Twitter Thread by Andrew Ewing

Andrew Ewing
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1/ Covid and the brain. I am updating my list of papers, which is extensive. But, in the meantime, here is a talk I gave recently, "What happens to the brain when we are on covid."
With links to references.

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Neurologic Conditions Associated with SARS-CoV-2 Infection

Disease entity	Presentation	Supportive Neurodiagnostic testing	Pathogenesis
Encephalopathy	Altered mental status	MRI: non-specific EEG: abnormal (slow) CSF: nl cells and Pro CSF SARS-CoV-2 RT-PCR: NEG	Multiple organ failure Hypoxemia Systemic Inflammation Endothelialitis
Encephalitis	Altered mental status and CNS dysfunction	MRI: non-specific (? WM changes) EEG: abnormal (slow, +focal) CSF: pleocytosis & elev. Pro CSF SARS-CoV-2 RT-PCR: NEG	CNS inflammation
Viral encephalitis	Altered mental status and CNS dysfunction	MRI: new abnormality EEG: abnormal (slow, ±focal) CSF: Pleocytosis and elev. Pro CSF SARS-CoV-2 RT-PCR: POS Brain Tissue: POS (Ag or RNA)	Brain parenchymal neuro-invasion
Viral meningitis	Headache, nuchal rigidity	MRI: meningeal enhancement, CSF: pleocytosis & elev. Pro CSF SARS-CoV-2 RT PCR: POS	Subarachnoid invasion
Stroke	Focal motor or sensory deficit	MRI: ischemia or bleed, abnormal coagulation factors, increased inflammatory markers	Coagulopathy

https://onlinelibrary.wiley.com/doi/epdf/10.1002/ana.25807

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https://t.co/i7jCFQvORw

Neurologic Conditions Associated with SARS-CoV-2 Infection

Disease entity	Presentation	Supportive Neurodiagnostic testing	Pathogenesis
Anosmia/ageusia	Olfactory or taste dysfunction	Abnormal smell/taste tests	? Peripheral vs central neuro-invasion
ADEM	Headache, acute neurologic symptoms	MRI: hyperintense FLAIR lesions with variable enhancement	Postinfectious
Guillain-Barre syndrome	Flaccid muscle weakness	CSF: increased protein, nl WBC CSF SARS-CoV-2 RT-PCR: NEG EMG/NCS: abnormal	Postinfectious
Muscle injury	Myalgia	CK elevated	Myopathy or myositis?

ADEM = acute disseminated encephalomyelitis; CNS = central nervous system; CK= creatinine kinase; CSF = cerebrospinal fluid; EEG = electroencephalogram; EMG = electromyogram; FLAIR = fluid-attenuated inversion recovery; MRI = magnetic resonance imaging; NCS = nerve conduction study; NEG = negative; POS = positive; pro = protein; RT-PCR = reverse transcriptase-polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus type 2; WBC = white blood cell; WM = white matter.

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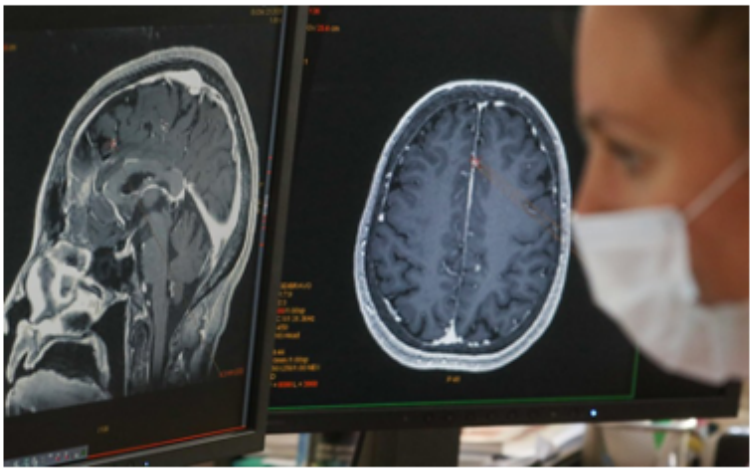
Nature news article July 2021

https://www.nature.com/articles/d41586-021-01693-6

- "How COVID-19 damages the brain is becoming clearer. New evidence suggests that the coronavirus's assault on the brain could be multipronged: it might attack certain brain cells directly, reduce blood flow to brain tissue or trigger production of immune molecules that can harm brain cells.
- Infection with the coronavirus SARS-CoV-2 can cause memory loss, strokes and other effects on the brain.
- With so many people affected — neurological symptoms appeared in 80% of the people hospitalized with COVID-19 who were surveyed in one study — researchers hope that the growing evidence base will point the way to better treatments.
- *"There is also growing evidence that some neurological symptoms and damage are the result of the body's own immune system overreacting and even misfiring after encountering the coronavirus."*



Chou, S. H.-Y. *et al. JAMA Netw. Open* **4**, e2112131 (2021).

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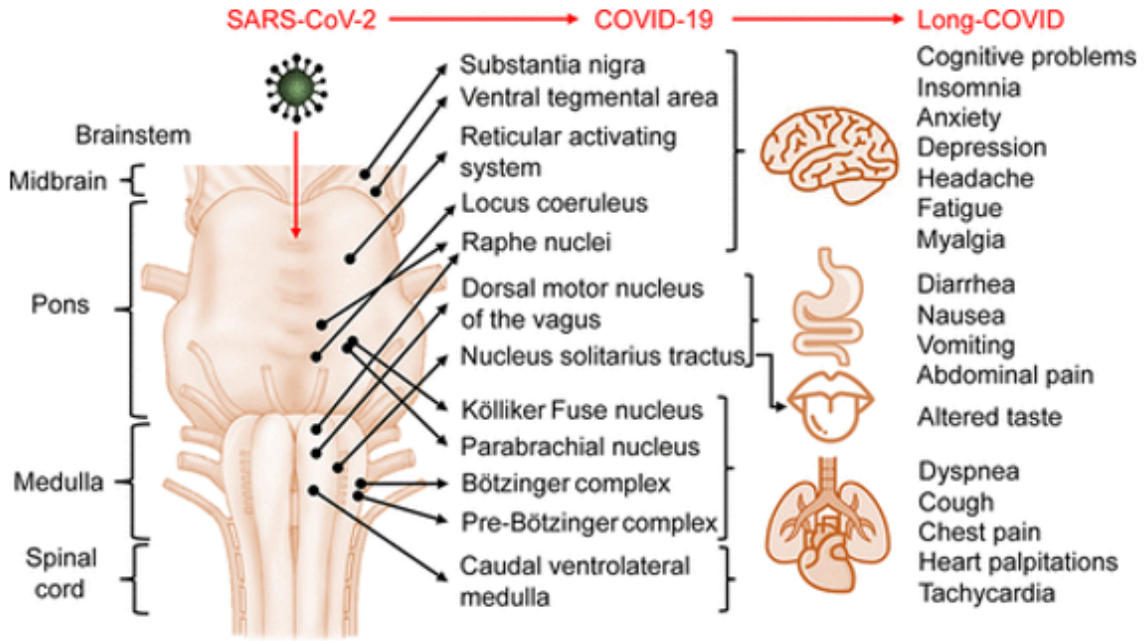
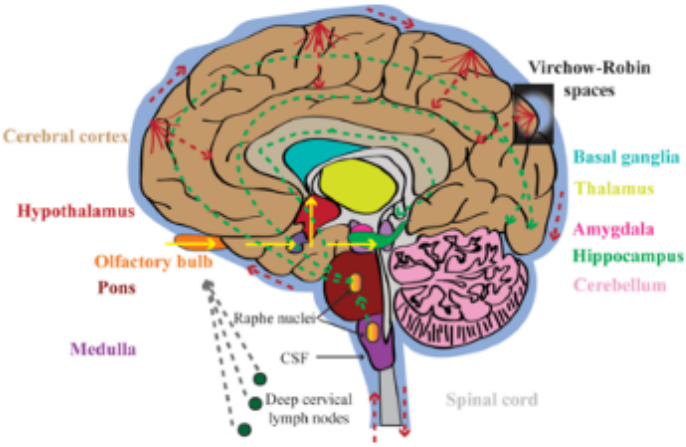
Mechanisms of SARS-CoV-2-induced brainstem dysfunction



Feb 2021, https://pubs.acs.org/doi/10.1021/acschemneuro.0c00793

7/

Possible dissemination routes of CNS infection with hCoVs



Route 1 (yellow solid arrows): olfactory nerve to olfactory cortex of temporal lobe to hippocampus to amygdala, or to hypothalamus
Route 2 (green dot arrows): via serotoninergic dorsal raphe system
Route 3 (red dot arrows): via hematogenous route and Virchow-Robin spaces
Route 4 (gray dot arrows): via lymphatic system.
***Route 5: Damaged blood vessels.**

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30174-2/fulltext

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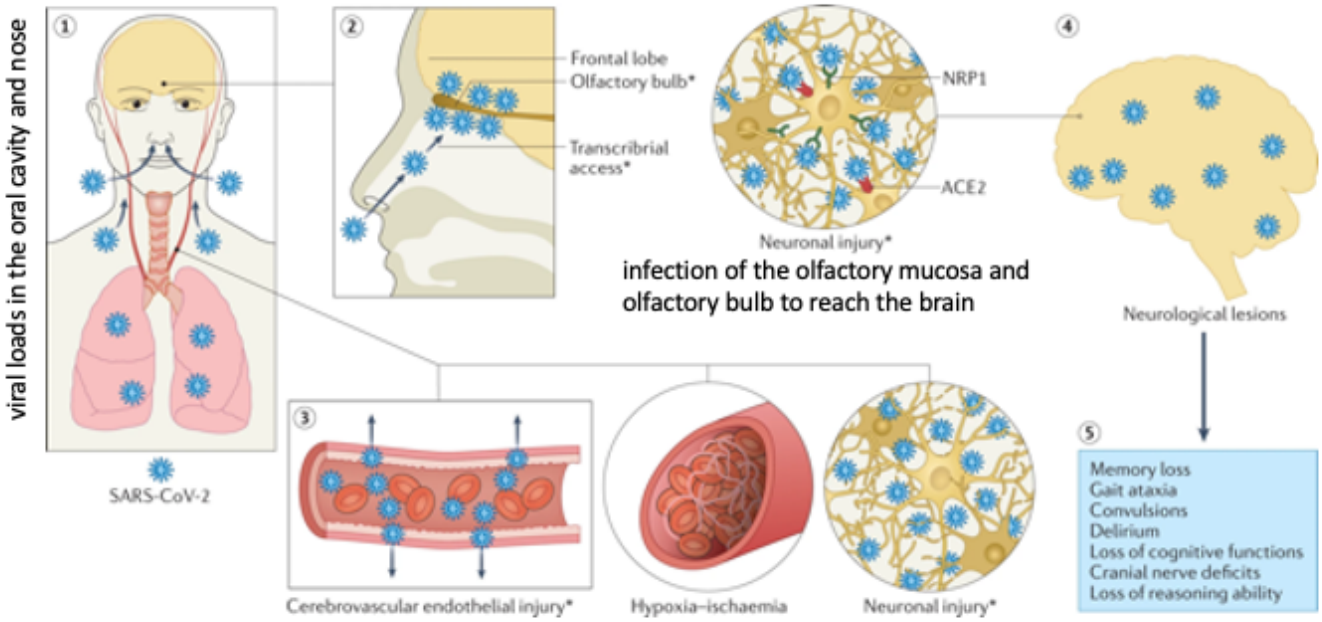
How does it get into and affect the brain?



Nature Reviews Neurology, November 2021, https://www.nature.com/articles/s41582-021-00593-7

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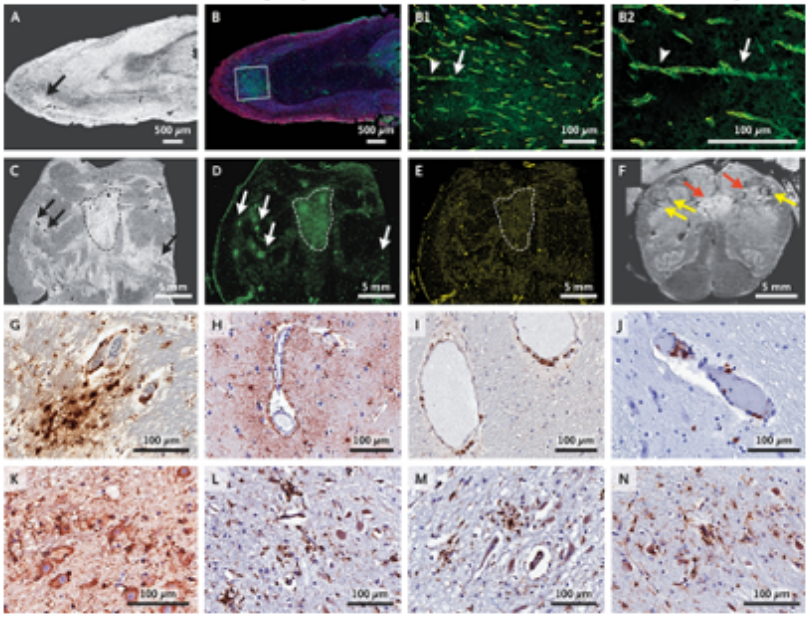
Pathological studies of microvascular injury in the brains of patients who died from Covid-19



https://www.nejm.org/doi/full/10.1056/NEJMc2033369

Several patients
Panel A (magnetic resonance microscopy of the olfactory bulb) shows an area of hyperintense signal (arrow).
Panel B immunofluorescence imaging -> fibrinogen leakage (in the box, fibrinogen is shown in green, collagen IV yellow, and nuclei blue.
Panel B1 leakage of fibrinogen in the parenchyma Panel B2 an enlarged view blood vessel staining for collagen IV.
Panel C magnetic resonance microscopy of the pons
Panel D (fibrinogen staining) vascular leakage
Panel E collagen IV shows fibrinogen leakage in blood vessels
Panel F shows magnetic resonance microscopy of the medulla in Patient IA3. The yellow arrows indicate linear hypointense signals, and the red arrows indicate linear hyperintense signals.
Panel G-N Stained brain tissue postmortem.
Panel G CD68+ perivascular macrophages in the pons
Panel H astrocytosis in the basal ganglia
Panel I perivascular CD3+ cells in the cerebellum. Panel J CD8+ cells in the pons
Panel K perineuronal IBA1 cells in the pons
Panel L CD68+ cells in the dorsal motor nucleus of the vagus nerve
Panel M a solitary nucleus in the medulla
Panel N a pre-Bötzinger complex (Diaminobenzidine staining was used in Panels G through N.)

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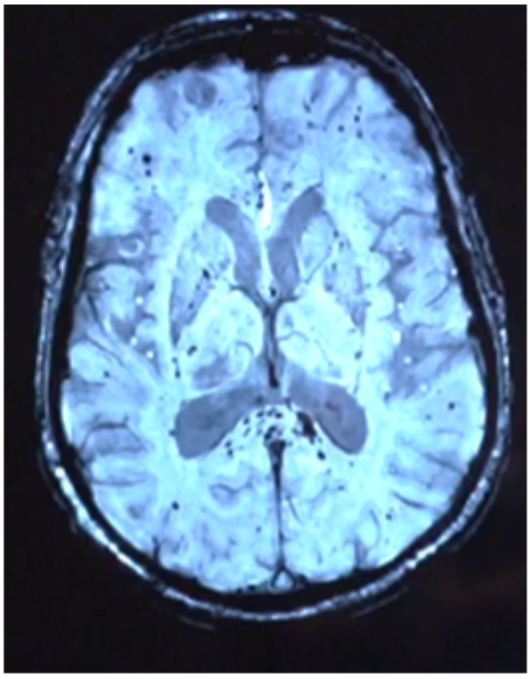
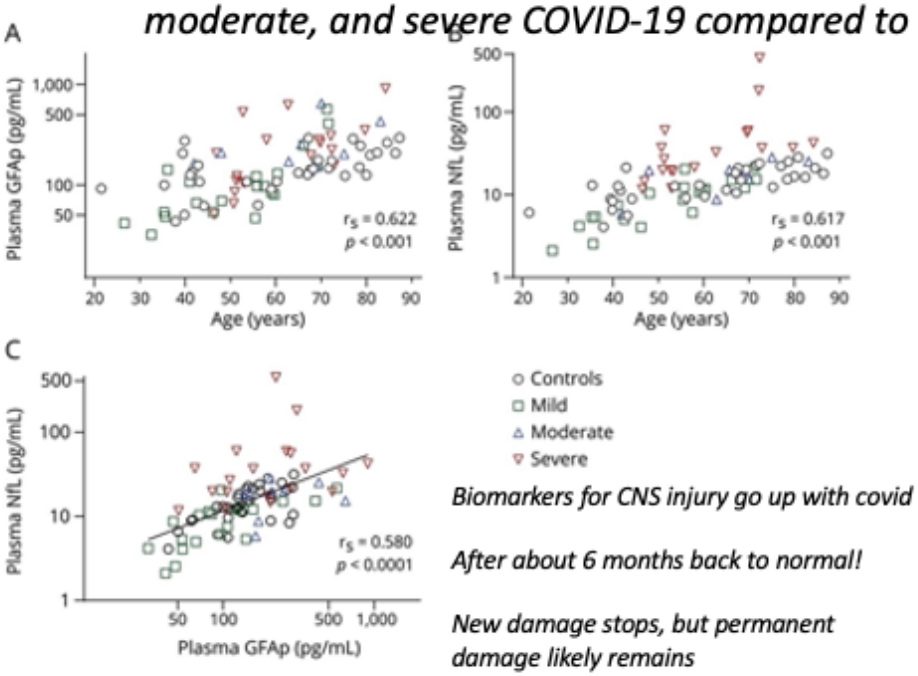
Blood vessel defects in the brain after covid



- Brain exhibits microthrombi and/or microbleeds in Splenium - May explain patients experiencing "Slowing of their thought-processes/thinking" Content owned by colleague Dr Granberg @TV4 & @ KI
- Posted on twitter.

11/

Plasma concentrations of blood-based CNS biomarkers in patients with mild, moderate, and severe COVID-19 compared to healthy controls



Biomarkers for CNS injury go up with covid

After about 6 months back to normal!

New damage stops, but permanent damage likely remains

Plasma concentrations of blood-based CNS biomarkers in patients with mild, moderate, and severe COVID-19 compared to healthy controls

Concentrations increased from a median of 20 (IQR 11–24) pg/mL in the first to 32 (IQR 16–60) pg/mL in last specimen (p = 0.002, figure 2D).
Plasma NfL concentration correlated inversely with the blood lymphocyte count, a negative prognostic factor11 (r = −0.37, p = 0.047); there was no significant correlation with C-reactive protein concentrations (data not shown).

Discussion

We have examined 2 blood-based biomarkers for CNS injury in patients with COVID-19. NfL and GFAp have historically been proven to be useful measures of CNS injury when assessed in CSF, but sampling of this fluid is challenging in the clinical COVID-19 setting. In contrast, measurement of these markers in the plasma is convenient and provides a practical method of

(A and B) Log10 plasma levels were analyzed with analysis of covariance, including interactions between age and group. Estimated geometric means at 70 years of age for the 3 coronavirus disease 2019 (COVID-19) groups were compared with controls. (A) Age and plasma glial fibrillary acidic protein (GFAp) were significantly correlated. Plasma levels of GFAp were significantly increased in the moderate and severe COVID-19 groups compared to controls (p = 0.03 and p = 0.001, respectively). (B) Age and plasma neurofilament light chain protein (NfL) were sig- nificantly correlated. Plasma levels of NfL were 3.1 times higher in patients with severe COVID-19 compared to controls (p < 0.001). (C) Correlation between log10 values of plasma GFAp and NfL in patients with COVID-19.

https://neurology.org/content/neurology/95/12/e1754.full.pdf

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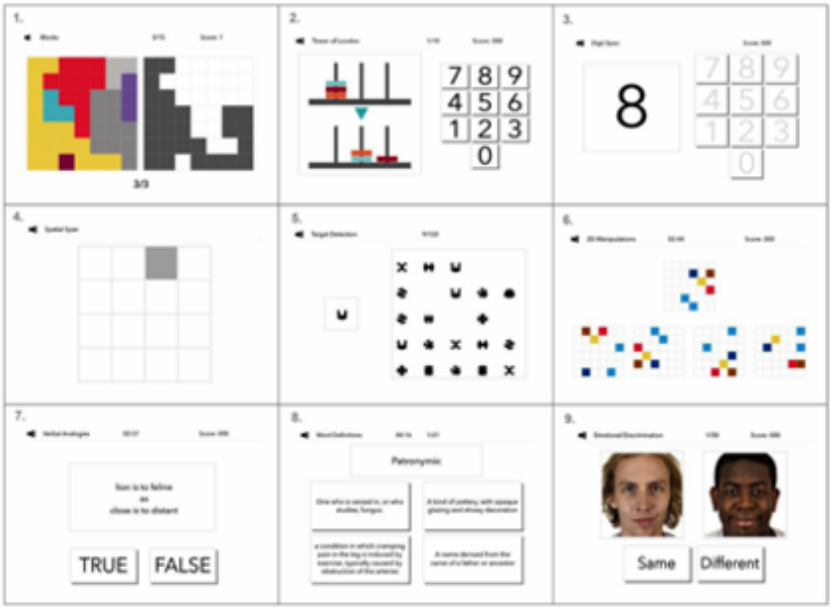
Cognitive effects caused by Covid



<u>Great British Intelligence Test</u>
-Spatial problem solving
-Spatial planning
-Working memory
-Short-term memory
-Visual attention
-Spaitially manipulate objects mentally
-Reasoning
-Identify word meaning
-Emotion identification

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00324-2/fulltext

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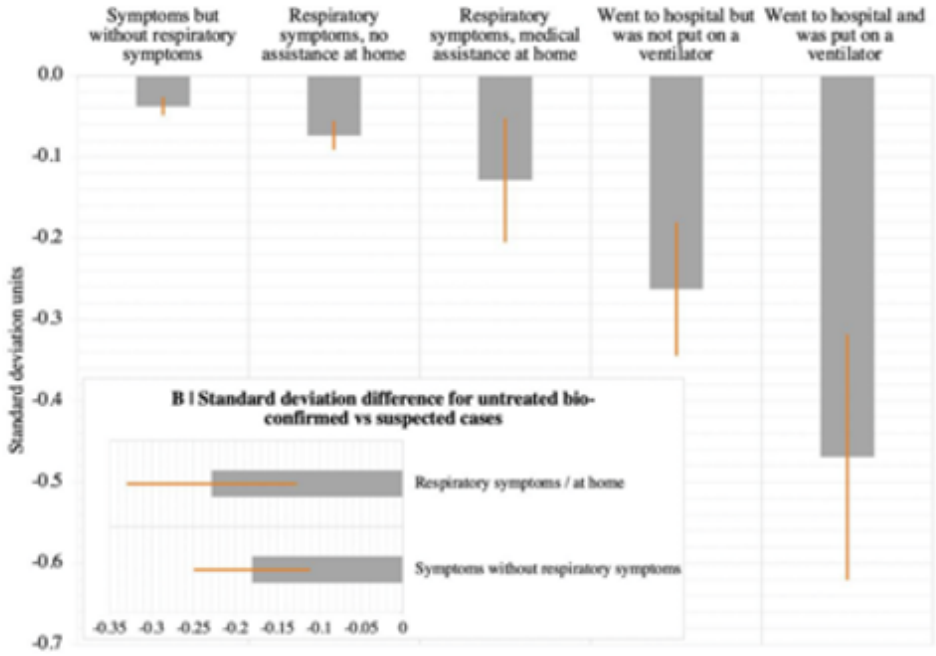
Cognitive deficits in recovered Covid patients



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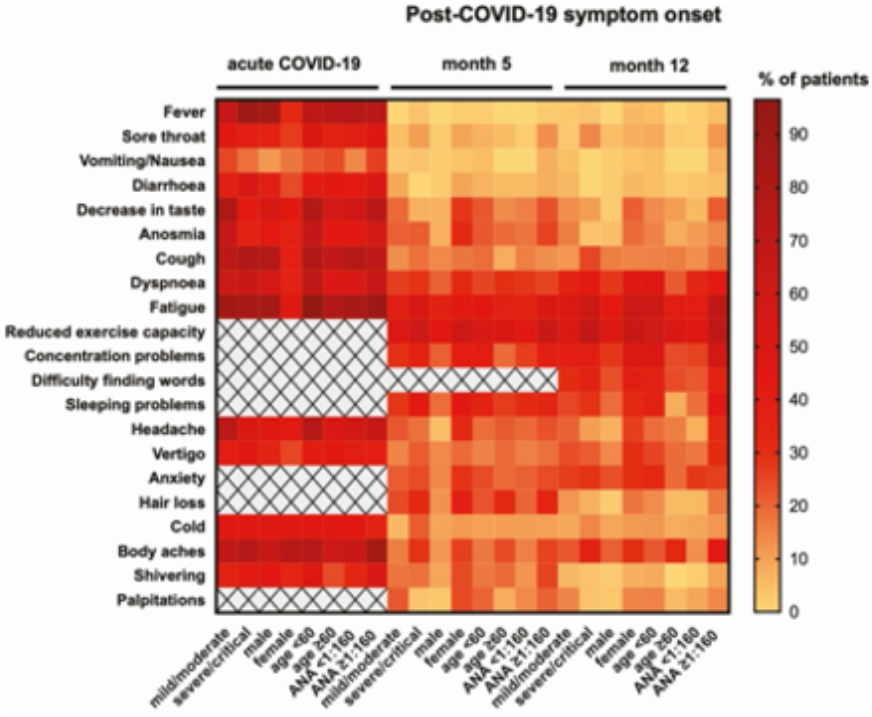
Neurocognitive long-COVID

- Neurocognitive long-COVID symptoms can persist ≥1 year after COVID-19 symptom onset and reduce life quality significantly. Several neurocognitive symptoms were associated with ANA titer elevations. This may indicate autoimmunity as a cofactor in etiology of long COVID.
- July 7, 2021
- https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab611/6315216



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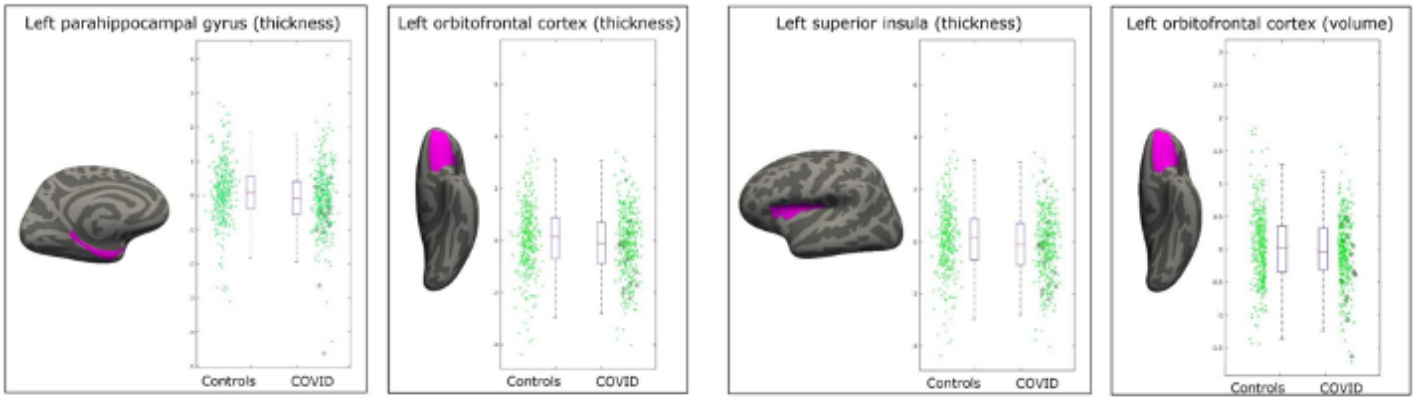
Even mild cases of COVID-19 leave a mark on the brain

Loss of grey matter after Covid infection

COVID patients were scanned before and after they contracted the disease
UK Biobank project, and its COVID-19 re-imaging study



Most significant longitudinal group comparison results.
3 main regions showing significant loss of grey matter (thickness, volume) between the two timepoints specifically for the COVID patients are the parahippocampal gyrus, the lateral orbitofrontal cortex, and the superior insula. All results were localised to the left hemisphere. For each region, the IDP spatial region of interest shown in magenta, overlaid on the FreeSurfer average inflated cortical surface; to the right are the scatter and box plots showing the difference in cortical thickness or volume between the two timepoints for the 388 controls and 394 COVID patients. In black circles are the 15 hospitalised COVID patients. All y axes are arbitrary units proportional to the original measures, due to the normalisation steps in the IDP preprocessing.

https://www.medrxiv.org/content/10.1101/2021.06.11.21258690v1.full.pdf (preprint, June 2021)

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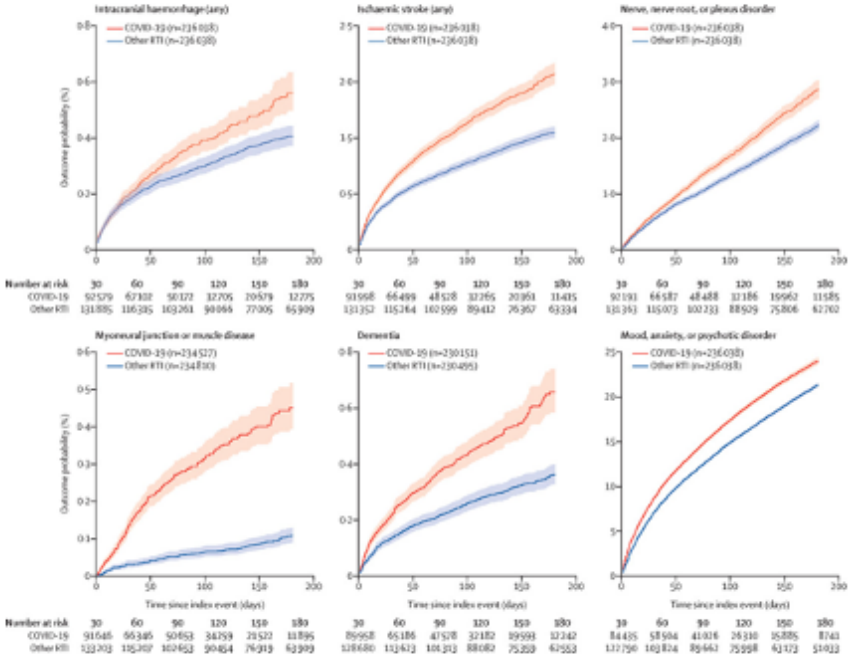
Psychiatric outcomes increase after covid infection



Among 236 379 patients diagnosed with COVID-19, the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months was 33·62% (95% CI 33·17–34·07), with 12·84% (12·36–13·33) receiving their first such diagnosis. For patients who had been admitted to an ITU, the estimated incidence of a diagnosis was 46·42% (44·78–48·09) and for a first diagnosis was 25·79% (23·50–28·25).

April 6 2021: https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(21)00084-5/fulltext

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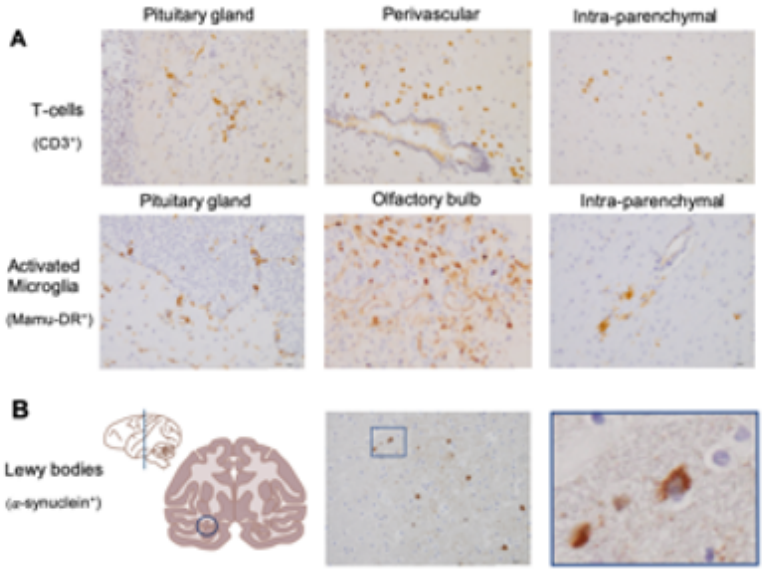
Several studies suggest Covid and Parkinsons disease are related

https://www.biorxiv.org/content/10.1101/2021.02.23.432474v2.full.pdf

- SARS-CoV-2 causes brain inflammation and Lewy bodies, a hallmark for Parkinson, after an asymptomatic infection in macaques.



Lewy bodies are protein inclusions containing disaggregated oligomers of many cellular proteins. They are associated with Parkinson's disease.

Alzheimers too?

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These patients might have something similar to what Robin Williams had – Lewy Body Disease

- *https://n.neurology.org/content/87/13/1308*
- ***Visual hallucinations.***
- ***Movement disorders.*** *Signs of Parkinson's disease (parkinsonian signs), such as slowed movement, rigid muscles, etc.*
- ***Poor regulation of body functions (autonomic nervous system).*** *Blood pressure, pulse, sweating and the digestive process, etc.*
- ***Cognitive problems.*** *Similar to those of Alzheimer's disease, such as confusion, poor attention, visual-spatial problems and memory loss.*
- ***Sleep difficulties.*** *You might have rapid eye movement (REM) sleep behavior disorder, which can cause you to physically act out your dreams while you're asleep.*
- ***Fluctuating attention.*** *Episodes of drowsiness, long periods of staring into space, long naps during the day or disorganized speech are possible.*
- ***Depression.*** *You might develop depression.*
- ***Apathy.***

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Neurotoxic Amyloidogenic Peptides Identified in the Proteome of SARS-COV2: Potential Implications for Neurological Symptoms in COVID-19

- *Tweet from Dec 2: Cytotoxic amyloid aggregates of #SarsCoV2 proteins are causing some of the neurological symptoms commonly found in #COVID19 and contributing to #LongCovid, possibly triggering progressive neurodegenerative disease!*
- "We introduce and support the idea that cytotoxic amyloid aggregates of SARS-CoV-2 proteins are causing some of the neurological symptoms commonly found in COVID-19 and contributing to long COVID, especially those symptoms which are novel to long COVID in contrast to other post-viral syndromes."
- *https://www.biorxiv.org/content/10.1101/2021.11.24.469537v1*

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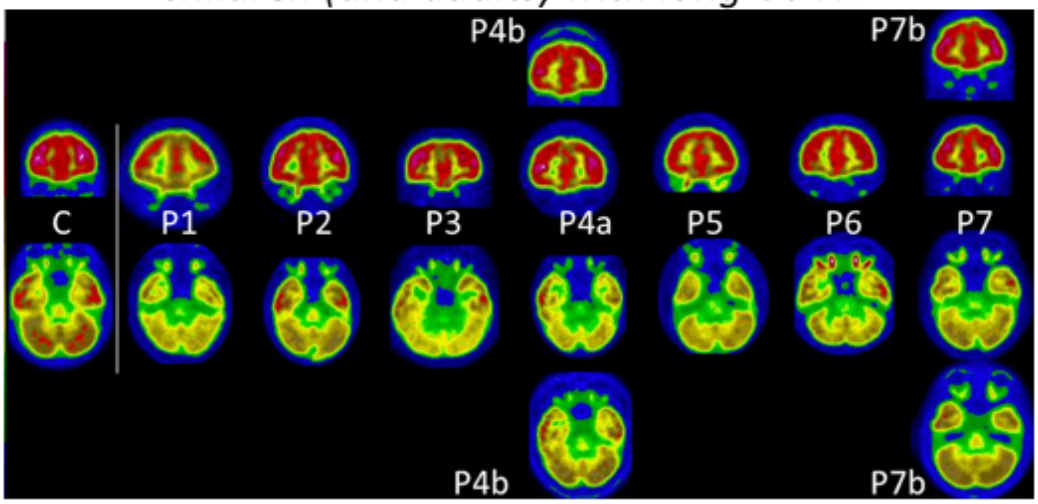
Similar patterns of 18F-FDG brain PET hypometabolism in children (and adults) with long COVID



Individual 18F-FDG PET of each of the seven children patient (#1 to #7), including the follow-up of two of them (#4b and #7b) An example of normal PET metabolism in a child of 10 years old is also presented. Hypometabolism is found in olfactory regions for children #1,3,4,5,6; in temporal regions for children #1,3,4,5,6,7; in the brainstem for children #1,3,4,5,6,7; in the cerebellum for all children. At follow-up, the brain metabolism was improved at least for the brainstem.

https://assets.researchsquare.com/files/rs-722537/v1/ab02cf89-2244-4e6a-ac95-49df657b9502.pdf?c=1631886443

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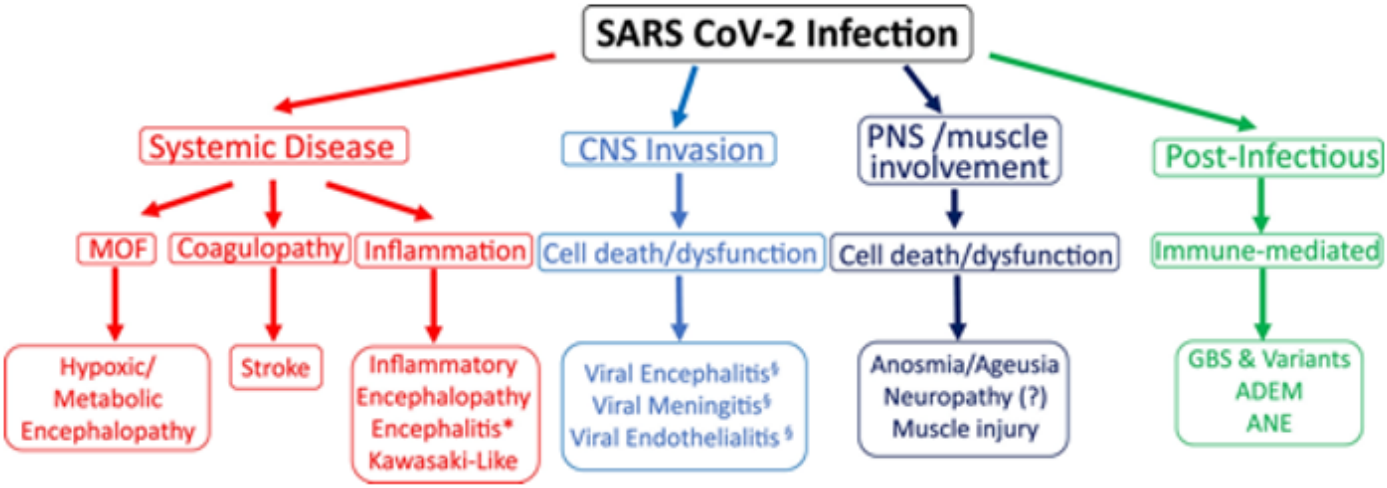
COVID-19: A Global Threat to the Nervous System



- FIGURE: Mechanisms of severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2) neuropathogenesis. SARS-CoV-2 pathogenic effects on the nervous system are likely multifactorial, including manifestations of systemic disease, direct neuro-invasion of the central nervous system (CNS), involvement of the peripheral nervous system (PNS) and muscle, as well as through a postinfectious, immune-mediated mechanism. MOF = multi-organ failure; GBS = Guillain-Barre syndrome. *CNS in□lammation (CSF pleocytosis and proteinorrachia) with no evidence of direct viral infection of CNS; direct evidence of viral invasion (reverse transcriptase-polymerase chain reaction positive [RT-PCR+], biopsy); ADEM = acute disseminated encephalomyelitis; ANE = acute necrotizing encephalopathy.
- https://onlinelibrary.wiley.com/doi/epdf/10.1002/ana.25807