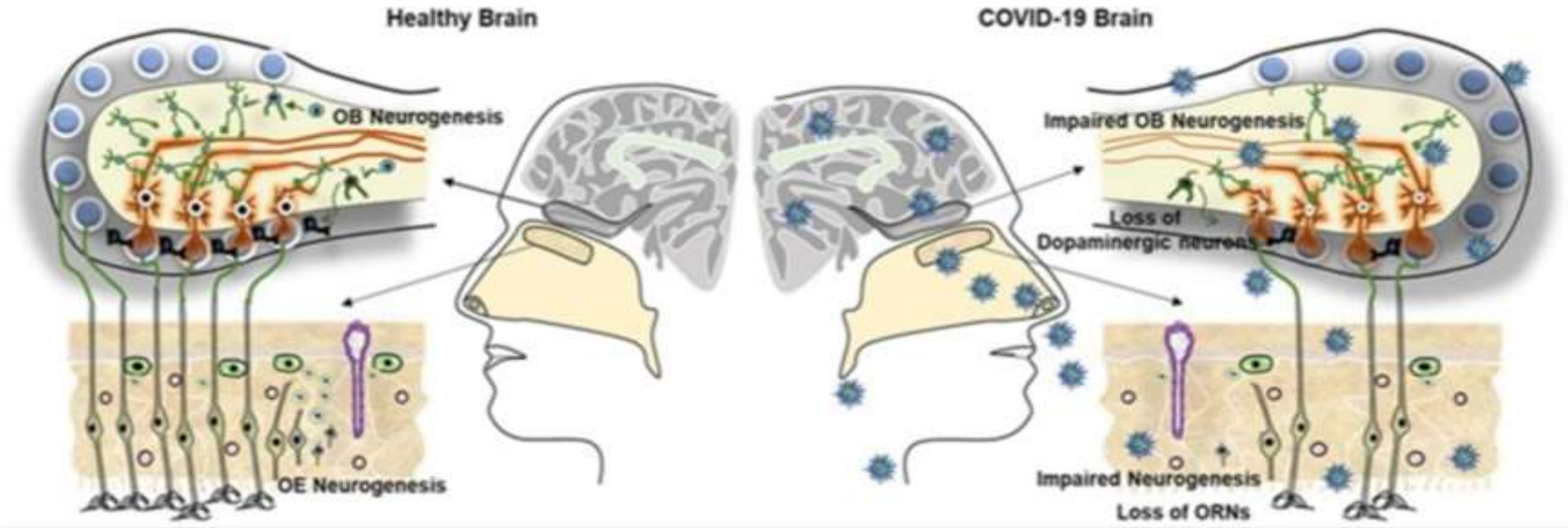
COVID-19, the Brain, and Long-Haulers



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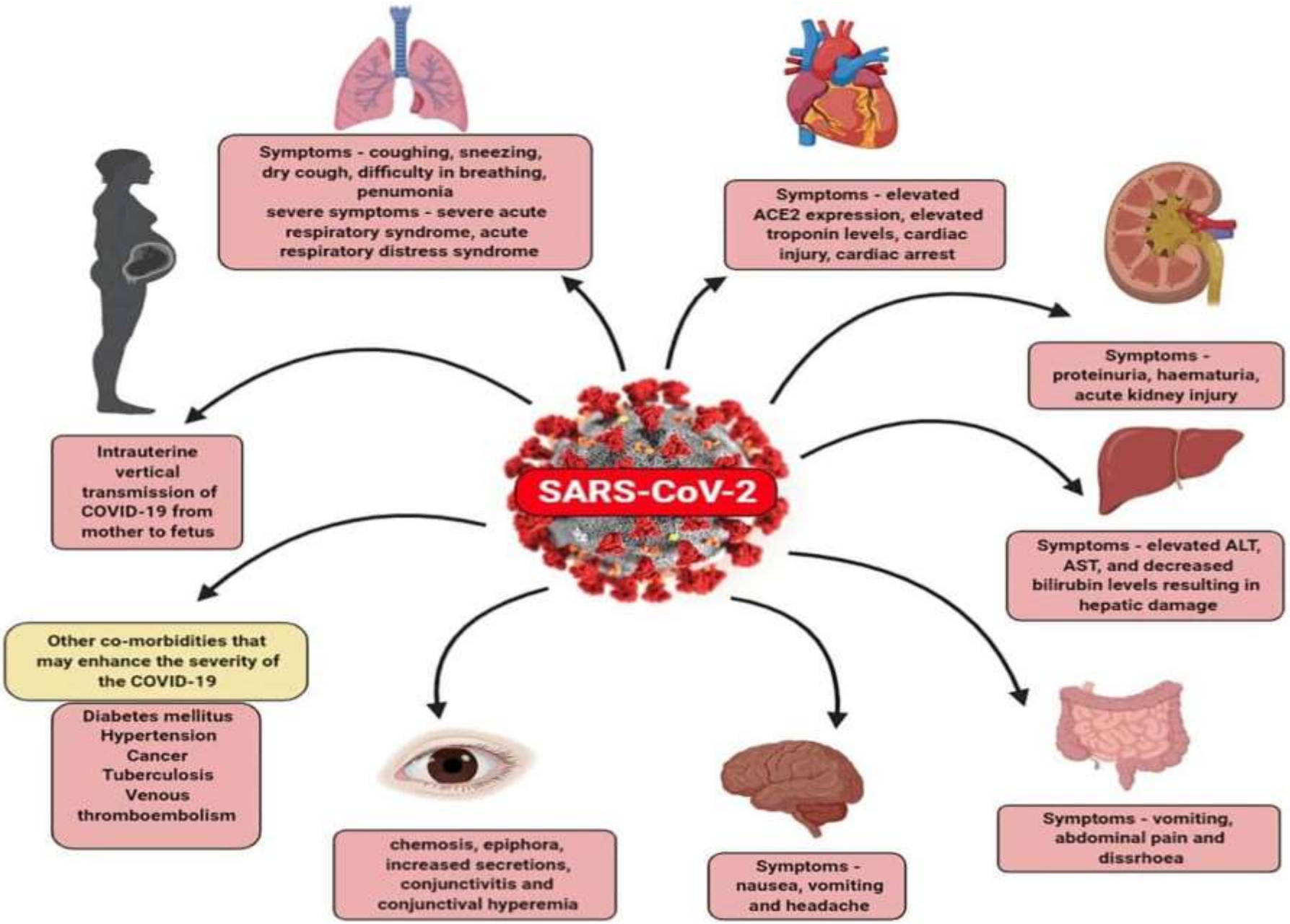
Outline

- Organs affected by COVID-19
- Long COVID-19 symptoms
- Why brain damage is the most likely cause of long COVID-19?
- Evidence for COVID-19 brain damage
- Comparison between COVID-19 and other neurodegenerative diseases.
- Location of ACE2 receptor in organs and various areas of the brain
- The most likely ports of entry of the virus into the brain
- Models of animals/human organoids to study COVID-19 infection
- Evidence for initial olfactory bulb infection and link to brain neurodegeneration, cognitive dysfunction and depression in humans.
- Vaccine as preventive measure and concerns that led to vaccine hesitancy.
- How to mitigate the COVID-19 irreversible brain damage?

COVID-19 symptoms in various organs: Acute and possible long-term effects (Renu et al. 2020)



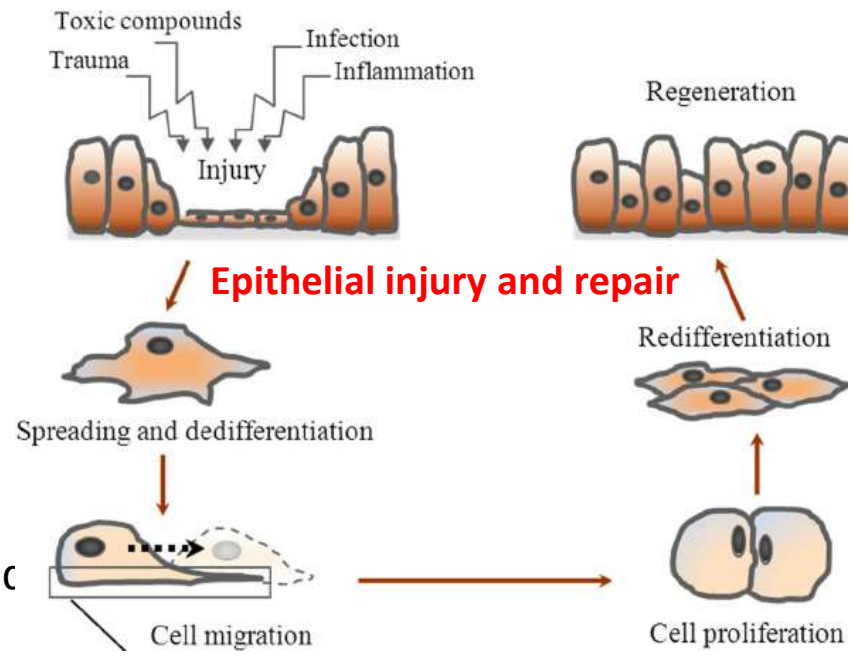
Why Doesn't Your Brain Heal Like Your Skin?

Skin and epithelial cells keep dividing and new cells can heal your wound after injury.

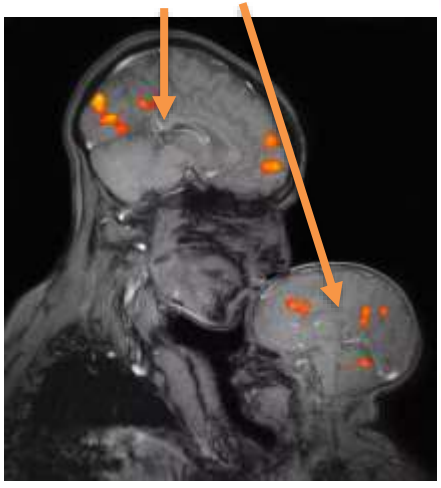
Neurons do not divide with very few exceptions. Nerve cells do not easily regrow damaged parts.

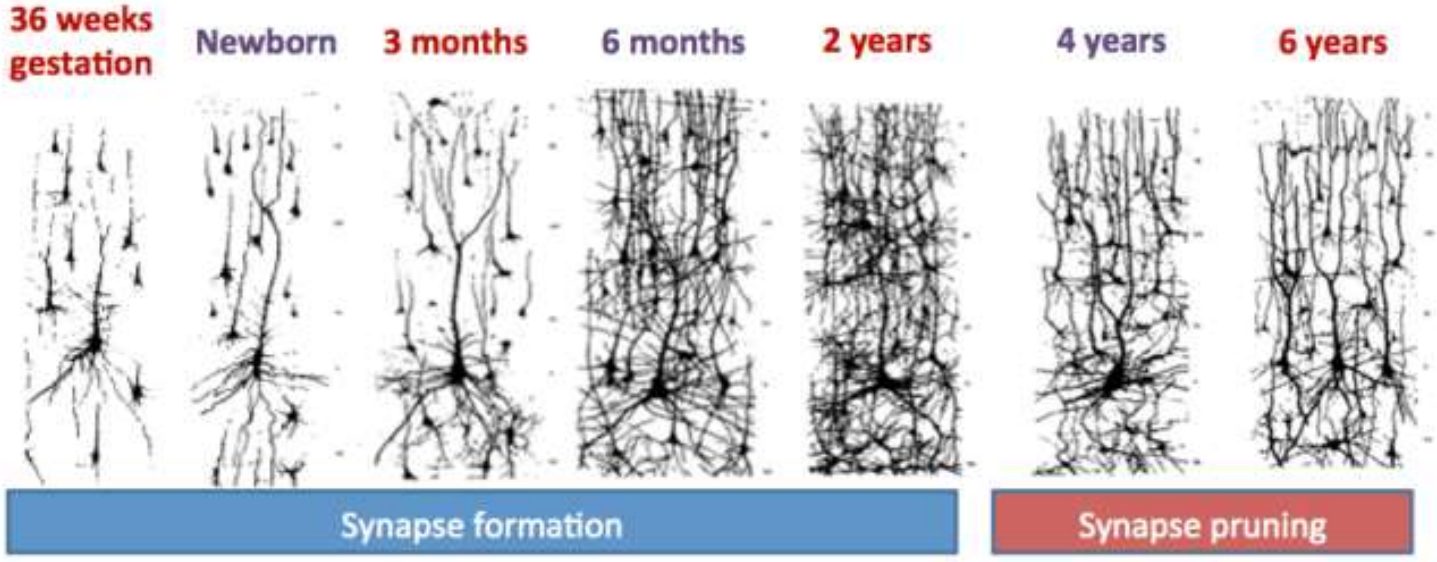
The immune response in the brain is different from that in other tissues. Brain activated immune cells may remain overactivated and kill healthy neurons.

Neurons can change their connections (plasticity), and it helps the brain to adapt to the loss of neurons, by building new connections between surviving neurons.

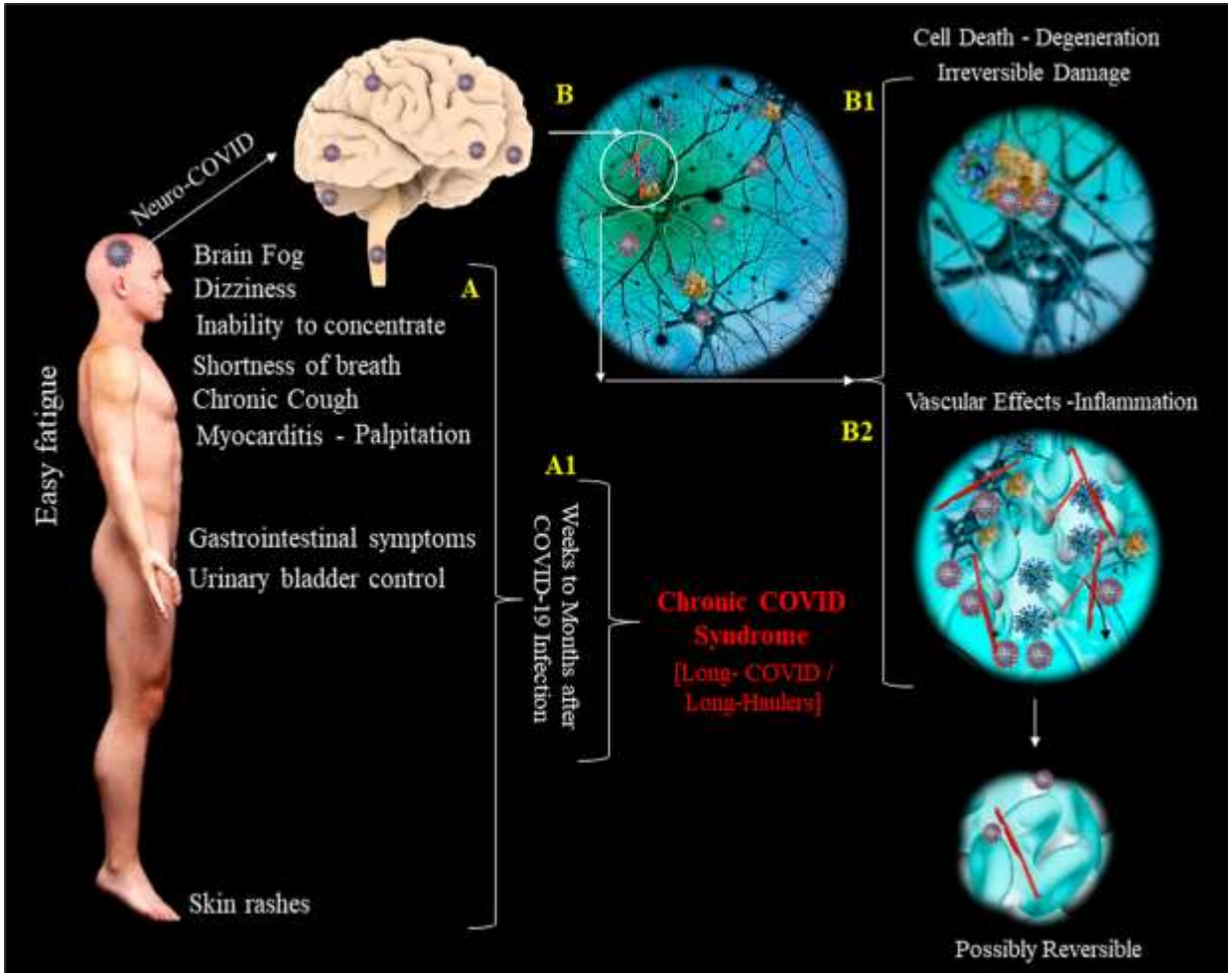


85 billion neurons





Chronic COVID syndrome and neuro-COVID in long-haulers



Chris Cuomo: "This virus creates emotional illness and psychological illness… I am telling you, it is in my head, it is causing people depression and creating brain fog."

The neurological syndrome seen in the long-haulers may be caused by:
-an underlying neurodegeneration,
-and/or a low-grade inflammation.

-The outcomes with cellular degeneration are most likely poor.
-In contrast, with therapy, the prognosis of an inflammatory cause of neuro-COVID without cell damage could be better with a reversal to symptoms to normal. (Baig 2020)

Predictors of Post-COVID-19 syndrome

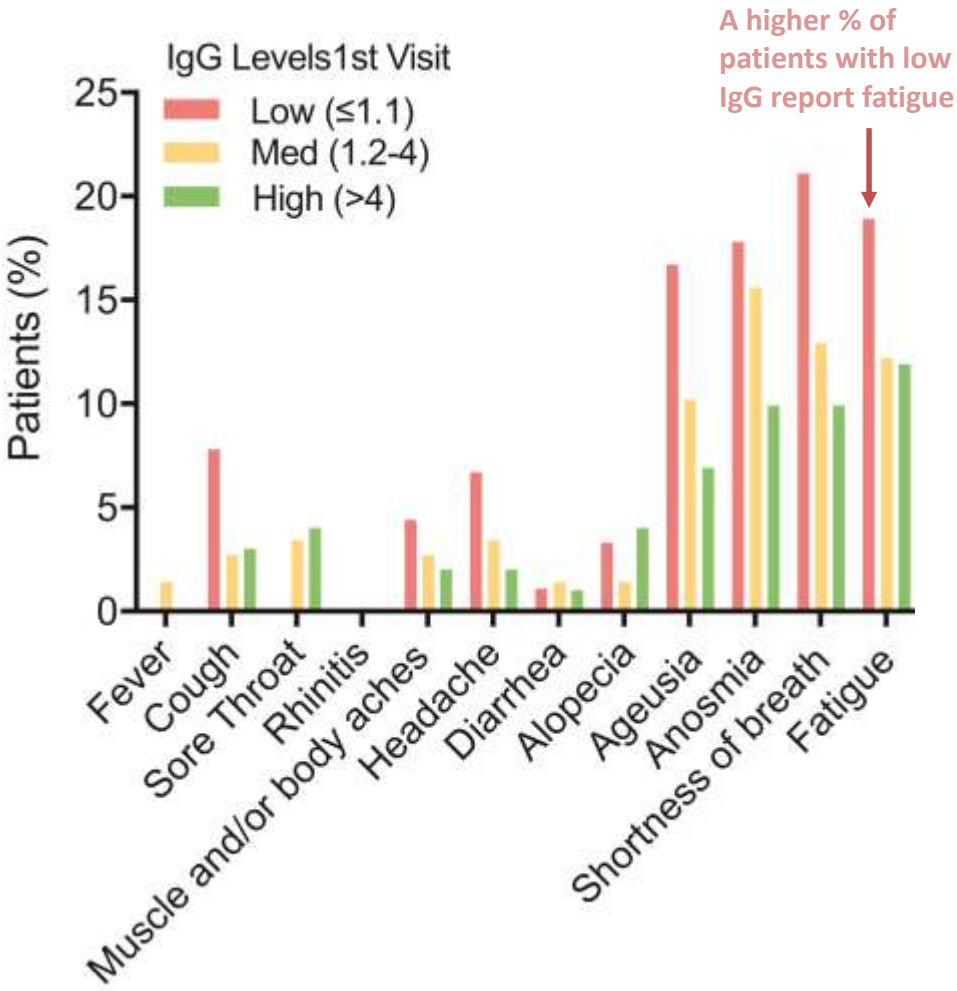
Post-Covid-19 syndrome can occur even after a very mild initial phase of COVID-19 in outpatient setting (Shah et al. 2021).

Post-Covid-19 syndrome is characterized by fatigue, anosmia, ageusia or shortness of breath, which cannot be explained by an alternative diagnosis. Symptoms persist after 4 to 7 months post-infection.

These symptoms are more frequent in SARS-CoV-2 infected female patients and are associated with lower serum IgG titers, anosmia and diarrhea at disease onset. IgG is the most abundant antibody in the blood. It helps prevent infections.

11% of patients in our cohort still could not fully participate in everyday and work life 7 months after disease onset (Augustin & al. 2021).

Augustin & al. 2021



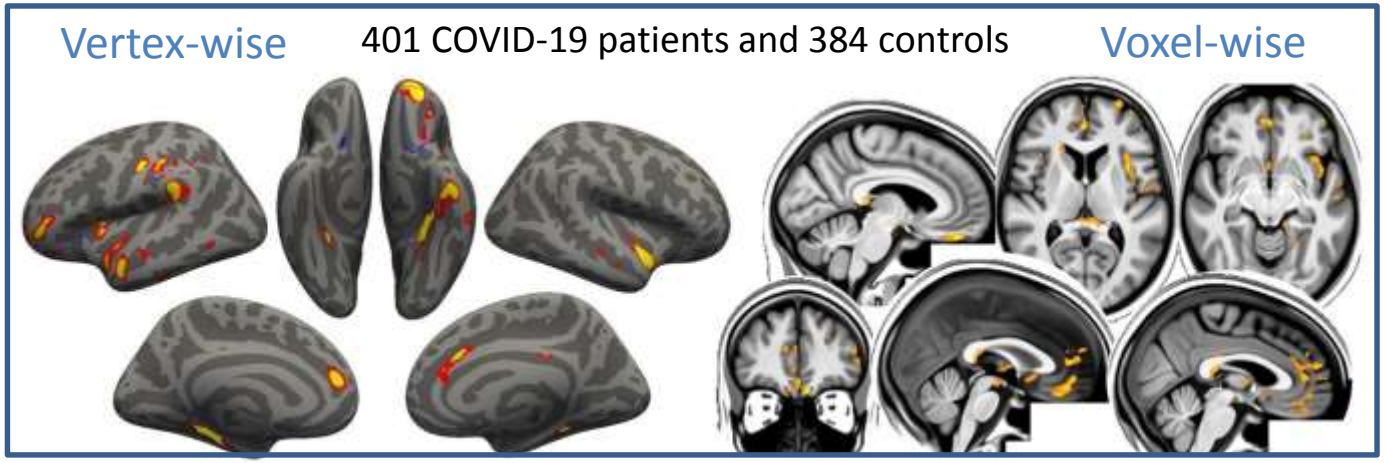
Bars show % of patients that reported the respective symptoms at their third visit.

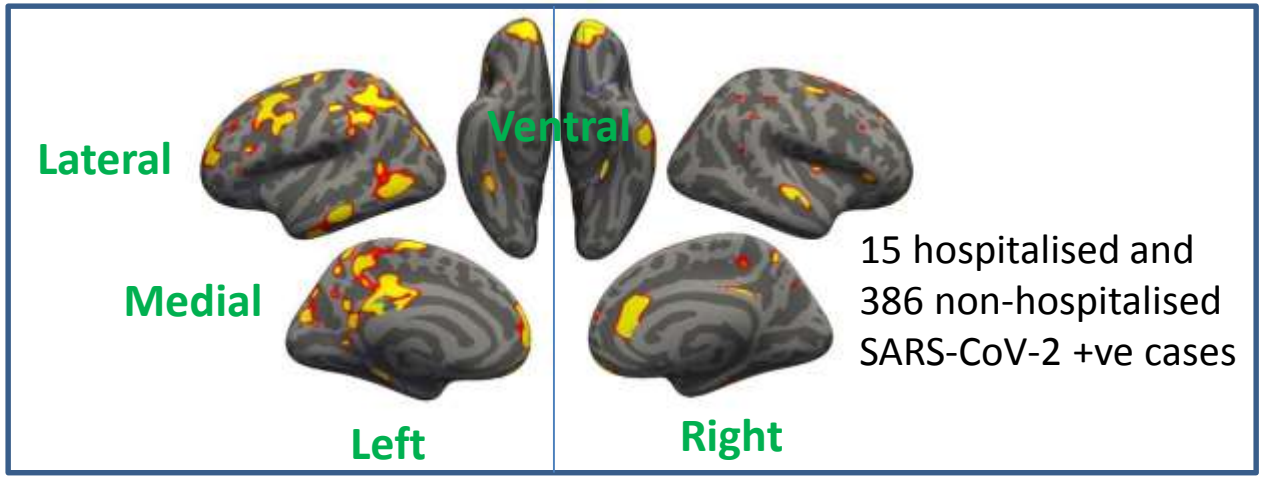
Brain imaging before and after COVID-19 in UK biobank (Douaud et al. preprint)

i) A more pronounced reduction in grey matter thickness and contrast in the lateral orbitofrontal cortex and parahippocampal gyrus,

ii) a relative increase of diffusion indices, a marker of tissue damage, in the regions of the brain functionally-connected to the piriform cortex, anterior olfactory nucleus and olfactory tubercle, and

iii) greater reduction in global measures of brain size and increase in cerebrospinal fluid volume suggesting an additional diffuse atrophy in the infected participants

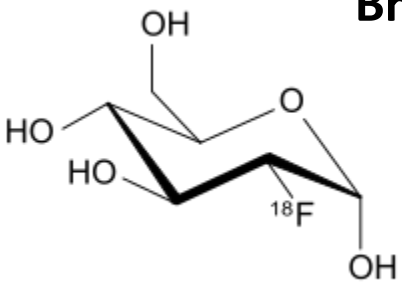




These brain imaging results may be the *in vivo* hallmarks of a degenerative spread of the disease — or of the virus itself — via olfactory pathways (a possible entry point of the virus to the central nervous system being via the olfactory mucosa), or of neuroinflammatory events due to the infection, or of the loss of sensory input due to anosmia.

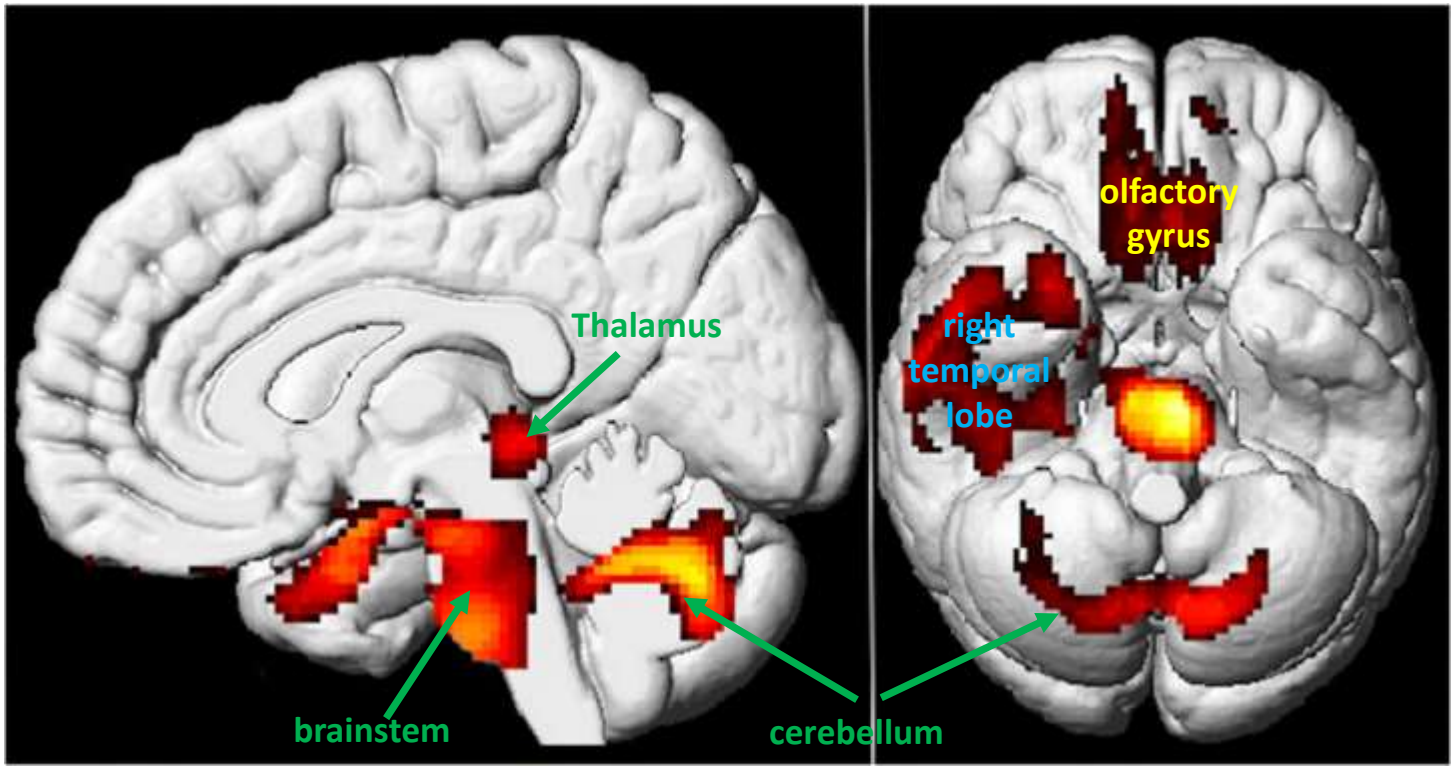
Brain 18F-FDG PET hypometabolism in patients with long-COVID

(Guedj et al. 2021)



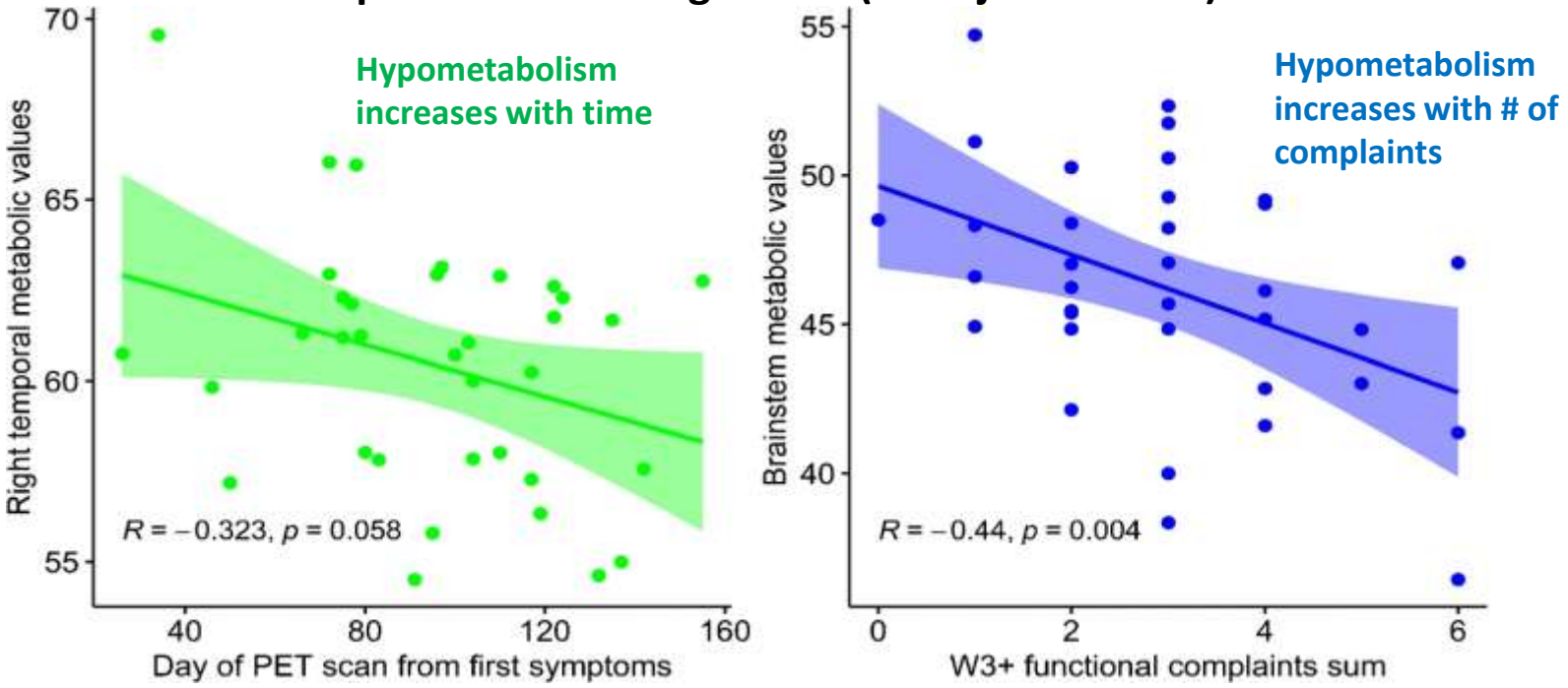
Fluorodeoxyglucose is a glucose analog, with the positron-emitting radionuclide fluorine-18. used in the medical imaging positron emission tomography (PET).

The uptake of 18F-FDG by tissues is a marker for the tissue uptake of glucose, which is correlated with tissue metabolism.



In comparison to 44 healthy subjects, 35 patients (26-155 days after infection) exhibit hypometabolism in the bilateral rectal/orbital gyrus, including the olfactory gyrus; the right temporal lobe, including the amygdala and the hippocampus, extending to the right thalamus; the bilateral pons/medulla brainstem; the bilateral cerebellum

Relationships between PET metabolic clusters and characteristics of patients with long COVID (Guedj et al. 2021)



An increased number of functional complaints at 3 weeks (W3+) after infection was correlated with a younger age and with a longer duration from the initial infection symptoms.

Patients with memory/cognitive impairment and more numerous complaints were younger.
Note: study may have limitations because bias of recruitment cannot be excluded.

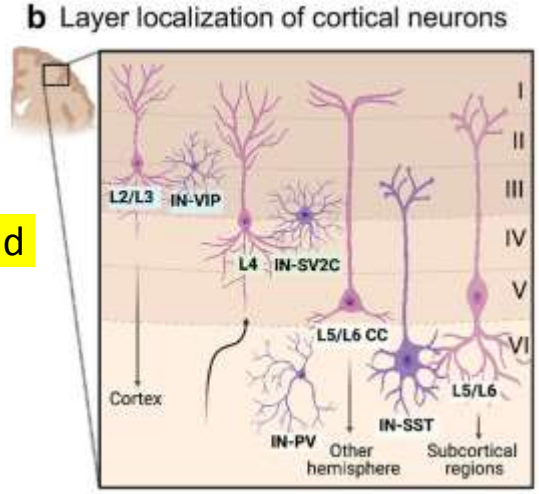
Absence of significant brain hypermetabolism suggests no brain inflammation.

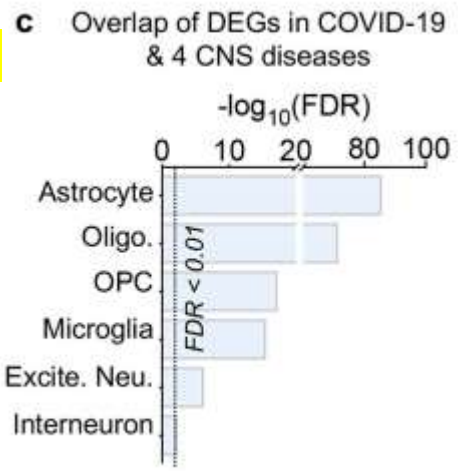
Hypothesis: Brain hypometabolic dysfunction at least partly involves remote functional effects from focal olfactory lesion through loss of function due to deafferentation (loss of inputs).

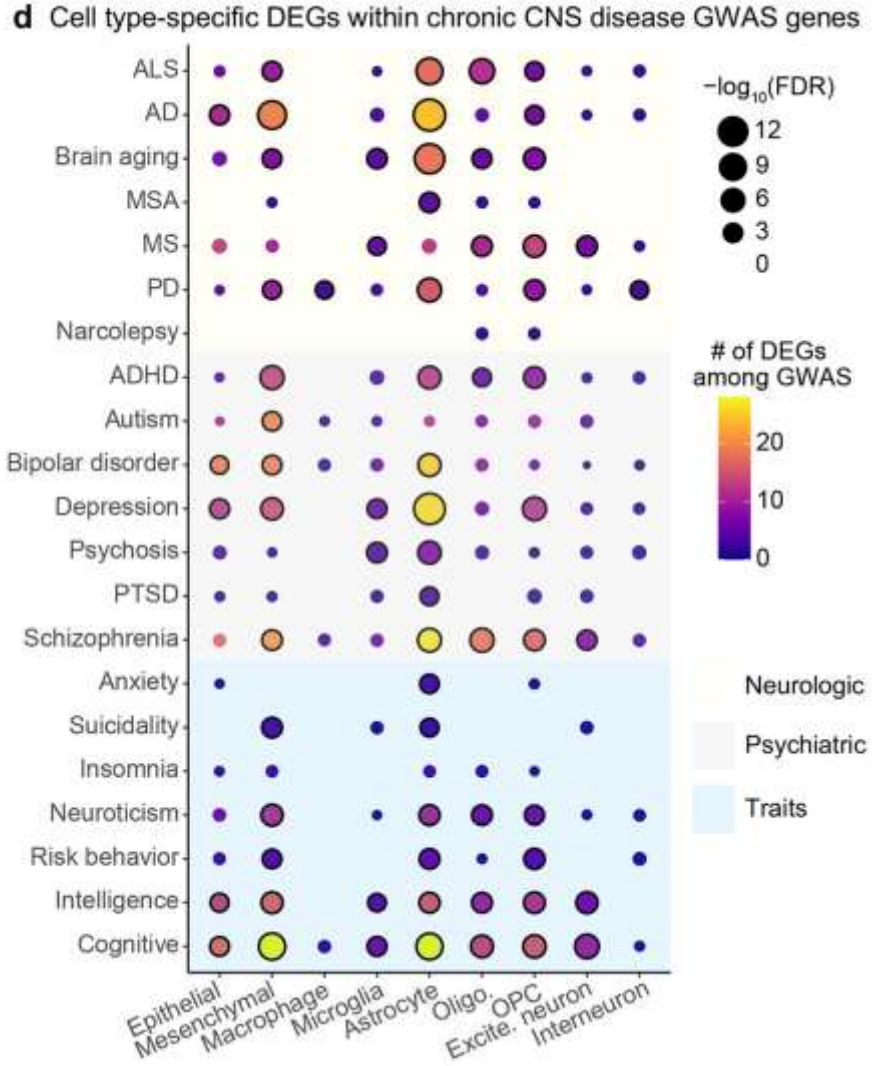
Molecular dysfunction in upper-layer neurons and links to long-term symptoms

Gene-expression changes linked to synaptic deficits particularly in L2/3 excitatory neurons and L2/3-residing VIP interneurons

L2/3 excitatory neurons are cortico-cortical projecting and already exhibit sparse action potential firing to generate a simple and reliable neural code for associative learning. Thus, this neuronal population may be particularly sensitive to deficits in neurotransmission by COVID-19.







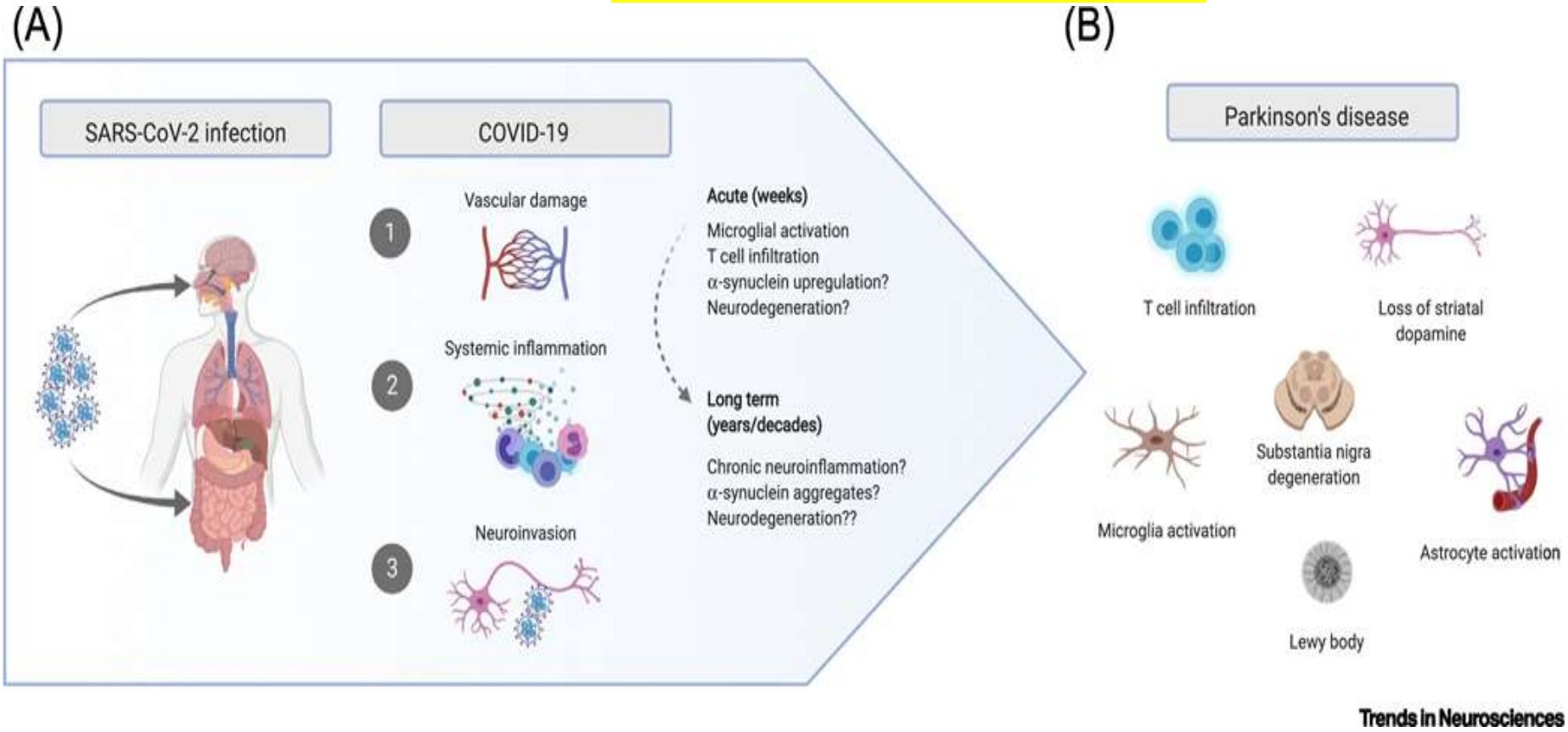
30 frontal cortex and choroid plexus samples across 14 control individuals and 8 patients with COVID-19

Perturbations associated with COVID-19 overlap with those found in chronic brain disorders and reside in genetic variants associated with cognition, schizophrenia and depression.

(Yang et al. 2021)

Is COVID-19 a Perfect Storm for Parkinson's Disease? Brundin et al. 2020

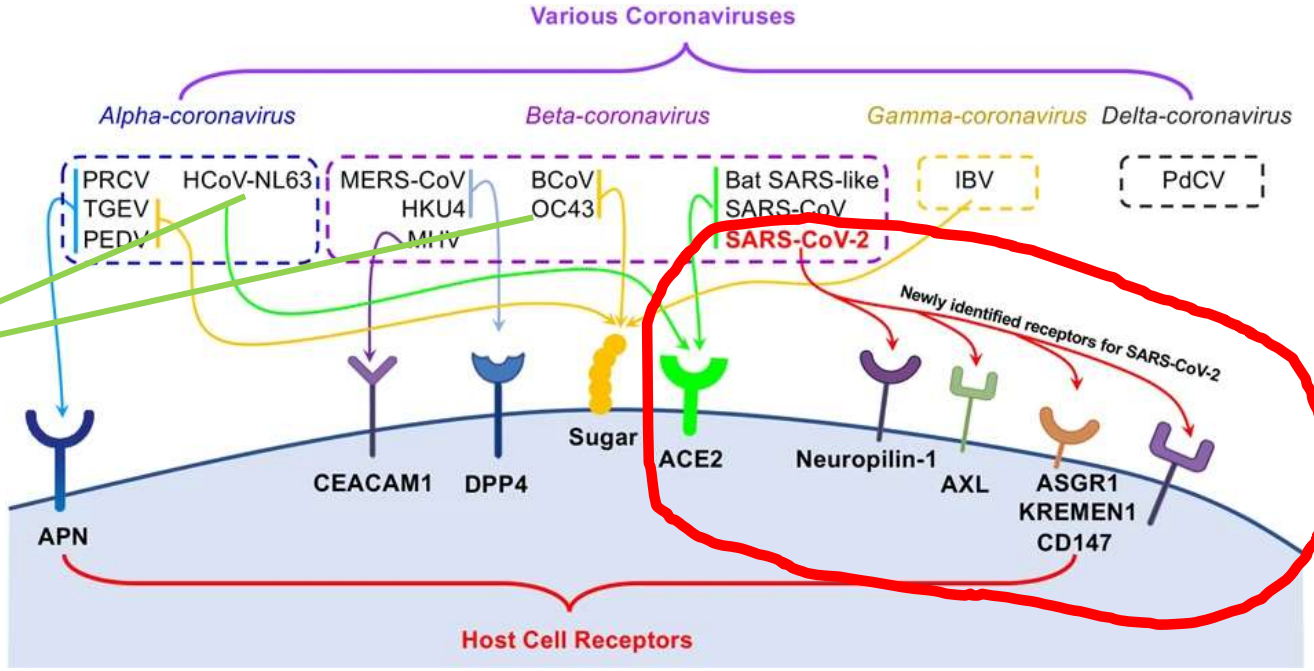
At least 3 case reports described the development of acute parkinsonism following COVID-19



(A) Initial viral infection of the respiratory tract and/or the gut in patients with coronavirus disease 2019 (COVID-19) could affect the brain in three ways: through vascular damage; systemic inflammation; and direct neuroinvasion (e.g., via the olfactory system or vagal nerve), which each might act alone or in concert.

Several of the brain changes that are commonly seen in PD have also been observed following infection with SARS-CoV-2.

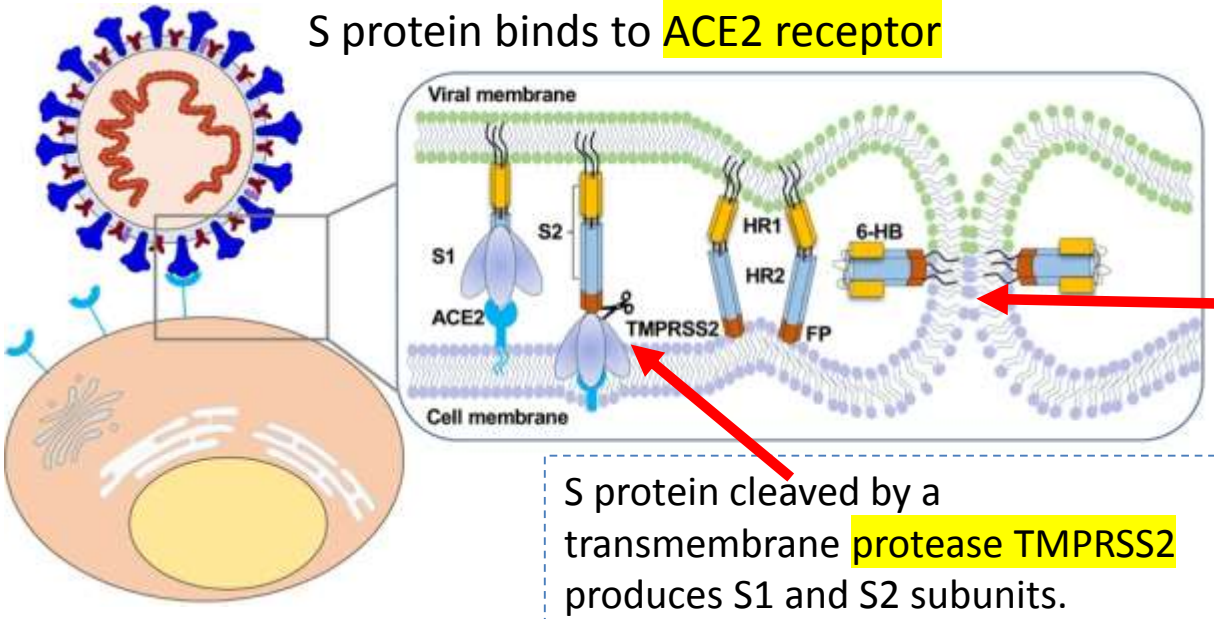
Different coronaviruses use a variety of receptors for viral attachment and entry



Cause common cold & may protect against COVID-19 (T-cells: Sagar et al. 2020; Mateus et a. 2020)

SARS-CoV2 may have many receptors

S protein binds to ACE2 receptor



S protein cleaved by a transmembrane protease TMPRSS2 produces S1 and S2 subunits.

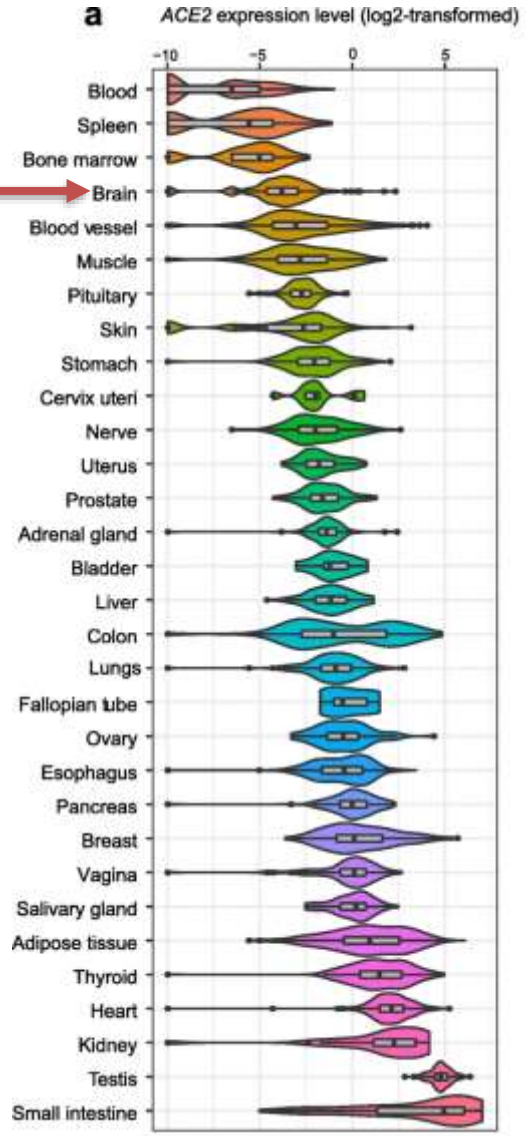
HR1 and HR2 of the S2 subunit gradually approach each other and form a six-helix bundle (6-HB), which causes the virus envelope and host cell membrane to fuse

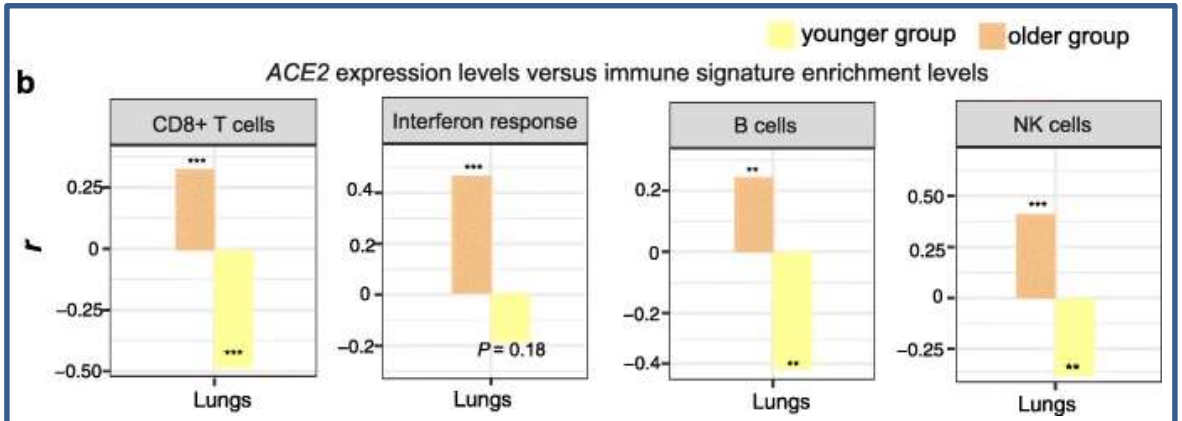
Zhang et al. 2021

Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues (Li et al. 2020, cited 455 times)

Comparison of ACE2 expression levels across 31 human tissues in Genotype-Tissue Expression (GTEx).

The brain has relatively low ACE2 expression





Correlation between *ACE2* expression levels and immune signature enrichment levels in the lungs of older (ages > 49 years) and younger (ages ≤49 years) populations.

-SARS-CoV-2 may infect persons with different sexes, ages, and races equally.

-Distinct disease severity may be explained by different host immune responses to SARS-CoV-2 between males and females, young and old persons.

The intestine, testis, kidney & heart have the highest ACE2 expression

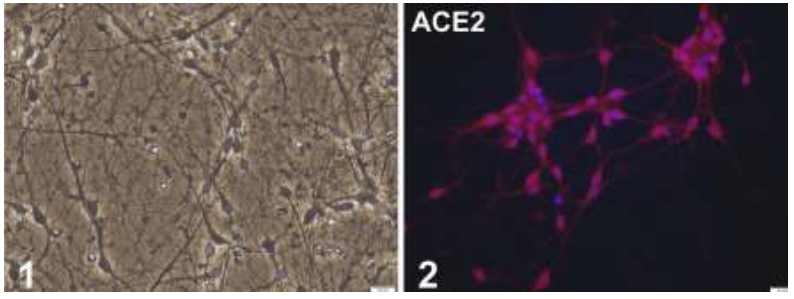
Expression of ACE2 in Human Neurons Supports the Neuro-Invasive Potential of COVID-19 Virus (Xu and Lazartigues 2020)

Tissue name	ACE2 protein expression	ACE2 protein expression levels	Related COVID-19 symptoms
Duodenum	✓	High	GI disturbance
Gallbladder	✓	High	NA
Heart	✓	High	Heart injury
Kidney	✓	High	Kidney injury
Small intestines	✓	High	Diarrhea and other GI disturbance
Testis	✓	High	NA
Adrenal gland	✓	Medium	NA
Colon	✓	Medium	Diarrhea
Rectum	✓	Medium	NA
Brain	✓ (validated via enzymatic activity assays)	Low	Loss of taste or smell, respiratory failure, and other neurological symptoms
Liver	✓	Low	Increased levels of liver enzymes (ALT, AST)
Lung	✓	Low	Pneumonia and respiratory symptoms
Oral mucosa	✓	Low	NA
Seminal vesicle	Only in glandular cells	Low	NA
Skin	✓	Low	A rash on skin, or discoloration of fingers or toes
Spleen	Only in vascular and red pulp sinus endothelium	Low	NA
Eye	NA	NA	Conjunctivitis
Adipose tissue	×		
Common blood cells	×		Abnormal blood clotting
Endometrium	×		
Esophagus	×		
Nasopharynx	×		
Stomach	×		

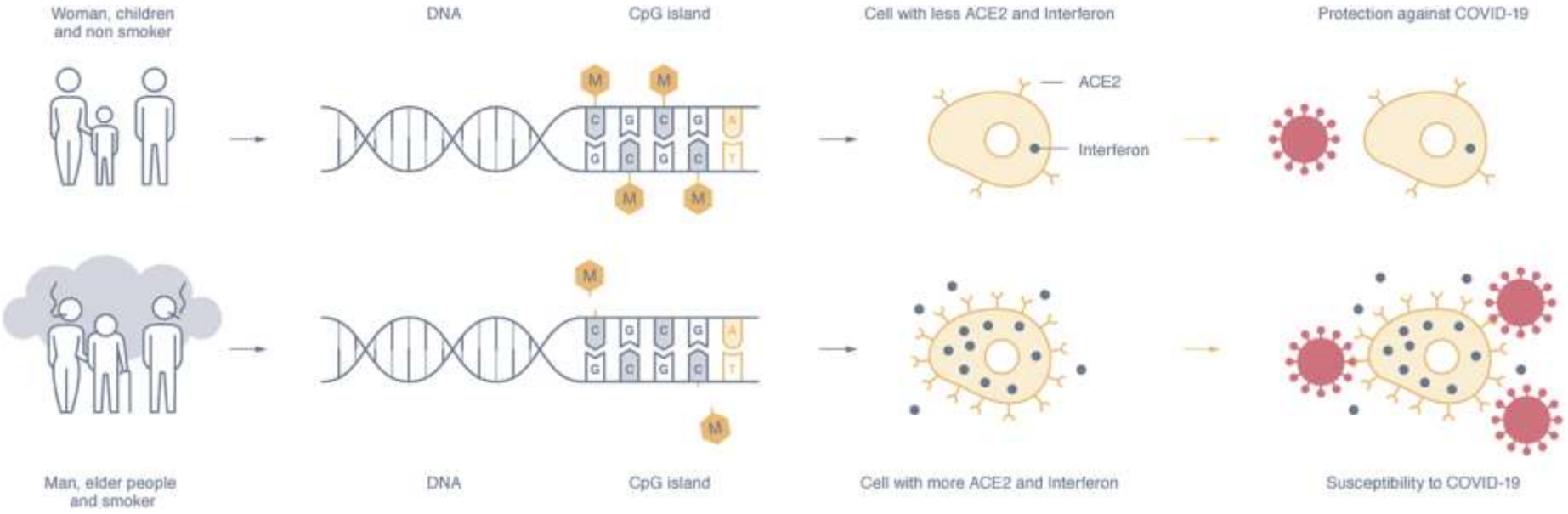
The data of ACE2 protein expression were obtained via published reports (Hamming et al. 2004; Kehoe et al. 2016; Xu et al. 2017; Hikmet et al. 2020) and version 19 of the Human Protein Atlas (https://www.proteinatlas.org). The data of related COVID-19 symptoms were obtained via the website of Centers for Disease Control and Prevention (CDC)

Low ACE2 expression in brain

ACE2 is expressed in cultured human pluripotent stem cell (PSC)-derived from forebrain-type neurons



Methylation Pathways and SARS-CoV-2 Lung Infiltration and Cell Membrane-Virus Fusion Are Both Subject to Epigenetics (Pruimboom 2020)

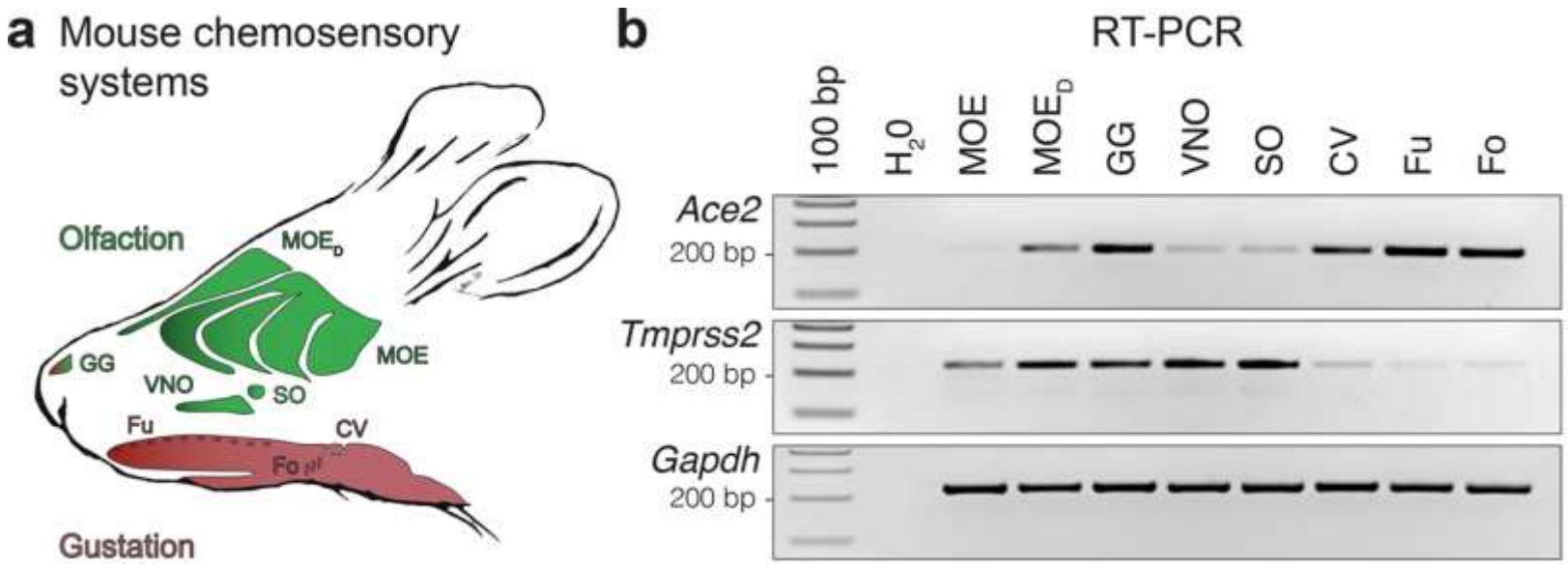


Susceptible individuals, mostly men, the elderly, and smokers, show a hypomethylation pattern of the ACE2 and interferon genes (lower part), whereas women, children, and non-smokers show DNA hypermethylation and lower expression of ACE2 and interferon proteins (upper part).

The higher presence of ACE2 on epithelial cells and interferon makes people more susceptible to SARS-CoV-2 infection and increases disease severity.

ACE2 variation may be one cause for COVID-19 severity: The ACE2 gene and protein show a high degree of genetic polymorphisms including single nucleotide variation, transcriptional variation, post-transcriptional modifications and putative protein mutations (Chen et al. 2020)

Age-dependent expression of SARS-CoV-2 entry site transcripts in the MOE_D, CV, and GG

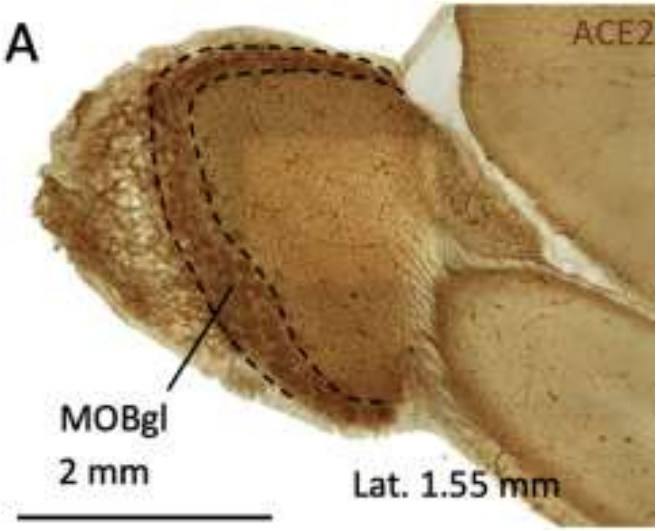


There is a direct correlation between human sensory-symptomatology and mice SARS-CoV-2-expressing entry cells providing a putative explanation for the observed anosmia and ageusia in COVID-19 patients.

From a clinical point of view, anosmia and ageusia have a low prevalence in infected children and increase with the age of the COVID-19 patient, which seems to be consistent with the protein expression of ACE2 observed in the mice olfactory system. Brechbühl et al. 2021

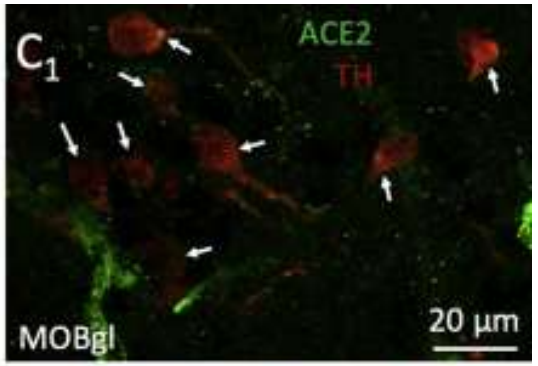
ACE2 is expressed in TH positive neurons of the rat main olfactory bulb (MOB).

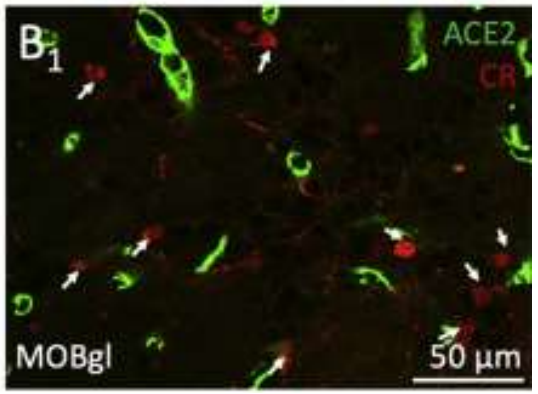
A) DAB developed immunoreaction against ACE2 in the olfactory bulb region. The highest expression of ACE2 was found in the glomerular layer (MOBgl).



Sections double-labeled against ACE2 and calretinin (CR, panel B) or tyrosine hydroxylase (TH, panel C).

ACE2 positive neurons were negative for CR (panel B1) in the glomerular layer but positive for TH (panel C1).

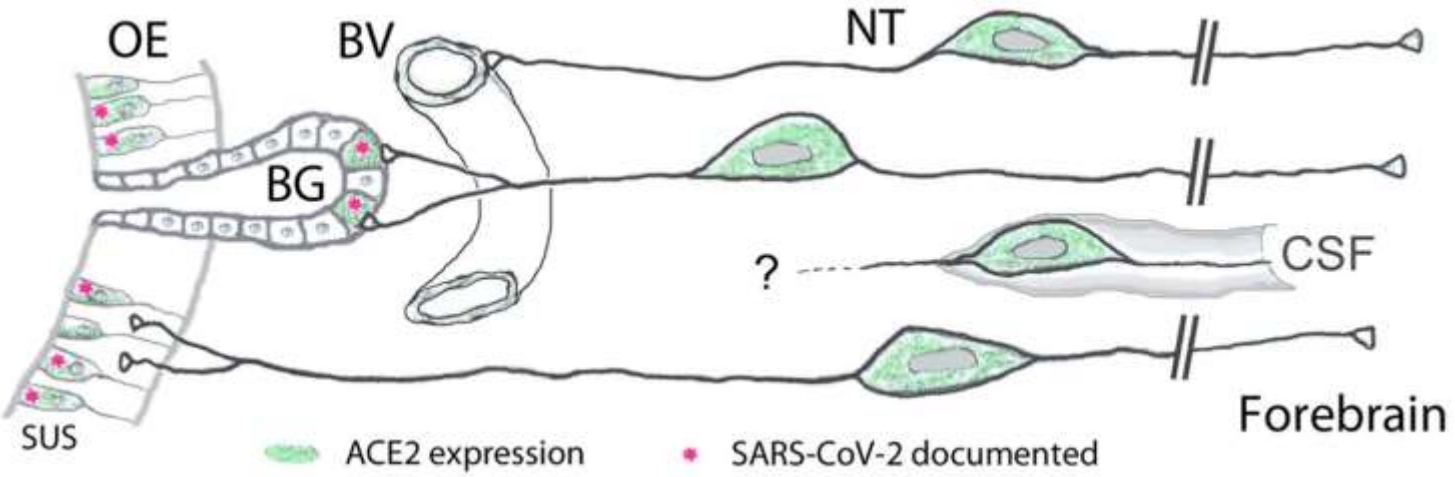




Hernández et al. 2021

Expression of the ACE2 Virus Entry Protein in the Nervus Terminalis Reveals the Potential for an Alternative Route to Brain Infection in COVID-19

Many peripheral processes of the nervus terminalis innervate the olfactory epithelium, the blood vessels below this epithelium, as well as cells in Bowman's glands (Larsell, 1950), and the central processes of some of these neurons extend to various targets in the forebrain as far caudal as the hypothalamus



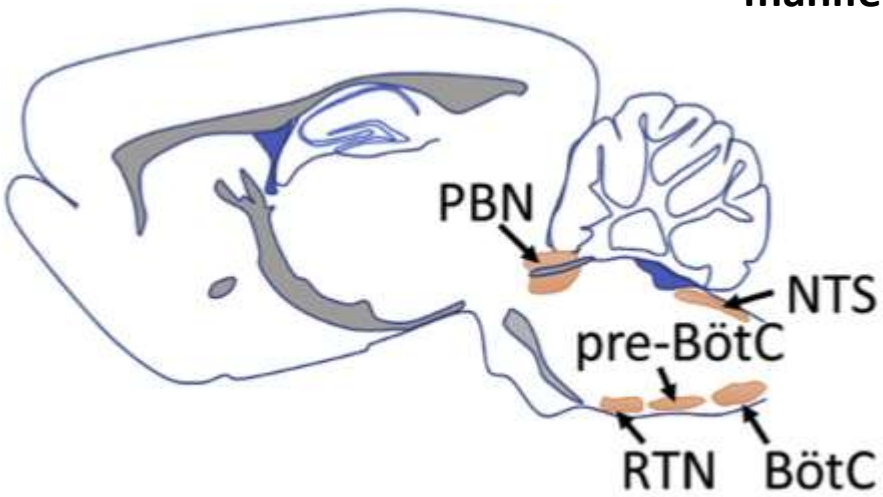
(Bilinska et al. 2021)

Peripheral projections of nervus terminalis (NT) neurons and their presumptive relationship with ACE2-expressing neurons in the olfactory epithelium.

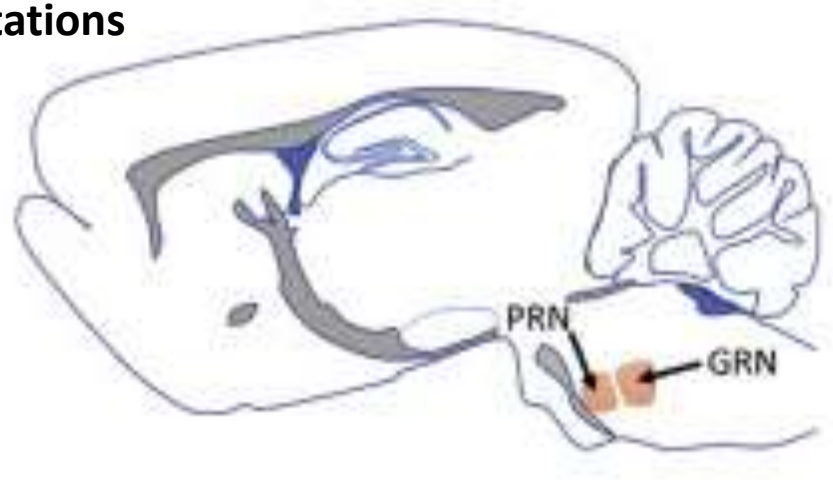
NT neurons innervate blood vessels (BV), Bowman gland (BG) cells, the olfactory epithelium (OE), and contact cerebrospinal fluid (CSF) spaces.

Cells expressing ACE2 are indicated in green, including sustentacular cells (SUS) and BG cells.

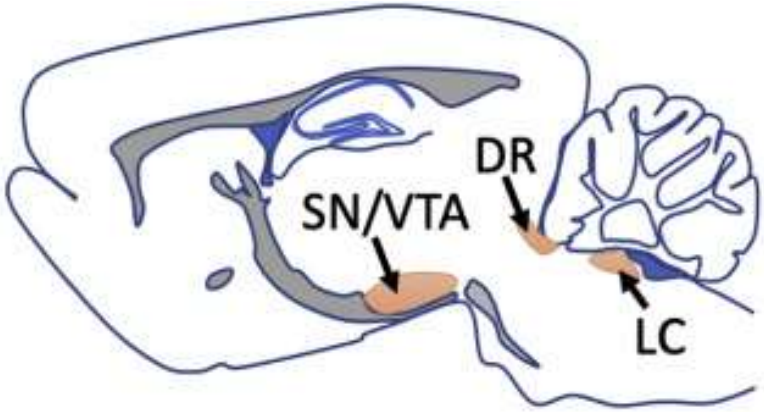
ACE2 expression in rat brain: Implications for COVID-19 associated neurological manifestations



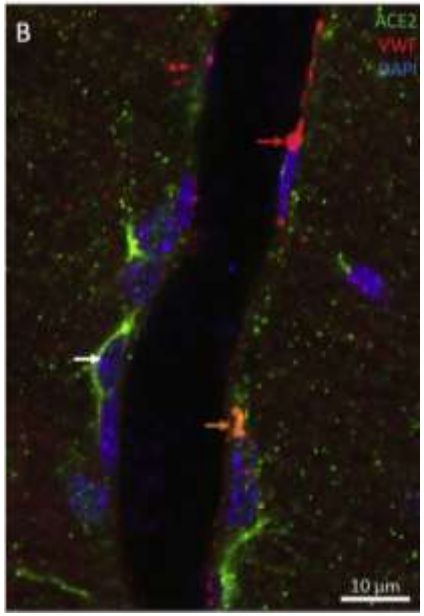
ACE2 is highly expressed in nuclei of the brainstem respiratory network.



ACE2 is highly expressed in arousal-related reticular formation pontomedullary nuclei.



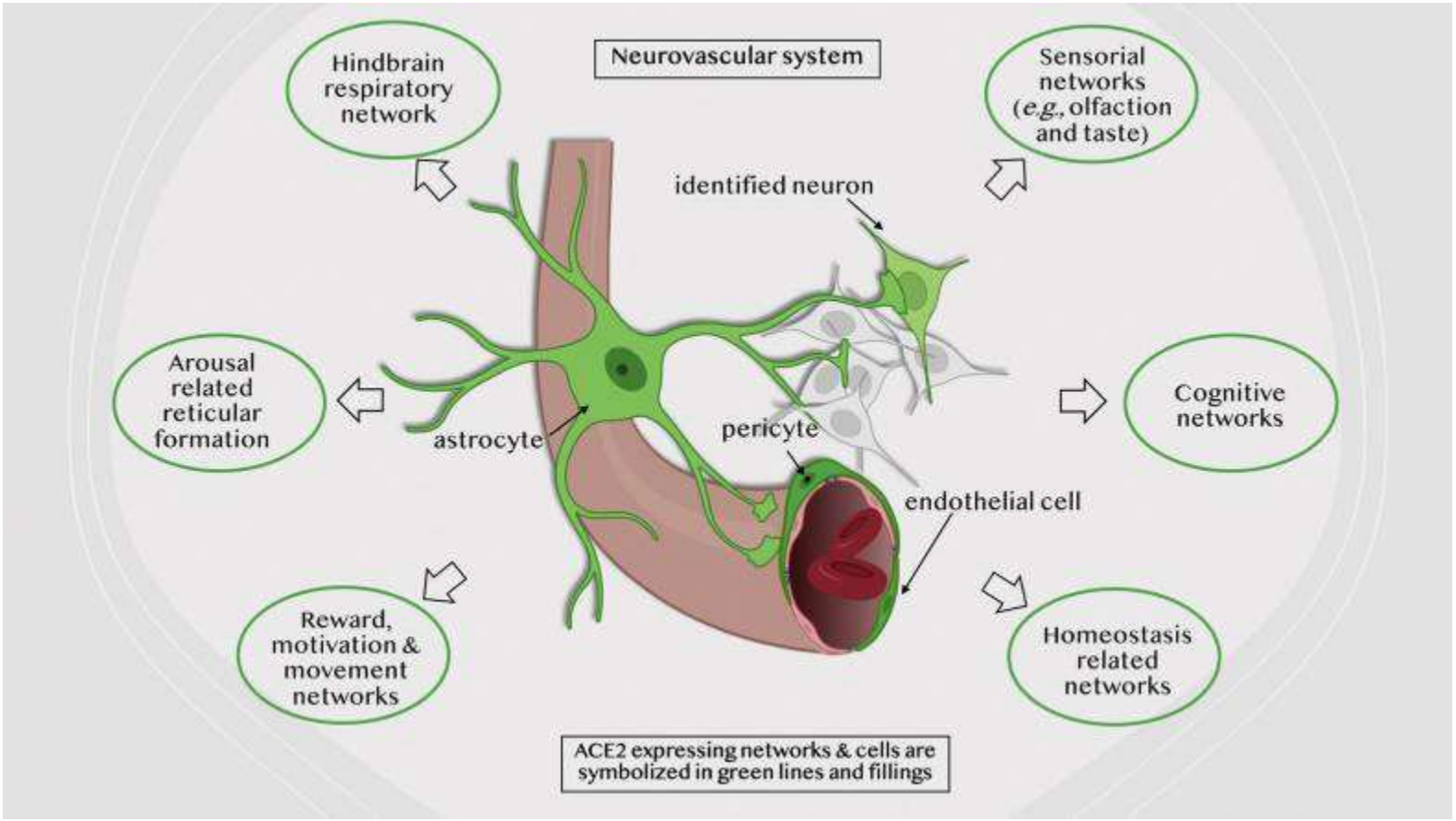
ACE2 is expressed in brainstem aminergic nuclei.



ACE2 is expressed in the components of the blood-brain barrier: astrocytes and astrocytic foot processes, pericytes and endothelial cells,

Hernández et al. 2021

Widespread expression of ACE2 immunoreaction in brain vasculature



In the brain vasculature, the constituent elements for the blood-brain barrier all expressed ACE2, with a particularly high density of immunopositive vasculatures in the olfactory bulb, the hypothalamic nuclei (homeostasis), the midbrain dopaminergic regions (reward), and in various brainstem respiratory nuclei associated with breathing regulation and arousal.

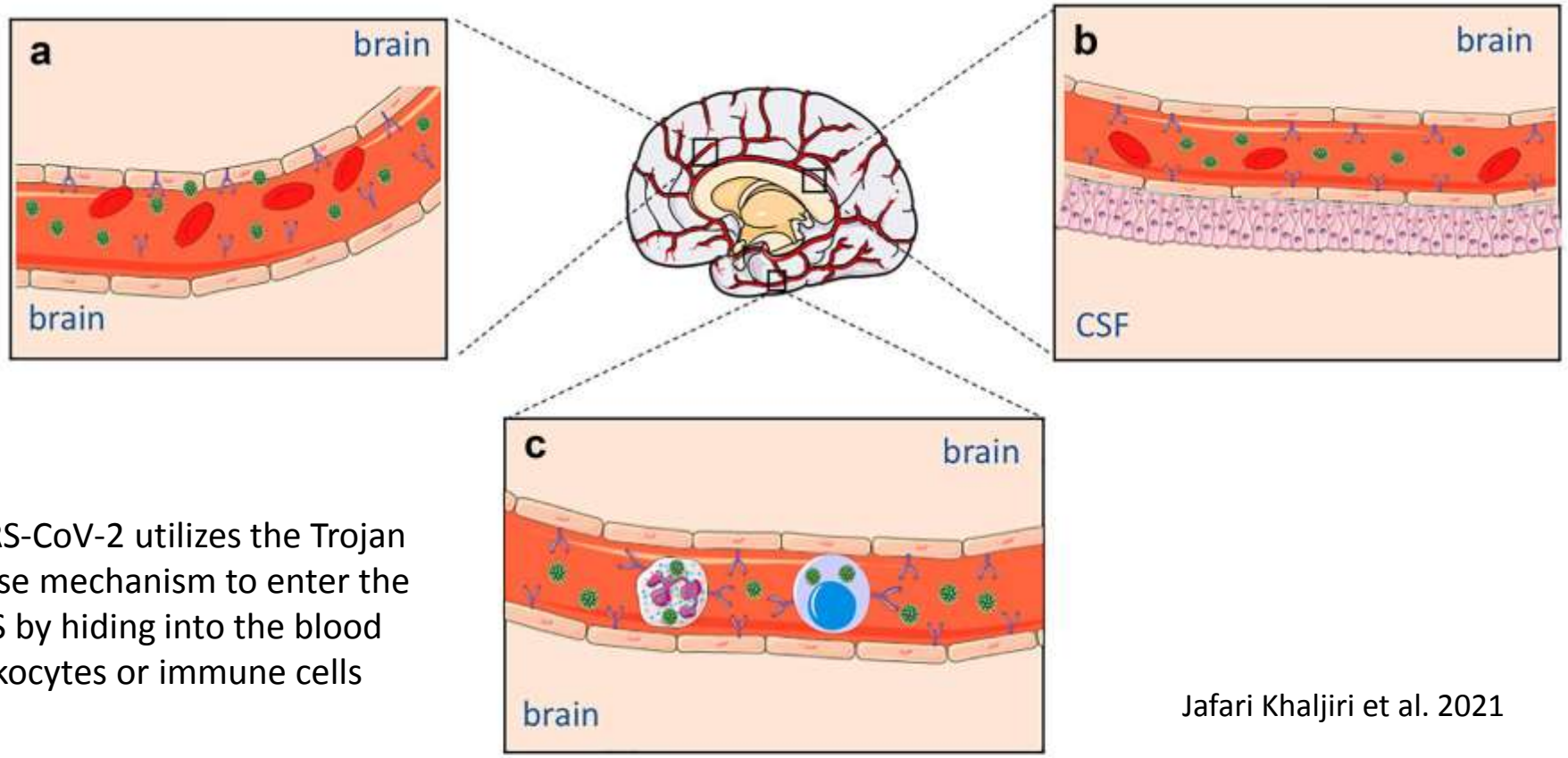
The potential impairment of these structures could be the neural substrate for the clinical manifestations of COVID-19 and the post-acute COVID-19 syndrome.

Hernández et al. 2021

Hematogenous route of SARS-CoV-2 entry into the CNS

SARS-CoV-2 can pass the blood–brain barrier from the cerebrospinal fluid into the brain tissue

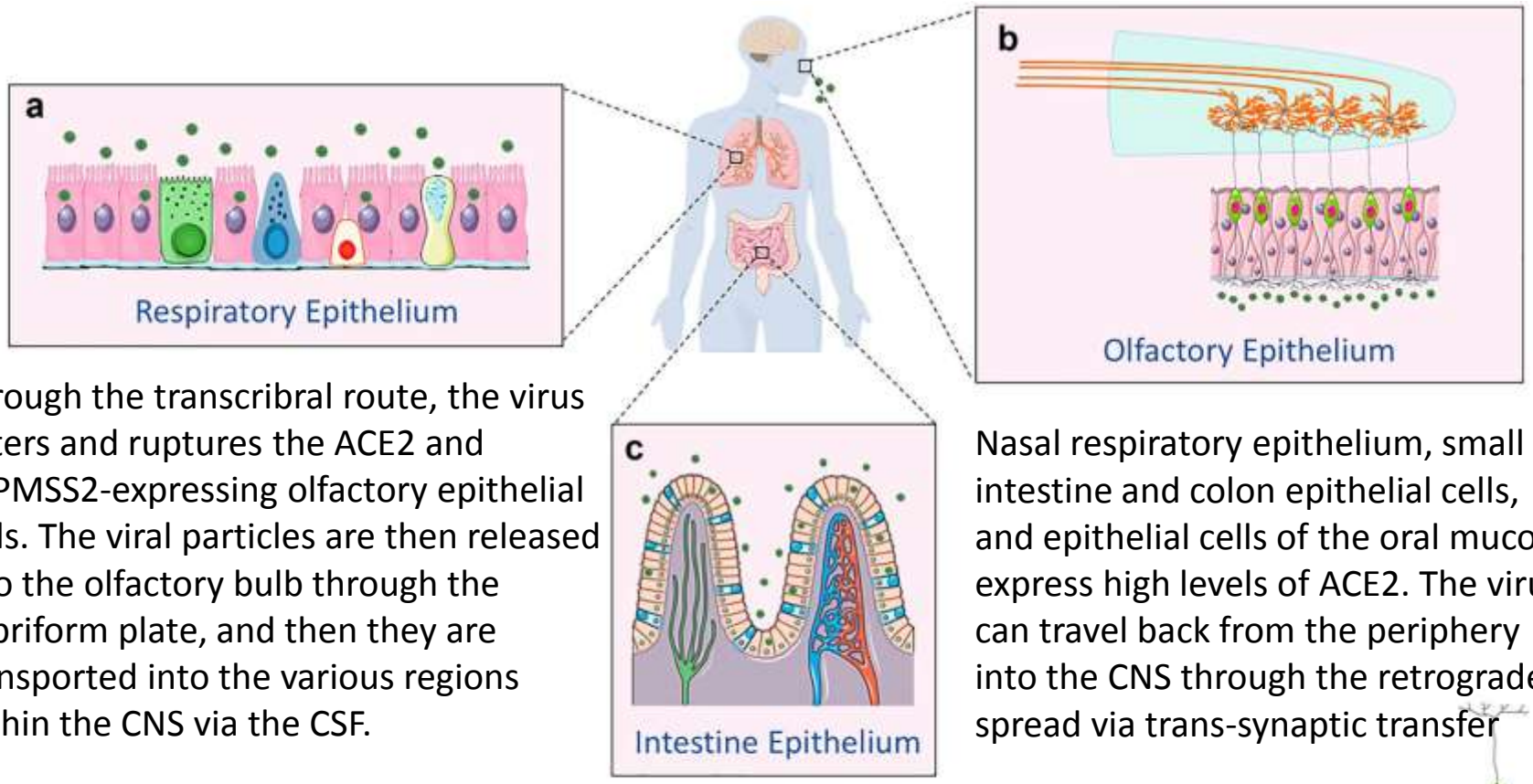
The epithelium of blood–cerebrospinal fluid barrier across the choroid plexus in the ventricles highly expresses ACE-2



SARS-CoV-2 utilizes the Trojan horse mechanism to enter the CNS by hiding into the blood leukocytes or immune cells

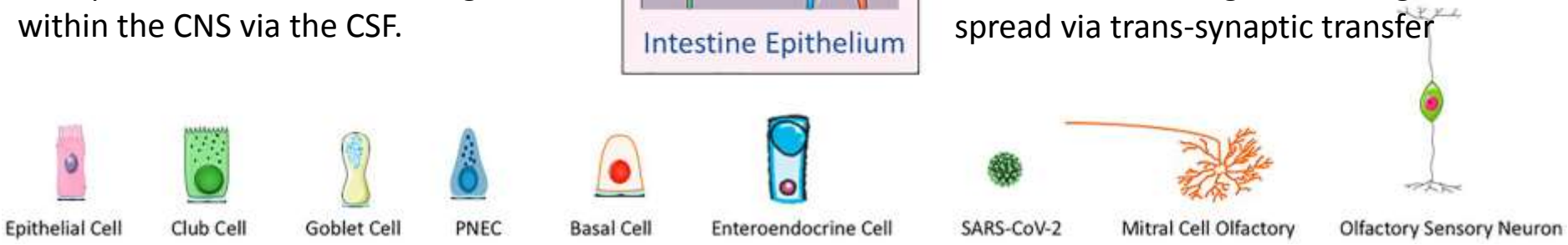
Jafari Khaljiri et al. 2021

Neuronal pathways of SARS-CoV-2 entry into the CNS



Through the transcribral route, the virus enters and ruptures the ACE2 and TRPMSS2-expressing olfactory epithelial cells. The viral particles are then released into the olfactory bulb through the cribriform plate, and then they are transported into the various regions within the CNS via the CSF.

Nasal respiratory epithelium, small intestine and colon epithelial cells, and epithelial cells of the oral mucosa express high levels of ACE2. The virus can travel back from the periphery into the CNS through the retrograde spread via trans-synaptic transfer



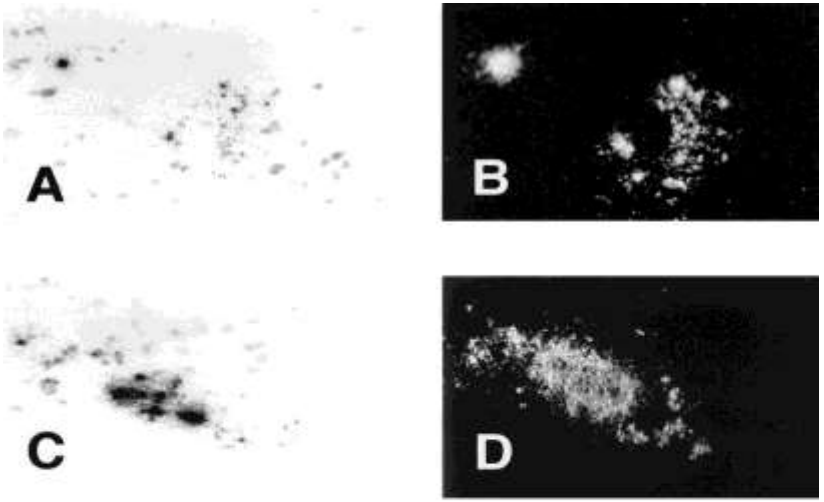
Jafari Khaljiri et al. 2021

Detection of coronaviruses in the human brain

HCoV-OC43: Arbour et al. 2000

bright-field dark-field

A,B,C,D: Two different blocks from the same multiple sclerosis patient



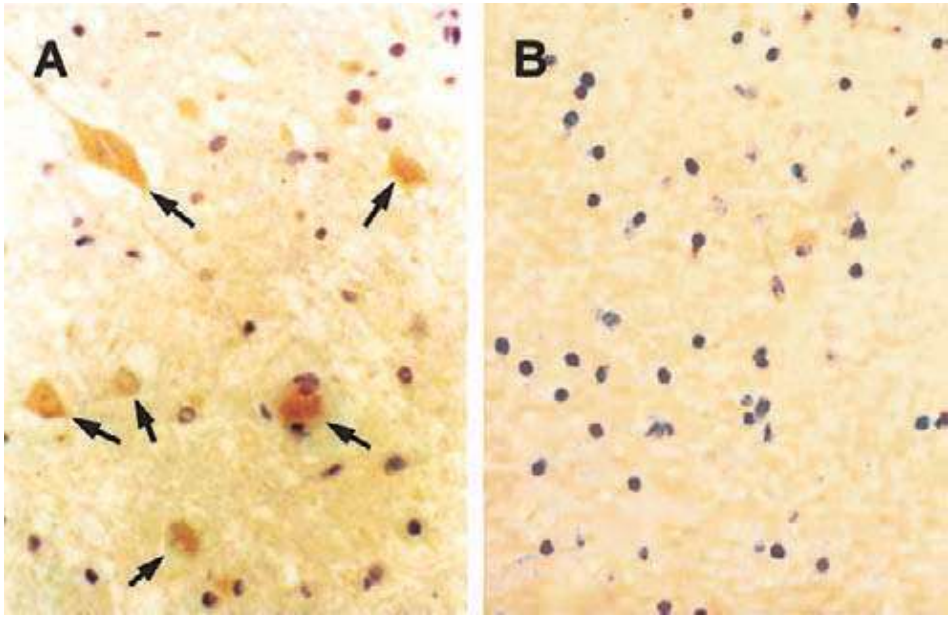
E,F: Negative control: treated by RNase

In situ hybridization for HCoV-OC43 RNA in human brain sections (autopsy), using a radiolabeled riboprobe for the viral N gene, confirmed the presence of viral RNA in brain parenchyma, outside blood vessels, suggesting persisting infection. 40 of 90 donors were positive for 229E and 21 of 90 were positive for OC43. Higher prevalence of OC43 in multiple sclerosis patients.

SARS-CoV: Xu et al. 2005

Patient with SARS-CoV

Patient who died in a car accident



-Immunohistochemistry stains for N protein SARS-CoV in brain tissue from a patient during autopsy. Both neurons and glial cells were labeled.

-Pathologic examination revealed necrosis of neurons cells and proliferation of glial cells.

-Direct evidence that SARS human coronavirus is capable of infecting the central nervous system

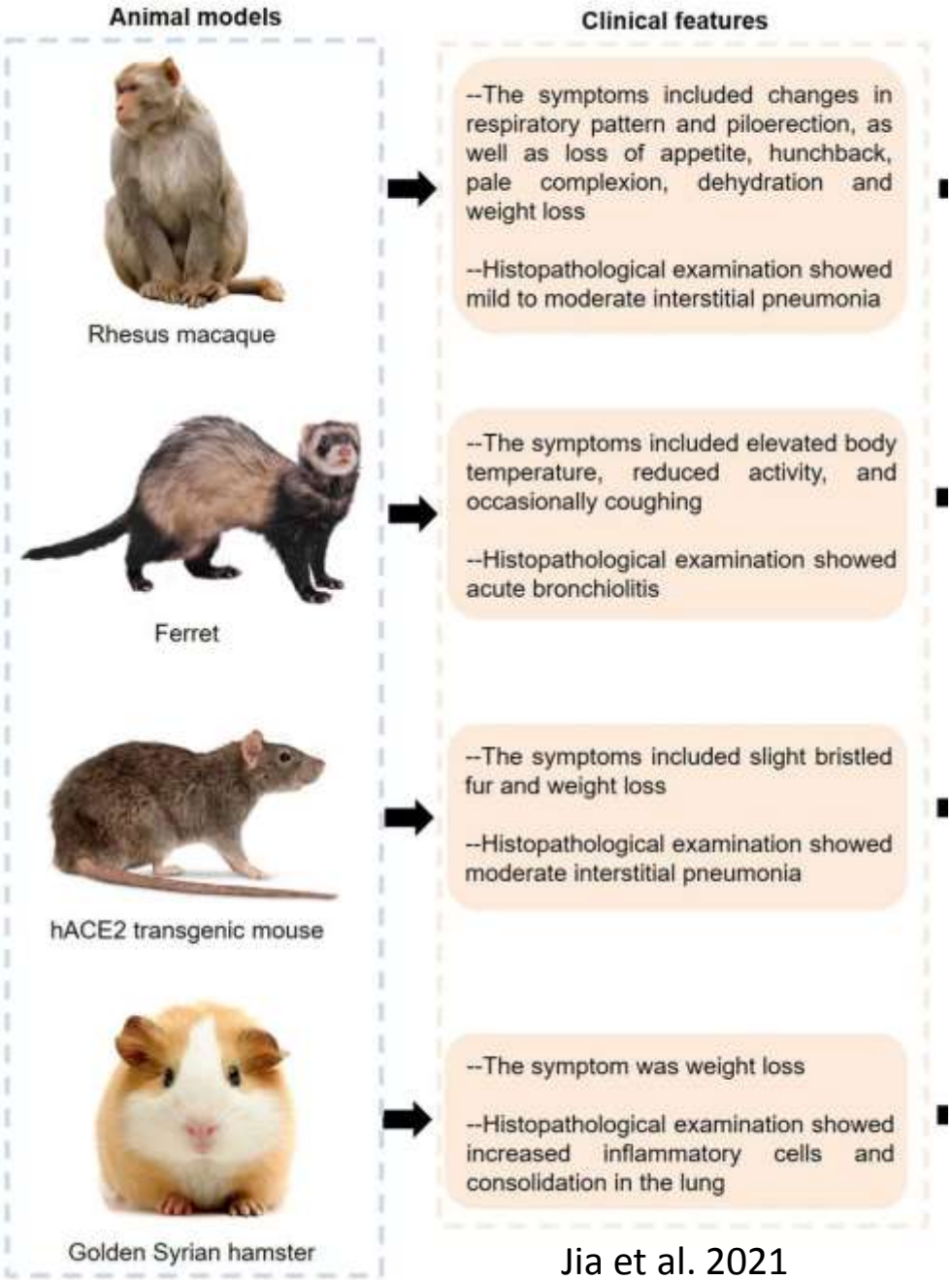
Animal Models of SARS-CoV-2 Infection

Good for testing vaccines, monoclonal antibodies and antiviral drugs.

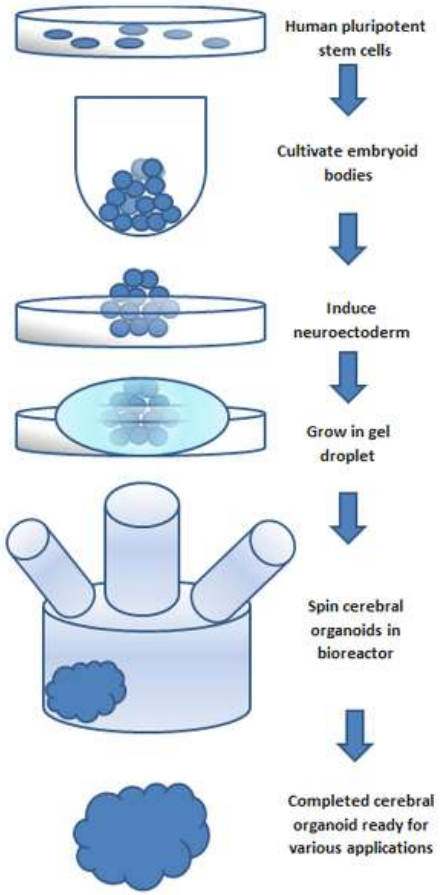
Good for studying viral transmission and prophylactic intranasal drug administration.

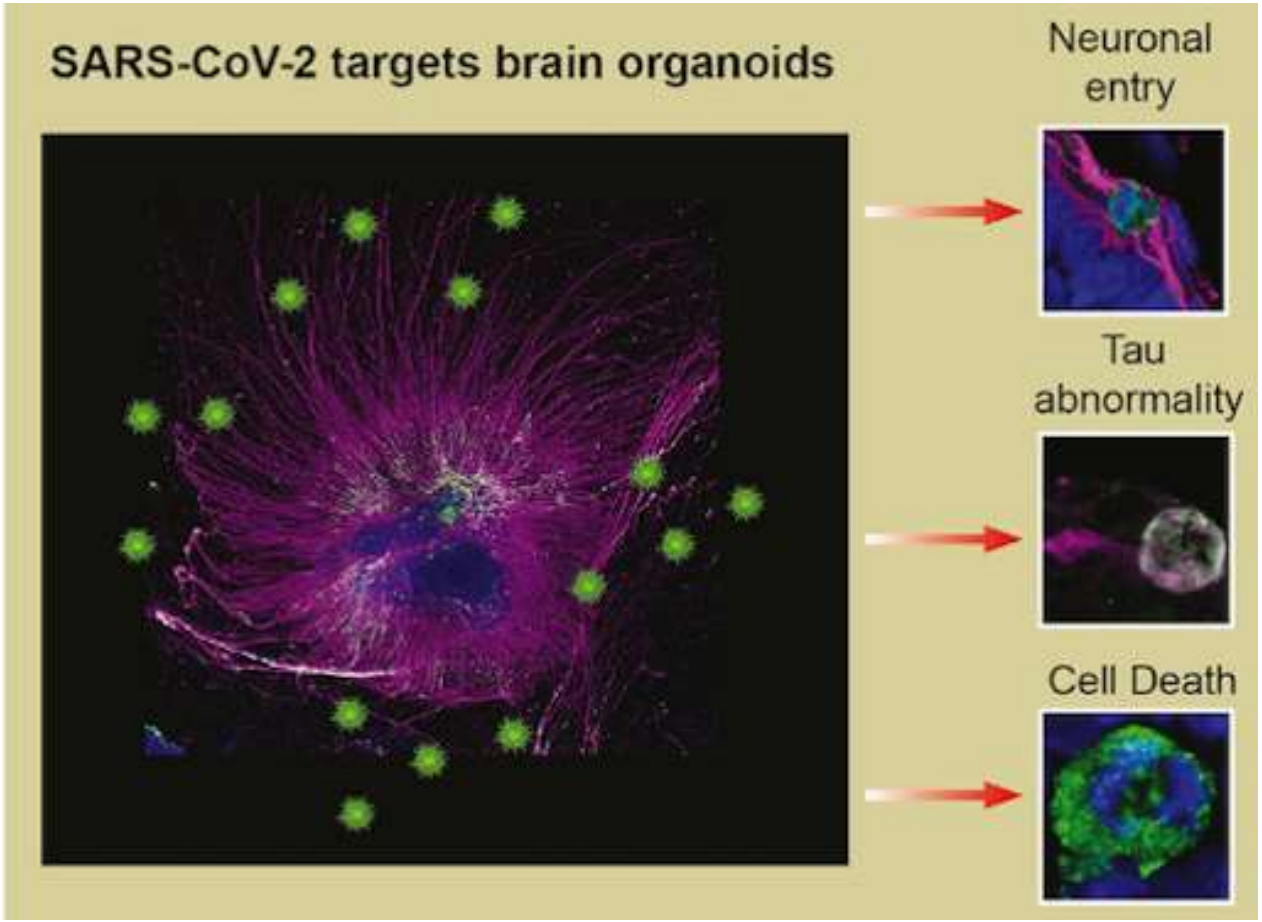
Genetically modified to have human ACE2 (hACE2) receptors allowing virus-entry into the cells. Relatively low cost and more practical. Lab mice, which could not be infected with original strains of SARS-CoV-2, can be infected with new virus variants (FDA, FAQ).

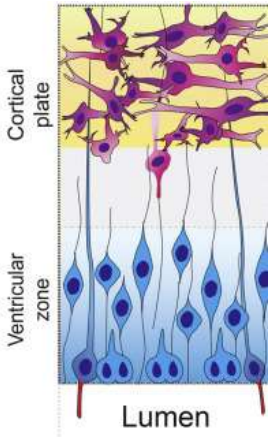
Good for studying SARS-CoV-2 transmission via direct contact or aerosols.



Jia et al. 2021







Modelling coronavirus exposure of the CNS is critical to assess the cellular tropism and potential neurological consequences of infection.
A Düsseldorf isolate of SARS-CoV-2 is shown to enter human cerebral organoids and preferably target neuronal cells.

- Clinical SARS-CoV-2 strain targets neurons of 3D human brain organoids.
- SARS-CoV-2 does not appear to actively proliferate in neurons.
- SARS-CoV-2 exposure is associated with altered distribution of Tau from axons to soma, hyperphosphorylation, and apparent neuronal death.

Ramani et al. 2020

Infection of Brain Organoids and 2D Cortical Neurons with SARS-CoV-2 Pseudovirus

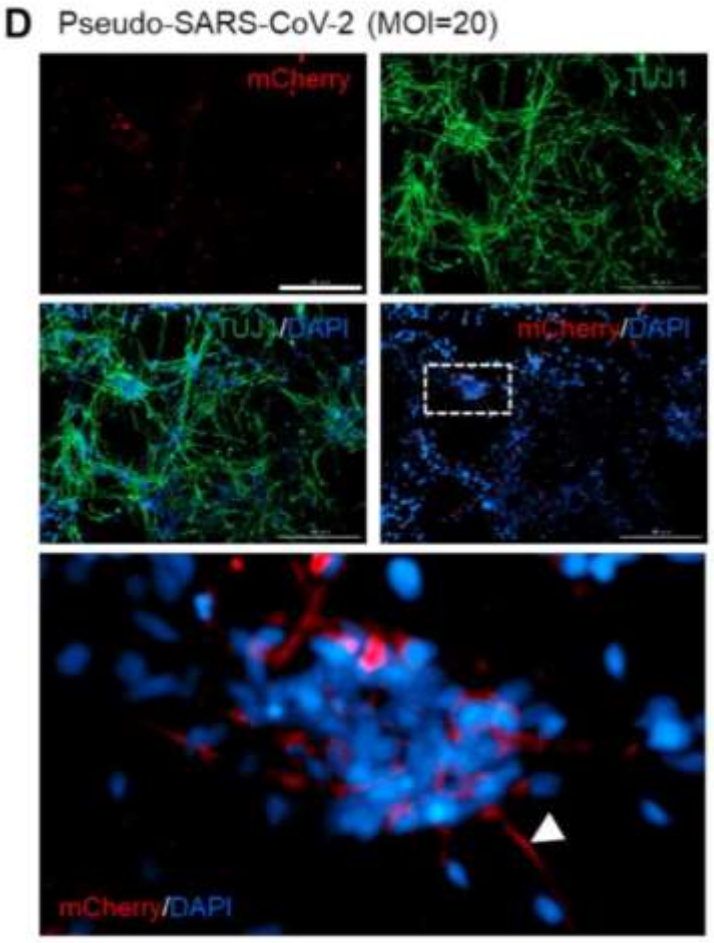
Pseudoviruses are safe to use because they lack all the genetic materials to replicate.

2D cortical neurons were treated with different doses (multiplicity of infection MOI = 1, 5, 20) of pseudotyped SARS-CoV-2

The pseudo-SARS-CoV-2-infected neurons exhibited a weak but clear mCherry signal, which indicates the infection by the viral particles

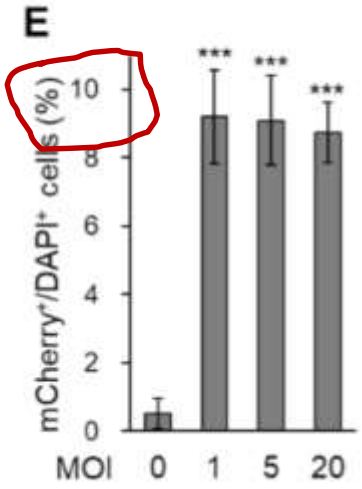
mCherry signal was detected in the axon of the neurons, despite the absence of ACE2 in the neural axon.

The infectivity of pseudo-SARS-CoV-2 on neurons was not elevated in proportion to the increase in viral loads, but remained at ~ 10%



DAPI stains cell nuclei in blue

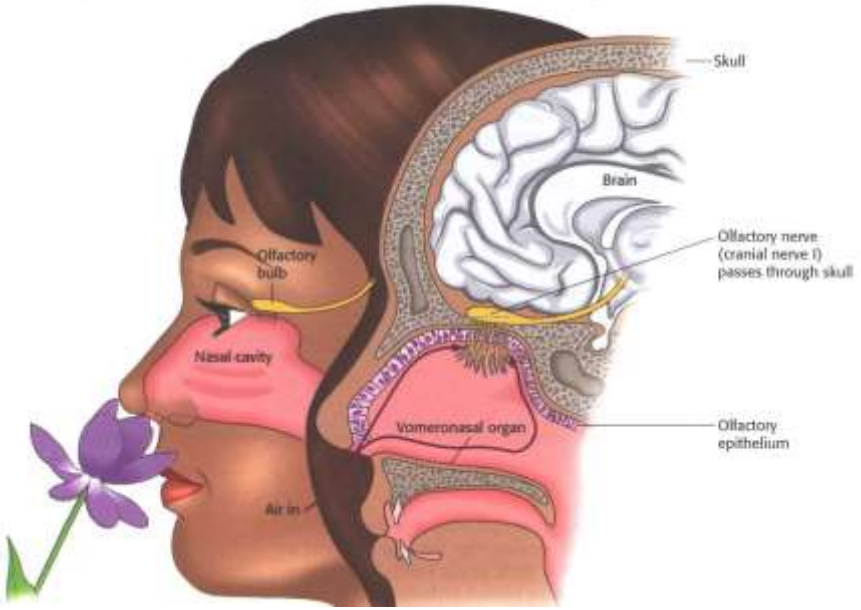
mCherry labels infected cells

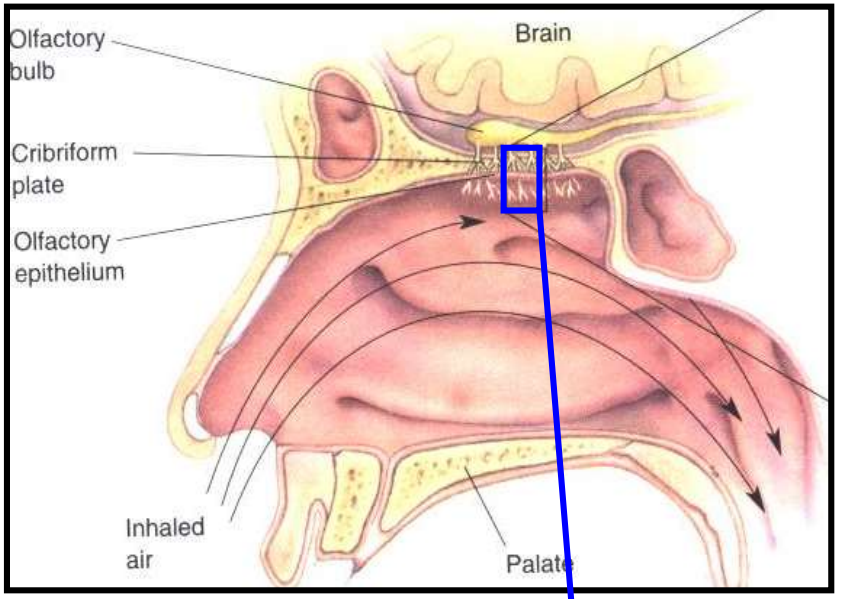


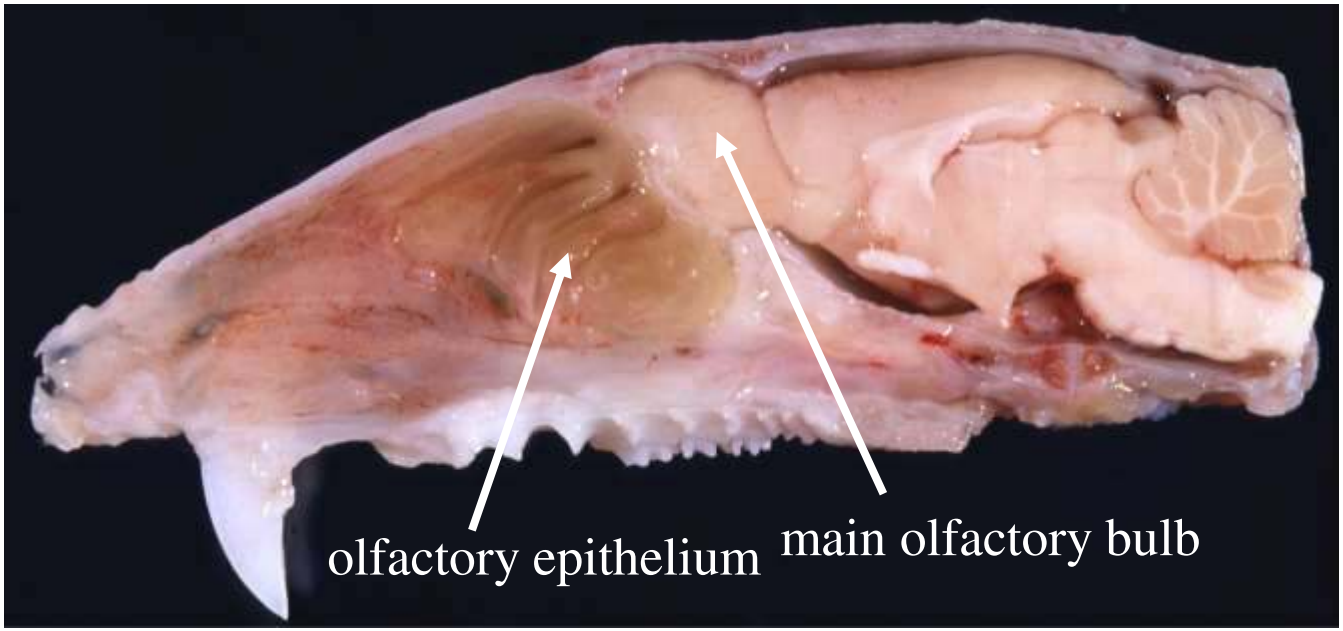
-Only limited portions of cortical neurons are susceptible to infection with the SARS-CoV-2 pseudovirus because cortical neurons expresses relatively low levels of ACE2.
-Virus can be translocated into axons/dendrites

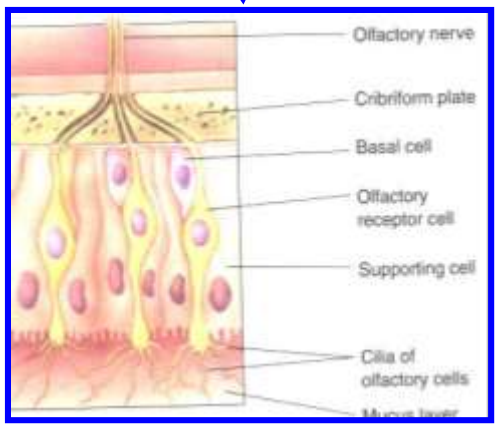
(Yi et al. 2020)

The human and rodent main olfactory system



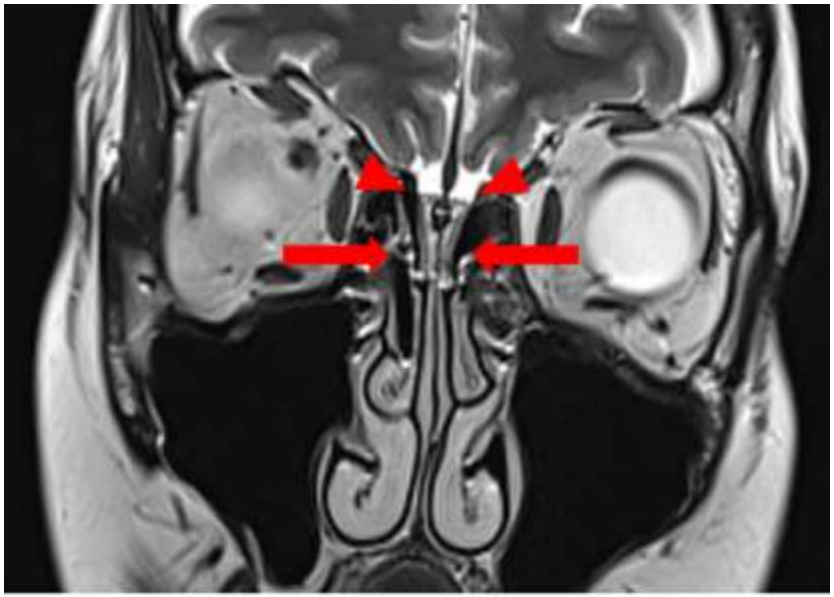






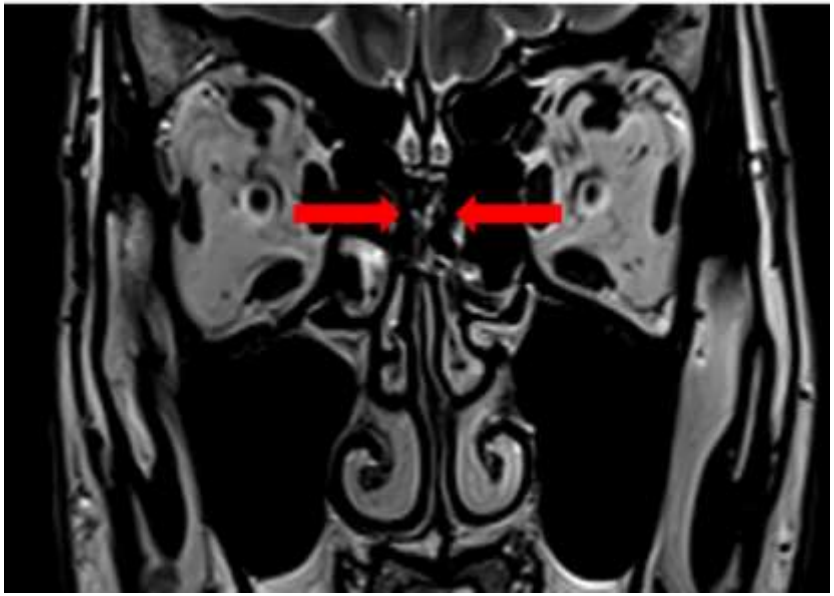
Olfactory bulb and mucosa abnormalities in persistent COVID-19-induced anosmia: a magnetic resonance imaging study

Adult, non-hospitalized patients who recovered from COVID-19 infection with olfactory dysfunction for ≥40 days after symptom onset



Coronal brain MRI of a patient with persistent anosmia and COVID-19 showing thickening and edema of the olfactory mucosa (arrows) and moderate visual atrophy of the olfactory bulbs (arrowheads).

Neuroimaging evaluation of the cases and of age- and sex-matched non-COVID-19 healthy historical controls (*n* = 8)



Coronal brain MRI of a control patient showing normal findings of the olfactory mucosa (arrows).

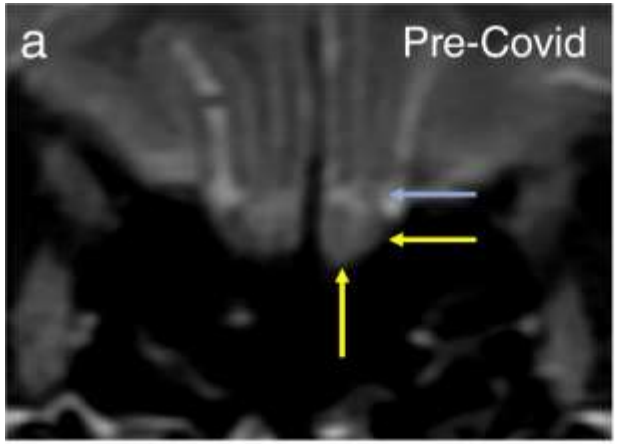
Tsivgoulis et al. 2020

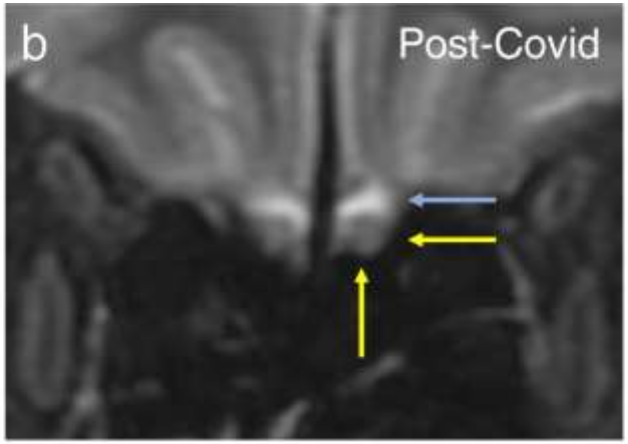
COVID-19-induced anosmia associated with olfactory bulb atrophy

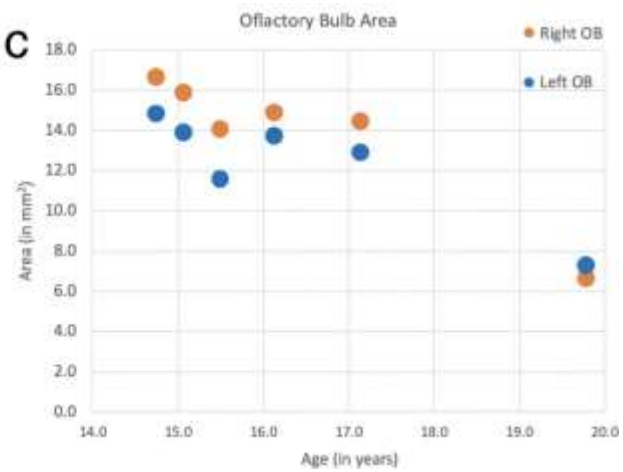
Chiu & al. 2020

The olfactory nerve is small and only well seen on dedicated skull base magnetic resonance imaging (MRI), so prospective assessments of its changes have been lacking.

19-year-old female: skull base MRI, 2 months after the onset of anosmia.



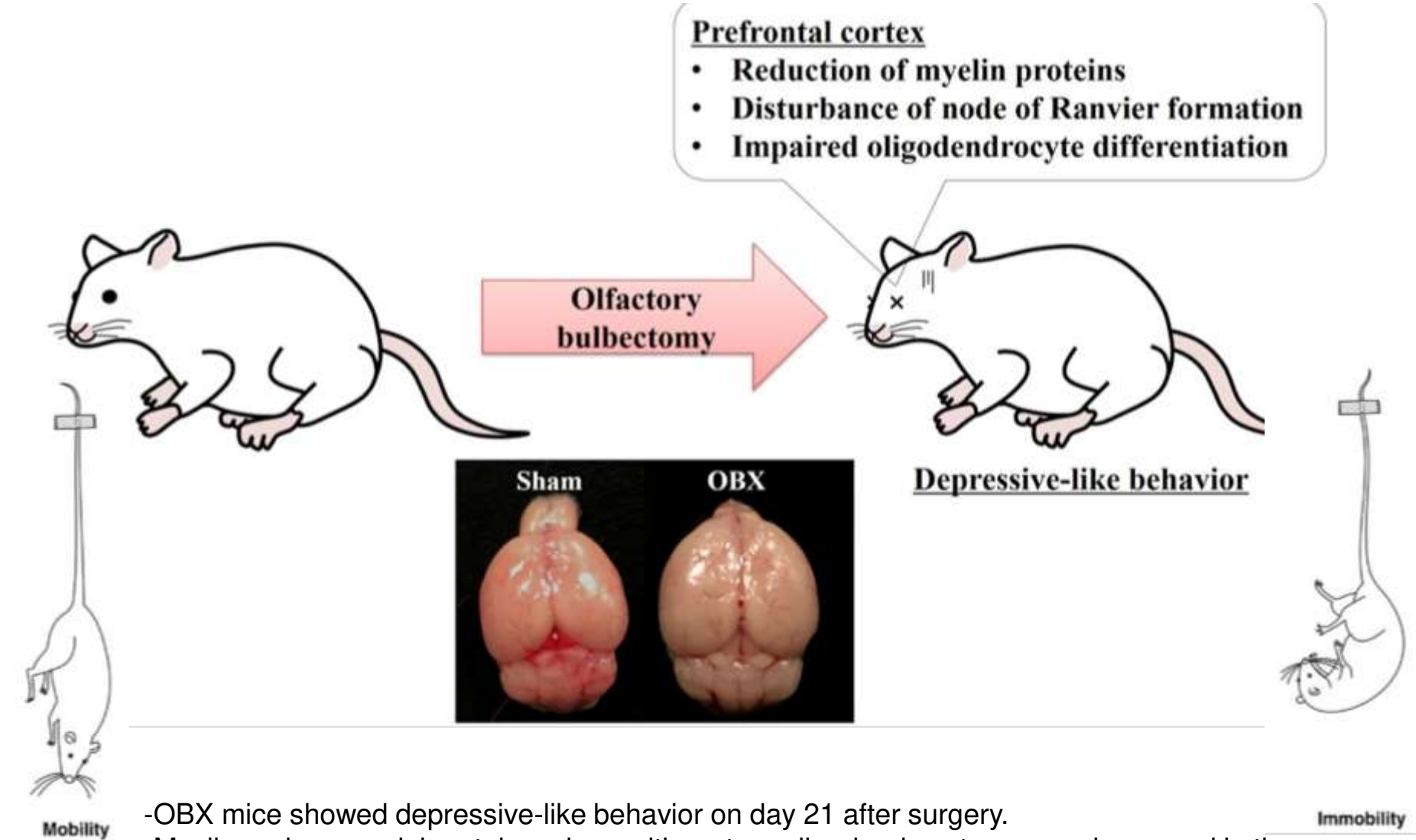




Coronal T2 fat-suppressed 3-mm thick images a before and b after diagnosis of COVID-19. Notice the smaller size of olfactory bulbs (anatomic left in yellow arrows) within the olfactory grooves, as evidenced by increased CSF (blue arrows) above the nerve.

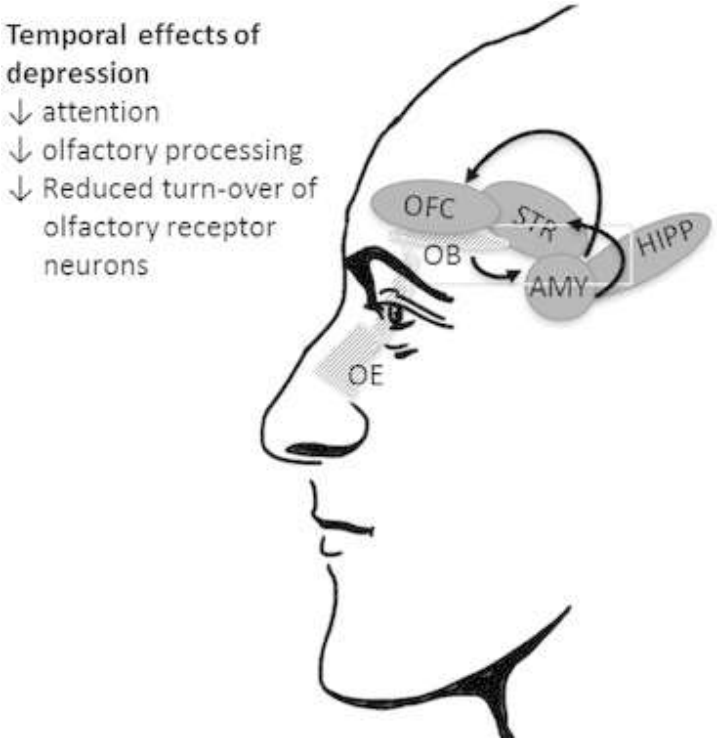
Time course of patient's olfactory bulb size over 5 years, with a pronounced decrease on the most recent timepoint on the far right, occurring after diagnosis of COVID-19

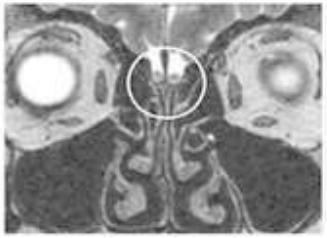
Disturbance of prefrontal cortical myelination in olfactory bulbectomized mice is associated with depressive-like behavior (Takahashi et al. 2021)



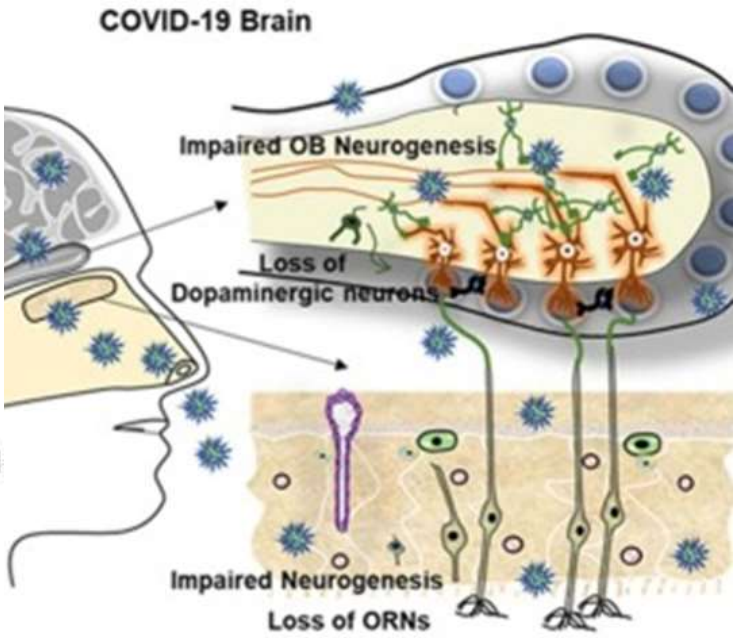
-OBX mice showed depressive-like behavior on day 21 after surgery.
-Myelin and paranodal proteins, along with mature oligodendrocytes, were decreased in the prefrontal cortex of OBX mice on day 21 after surgery.
-Imipramine improved OBX-induced depressive-like behavior and abnormal myelination.
-Oligodendrocytes and myelin may be new therapeutic targets in depression.

Olfaction as a marker for depression (Croy and Hummel 2016)





Stable effects of reduced OB volume
↓ Dopamin, ↓ Serotonin
↓ signaling to limbic and reward neurocircuits
↓ interoceptive awareness
↑ Depression

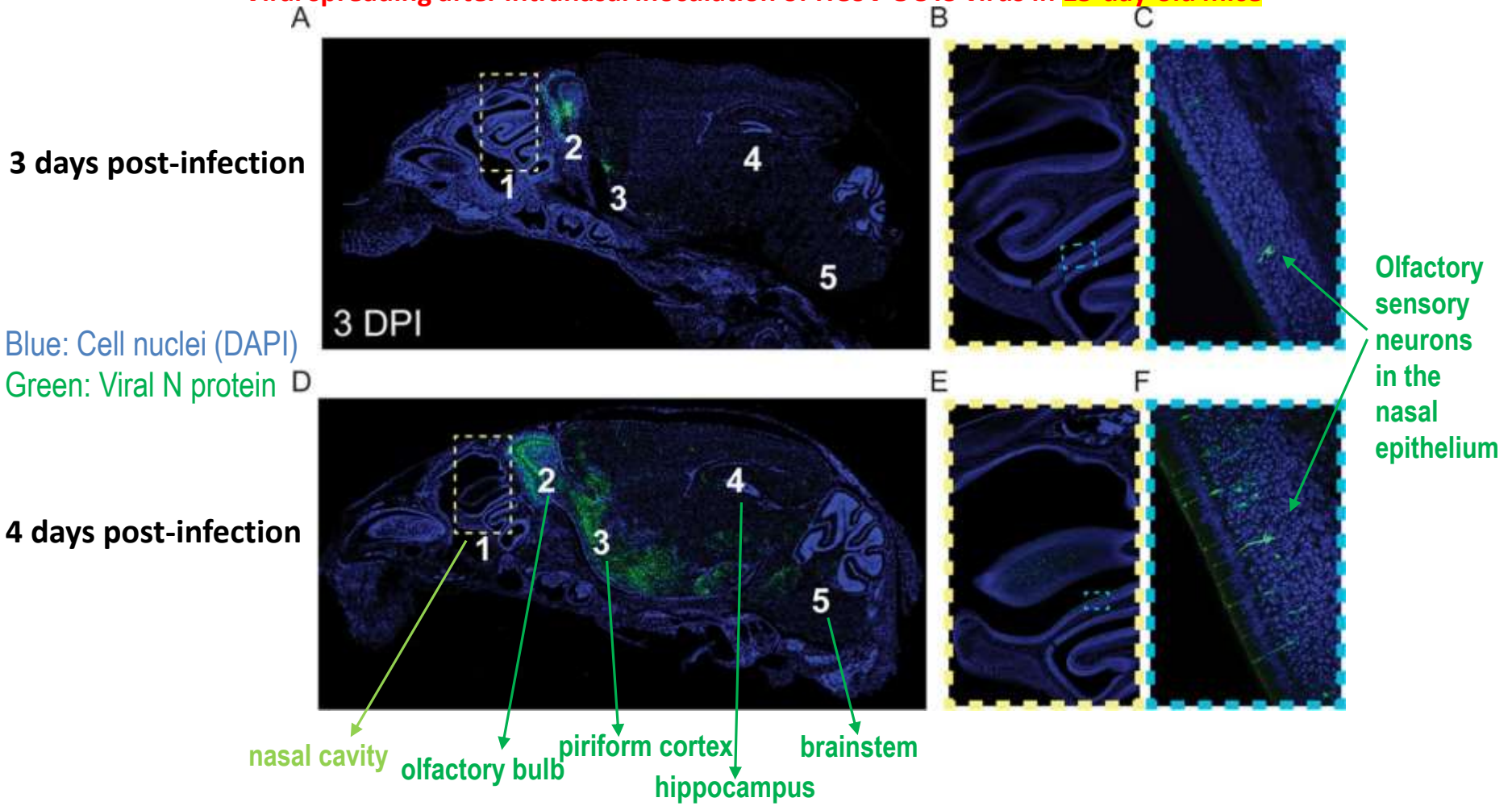


Temporal and stable relation between olfaction on depression. Reduced olfactory function in depression is potentially caused by reduced attention and reduced turn-over rate of olfactory receptor neurons in the olfactory epithelium (OE). Those effects are temporal and diminish after remission.

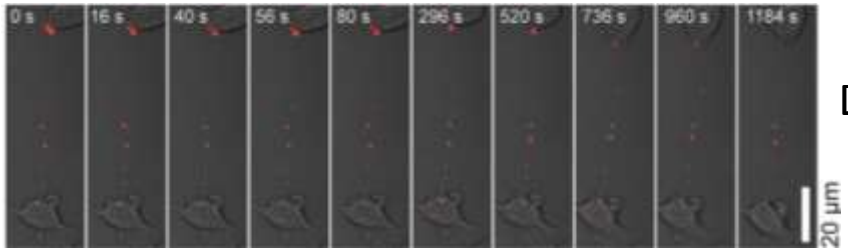
In contrast, smaller olfactory bulb (OB) volume is stable and relates to enhanced depression rates, potentially caused by mechanisms of reduced signaling from OB to amygdala (AMY), hippocampus (HIP), striatum (STR) and orbitofrontal cortex (OFC)

Human coronavirus OC43 neuroinvasion of the CNS initiates at the olfactory bulb: Propagation via passive diffusion of released viral particles and axonal transport

Viral spreading after intranasal inoculation of HCoV OC43 virus in 15-day-old mice



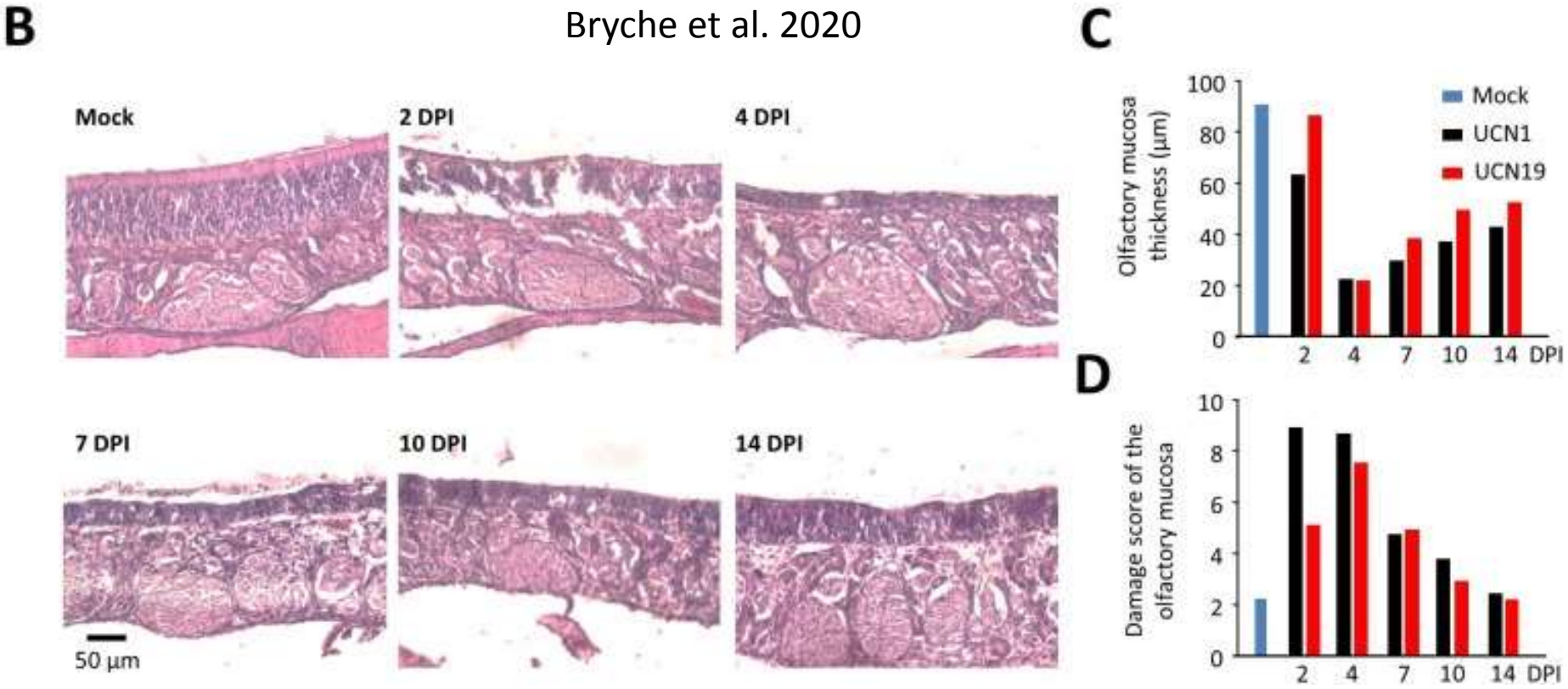
Viral movement (red dots) along the axon was assessed by live cell confocal microscopy in human neuroblastoma cell line.



Dubé et al. 2018

In hamsters, SARS-CoV-2 nasal instillation induces massive damage of the olfactory epithelium 2 days post infection (DPI) which has partially healed 14 DPI

Bryche et al. 2020



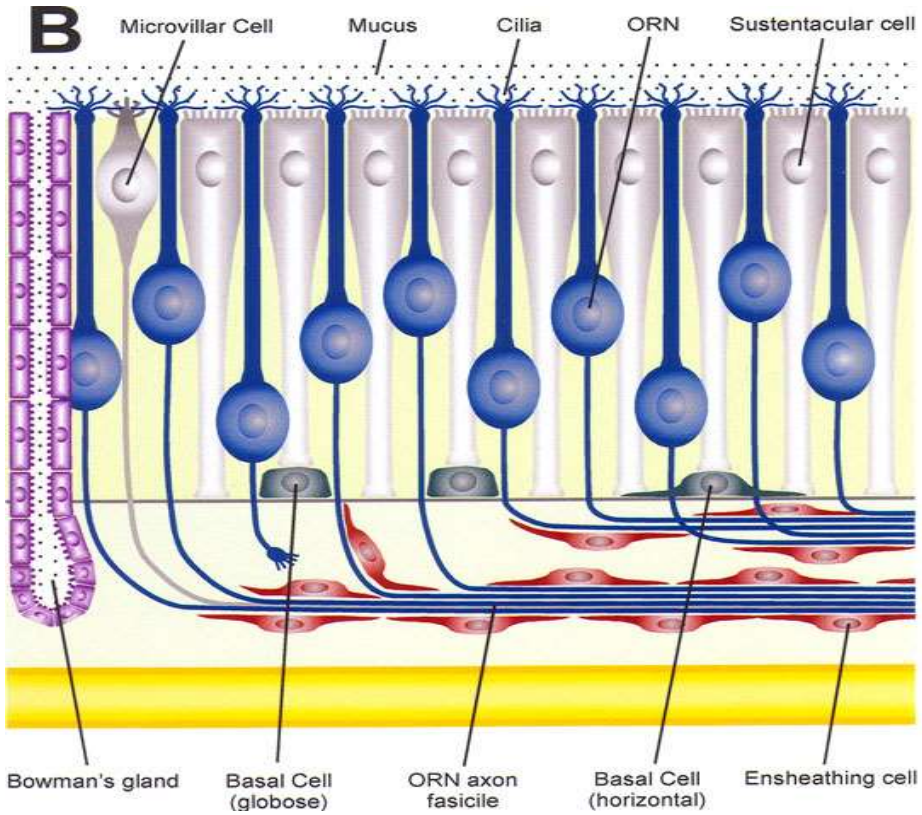
-Evolution of the nasal cavity from mock infected hamsters to 14 days post infection (DPI) in UCN19 virus-infected hamsters.

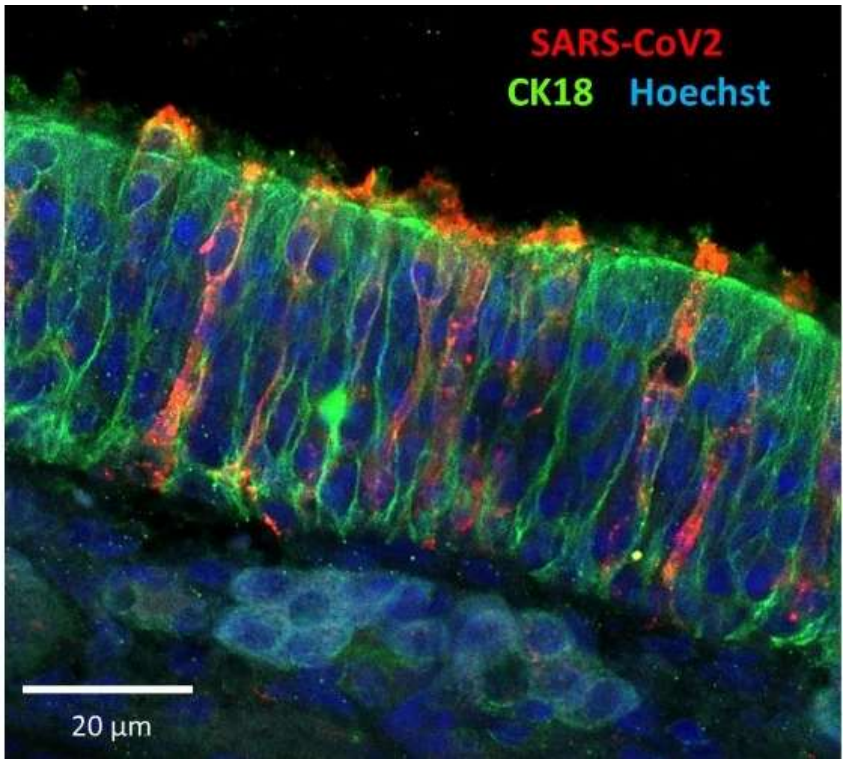
-Massive destruction of the olfactory epithelium and the cilia layer of the olfactory sensory neurons.

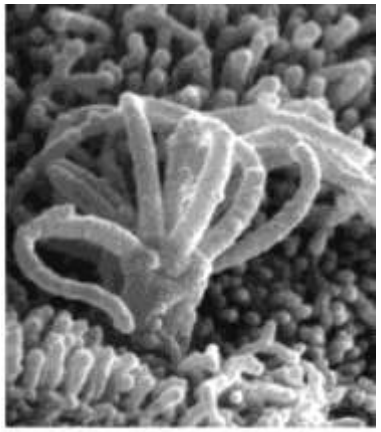
-Olfactory transduction is not functional because the cilia have the receptors that bind odors.

Notes: Biosafety level 3 facility, France; Hamsters (UCN1 &19 strains) were ~ 2 months old

Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in hamsters







-Double staining of the olfactory mucosa against **SARS-CoV-2** and a marker of sustentacular cells (CK18, 4 DPI, UCN19) which colocalize.
-In golden Syrian hamsters, massive damage of the OE as early as 2 days post-nasal instillation of SARS-CoV-2, resulting in a major loss of cilia necessary for odor detection.
-Infection of a large proportion of sustentacular cells but not of olfactory neurons, and the virus was not detected in the olfactory bulbs.

Bryche et al. 2020

Clinical Outcomes for Patients With Anosmia 1 Year After COVID-19 Diagnosis (Renaud & al. 2021)

97 patients (67 women) <50 years old. only one-half of the cohort underwent objective olfactory testing. However, all participants were contacted at 12 months and almost all reported a subjective return of smell.

At 8 months, objective olfactory assessment confirmed full recovery in 49 of 51 patients (96.1%). Two patients remained hyposmic at 1 year, with persistent abnormalities

Patterns and clinical outcomes of olfactory and gustatory disorders in six months: Prospective study of 1031 COVID-19 patients (Teaima et al. 2021)

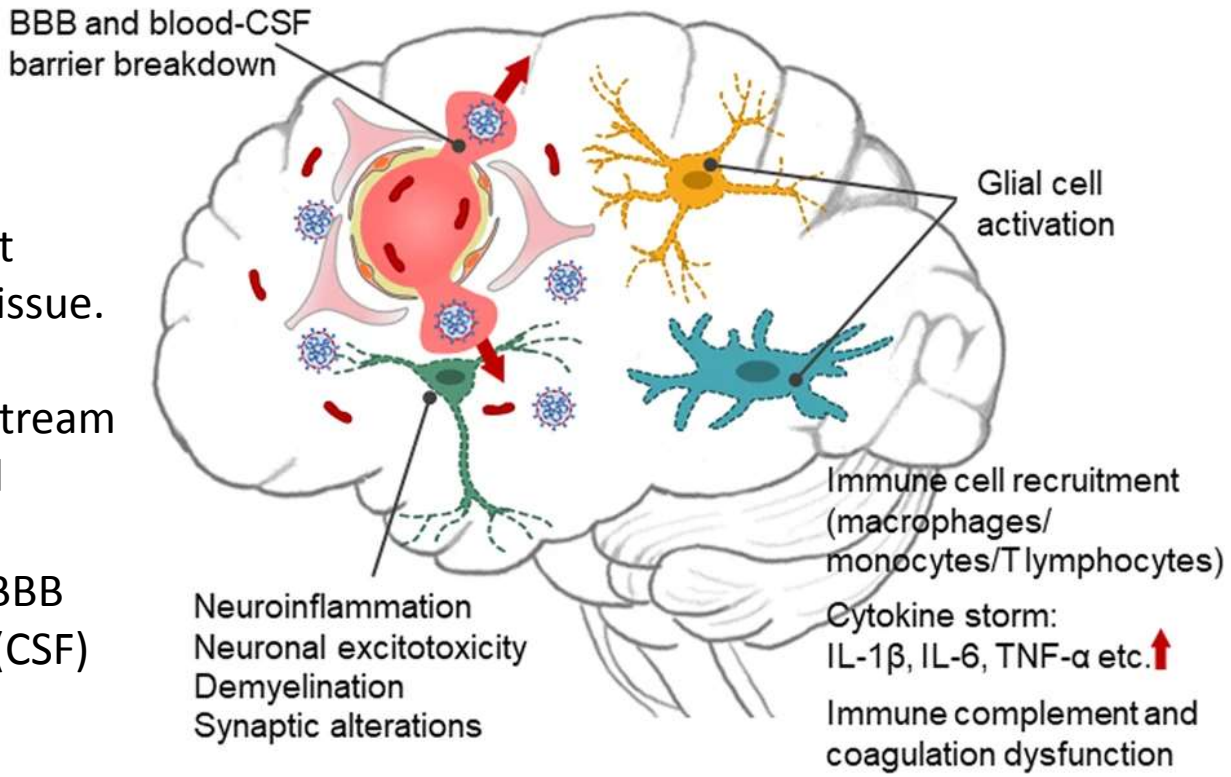
1031 patients were included in the study, aged 18 to 69 years old, with 31.8% were male. Olfactory/gustatory dysfunctions occurred after other COVID-19 symptoms in 43.5% of cases, occurred suddenly in 80.4% and gradually in 19.6%.

At 6-month follow up, 680 patients (66%) recovered completely, 22.1% recovered partially while 11.9% did not recover. Most improvement occurred in the first two weeks.

Parosmia (distorted smell perception) is an independent predictor for complete recovery, while phantosmia (olfactory hallucination) is significantly associated with lower probability of complete recovery.

Proposed consequences of SARS-CoV-2 neuroinvasion

(Han et al. 2021)



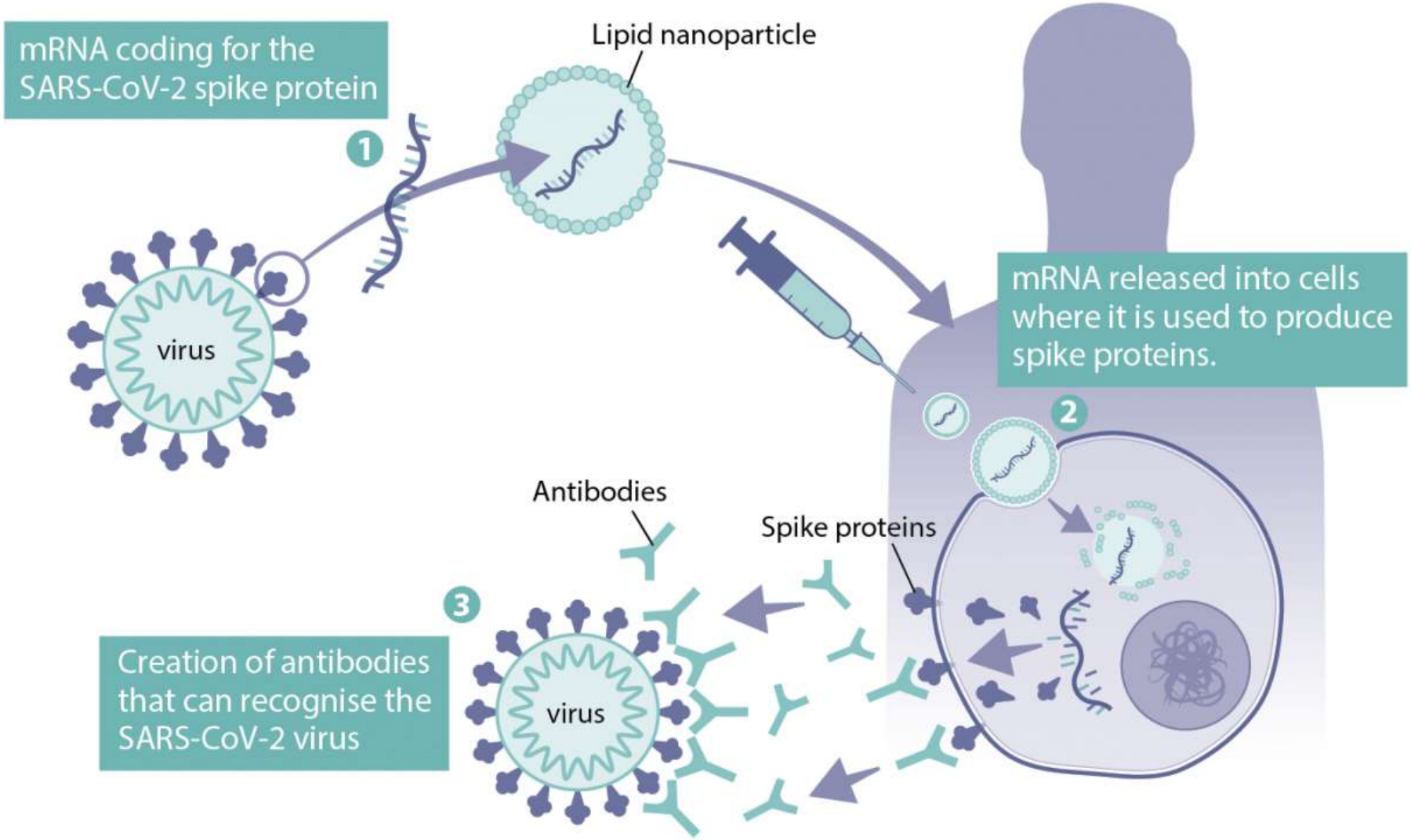
Growing evidence suggests that SARS-CoV-2 may invade brain tissue.

The virus may enter the bloodstream through multiple pathways and infect the neurovascular cells, causing the breakdown of the BBB and blood–cerebrospinal fluid (CSF) barrier.

This will further trigger the inflammatory responses, including the recruitment of macrophage and T lymphocytes, activation of astrocytes and microglia, and it will cause a vicious cycle of the cytokine storm.

The infection may also cause immune-mediated demyelination, neuronal excitotoxicity, and dysfunction of synaptic plasticity, which ultimately contributes to worsened neurological and neuropsychiatric symptoms in COVID-19 patients.

How do mRNA vaccines work?



-Vaccines work by mimicking an infection and training the immune system to recognize a disease-causing agent, such as viruses or bacteria.

-Instead of including a protein from the pathogen or the pathogen itself in the vaccine, mRNA vaccines contain the genetic instructions for producing that protein in our own cells.

Vaccine hesitancy: Concerns, misinformation and conspiracy theories

Vaccine hesitancy is a worldwide issue that has existed since the invention of vaccination, and it resulted in unnecessary deaths that were preventable
Conspiracy theories & misinformation: falsehood spread at least six times faster than the truth (Vosoughi et al 2018).

Can mRNA vaccines alter human genome?
No, because we do not have an enzyme "reverse transcriptase" which converts RNA to DNA. Our genes are more likely to be altered by COVID-19 virus and some other viruses. About 8 - 40% of our DNA consists of remnants of ancient viruses (Griffith 2001)

Do you need the vaccine if you are healthy or if you have been already infected?
Vaccines can much better boost the immune system against the original virus and its variants than the natural infection. Re-infection can occur within 3 months with more severe symptoms (Natasha Hinde 2021).

Can COVID-19 vaccines affect fertility?
It is actually the virus, not the vaccine, that is likely to cause problems of infertility. (Sharma et al. 2021).

Human beings have only two choices: the virus or the vaccine. The COVID-19 adverse effects could be long-lasting or irreversible. In contrast, mRNA vaccines are 99.999% safe, effective and biodegradable.

Safety of COVID-19 Vaccines

COVID-19 vaccines are as safe as flu vaccines and other vaccines that are routinely administered to our children before they are admitted to schools.

According to CDC, as of Nov. 1, 2021, 423 million doses of COVID-19 vaccines have been administered so far in the U.S. under the most intense safety monitoring system.

Reports of adverse events to Vaccine Adverse Event Reporting System (VAERS) following vaccination, including deaths (0.0018%), do not necessarily mean that the vaccine is the culprit (CDC 2021).

Arkansas
Immunization Record
Official Document

istory/Allergies/Precautions/Contraindications

	Vaccine	Date Given MM/DD/YYYY	Doctor or Clinic	Date Next Due MM/DD/YYYY
Influenza (Five Most Recent)				
1	Influenza Quad Inj PF	10/09/2017	LITTLE ROCK9	08/05/2021
2	Influenza Quad Inj PF	10/15/2016	LITTLE ROCK9	
3				
4				
5				
COVID-19 (Five Most Recent)				
1				07/20/2022
2				
3				
4				
5				
Travel				
1				
2				
3				
Other				

★ = Adverse reaction ! = Invalid Min Age/Interval ⊘ = Determined Invalid by Provid

	Vaccine	Date Given MM/DD/YYYY	Doctor or Clinic	Date Nex MM/DD/Y
DTaP / TD / Tdap				
1	DTaP-Hib-IPV (Pentac	09/20/2010	LITTLE ROCK9	08/05/20
2	DTaP-Hib-IPV (Pentac	11/19/2010	LITTLE ROCK9	
3	DTaP-Hib-IPV (Pentac	01/24/2011	LITTLE ROCK9	
4	DTaP (Daptacel)	10/21/2011	LITTLE ROCK9	
5	DTaP (Daptacel)	07/24/2014	LITTLE ROCK9	
6				
Polio				
1	DTaP-Hib-IPV (Pentac	09/20/2010	LITTLE ROCK9	
2	DTaP-Hib-IPV (Pentac	11/19/2010	LITTLE ROCK9	
3	DTaP-Hib-IPV (Pentac	01/24/2011	LITTLE ROCK9	
4	Polio-IPV	08/29/2014	LITTLE ROCK9	
5				
Hib				
1	DTaP-Hib-IPV (Pentac	09/20/2010	LITTLE ROCK9	
2	DTaP-Hib-IPV (Pentac	11/19/2010	LITTLE ROCK9	
3	DTaP-Hib-IPV (Pentac	01/24/2011	LITTLE ROCK9	
4	Hib (PRP-T) (ACTHIB)	10/21/2011	LITTLE ROCK9	
5				
Pneumococcal				
1	PCV13	09/20/2010	LITTLE ROCK9	07/20/20
2	PCV13	11/19/2010	LITTLE ROCK9	
3	PCV7	01/24/2011	LITTLE ROCK9	
4	PCV13	07/26/2011	LITTLE ROCK9	
5				
Rotavirus				
1	Rotavirus (RotaTeq)	09/20/2010	LITTLE ROCK9	
2	Rotavirus (RotaTeq)	11/19/2010	LITTLE ROCK9	
3	Rotavirus (RotaTeq)	01/24/2011	LITTLE ROCK9	
4				
Hep A				
1	Hep A, ped/adol, 2D	07/26/2011	LITTLE ROCK9	
2	Hep A, ped/adol, 2D	01/26/2012	LITTLE ROCK9	
3				
Hep B				
1	Hep B, ped/adol	12/14/2012	PR	
2	Hep B, ped/adol	01/18/2013	LITTLE ROCK9	
3	Hep B, ped/adol	07/24/2013	LITTLE ROCK9	
4				
MMR				
1	MMR	10/21/2011	LITTLE ROCK9	
2	MMR	07/24/2014	LITTLE ROCK9	
3				
Varicella (CPOX)				
1	Varicella	07/26/2011	LITTLE ROCK9	
2	Varicella	08/29/2014	LITTLE ROCK9	
3				
Meningococcal				
1				08/05/20
2				
HPV				
1				08/05/20

Olfactory training using odorants

Odorant categories include floral, fruity, spicy, resinous, burnt and foul. Only more pleasant odorants have been used.

Olfactory training is a treatment for patients with olfactory dysfunction that was first suggested by Hummel et al. (2009) using eucalyptus, clove, lemon, and rose. In Korea, Kim et al. (2016) suggested the four familiar odorant regimens as pine, cinnamon, lemon, and peppermint.

They reported successful results on olfactory function improvement in post-infectious olfactory dysfunction patients using these odorants.

The patients had to sniff each odorant for 10 seconds with a rest period 30 seconds to prevent olfactory fatigue twice a day (morning and evening) for 2 months.

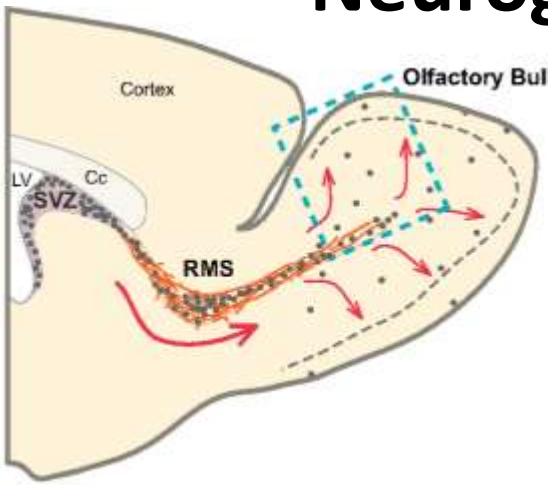
Only observational studies indicating beneficial effects in COVID-19 patients:

-548 patients, the recovery rate was 73.3% in the group of patients who trained for > 28 days, and 59% in the group who trained for < 28 days (Denis et al. 2021)

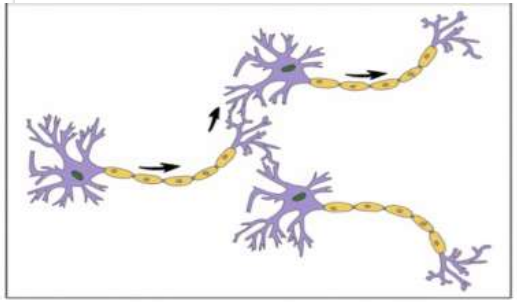
-7 of 10 patients with olfactory training recovered to normal olfaction (Seo et al. 2021)

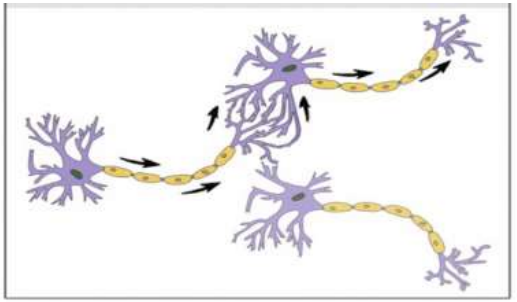
Smell Training Kit
Amazon $30

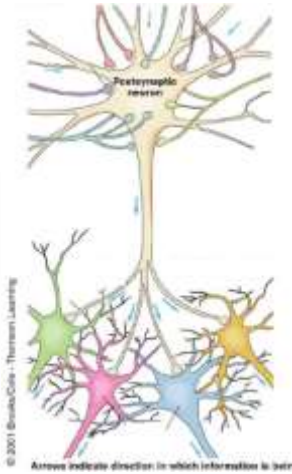
Neurogenesis and neuroplasticity

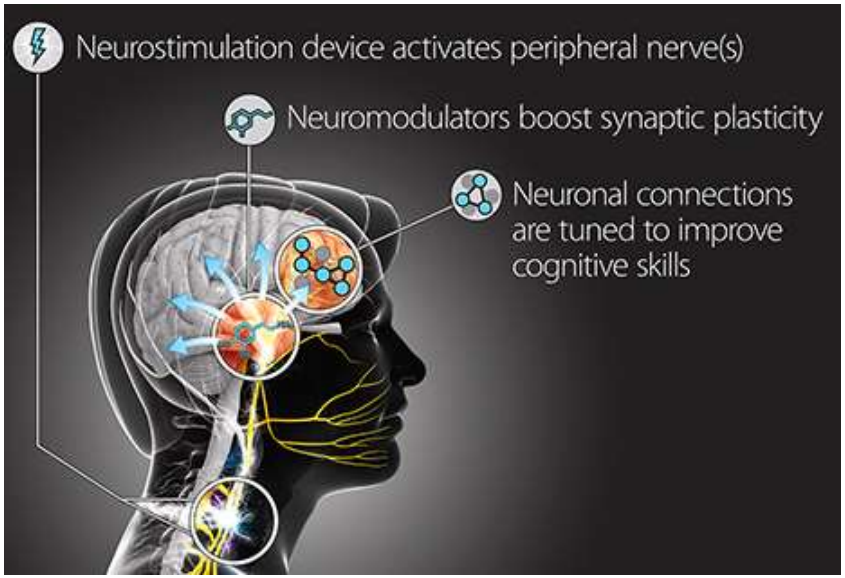


Neurons that fire together wire together: Donald Hebb









Precise activation of peripheral nerves through stimulation can boost neurotransmitter release which promote and strengthen neuronal connections.

Playing Super Mario 64 increases hippocampal grey matter in older adults. (West et al. 2017)

Exercise: a neglected intervention in mental health care?

-Exercise is beneficial for mental health; it reduces anxiety, depression, and negative mood, and improves self-esteem and cognitive functioning (Callaghan 2004; Sharma et al. 2006; Kvam et al. 2016).

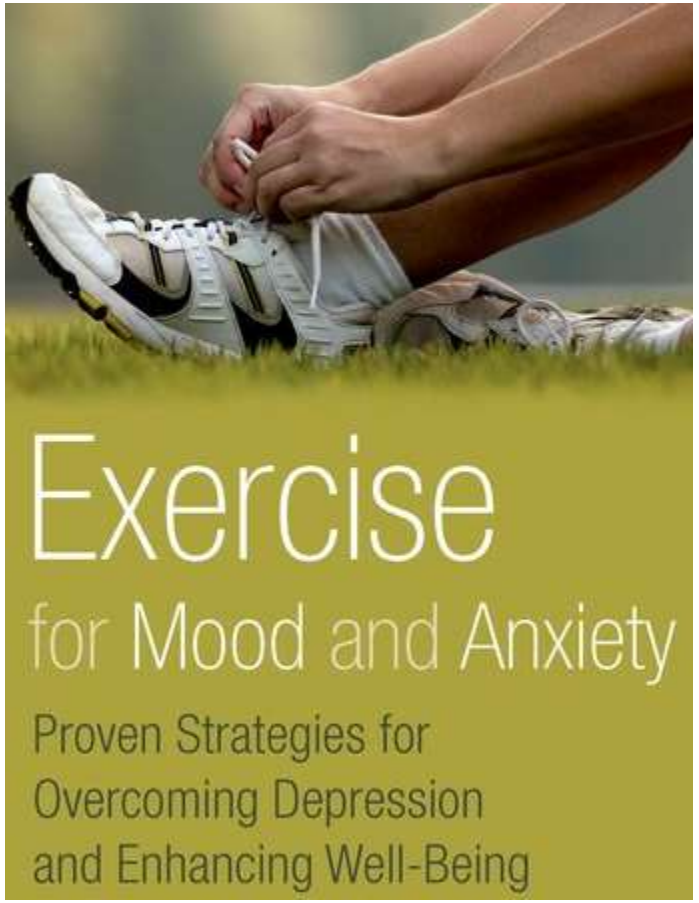
-Aerobic exercises, including jogging, swimming, cycling, walking, gardening, and dancing, have been proved to reduce anxiety and depression (Guszkowska 2004).

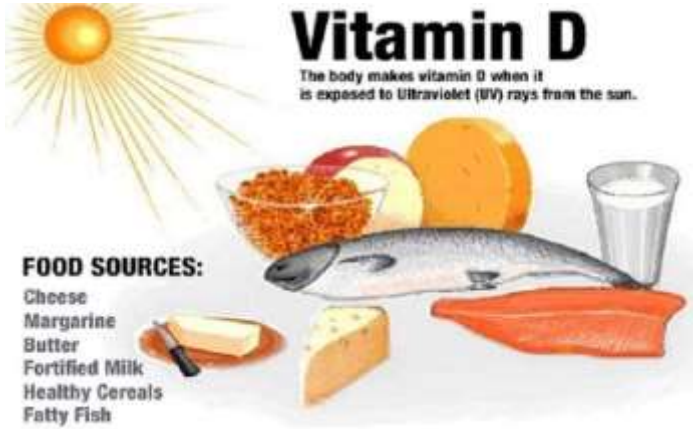
-These improvements in mood are proposed to be caused by exercise-induced increase in blood circulation to the brain and by an influence on the hypothalamic-pituitary-adrenal (HPA) axis and, thus, on the physiologic reactivity to stress.

-Other hypotheses: distraction, self-efficacy, and social interaction (Peluso and Andrade 2005)

-Exercise increases endorphin which reduces pain and contributes to feelings of euphoria. It also increases level of dopamine, norepinephrine, serotonin.

-More sunlight exposure and Vitamin D intake: Synthesis of Vit. D in response to sunlight decline with age (Heaney 2006). Deficiency in Vit. D is linked to depression (Silva et al. 2021) and COVID-19 severity (Margarucci et al. 2021).





Curious questions?