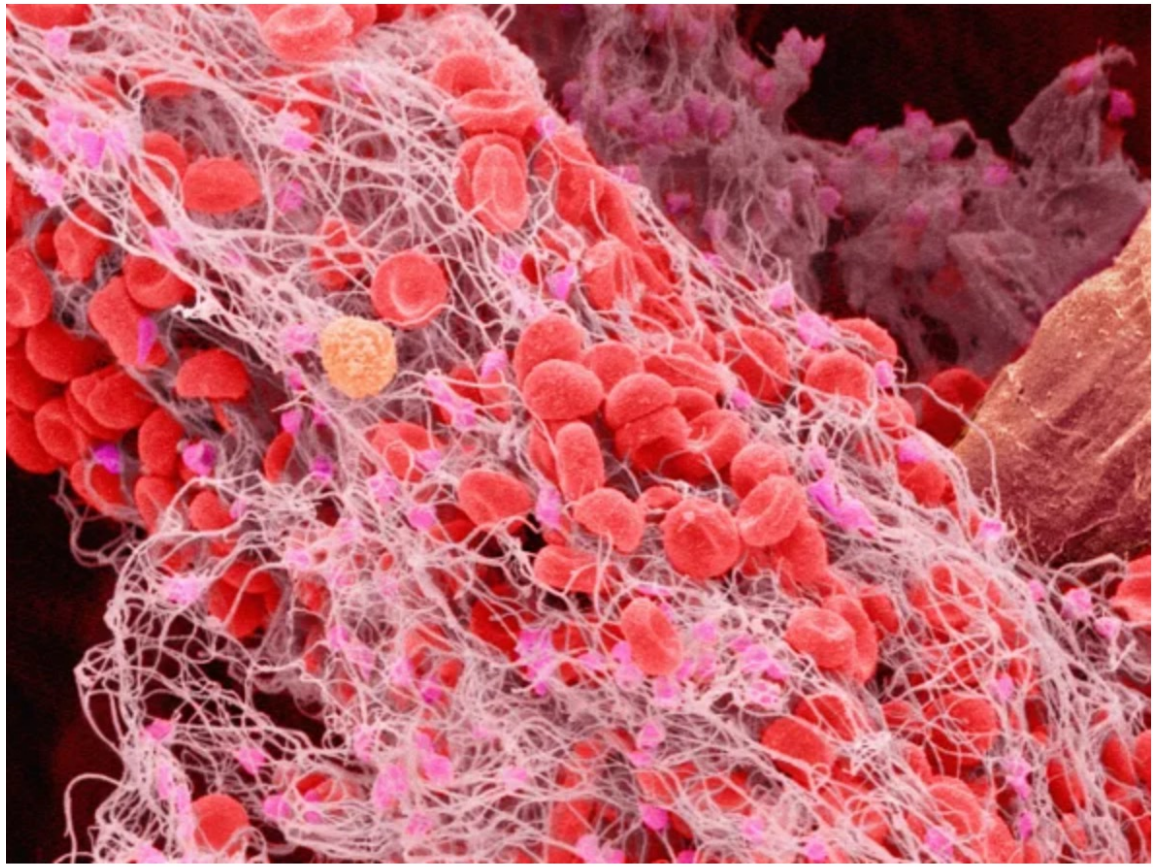
Association Between Midlife Vascular Risk Factors and Estimated Brain Amyloid Deposition Gottesman R et al JAMA 2017

The contribution of vascular risk factors in neurodegenerative disorders: from mild cognitive impairment to Alzheimer's disease Cheng Y et al Alzheimer's Research 2020

Associations between Cerebrovascular Risk Factors and Parkinson Disease Kummer B et al Ann Neurology 2019

Long COVID and Clotting

- Dr Resia Pretorius in South Africa, found significant micro-clot formation in people with long COVID including VAX injured
- The clots can reduce the supply of oxygen and nutrients to different parts of the body, & cause brain fog and fatigue
- Clots themselves have been found to be immunogenic & can stimulate the **production of antibodies** and give rise to autoimmune phenomena
- The amyloid/ fibrin clots are tough to breakdown

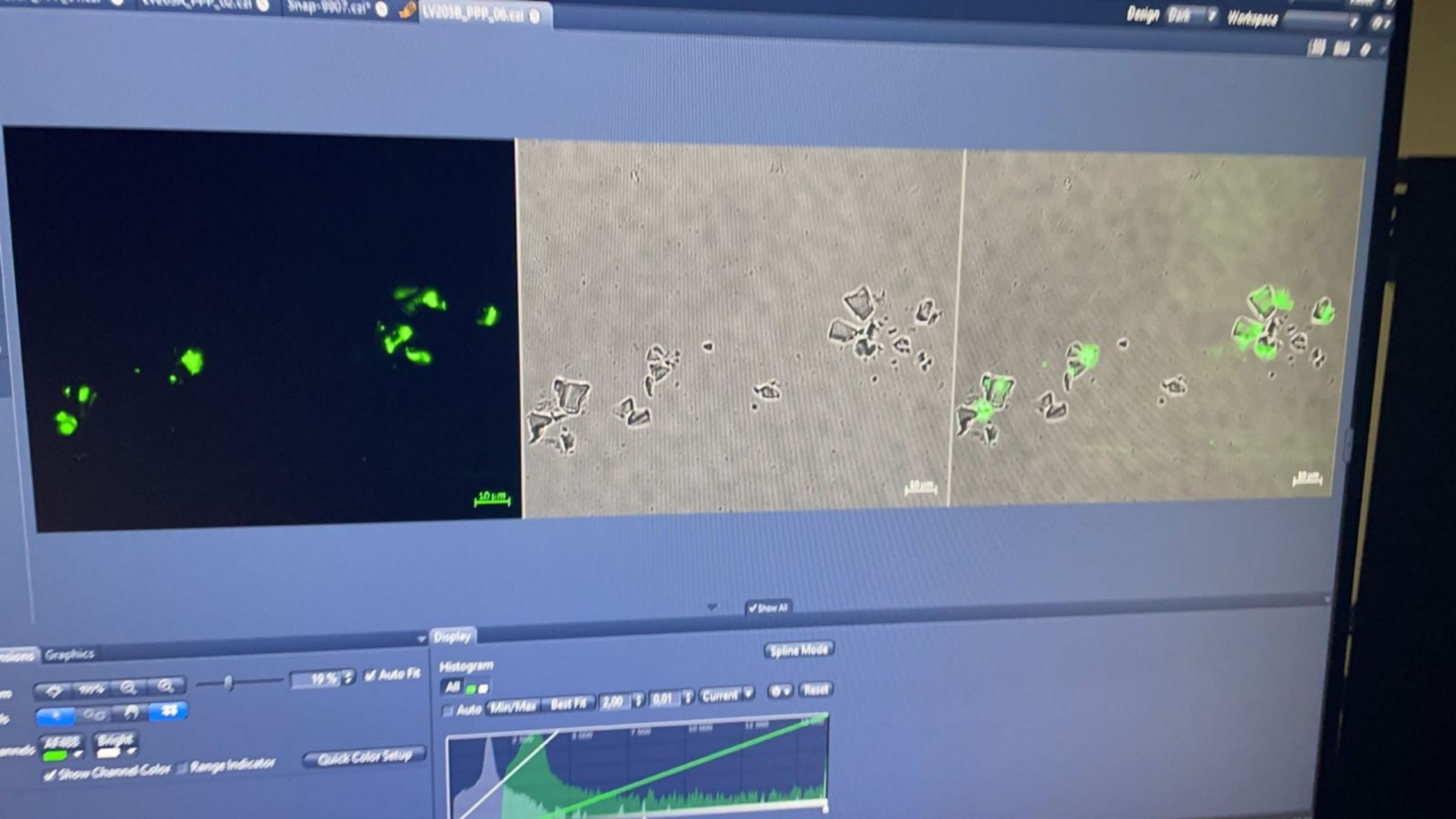


Scanning electron micrograph of a blood clot in human blood. Credit: Getty Images

Could microclots help explain the mystery of long Covid? Resia Pretorius 2022 The Guardian

Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin Pretorius R Caridovas Diabetol 2021

Network medicine links SARS-CoV-2/COVID-19 infection to brain micro vascular injury and neuroinflammation in dementia-like cognitive impairment Alzheimers and Therapeutics 2021



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Design
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Histogram
Spline Mode
All
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0,01
Current
Reset
19 %
Auto Fit
AF488
Bright
Show Channel Color
Range Indicator
Quick Color Setup

Damage to DNA can fuel Neurodegenerative Disease and More

- Spike protein localizes in the nucleus & impairs our cells' ability to repair DNA by Impeding 2 key DNA repair proteins, BRCA1 and 53BP1 recruitment to the damage site
- Segments of SARS-CoV-2 Viral RNA can become integrated into human genomic DNA.
- 53BP1 is called the Guardian of the Genome

SARS-CoV-2 Spike Impairs DNA Damage Repair and Inhibits V(D)J Recombination In Vitro Jiang Hu et al : Viruses 2021 Oct 13;13(10):2056.

Intracellular Reverse Transcription of Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line, Alden et al Jan 2022 Current Issues of Biology

Advanced Senescence

- Advanced senescence may well be one of the many reasons why older patients, especially those who are frail and/or who have underlying medical problems, are most susceptible to COVID
- Senescent cells trigger inflammation and immune dysregulation
- Numerous studies suggest S1 drives senescence
- Advanced senescence is linked to NDG disease

SARS-CoV-2 Spike Protein Induces Paracrine Senescence and Leukocyte Adhesion in Endothelial Cells Meyer, K et al ASM Journals Journal of Virology Vol. 95, No. 17 August 2021

Where Do We Go From Here?

- We are facing an eponymous tidal wave and are standing in the path of a tsunami, the might of which has never been seen
- Never has humanity faced the health challenges that we are facing now and going forward
- Behind the veil that is lifting, is an approaching tsunami of neurodegenerative disease and other health problems inflicted upon humanity
- It seems, more important than ever to truly see the landscape in front of us and come together as one
- UBUNTU

References for Immune Dysregulation

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Spike Protein Crossing the BBB

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