Effects of Long COVID on Brain and Mental Health

J. Douglas Bremner, M.D

Professor of Psychiatry and Radiology,
Emory University School of Medicine,
Atlanta, GA

Staff Psychiatrist
Atlanta Veterans Center (AVC)
General Mental Health (GMH)
Atlanta VA Medical Center, Decatur, GA

EMORY UNIVERSITY

VA | U.S. Department of Veterans Affairs
Atlanta VA Medical Center

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- Research Support from the National Institute on Drug Abuse (NIDA) Helping End Addictions Long Term (HEAL) Program for Opioid Withdrawal studies
- Sham and active transcutaneous Vagal Nerve Stimulation (tcVNS)devices provided free of charge by ElectroCore LLC
- Subcontracts to study tcVNS with the Georgia Institute of Technology and City University of New York
- Scientific Advisory Board for Evren
- No stock or financial interest in any device manufacturer or product

Symptoms of COVID-19 Infection

- Fever or chills
- Cough
- Shortness of breath
- Fatigue
- Muscle aches
- Headache
- Loss of taste and smell
- Sore throat
- Congestion
- Nausea or vomiting
- Diarrhea.

Symptoms of acute COVID begin 2-14 days after exposure and last 2-4 weeks

COVID-19 Worldwide Distribution

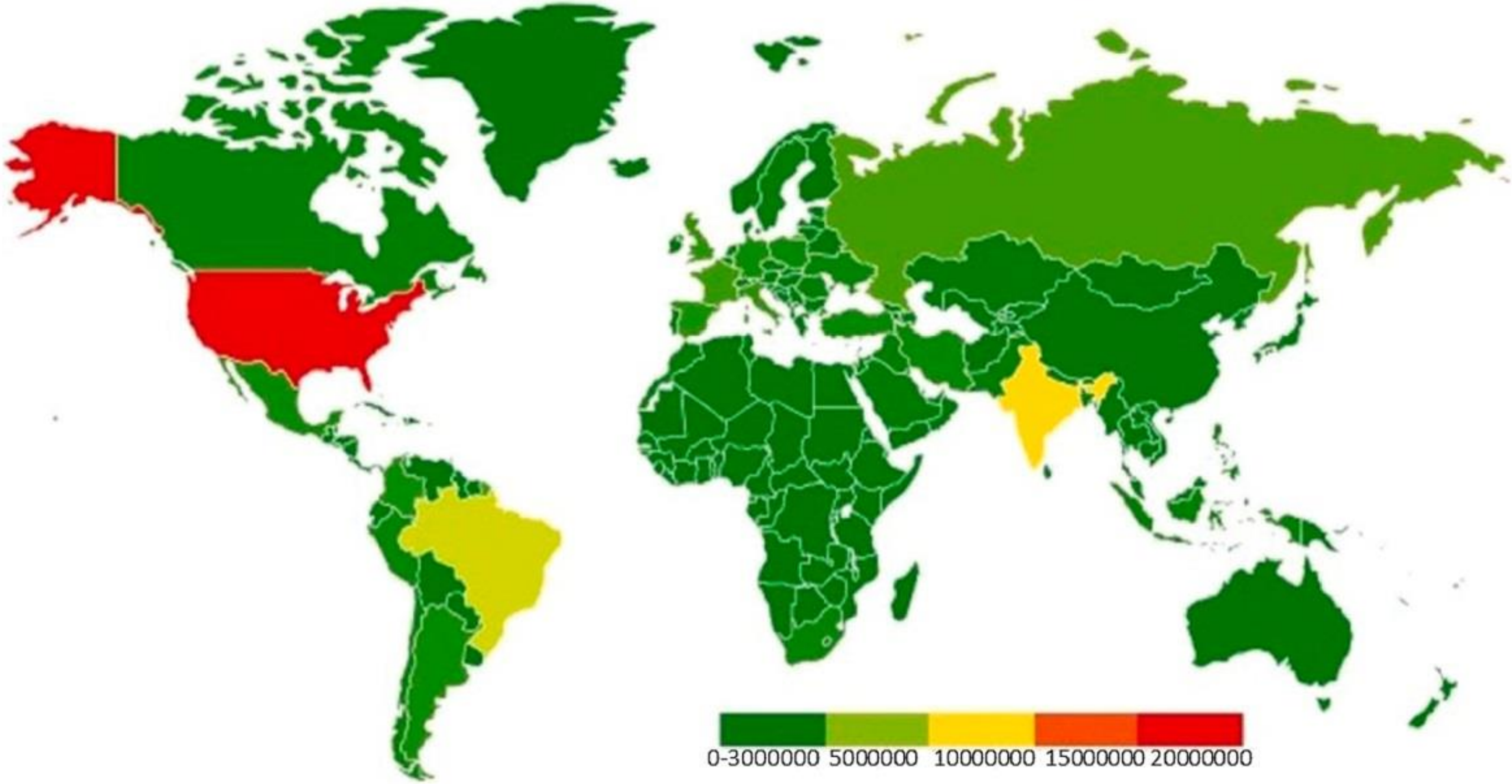


Fig. 1. Global cumulative COVID-19 confirmed cases as of 12/20/2020. https://www.who.int/publications/m/item/weekly-epidemiological-update—22-december-2020.

COVID-19 Trajectories

- National Health Service (NHS) in England
- 57,032,174 persons identified on Jan 23, 2020 and followed until Nov 30, 2021
- 7,244,925 infected during that time, for a rate of 12.7%
- 6.4% of infected persons hospitalized, of whom 10.6% admitted to ICU, 5.6% received ventilation, 2.2% died
- Thygesen et al 2022, The Lancet

Long COVID/PASC

- PASC: Post-acute Sequelae of SARS Cov-2 infection (aka Long COVID, Long hauler syndrome)
- Persistent symptoms beyond acute phase (4 weeks per CDC)
- More common in patients with severe infection, hospitalization, ICU course
- 13% at one month, 2.5% at three months
- 30% at 6 months in hospitalized

Long COVID/PASC Symptoms

- Tiredness or fatigue that interferes with daily life
- Symptoms get worse after physical or mental exertion
- Respiratory/heart: Difficulty breathing or shortness of breath, cough, chest pain, palpitations
- Digestive: diarrhea, stomach pain
- Joint, muscle pain, rash, change in menstruation

Long COVID in June of 2022

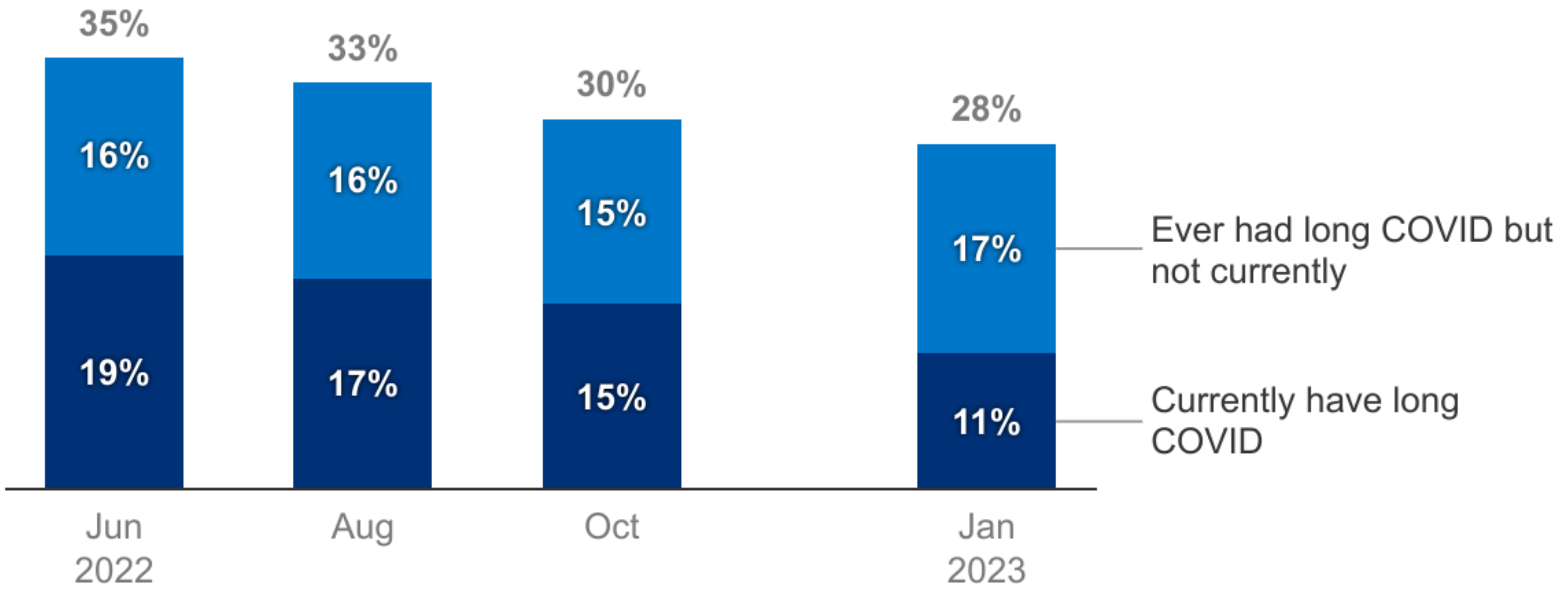
- Affected 7.5% of Americans
- 19% of those who ever had COVID
- Occurred in 35% of infected at some point
- More common in women than men (9.4% v 5.5%)
- More common in Hispanics (9%) than Whites (7.5%), Blacks (6.8%) or Asians (3.7%)

National Center for Health Statistics, June 22, 2022, accessed at cdc.gov

Figure 1

Among People Who Have Had COVID, the Percentage who Currently Have Long COVID is Declining

Percentage of people reporting that they currently have or ever had long COVID among those who have had COVID as of January 16, 2023



NOTE: The Pulse Survey, an experimental survey conducted by the Census Bureau and National Center for Health Statistics, asked respondents whether they had any symptoms of COVID that had lasted longer than 3 months. This figure reports the findings as of 6/13/2022, 8/8/2022, 10/17/2022, and 1/16/2023.
SOURCE: National Center for Health Statistics. Post-COVID Conditions. Data accessed Jan 26, 2023. Available from: https://data.cdc.gov/d/gsea-w83j.

KFF

COVID Neurological Complications

- Impairment in cognition
- Headache
- Encephalitis
- Ischemic Stroke
- Olfactory (smell) impairment
- Microbleeds in brain
- Inflammation of blood vessels in the brain
- Viral neuronal infiltration

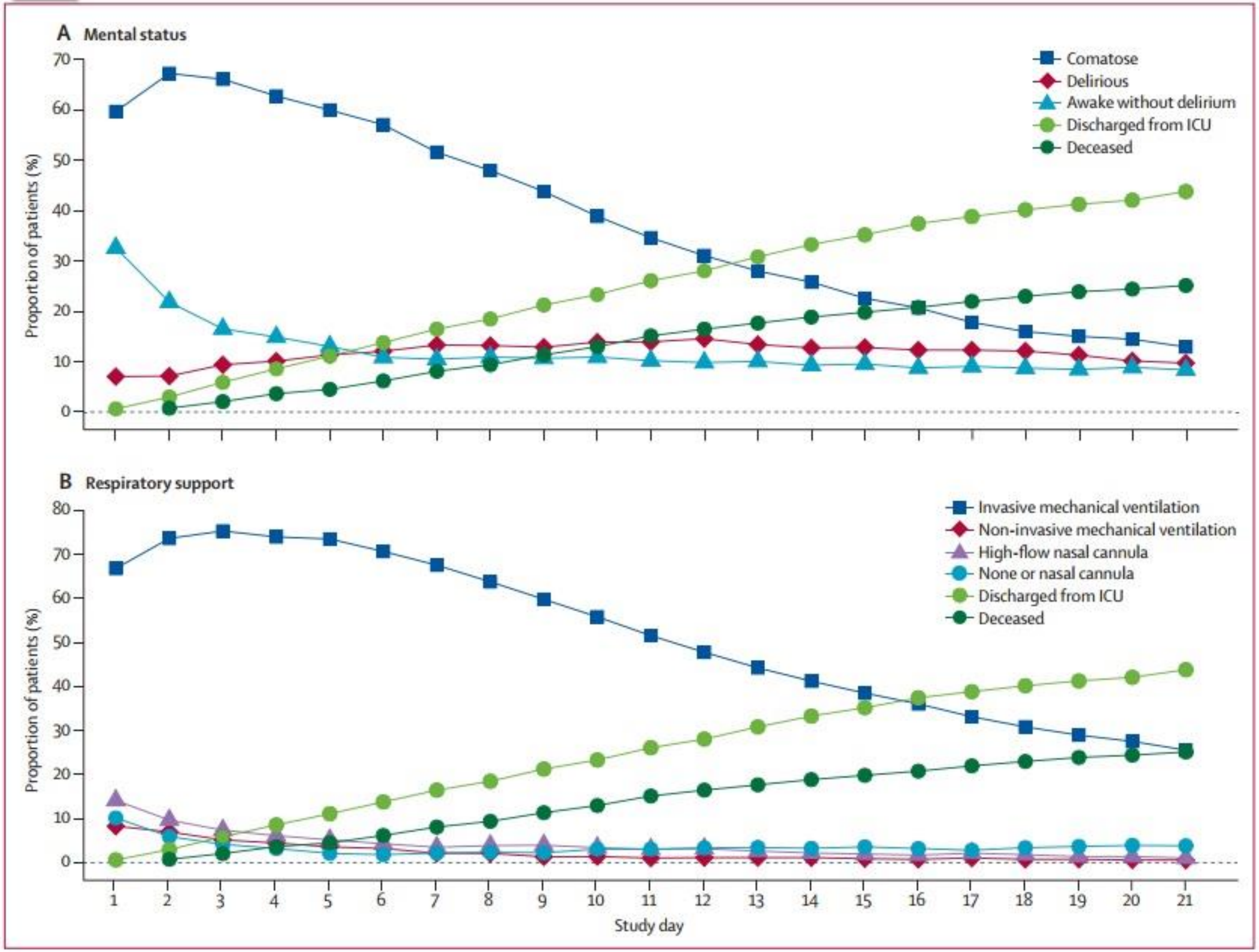
Most Common Neurological and Psychiatric Symptoms Associated with COVID

- Anosmia (43%)
- Weakness (40%)
- Fatigue (38%)
- Dysgeusia (37%)
- Myalgia (25%)
- Depression (23%)
- Anxiety (16%)
- Altered Mental Status (8%)

Rogers et al 2021 Meta-analysis, J Neurol Neurosurg Psychiatry

Prevalence of Delirium with Severe Acute Respiratory Syndrome COVID

Pun et al
2021 Lancet
Resp Med



2088 patients admitted to ICU

88% ventilated

82% comatose

55% delirious

29% died

Family visits protective for delirium

Use of benzodiazepines nonprotective

Long COVID Neurological Symptoms

- Brain fog: difficulty thinking or concentrating
- Headache
- Sleep problems
- Dizziness
- Pins and needles (paresthesia)
- Change in smell or taste (olfaction)
- Depression or anxiety

Long COVID Symptoms

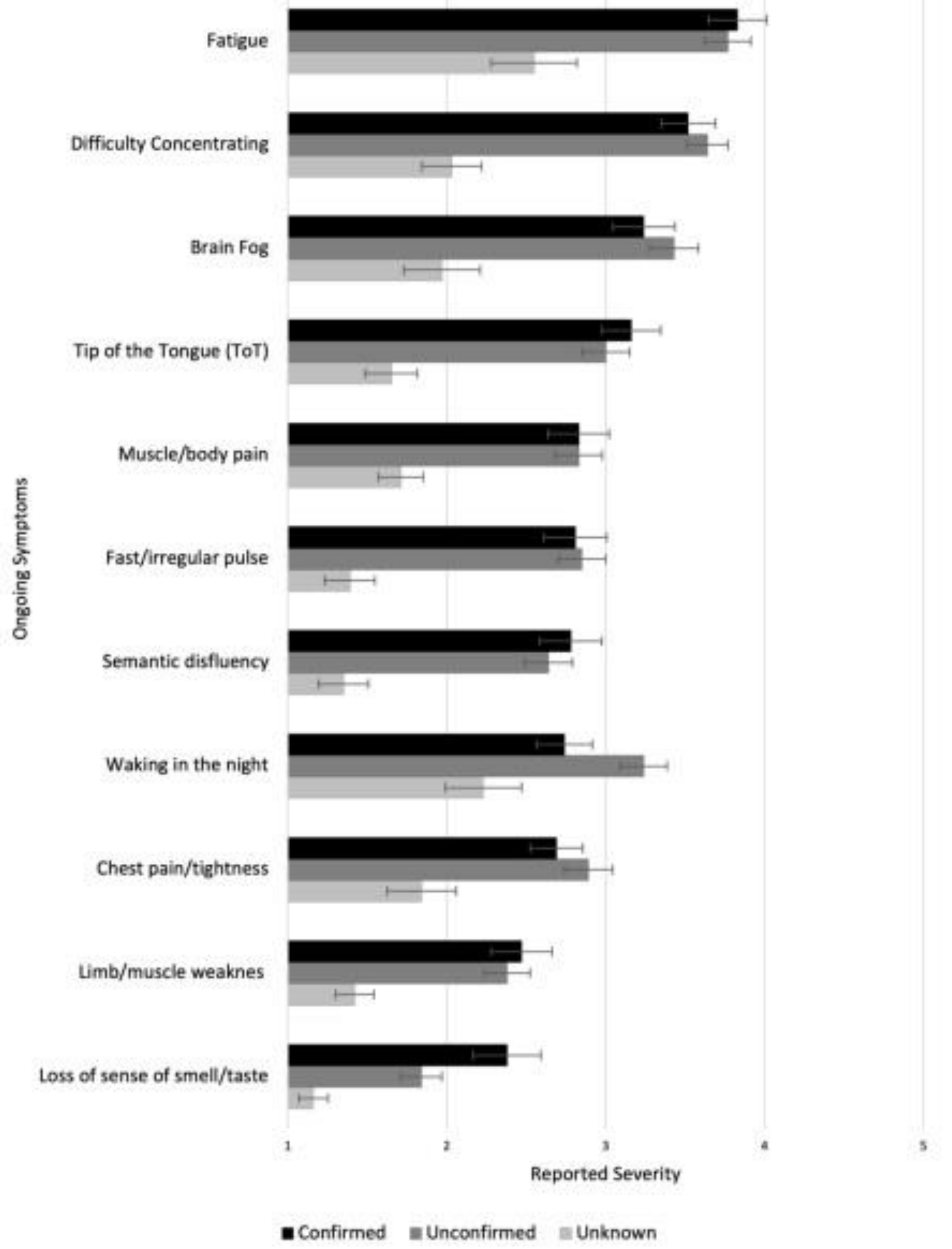


FIGURE 5 | Experience of ongoing symptoms in Unknown, Unconfirmed COVID, and Confirmed COVID groups.

Guo et al 2021

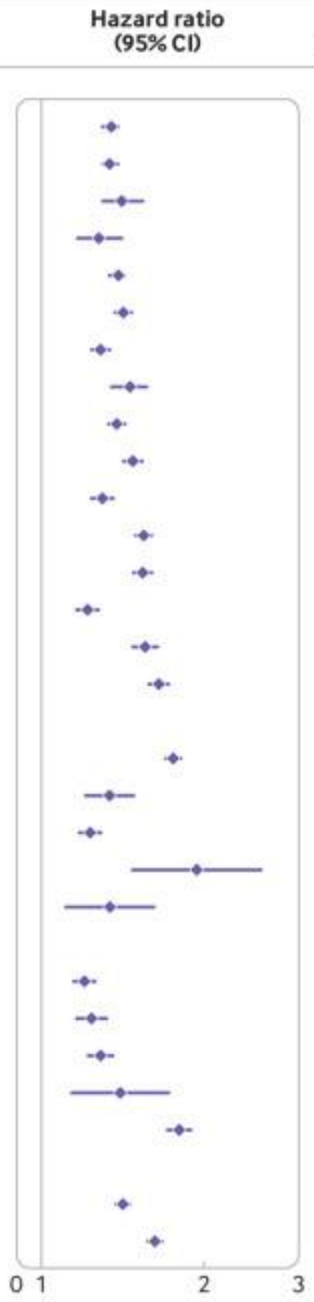
Long-term Mental Health Effects of COVID

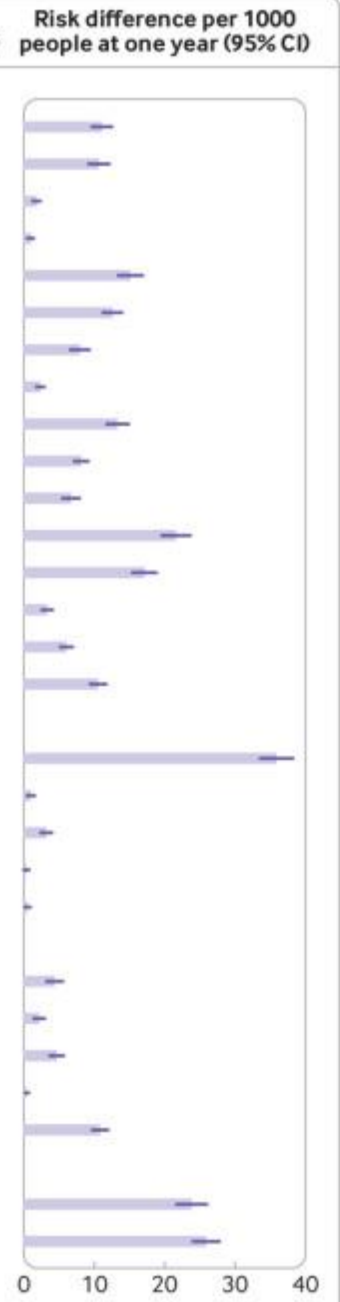
- Study of 153,848 patients in VA who survived 30 days of SARS-CoV-2 infection and two non-infected control groups
- Incident mental health outcomes (new disorder)
- Increased risk of anxiety disorders (hazard ratio (HR) 1.35, depressive disorders (HR 1.39)
- Increased use of antidepressants (HR 1.55)
- Neurocognitive decline (HR 1.8), sleep disorders (HR 1.41)
- Greater risk for hospitalization due to Covid than other cause
- Xie et al BMJ 2022

Long-term Mental Health Consequences of COVID

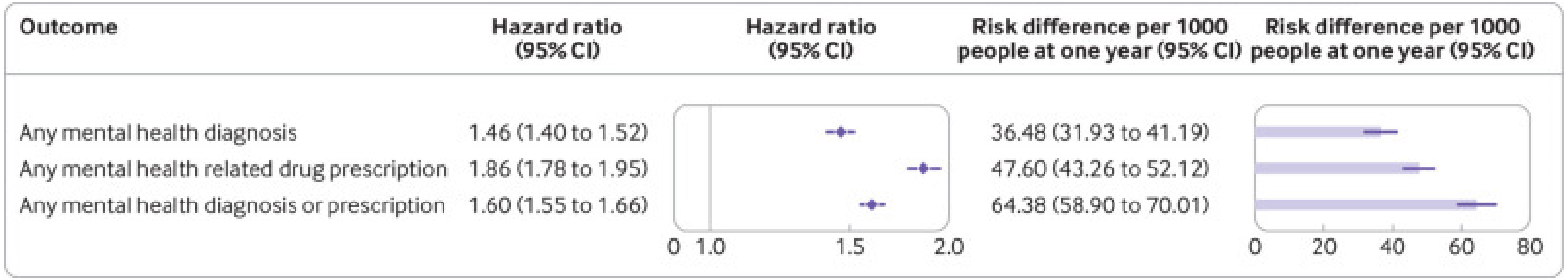
Xie et al 2022 BMJ

Outcome	Hazard ratio (95% CI)	Risk difference per 1000 people at one year (95% CI)
Anxiety disorders	1.35 (1.30 to 1.39)	11.06 (9.64 to 12.53)
Generalized anxiety disorder	1.34 (1.30 to 1.39)	10.56 (9.18 to 11.99)
Mixed anxiety disorder	1.41 (1.30 to 1.54)	1.66 (1.21 to 2.15)
Panic disorder	1.28 (1.17 to 1.41)	0.84 (0.49 to 1.22)
Depressive disorders	1.39 (1.34 to 1.43)	15.12 (13.38 to 16.91)
MDD - single episode	1.42 (1.37 to 1.47)	12.53 (11.15 to 13.95)
MDD - recurrent	1.29 (1.24 to 1.34)	7.86 (6.58 to 9.18)
Suicidal ideation	1.46 (1.35 to 1.57)	2.25 (1.73 to 2.81)
Stress and adjustment disorders	1.38 (1.34 to 1.43)	13.29 (11.71 to 14.92)
Acute stress and adjustment disorder	1.48 (1.42 to 1.54)	8.05 (7.08 to 9.07)
PTSD	1.30 (1.24 to 1.36)	6.60 (5.39 to 7.85)
Antidepressants	1.55 (1.50 to 1.60)	21.59 (19.63 to 23.60)
SSRI	1.54 (1.49 to 1.60)	17.13 (15.47 to 18.84)
SNRI	1.22 (1.17 to 1.28)	3.23 (2.45 to 4.06)
Other antidepressants	1.56 (1.48 to 1.64)	5.98 (5.14 to 6.86)
Benzodiazepines	1.65 (1.58 to 1.72)	10.46 (9.37 to 11.61)
Opioids		
Opioid prescription	1.76 (1.71 to 1.81)	35.90 (33.61 to 38.25)
Opioid use disorder	1.34 (1.21 to 1.48)	0.96 (0.59 to 1.37)
Naloxone or naltrexone	1.23 (1.18 to 1.29)	3.08 (2.32 to 3.86)
Methadone	1.94 (1.47 to 2.56)	0.27 (0.14 to 0.46)
Buprenorphine	1.34 (1.12 to 1.62)	0.45 (0.15 to 0.80)
Substance use disorders		
Any substance use disorder	1.20 (1.15 to 1.26)	4.34 (3.22 to 5.51)
Illicit drug disorder	1.24 (1.16 to 1.32)	2.12 (1.42 to 2.87)
Alcohol use disorder	1.29 (1.22 to 1.35)	4.60 (3.61 to 5.65)
Sedative or hypnotics use disorder	1.40 (1.14 to 1.72)	0.28 (0.10 to 0.51)
Neurocognitive decline	1.80 (1.72 to 1.89)	10.75 (9.65 to 11.91)
Sleep		
Sleep disorders	1.41 (1.38 to 1.45)	23.80 (21.65 to 26.00)
Sleep medications	1.63 (1.58 to 1.67)	25.87 (24.01 to 27.78)





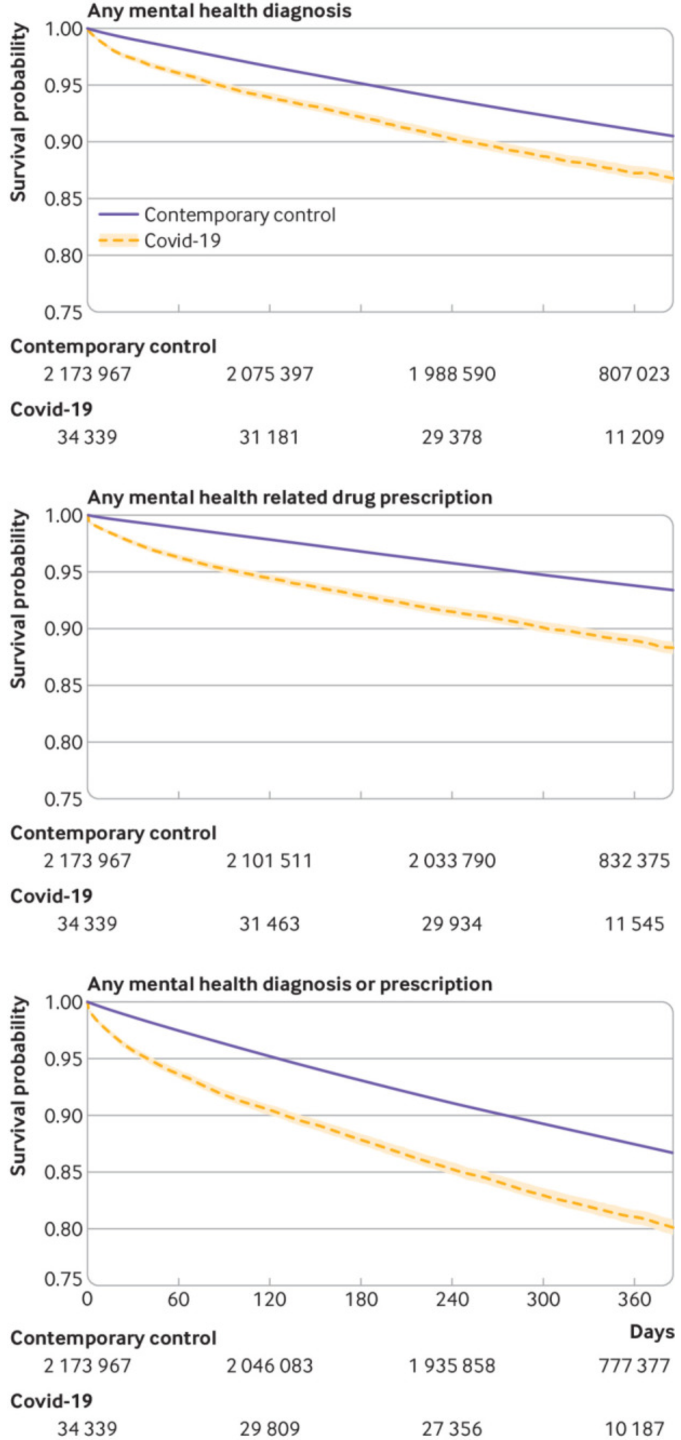
Long-term Mental Health Consequences of COVID



Xie et al 2022 BMJ

Long-term Mental Health Consequences of COVID

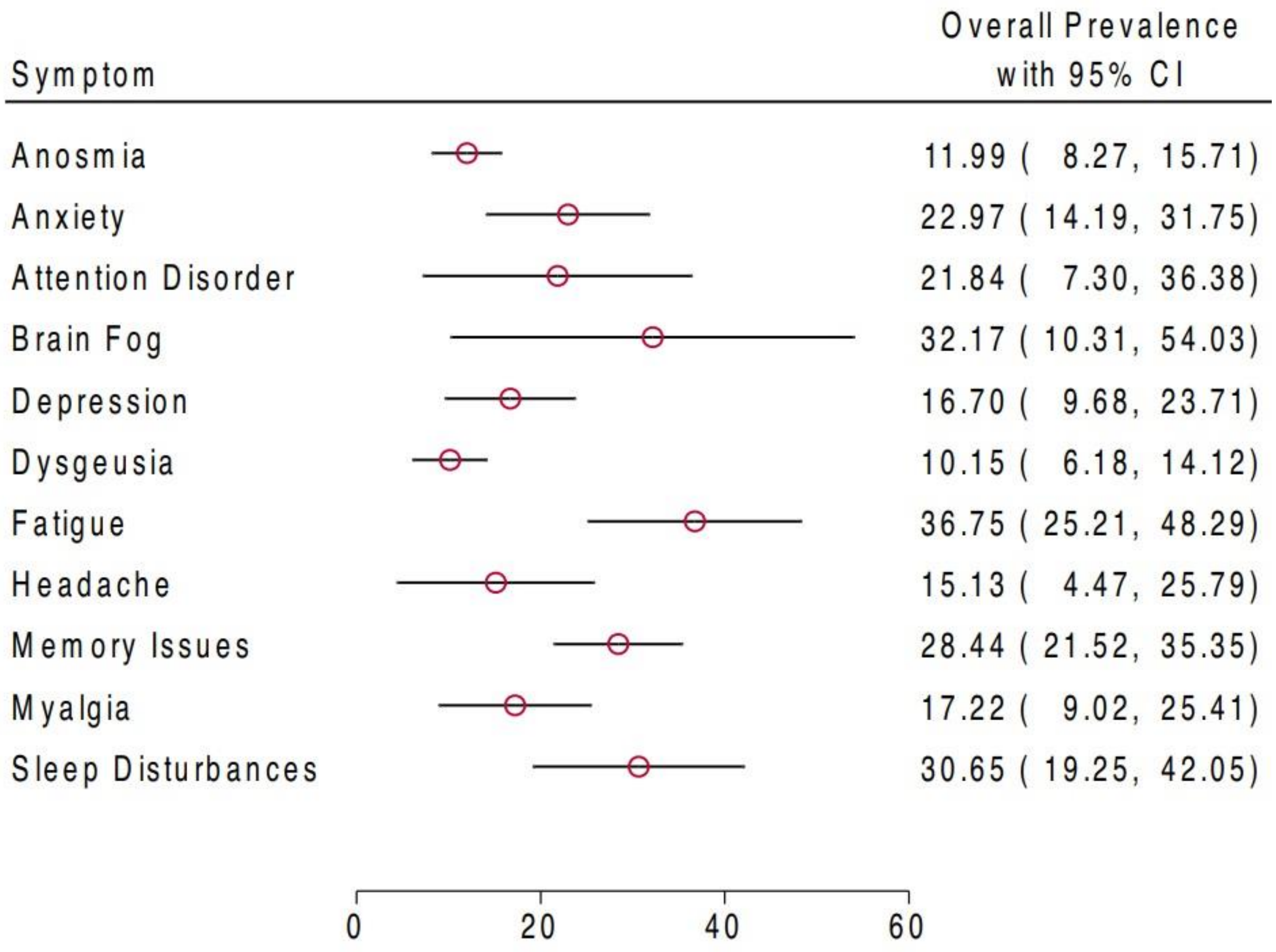
Xie et al 2022 BMJ



Long-term Psychiatric Effects of COVID

- Schou et al 2021-meta-analyses, post discharge from hospital to 6 months
- PTSD: 7-43%, increased after ICU admissions
- Depression: >30% in most studies
- Anxiety elevated over controls at 60 days, associated with physical symptoms, immune response
- Increased OCD and psychosis
- 11 studies report cognitive deficits in >25%
- 12 studies >45% with fatigue; increased sleep disorders
- Most studies show improvement over time

Long-term Psychiatric Effects of COVID



Premraj et al 2022 Three months post COVID

Long-term Psychiatric Effects of COVID

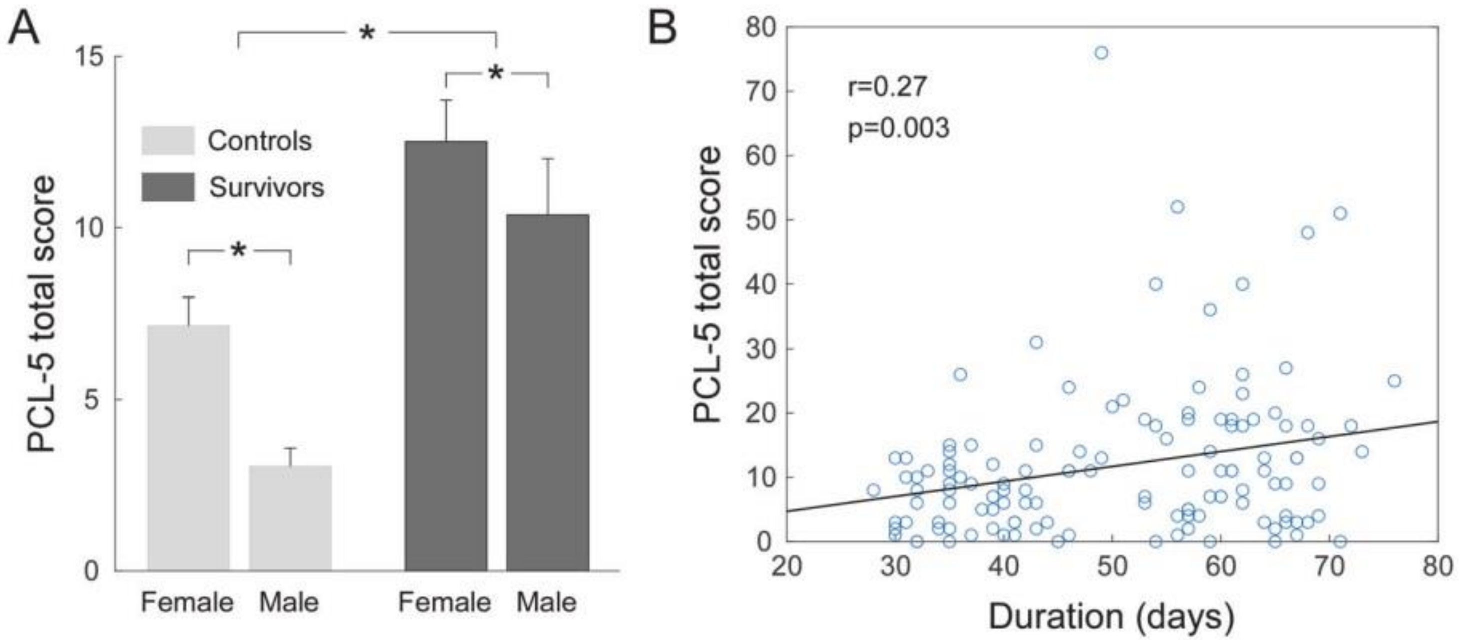


Fig. 1 PCL-5 total score of COVID-19 survivors and controls in Session 1. A. COVID-19 survivors had significantly higher scores than controls, and females had significantly higher scores than males. **B.** The score of COVID-19 survivors was significantly positively correlated with the duration from discharge to the date of participating in Session 1. Error bars represent the standard error of the mean. Asterisks represent $p < 0.05$.

Tu et al 2021 Three and six months post COVID; PCL=PTSD checklist

Long-term Psychiatric Effects of COVID

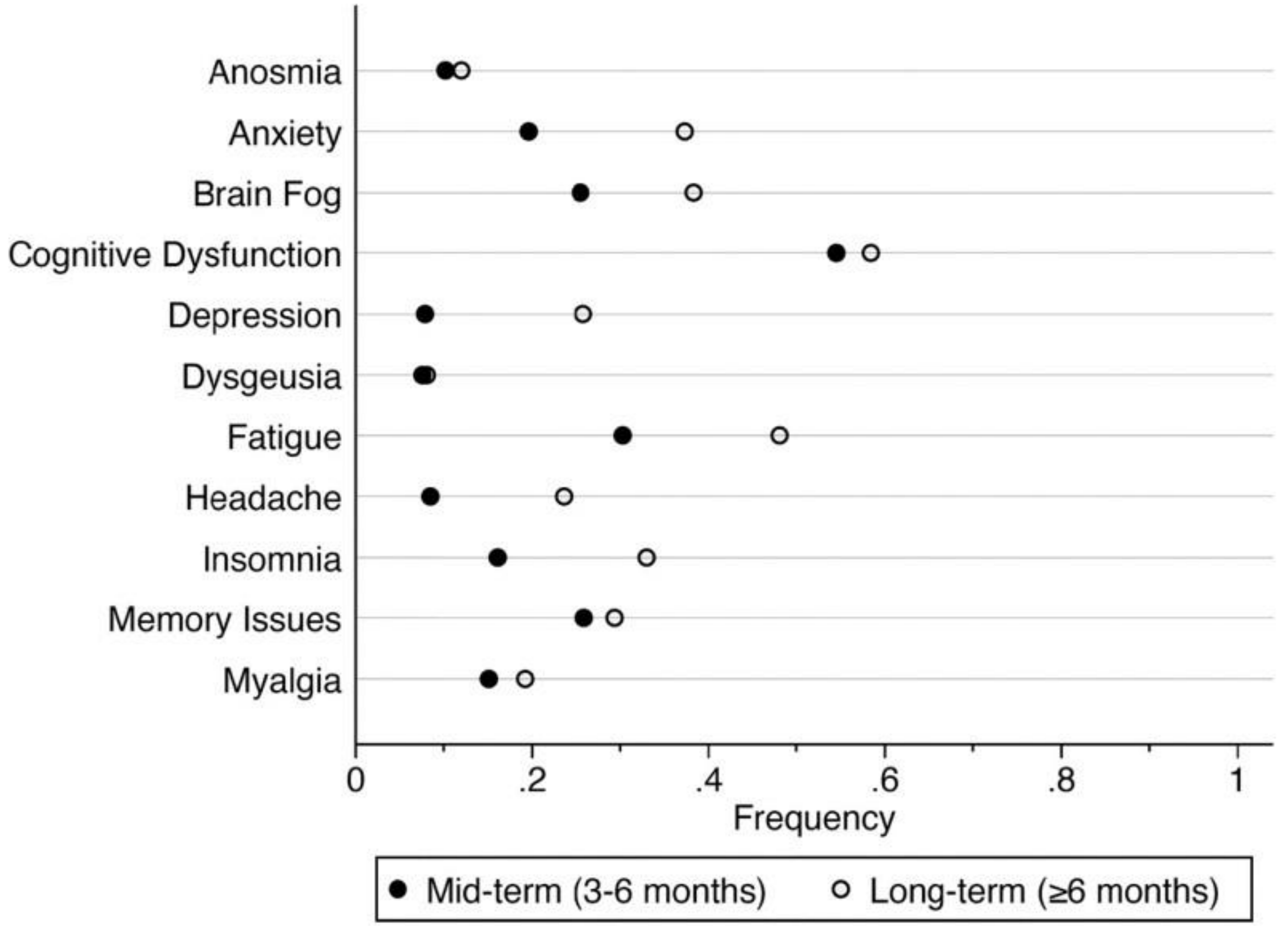
Taquet et al 2021 Psychiatric diagnoses at six months

	COVID-19 vs influenza (N=105 579)*		COVID-19 vs other RTI (N=236 038)*	
	HR (95% CI)	p value	HR (95% CI)	p value
Intracranial haemorrhage (any)	2·44 (1·89–3·16)	<0·0001	1·26 (1·11–1·43)	0·0003
Intracranial haemorrhage (first)	2·53 (1·68–3·79)	<0·0001	1·56 (1·27–1·92)	<0·0001
Ischaemic stroke (any)	1·62 (1·43–1·83)	<0·0001	1·45 (1·36–1·55)	<0·0001
Ischaemic stroke (first)	1·97 (1·57–2·47)	<0·0001	1·63 (1·44–1·85)	<0·0001
Parkinsonism	1·42 (0·75–2·67)	0·19	1·45 (1·05–2·00)	0·020
Guillain-Barré syndrome	1·21 (0·72–2·04)	0·41	2·06 (1·43–2·96)	<0·0001
Nerve, nerve root, or plexus disorders	1·64 (1·50–1·81)	<0·0001	1·27 (1·19–1·35)	<0·0001
Myoneural junction or muscle disease	5·28 (3·71–7·53)	<0·0001	4·52 (3·65–5·59)	<0·0001
Encephalitis	1·70 (1·04–2·78)	0·028	1·41 (1·03–1·92)	0·028
Dementia	2·33 (1·77–3·07)	<0·0001	1·71 (1·50–1·95)	<0·0001
Mood, anxiety, or psychotic disorder (any)	1·46 (1·43–1·50)	<0·0001	1·20 (1·18–1·23)	<0·0001
Mood, anxiety, or psychotic disorder (first)	1·81 (1·69–1·94)	<0·0001	1·48 (1·42–1·55)	<0·0001
Mood disorder (any)	1·47 (1·42–1·53)	<0·0001	1·23 (1·20–1·26)	<0·0001
Mood disorder (first)	1·79 (1·64–1·95)	<0·0001	1·41 (1·33–1·50)	<0·0001
Anxiety disorder (any)	1·45 (1·40–1·49)	<0·0001	1·17 (1·15–1·20)	<0·0001
Anxiety disorder (first)	1·78 (1·66–1·91)	<0·0001	1·48 (1·42–1·55)	<0·0001
Psychotic disorder (any)	2·03 (1·78–2·31)	<0·0001	1·66 (1·53–1·81)	<0·0001
Psychotic disorder (first)	2·16 (1·62–2·88)	<0·0001	1·82 (1·53–2·16)	<0·0001
Substance use disorder (any)	1·27 (1·22–1·33)	<0·0001	1·09 (1·05–1·12)	<0·0001
Substance use disorder (first)	1·22 (1·09–1·37)	0·0006	0·92 (0·86–0·99)	0·033
Insomnia (any)	1·48 (1·38–1·57)	<0·0001	1·15 (1·10–1·20)	<0·0001
Insomnia (first)	1·92 (1·72–2·15)	<0·0001	1·43 (1·34–1·54)	<0·0001
Any outcome	1·44 (1·40–1·47)	<0·0001	1·16 (1·14–1·17)	<0·0001
Any first outcome	1·78 (1·68–1·89)	<0·0001	1·32 (1·27–1·36)	<0·0001

Additional details on cohort characteristics and diagnostic subcategories are presented in the appendix (pp 29–33). HR=hazard ratio. RTI=respiratory tract infection. *Matched cohorts.

Table 3: HRs for the major outcomes in patients after COVID-19 compared with those after influenza and other RTIs

Long-term Psychiatric Effects of COVID

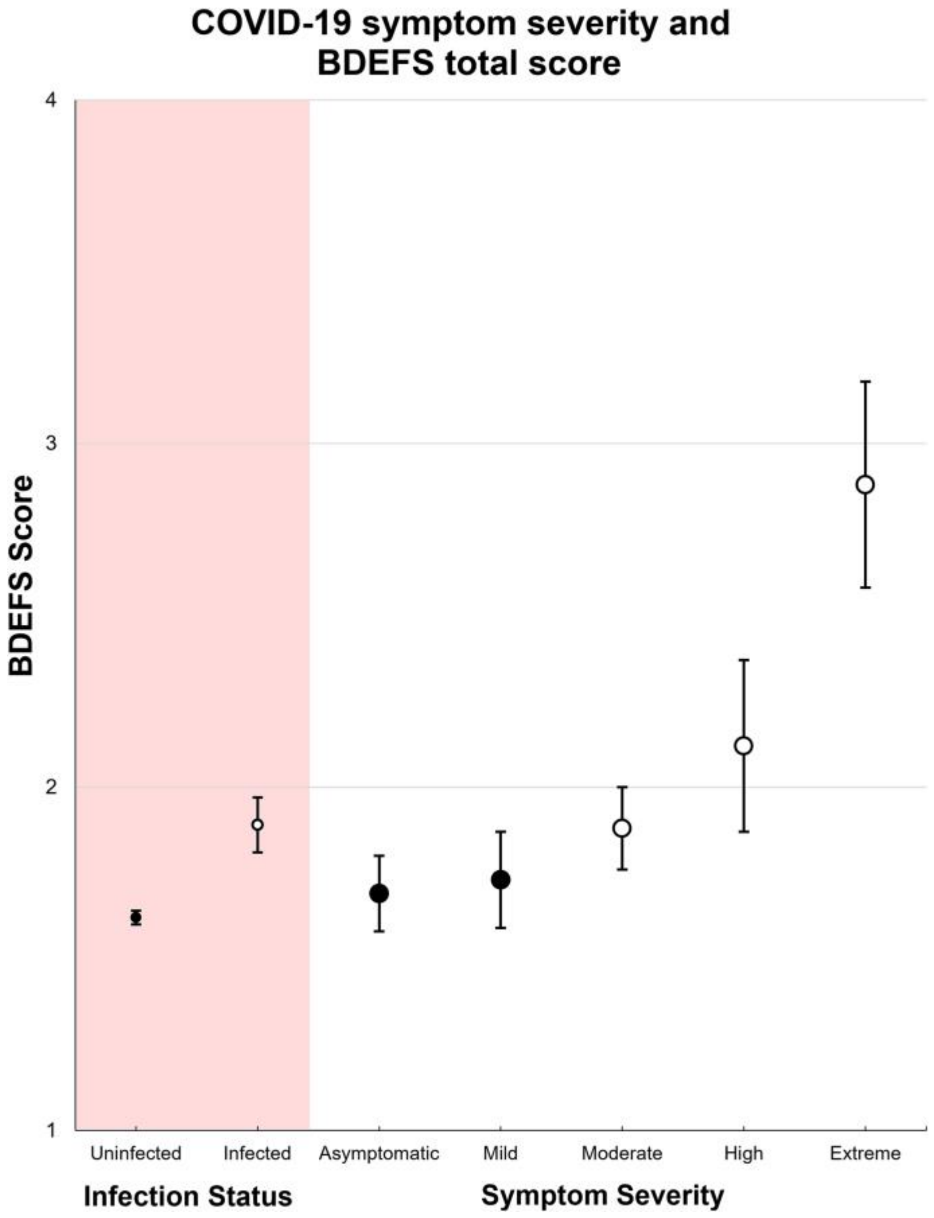


Premraj et al 2022 Three months and six months post COVID

Long-term Cognitive Effects of COVID

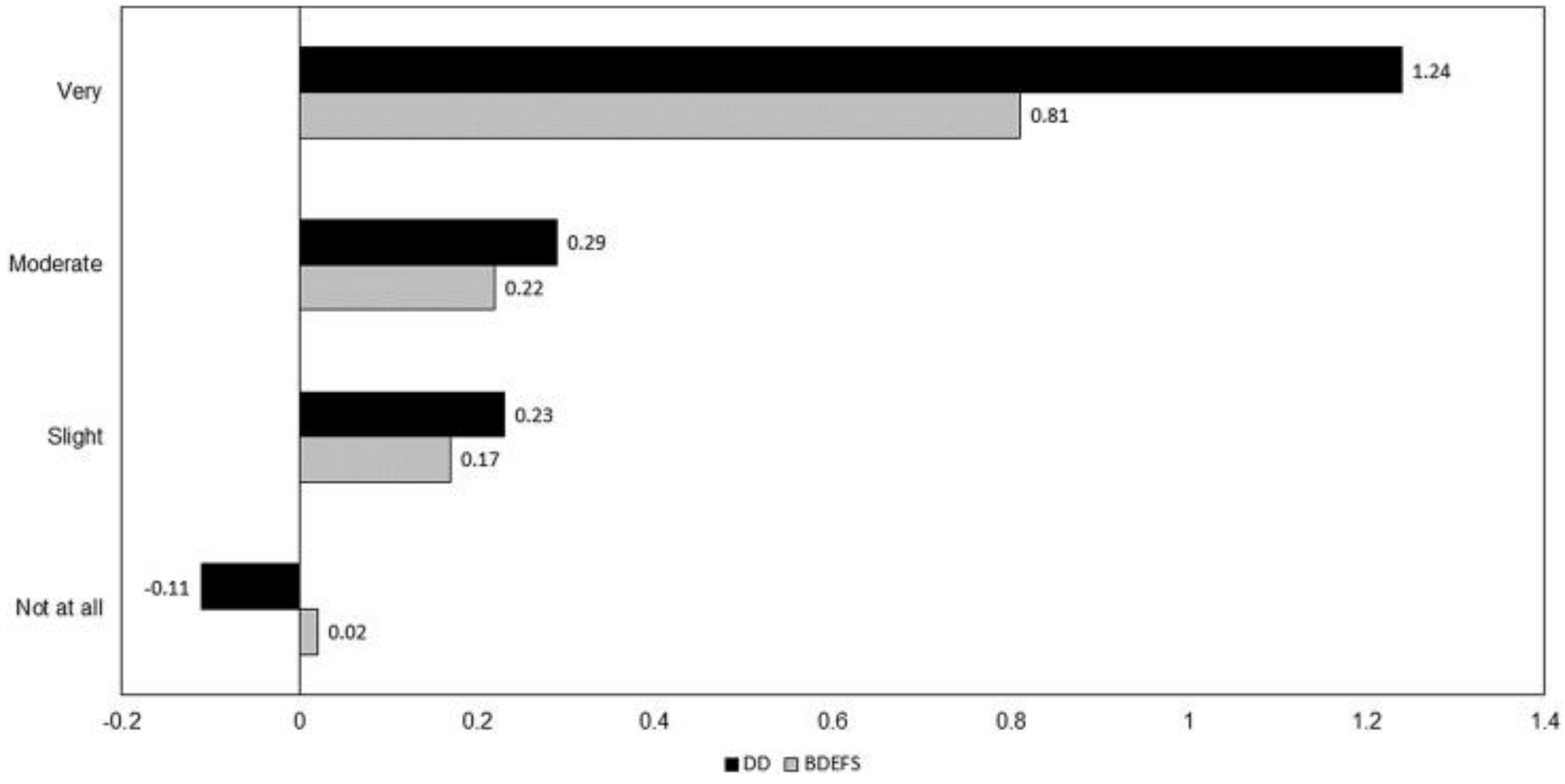
- Study of 1958 adults self reporting COVID infection and severity, cognitive impairment
- Tested on validated decision making task
- Dose response increase in cognitive dysfunction with increasing symptom severity
- Worse performance on decision task with increased symptom severity
- Hall et al 2022 BBI-H

Self-reported Symptom Severity Correlates with Self Report Cognitive Dysfunction



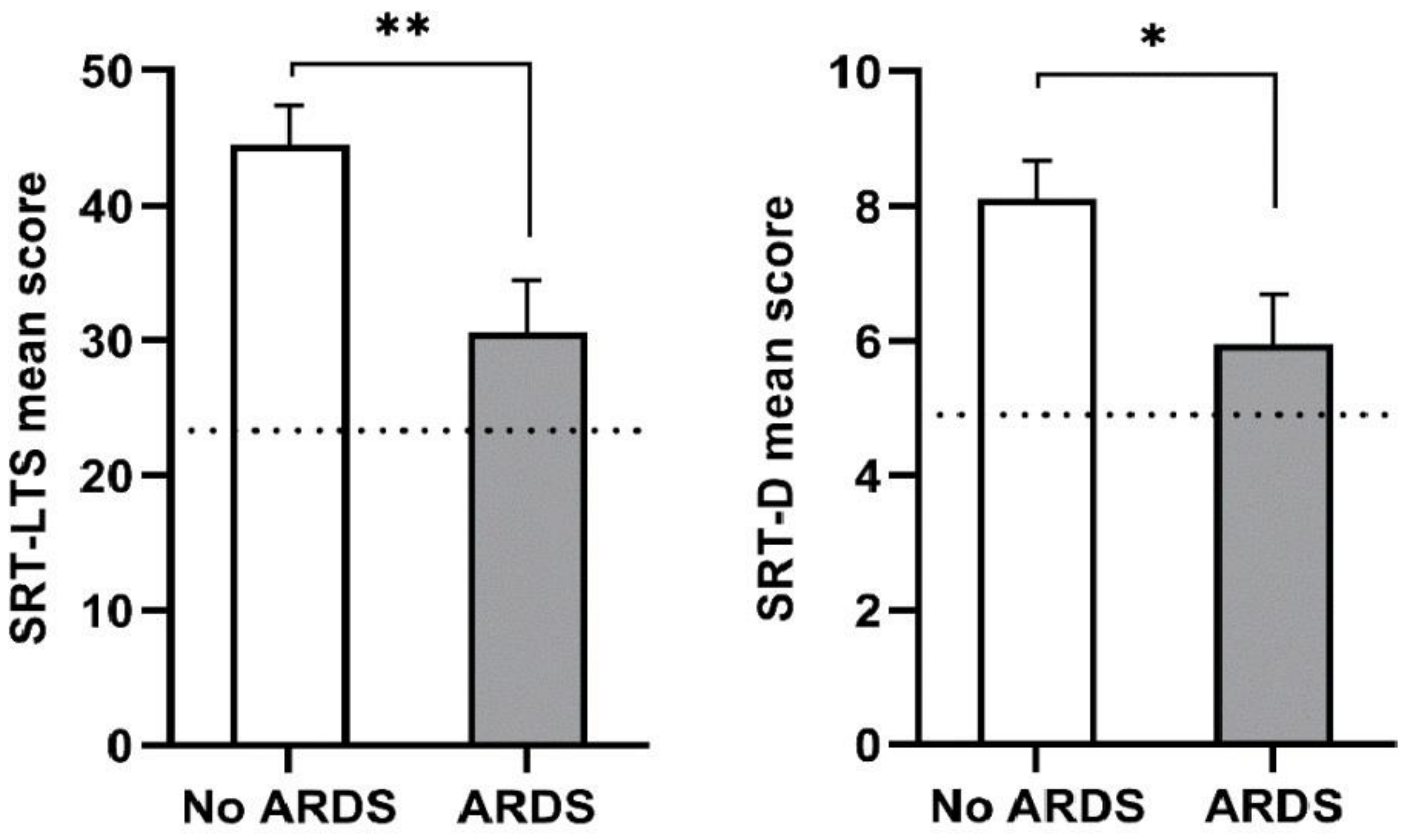
Hall et al 2022 Brain, Behavior & Immunity – Health; BDEFS=Barkley Deficits in Executive Functioning Scale

COVID Severity Correlates with Cognitive Impairment



Hall et al 2022 Brain, Behavior & Immunity – Health; BDEFS=Barkley Deficits in Executive Functioning Scale; ; DD=Delay discounting task

Long Term Declarative Memory Impairment Following Hospitalization for COVID



Ferrucci et al 2022 Eur J Neurol Five months after hospitalization 42% had processing speed deficits, 26% declarative memory deficits. ARDS=Acute Respiratory Distress Syndrome; SRT=Selective Reminding Test

Declarative Memory Impairment Post COVID Correlates with Oxygen Availability

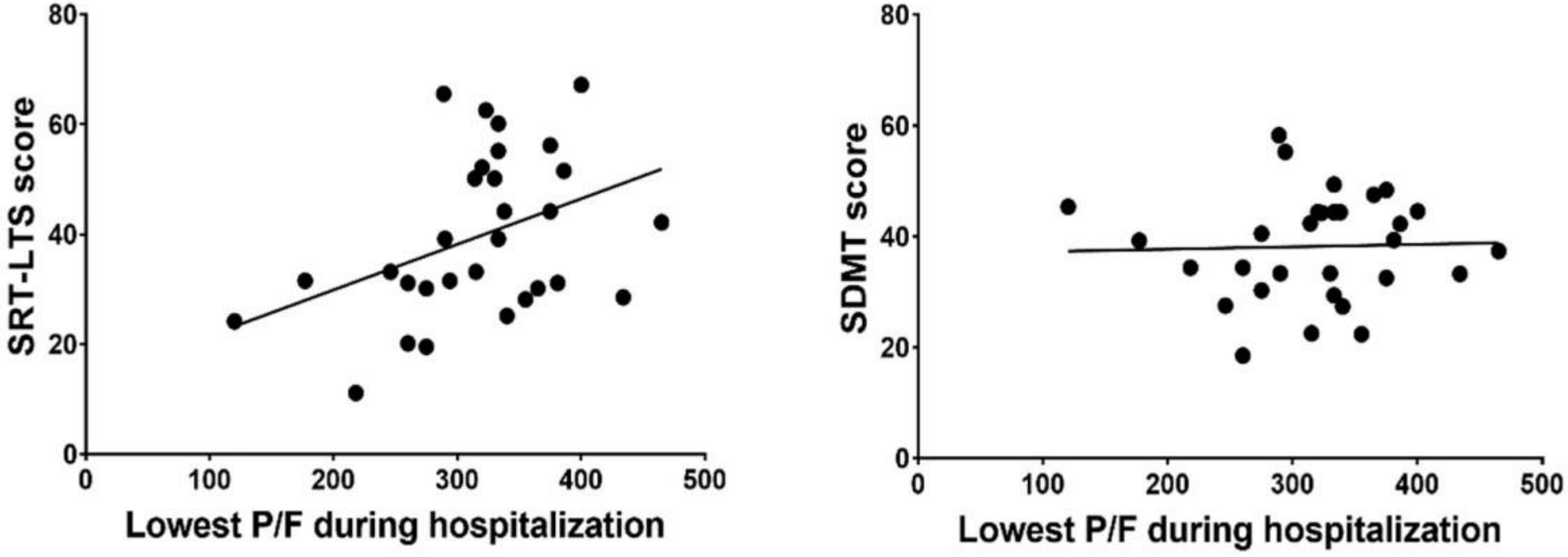
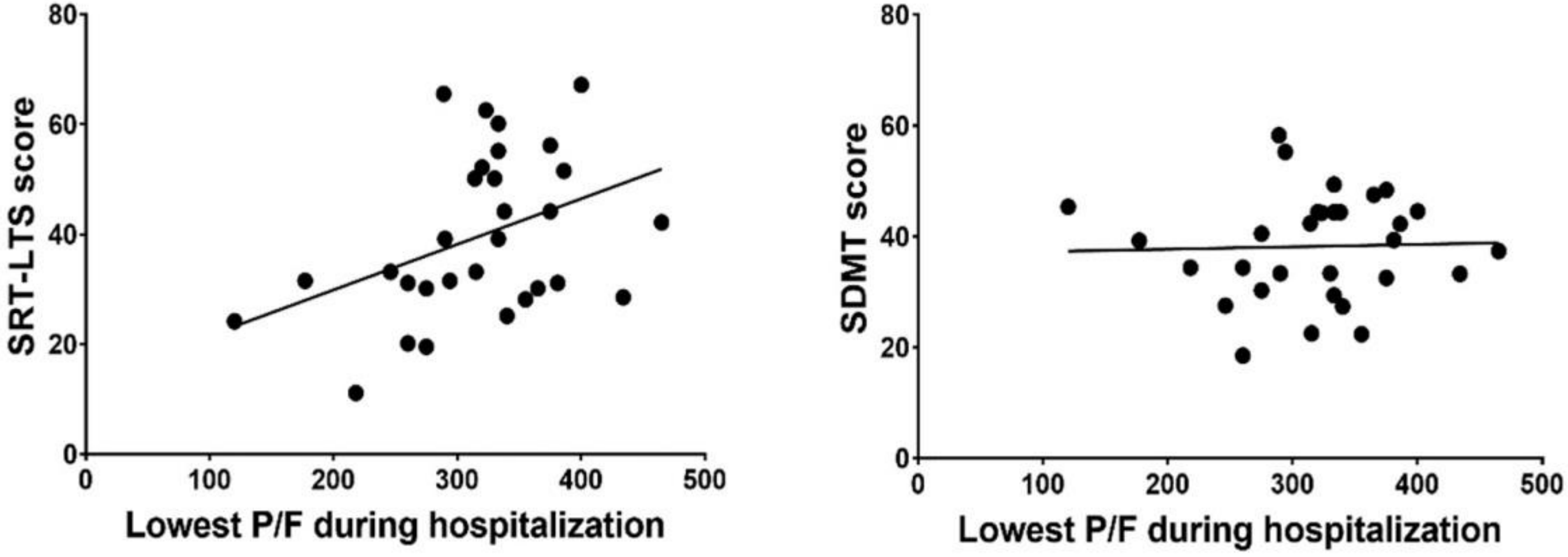


Figure 1. P/F = arterial oxygen partial pressure (PaO_2)/fractional inspired oxygen (FiO_2) ratio; SRT-LTS = Serial Recall Test Long-Term Storage; SDMT = Symbol-Digit Modalities Test.

Ferrucci et al 2021 Low oxygen availability correlates with verbal declarative memory deficits. SRT=Selective Reminding Test

Declarative Memory Impairment Post COVID Correlates with Oxygen Availability



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Ferrucci et al 2021 Low oxygen availability correlates with verbal declarative memory deficits. SRT=Selective Reminding Test

Increased Functional Impairment at Six Months Post COVID with Neurological Symptoms

J.A. Frontera et al. | Journal of the Neurological Sciences 426 (2021) 117486

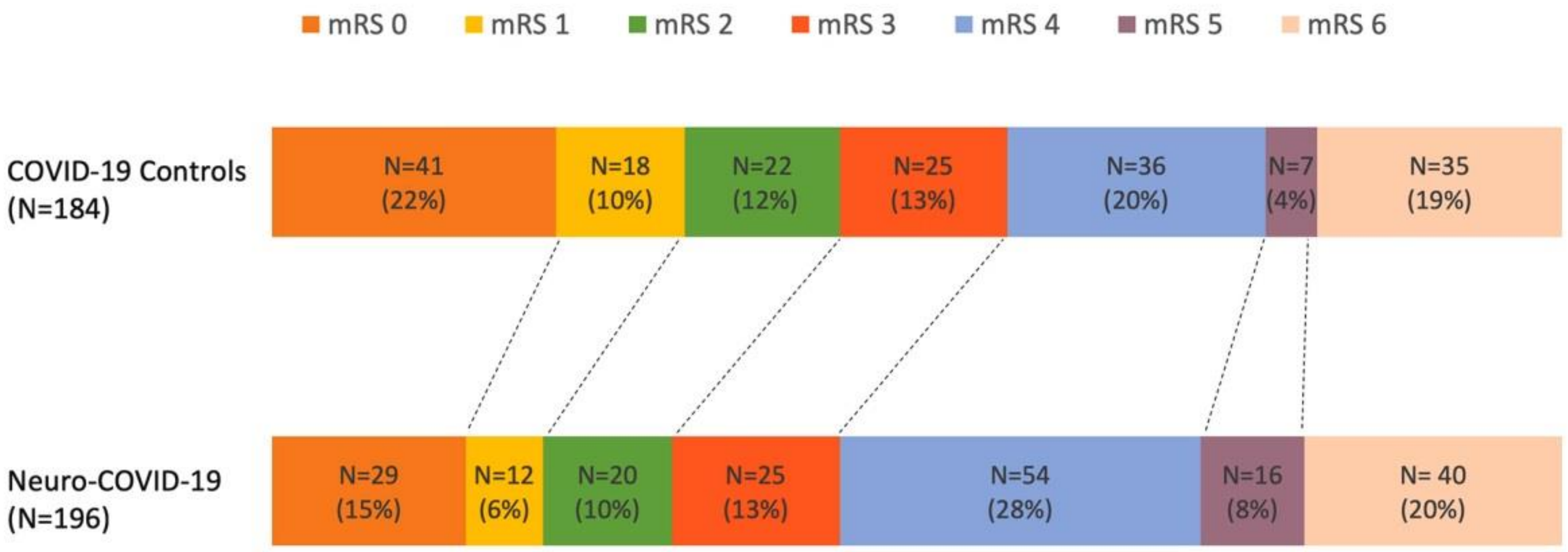
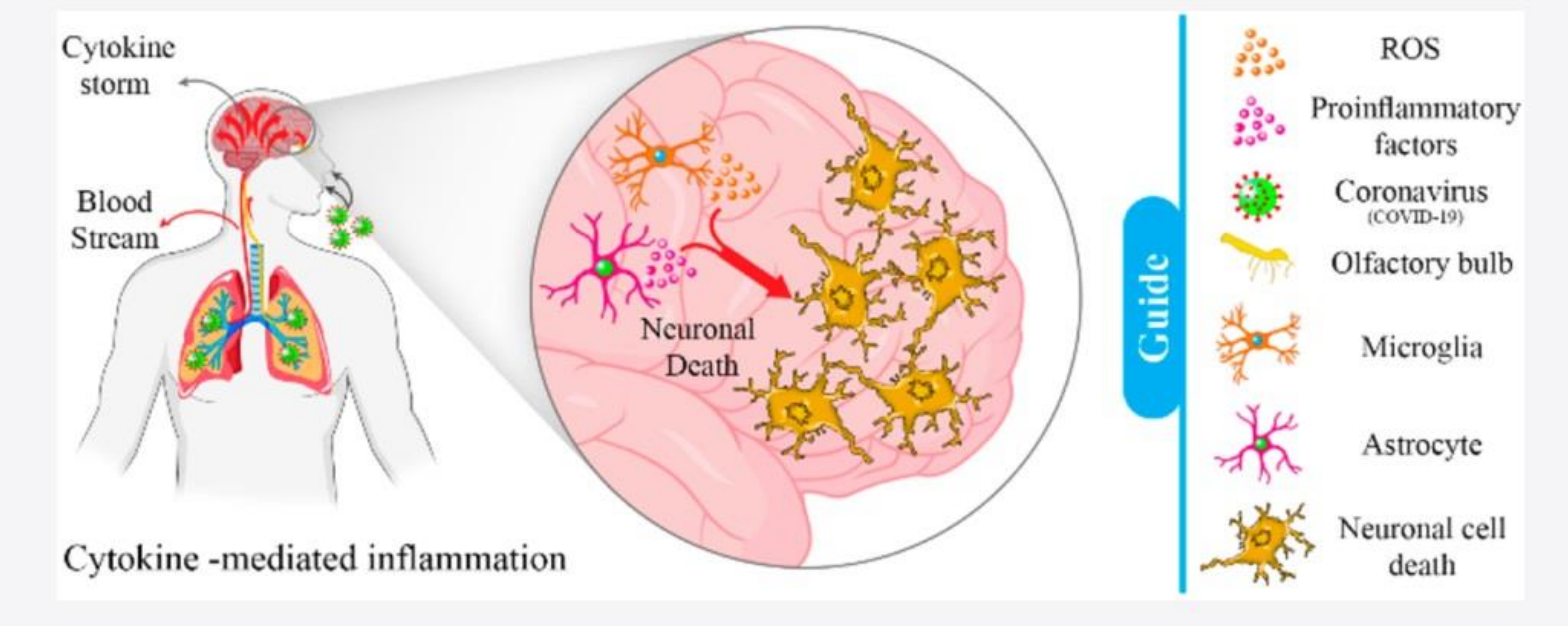


Fig. 2. Ordinal logistic regression analysis of 6-month modified Rankin scores among patients with and without neurological disorders during hospitalization for COVID-19. (Adjusted odds ratio OR 1.98, 95% confidence interval 1.23–3.48, $P = 0.02$).

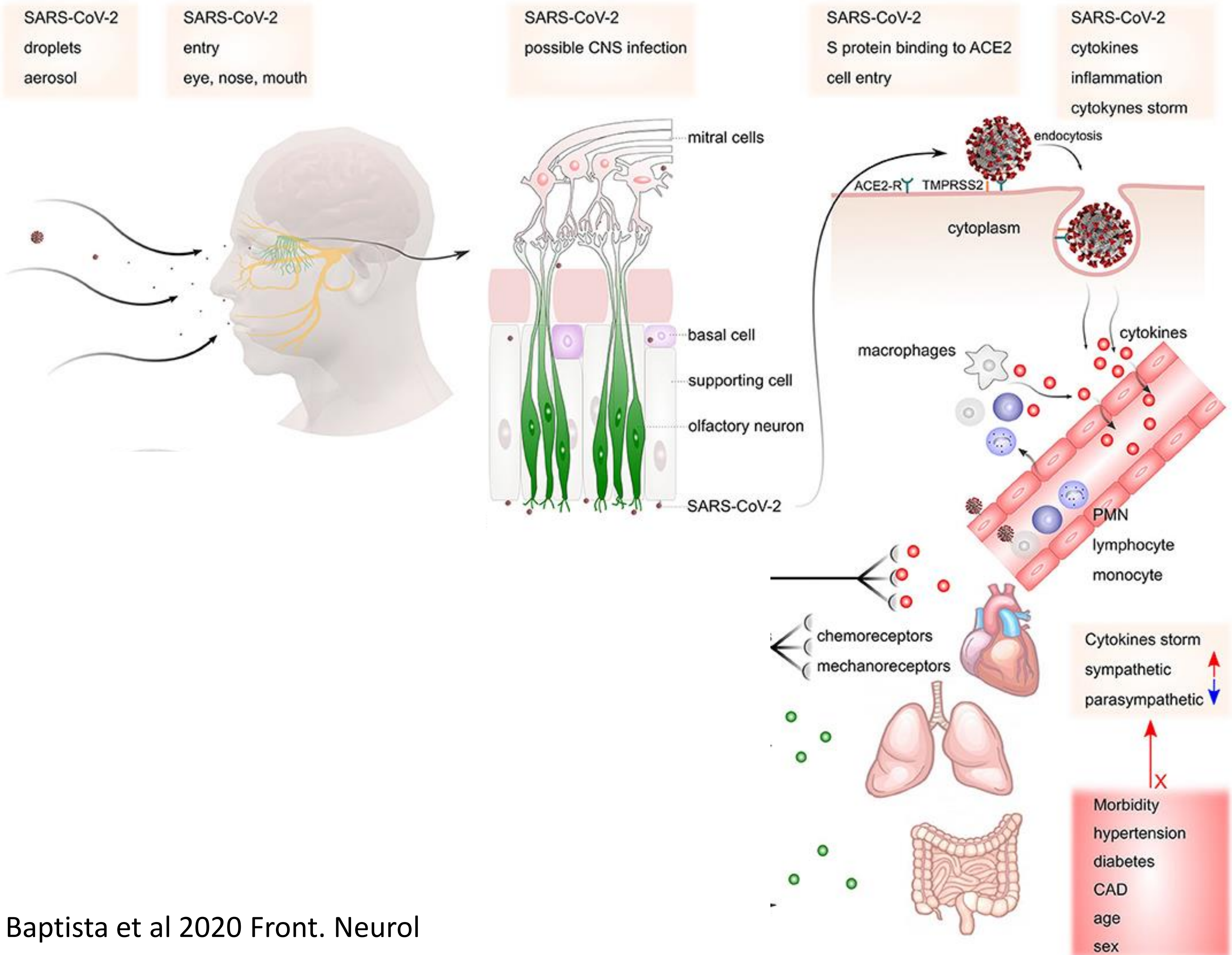
Frontera et al 2021

Mechanisms of Neuronal Injury with SARS-CoV-2



Boroujeni et al 2021

Mechanisms of Neuronal Injury with SARS-CoV-2



Virus binds to Angiotensin Converting Enzyme (ACE2) Receptor to enter cell

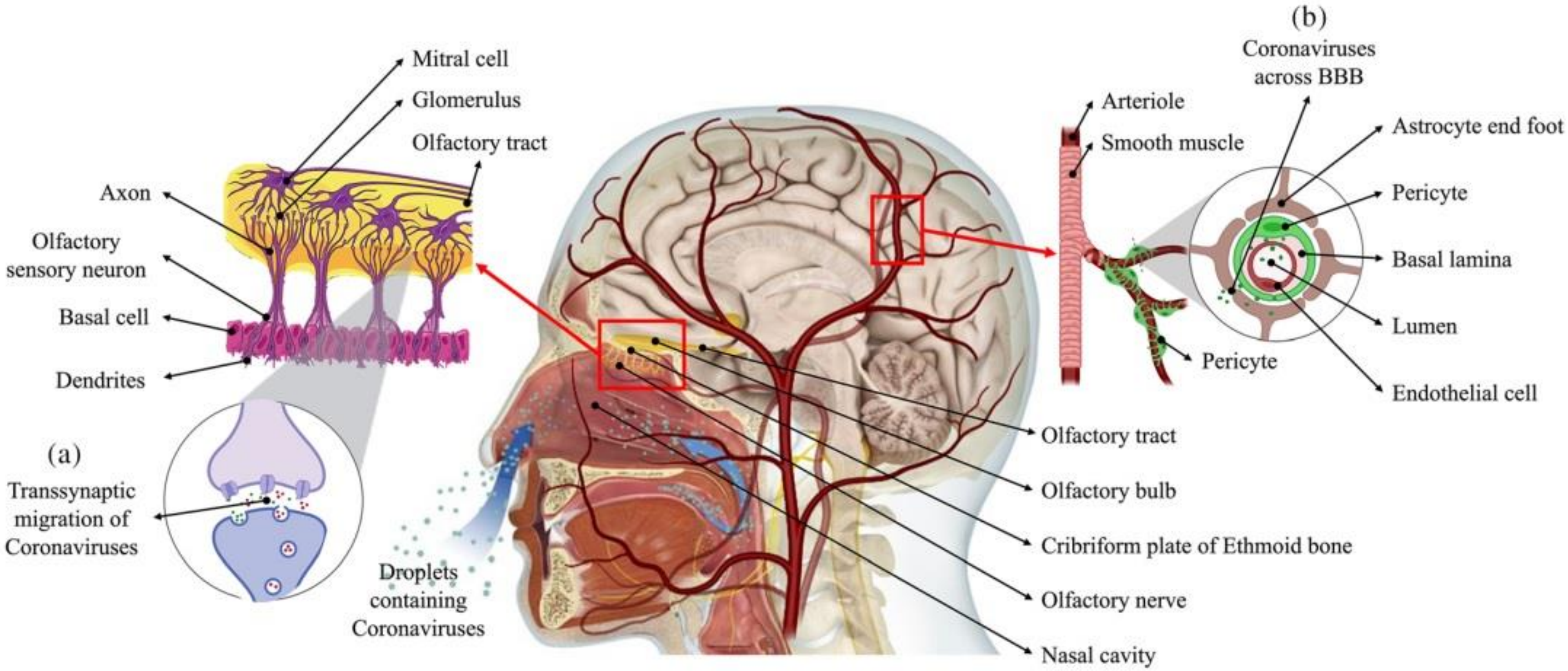
Transcription of Ribonucleic Acid (RNA) with COVID virus replication

Inflammatory reaction ensues with release of cytokines including Interleukin 6 (IL-6) "cytokine storm"

Inflammation of vessels and microbleeds in the brain, effects on peripheral organs

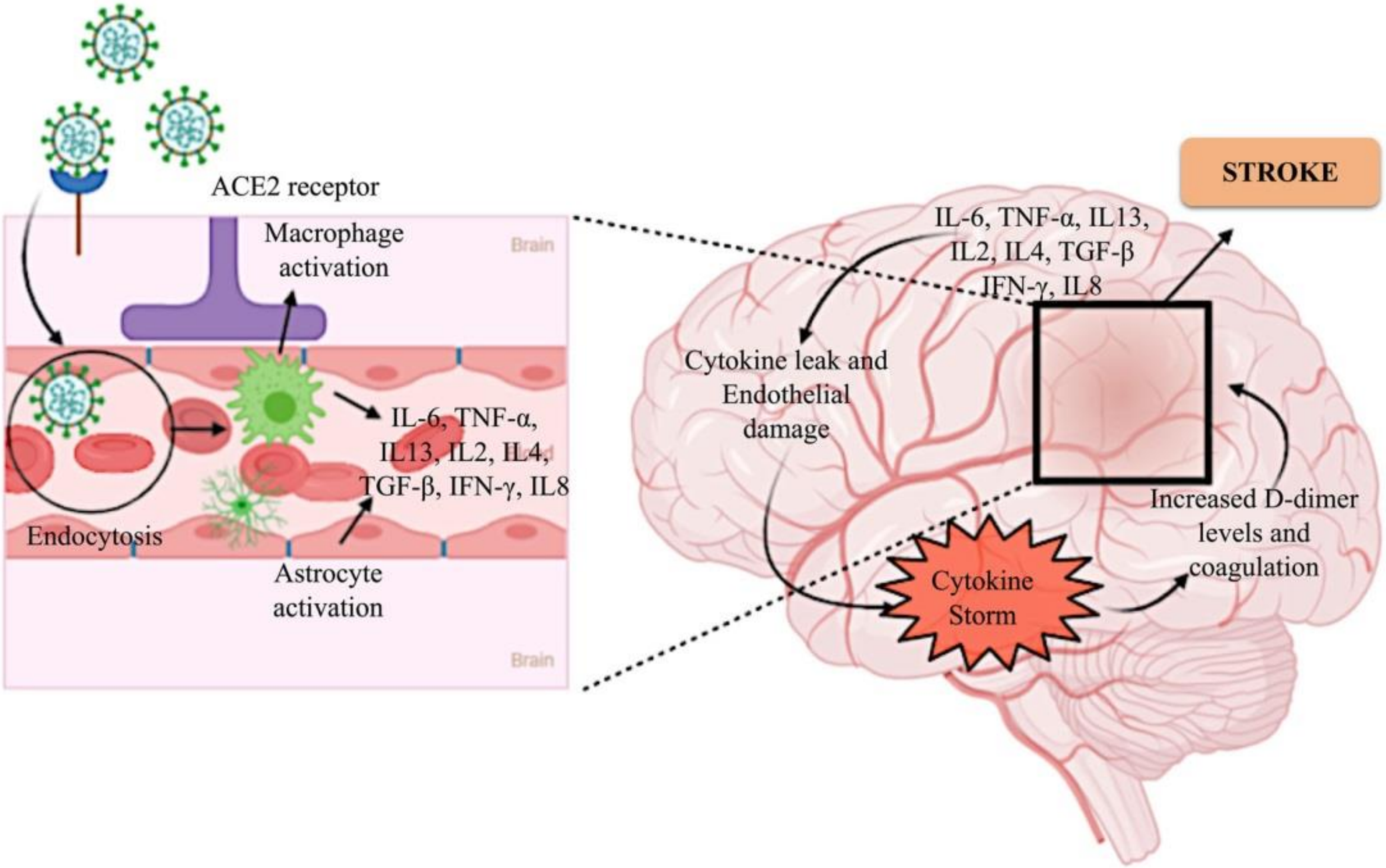
Baptista et al 2020 Front. Neurol

Mechanisms of Neuronal Injury with SARS-CoV-2



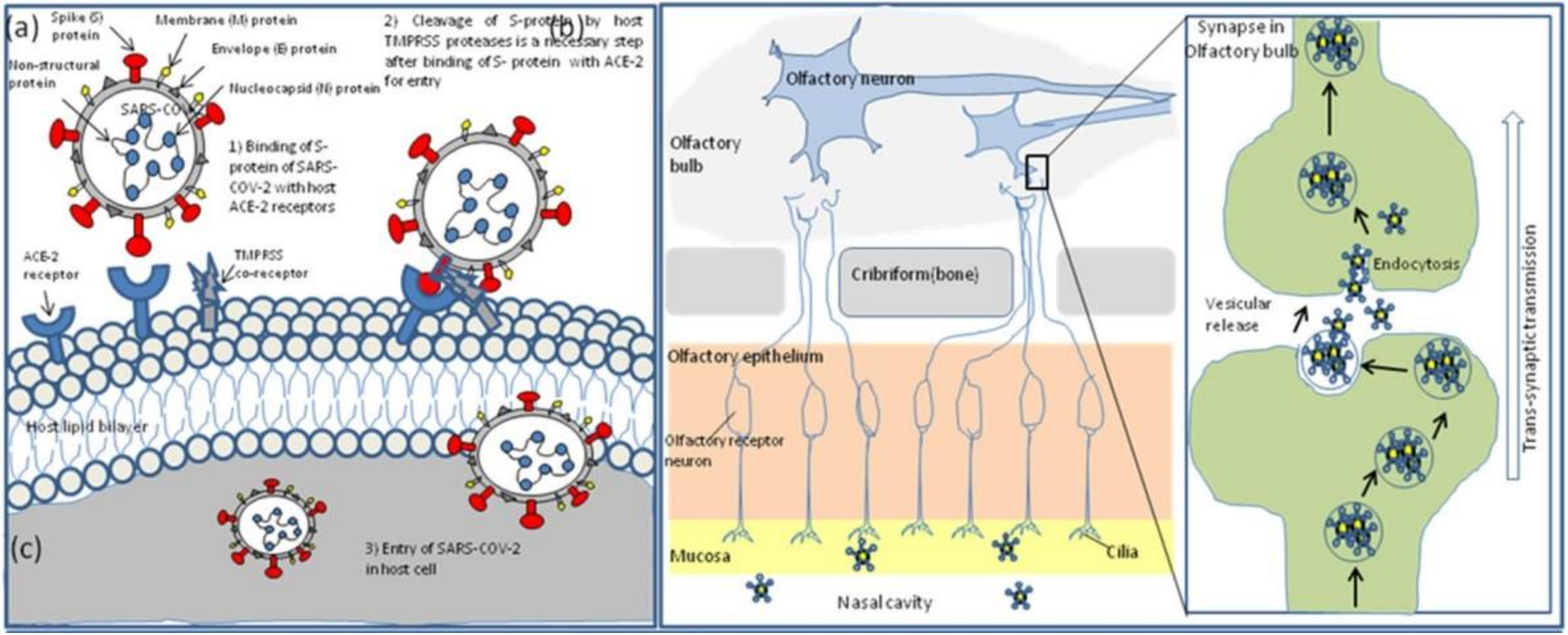
Kumar et al 2021

Mechanisms of Neuronal Injury with SARS-CoV-2



Kumar et al 2021

Mechanisms of Neuronal Injury with SARS-CoV-2



Kumar et al 2022

Mechanisms of Neuronal Injury with SARS-CoV-2

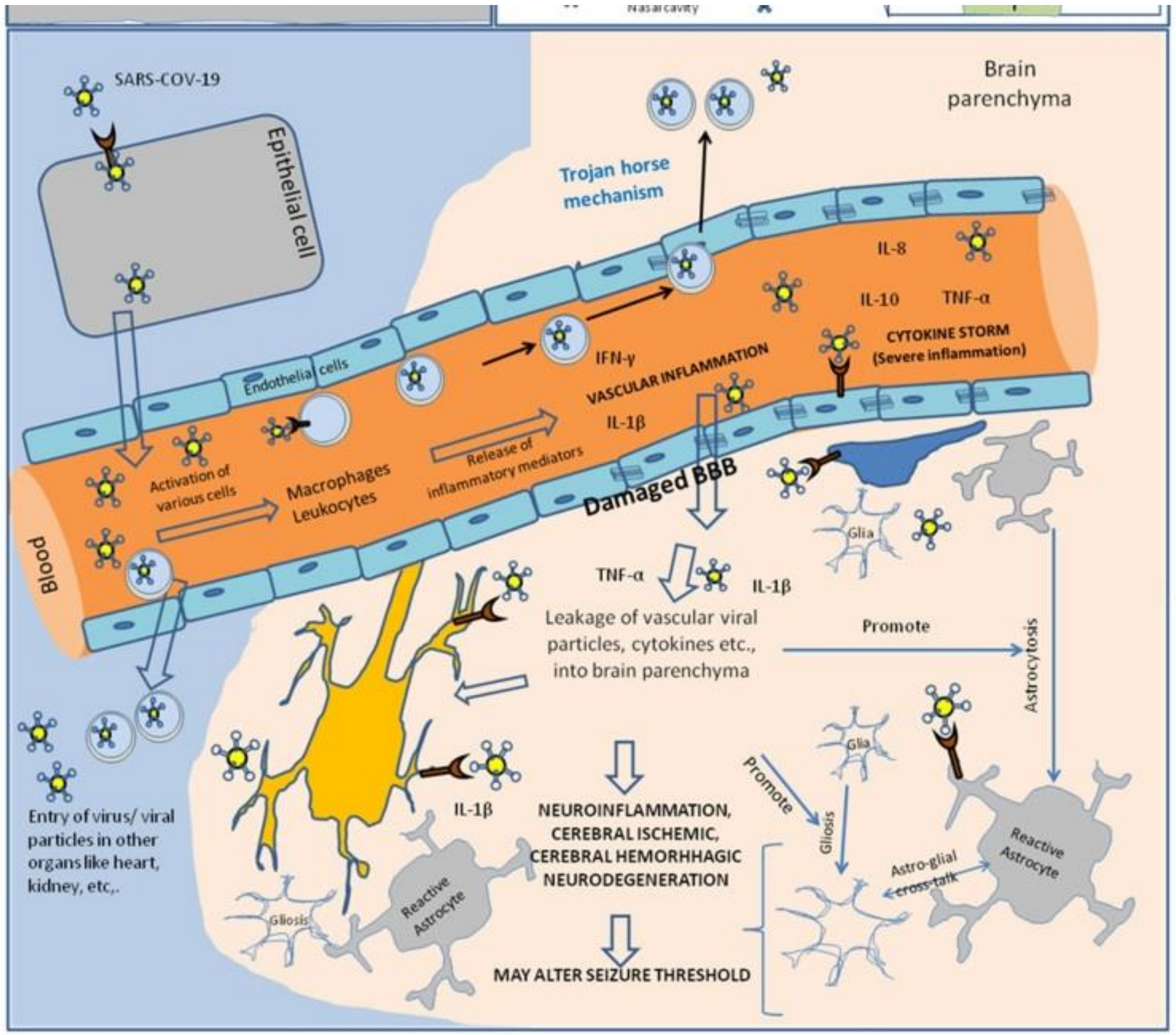


Figure 1. Mechanism of neuroinvasion of SARS-CoV-2 and associated neuropathological changes. (a) Entry of SARS-CoV-2 inside host cell after binding with host cell receptor, ACE-2 and co-receptor, TMPRSS, (b) olfactory retrograde transsynaptic route and (c) vascular route of viral neuroinvasion.

Kumar et al 2021

Mechanisms of Neuronal Injury with SARS-CoV-2

Tremblay et al 2020

A=astrocyte

L=leukocyte

M=Microglia

N=neuron

O=oligodendrocyte

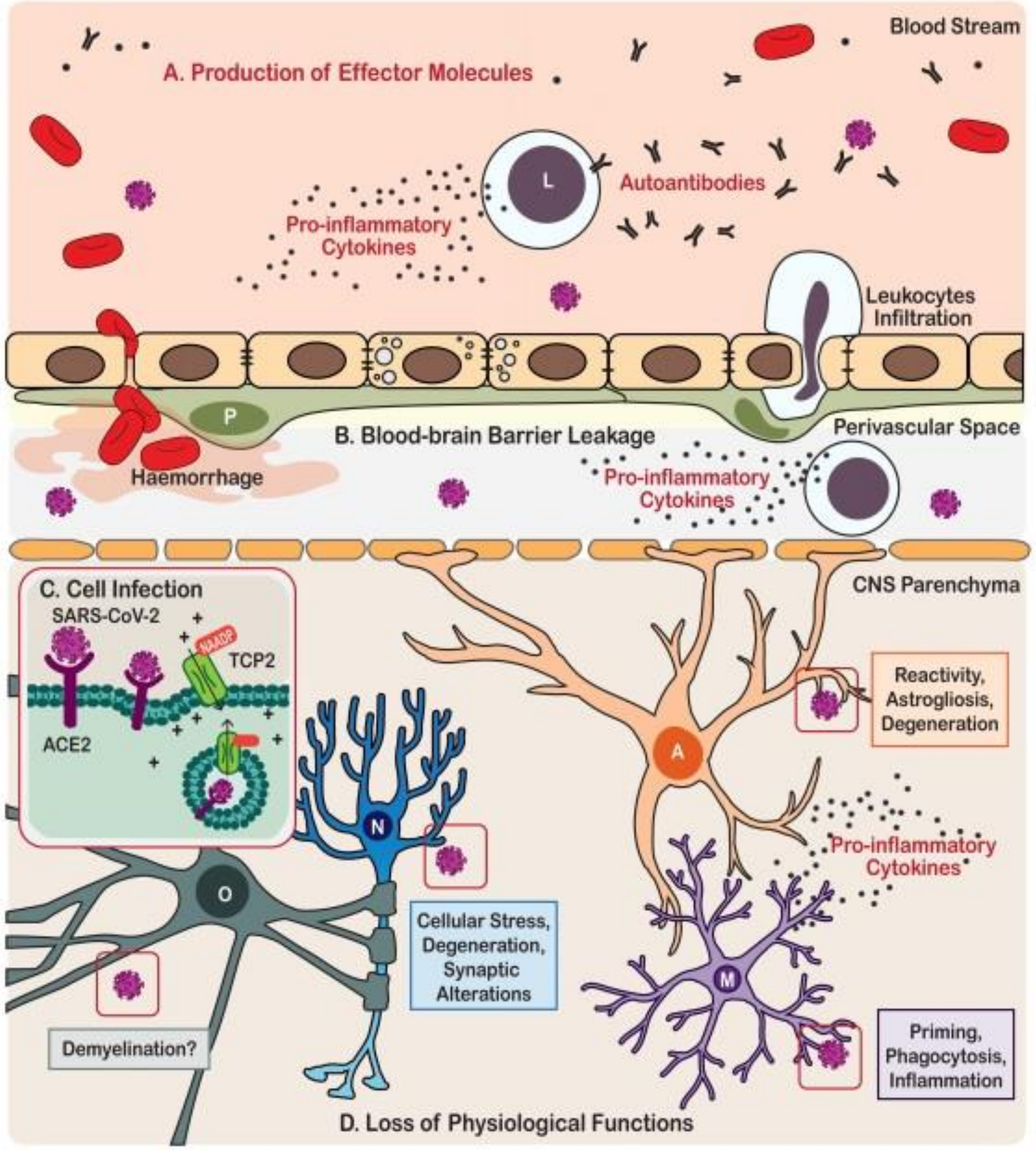


FIGURE 1 | Scheme illustration of the neurotropism, neuroinflammatory processes, and effects on brain cells triggered by COVID-19 in patients. **(A)** Immune cells from the periphery and the central nervous system (CNS) produce effector molecules that include pro-inflammatory cytokines and autoantibodies. **(B)** SARS-CoV-2 infection also causes leakage of the blood-brain barrier leading in some cases to haemorrhage and cerebral infarct, as well as eliciting leukocytes infiltration. **(C)** In the parenchyma, the CNS cells become infected by SARS-CoV via angiotensin-converting enzyme 2 (ACE2) endocytosis mediated by the two-pore channel 2 (TCP2). **(D)** SARS-CoV-2 infection leads to loss of physiological functions of the brain cells, including neurones, astrocytes, microglia, and oligodendrocytes. Cell types are identified in the following manner; A, Astrocyte; L, Leukocyte; M, Microglia; N, Neurone; O, Oligodendrocyte.

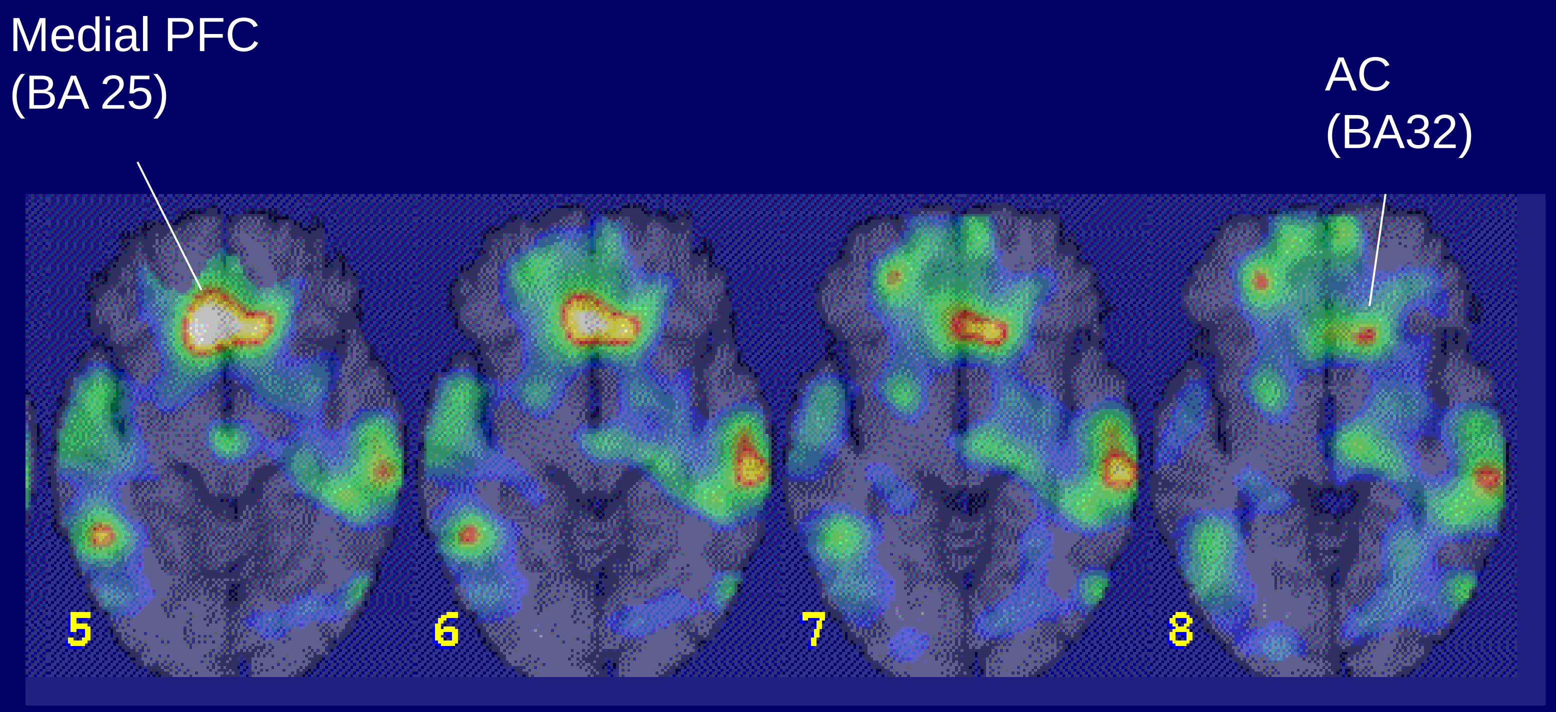
Brain Areas Involved in Long COVID

- Brain areas involved in memory and emotion
- Olfactory Cortex: sense of smell, linked to orbitofrontal cortex
- Medial prefrontal cortex and anterior cingulate: emotion, extinction of fear
- Amygdala: fear learning
- Hippocampus: memory
- Also involved in PTSD and depression

Medial Prefrontal Cortex (mPFC)

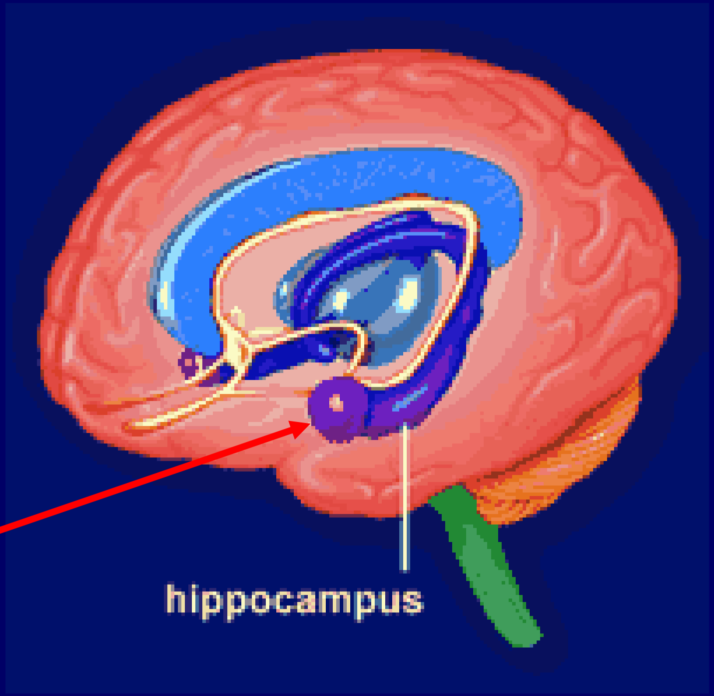
- Inhibits fear through inhibition of the amygdala
- Involved in regulation of emotion
- Modulates emotion

Medial Prefrontal Cortical Dysfunction with Traumatic Memories in PTSD



Decreased function in medial prefrontal cortical areas
Anterior Cingulate BA 25, BA 32 in veterans with PTSD compared to Veterans without PTSD during viewing of combat-related slides & sounds
Z score >3.00; p<.001

Hippocampus

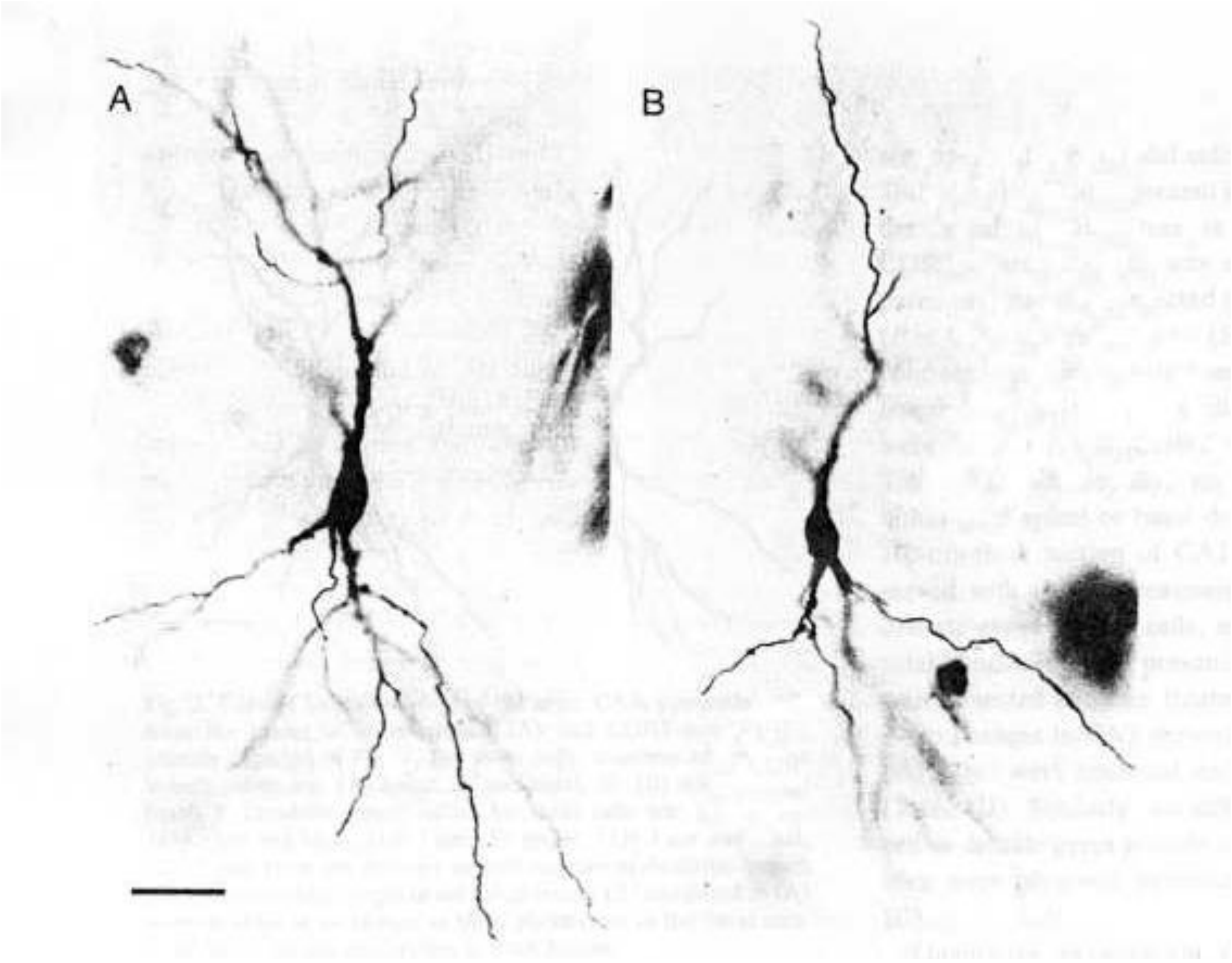


Amygdala –
fear learning

“Sea horse”

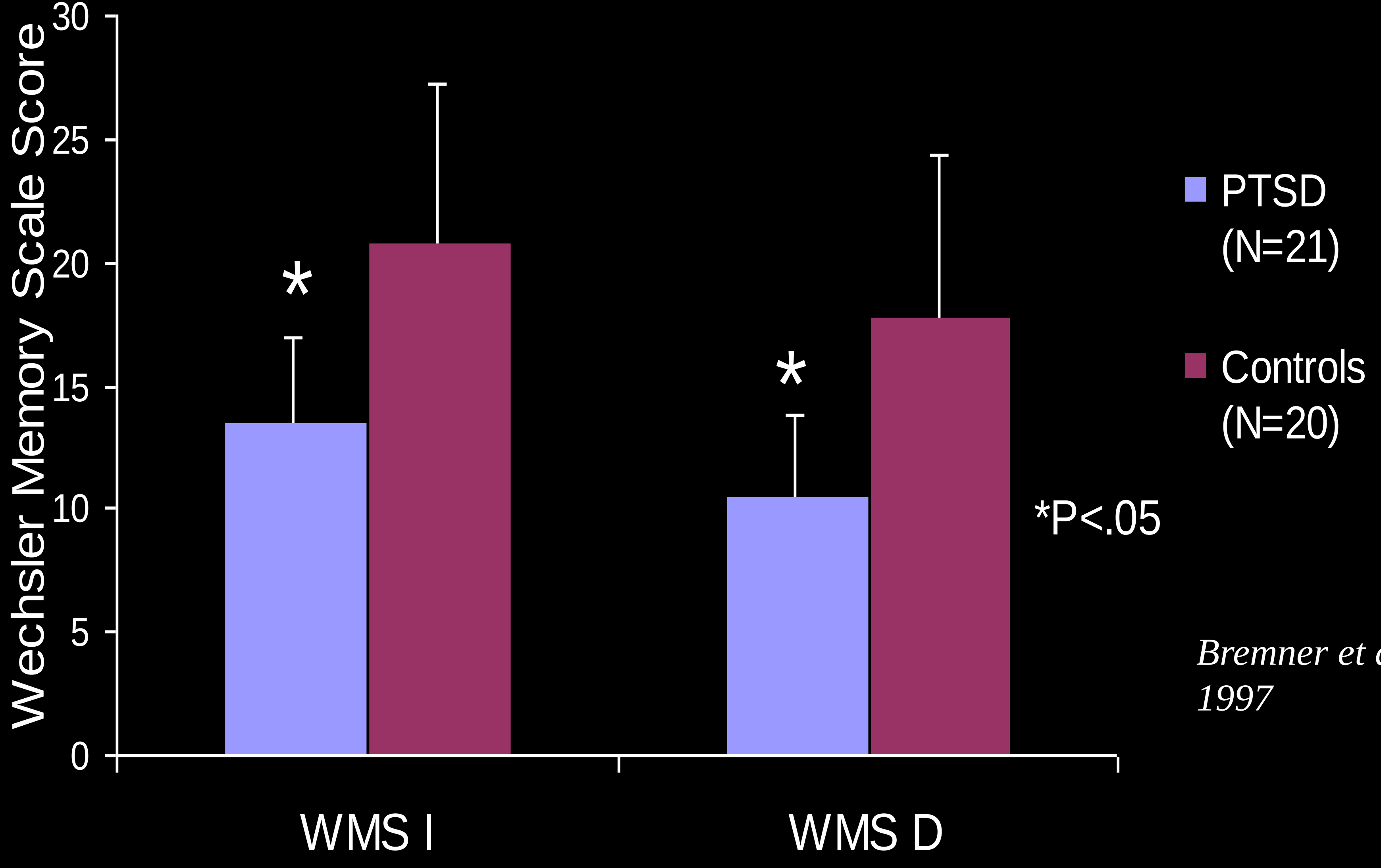
- Plays a critical role in learning and memory
- Creates a mental map of events in space and time
- Sensitive to stress
- Involved in dissociation and fear inhibition

Non-Stressed **Stressed**



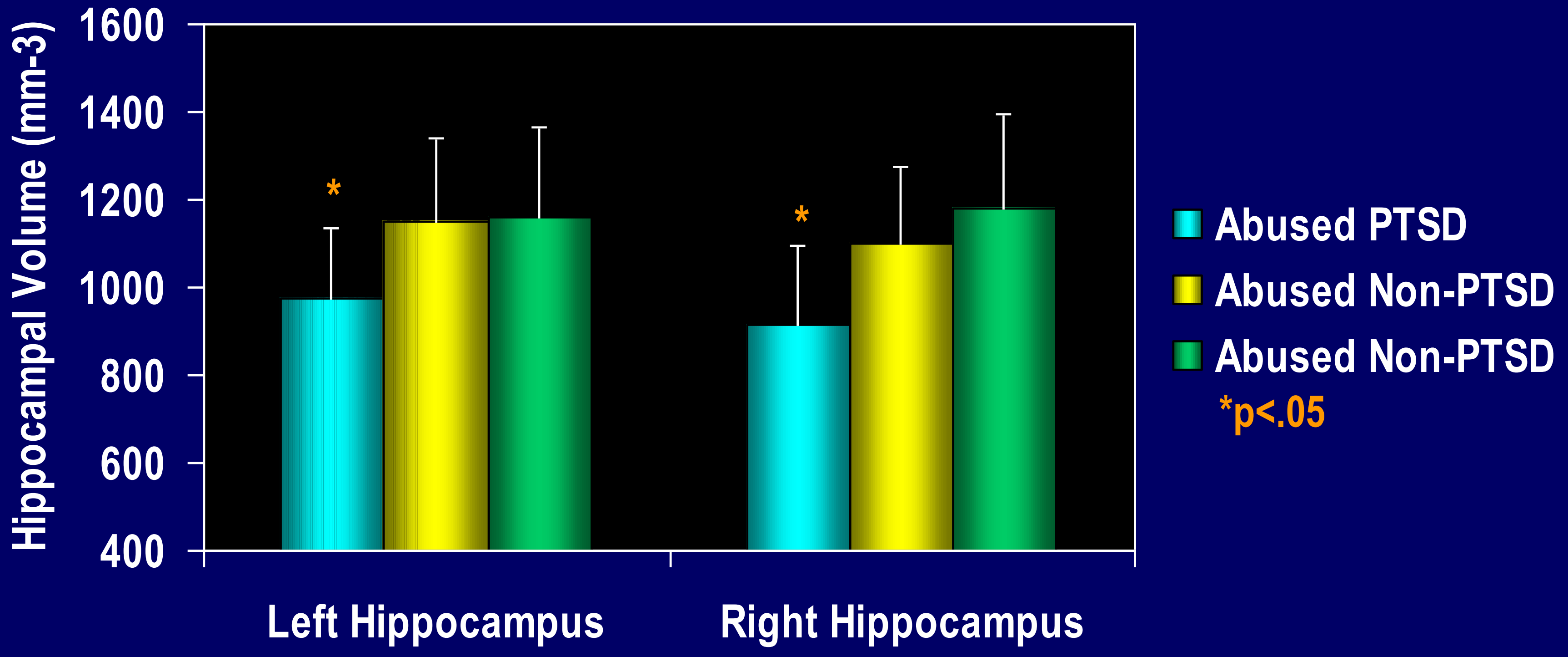
Stress results in decreased dendritic branching of neurons in the CA3 region of the hippocampus (Woolley et al. 1990)

Verbal Memory Deficits in Childhood Abuse-related PTSD



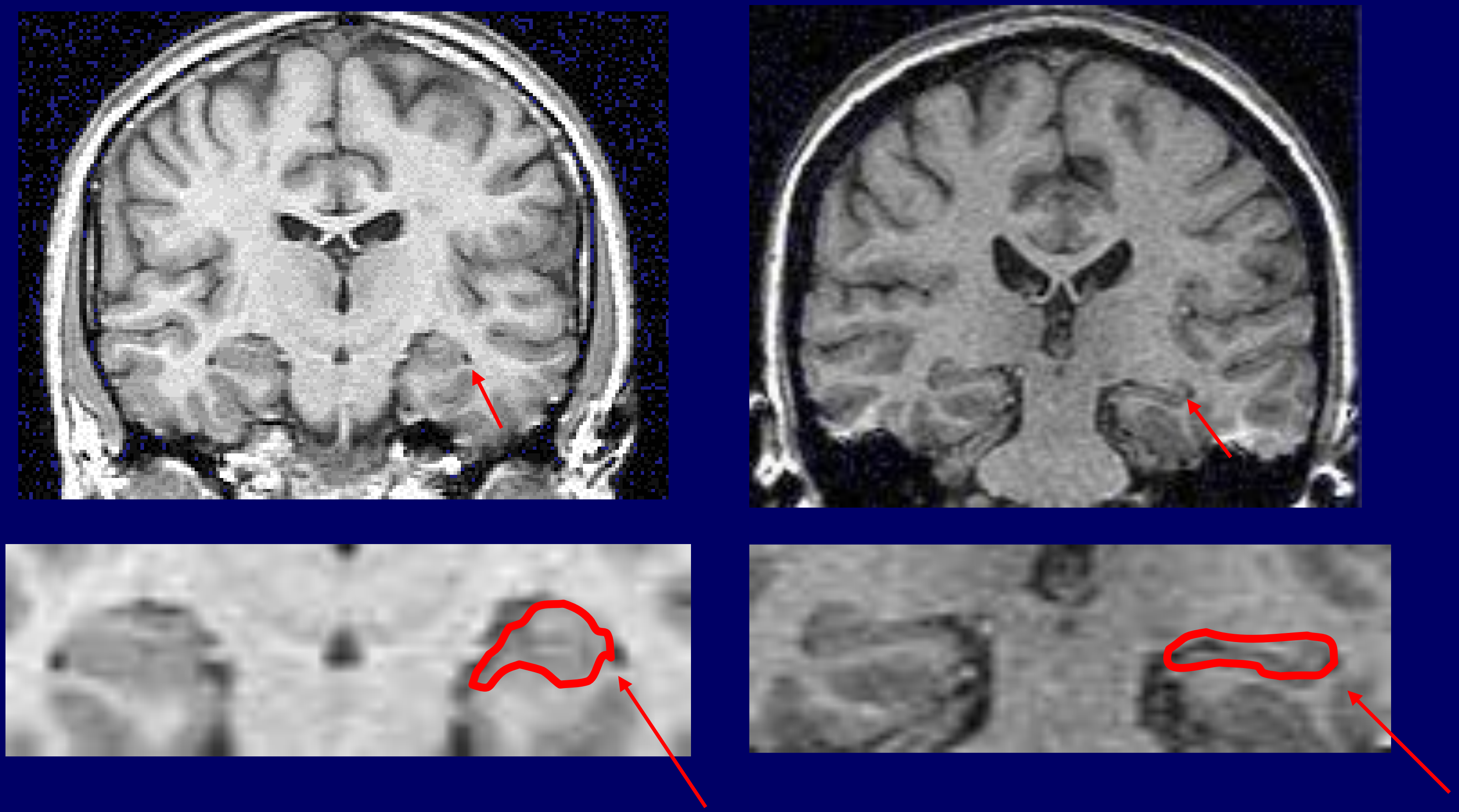
Bremner et al 1997

Smaller Hippocampal Volume in Women With Early Childhood Sexual Abuse-Related PTSD



Hippocampal volume measured with Magnetic Resonance Imaging (MRI)
Bremner et al. Unpublished data, 2000.

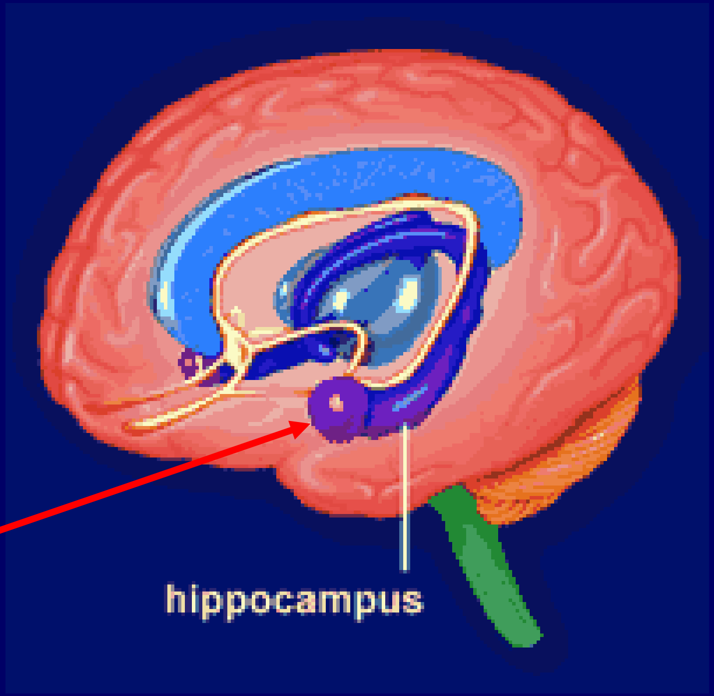
Hippocampal Volume Reduction in PTSD



NORMAL PTSD

J Douglas Bremner, MD, Emory University

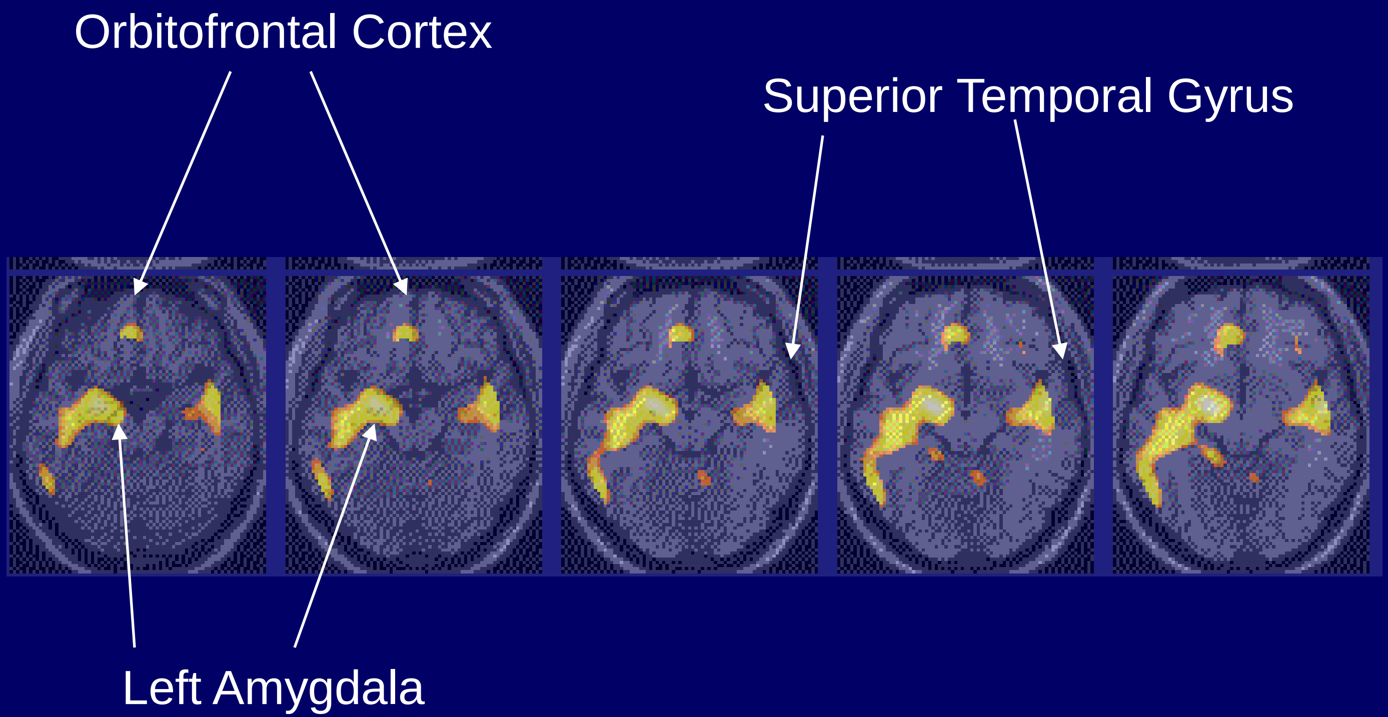
Amygdala



Amygdala – fear learning

- Involved in fear learning
- Pairing of light and shock results in fear response to light alone
- Lesions of the amygdala eliminate this

Increased Blood Flow with Fear Acquisition versus Control in Abuse-related PTSD



Yellow areas represent areas of relatively greater increase in blood flow with paired vs. unpaired US-CS in PTSD women alone, z>3.09; p<0.001

Acute Effects of COVID on the Brain in Critically Ill Patients

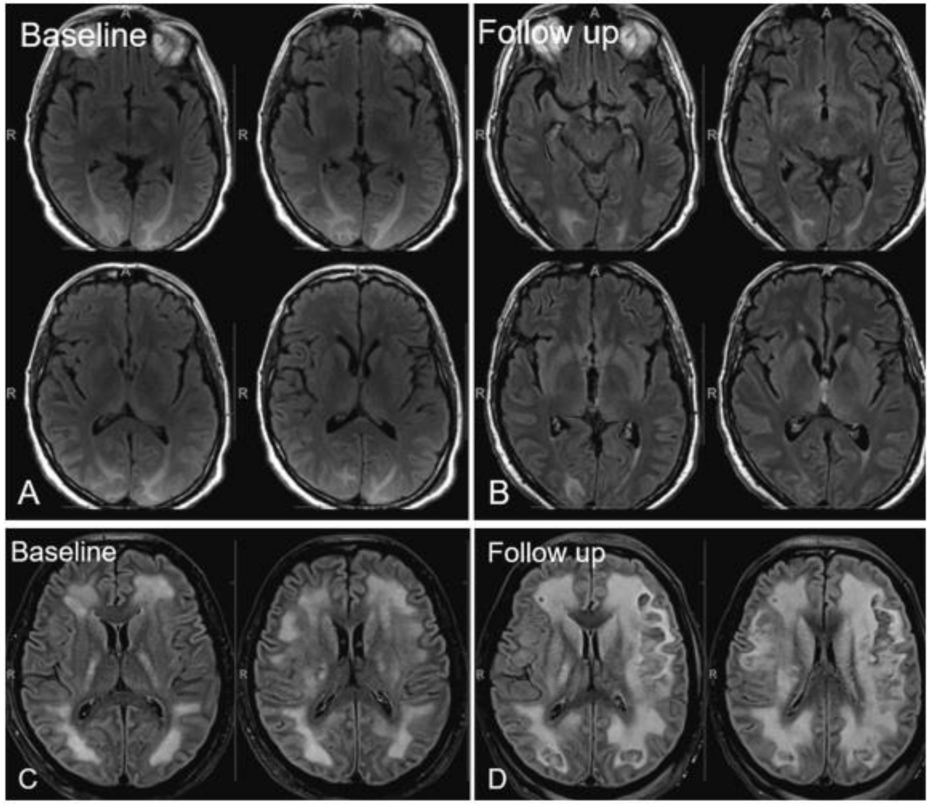


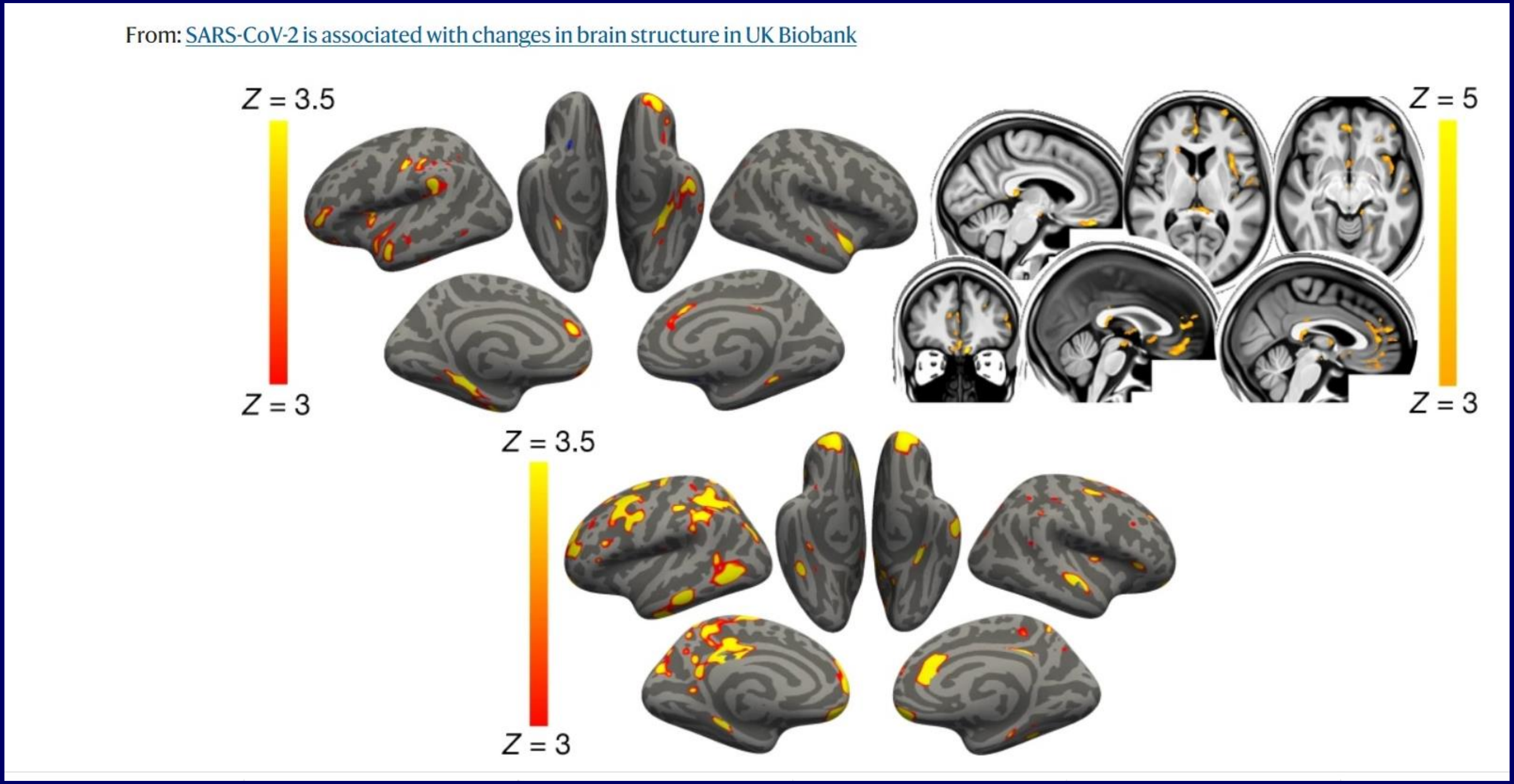
Fig. 2 White matter changes and increase in ventricle size from initial to final MRI. **a, b** Patient 6, a 61-year-old man with a history of hypertension, had an initial MRI **a** 17 days after admission and a final MRI **b** 24 days later. There were confluent posterior juxtacortical white matter changes present on the initial MRI which improved on the final MRI, consistent with posterior reversible encephalopathy syndrome. There was a notable increase in ventricular size between the MRIs (increase in the bicaudate index by 36.59% and in the third ventricular diameter by 44.64%). His course was complicated by a cardiac arrest with return of spontaneous circulation after 15 min prior to the initial MRI and renal failure requiring dialysis both prior to the initial MRI and between the initial and final MRI. He was ultimately declared brain dead following multifocal intracranial hemorrhage. **c, d** Patient 8, a 50-year-old man with a history of hypertension and diabetes (whose initial imaging was also described by Radmanesh et al. [12]) had an initial MRI **c** 21 days after admission and a final MRI **d** 11 days later. There were prominent symmetric confluent white matter changes present on the initial MRI which worsened on the final MRI and demonstrated progressive development of necrosis/cystic changes. His course was complicated by renal failure requiring dialysis prior to the initial MRI and a cardiac arrest with return of spontaneous circulation after 2.5 min between the initial and final MRI. He was discharged to a subacute rehab after 52 days with GCS score of 3 and mRS score of 5

- Agarwal et al 2021. Critically ill patients with two MRI scans 22 days apart on average

Long-term Cognitive and Brain Effects of COVID

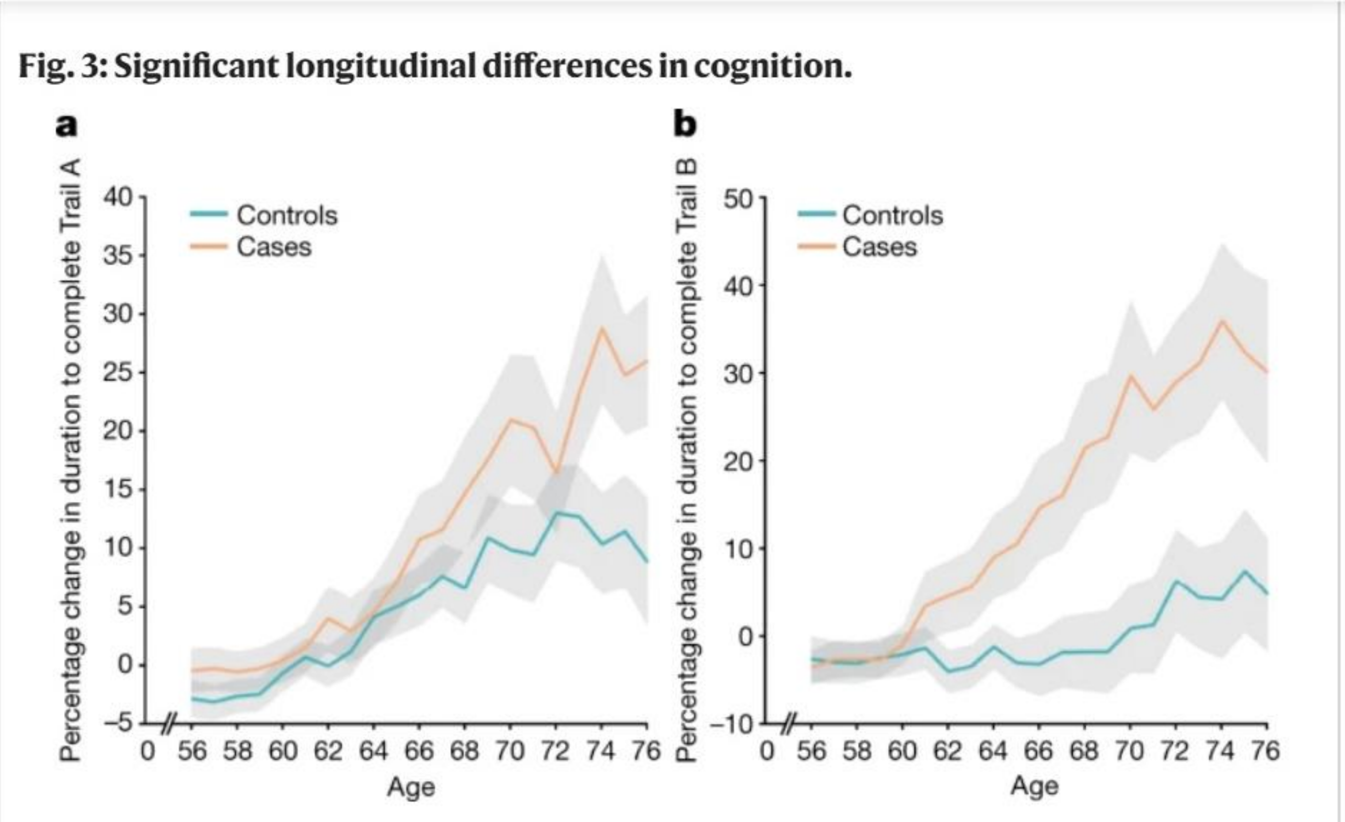
- 785 participants age 51-81 in UK Biobank scanned twice with magnetic resonance imaging (MRI)
- 401 tested positive for COVID infection some time between their two scans
- Greater reduction in gray matter thickness in infected persons in orbitofrontal cortex and parahippocampal gyrus
- Greater changes in markers of tissue damage in areas related to primary olfactory cortex
- Greater reduction in global brain size
- Douaud et al 2022 Nature

Reductions in Gray Matter Volume with COVID Infection



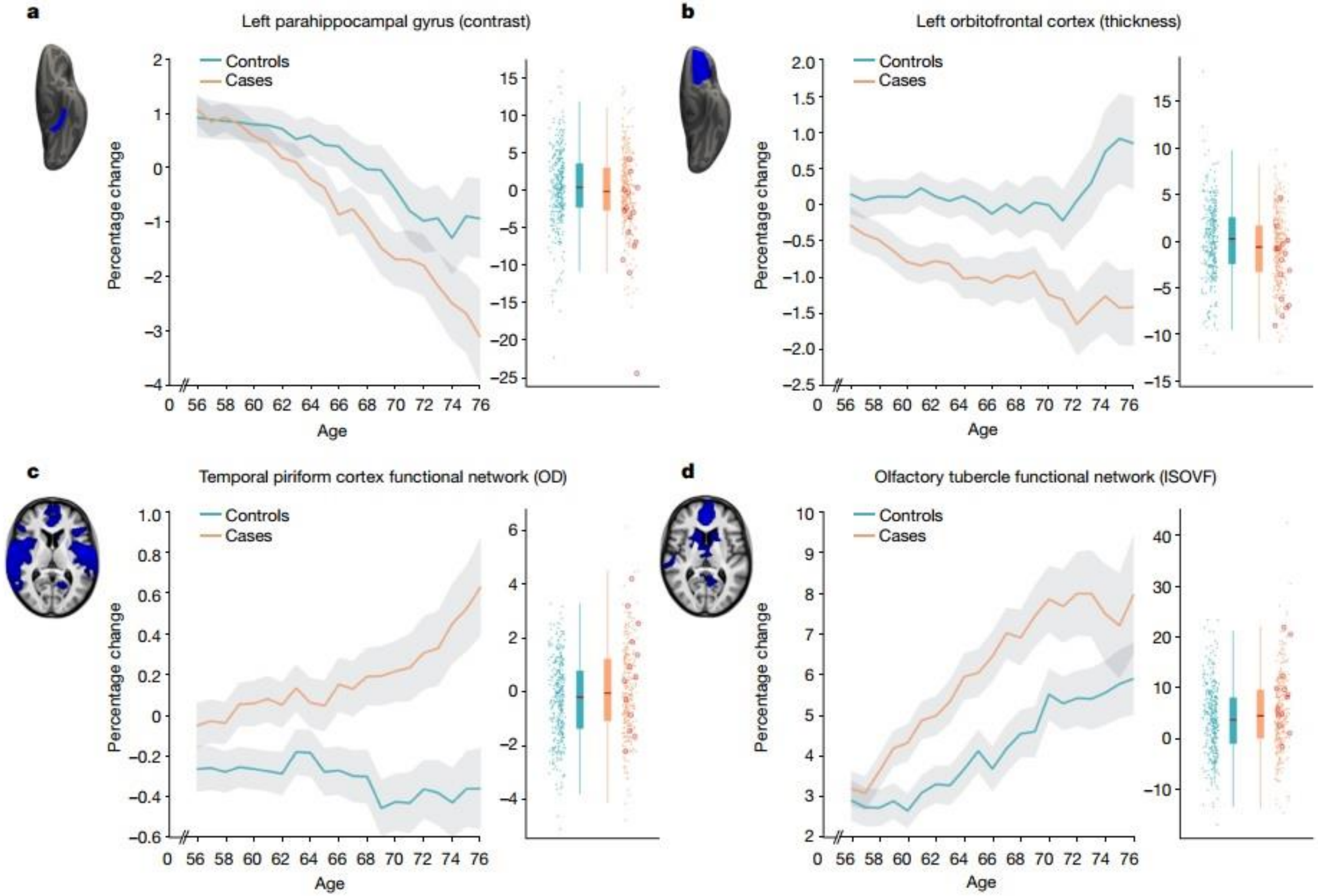
Douaud et al 2022 Nature; yellow and red areas represent significant difference in volumes with Covid infection

COVID Infection and Cognitive Impairment



Douaud et al 2022 Nature; Trail making task is a test of executive function and cognition

COVID Infection and Brain Changes



Douaud et al 2022 Nature;

Decreased Water Diffusion in White Matter Tracts in Long COVID at One Year

- Huang et al 2022

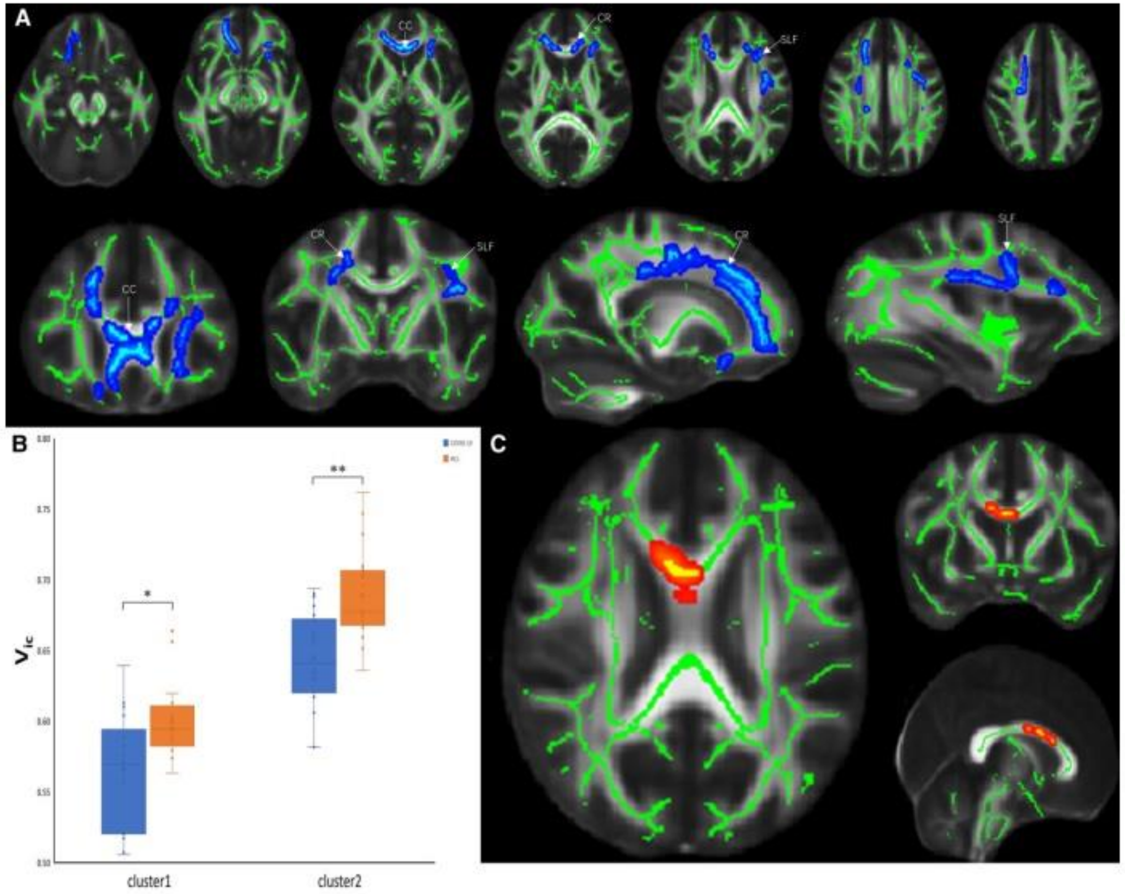


Figure 2 Results of TBSS analysis and *post hoc* regions of interest analysis. (A) TBSS results for V_{ic} between recovered COVID-19 patients and healthy controls (HCs). The TBSS analyses revealed decreased V_{ic} in patients than in controls. Green represents white matter skeleton. Blue-light blue represents areas of significant differences. Blue represents higher V_{ic}, and light blue represents lower V_{ic}. These tracts are named after significant fibre tracts in Table 4. (B) *Post hoc* region of interest (ROI) analysis results. Clusters are significant tracts in TBSS. The blue boxes represent recovered COVID-19 group, and the orange boxes represent healthy controls. Cluster 1 of recovered COVID-19 group: median = 0.570, interquartile interval (IQR) = 0.072, minimum = 0.506, maximum = 0.639; Cluster 2 of recovered COVID-19 group: median = 0.641, interquartile interval = 0.052, minimum = 0.582, maximum = 0.694;

Hypometabolism After Anosmia in Long COVID

- Donegani et al 2021
- 14 patients with one month of anosmia post COVID

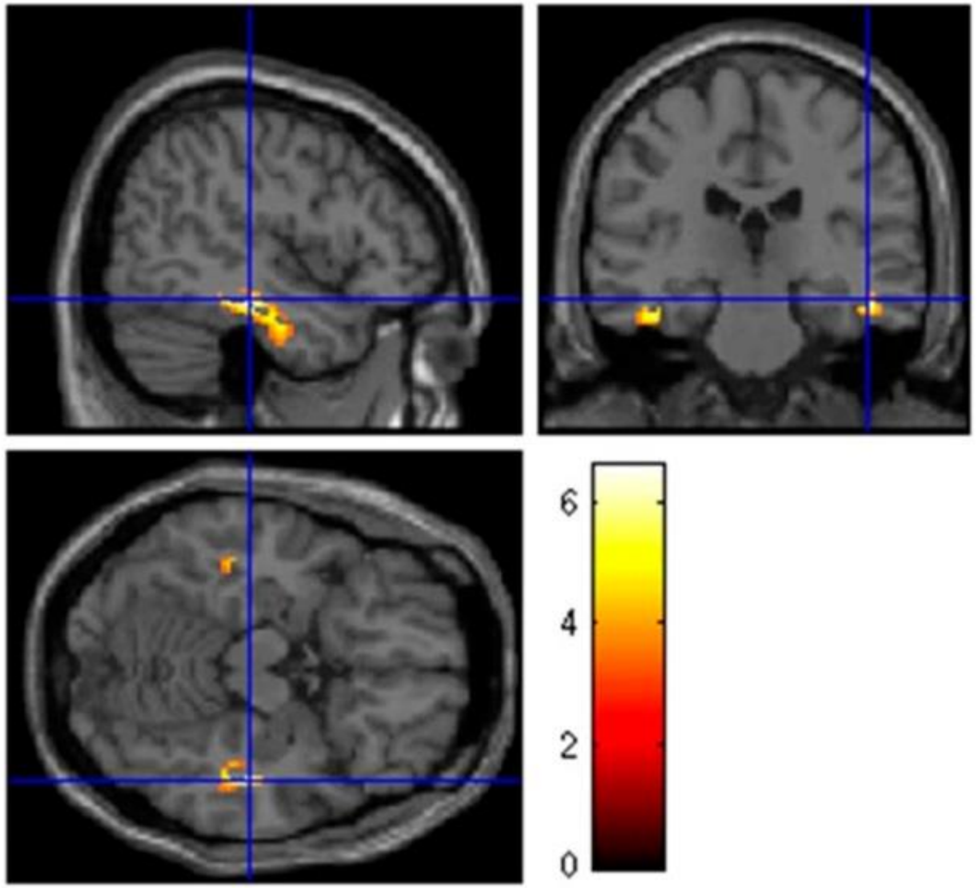
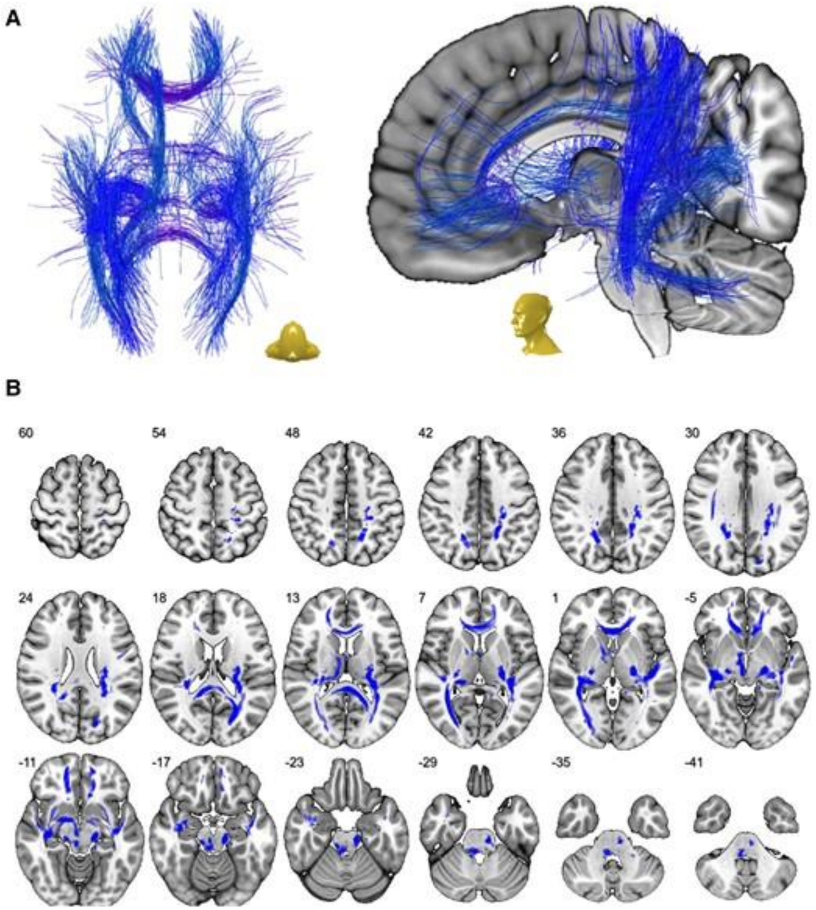


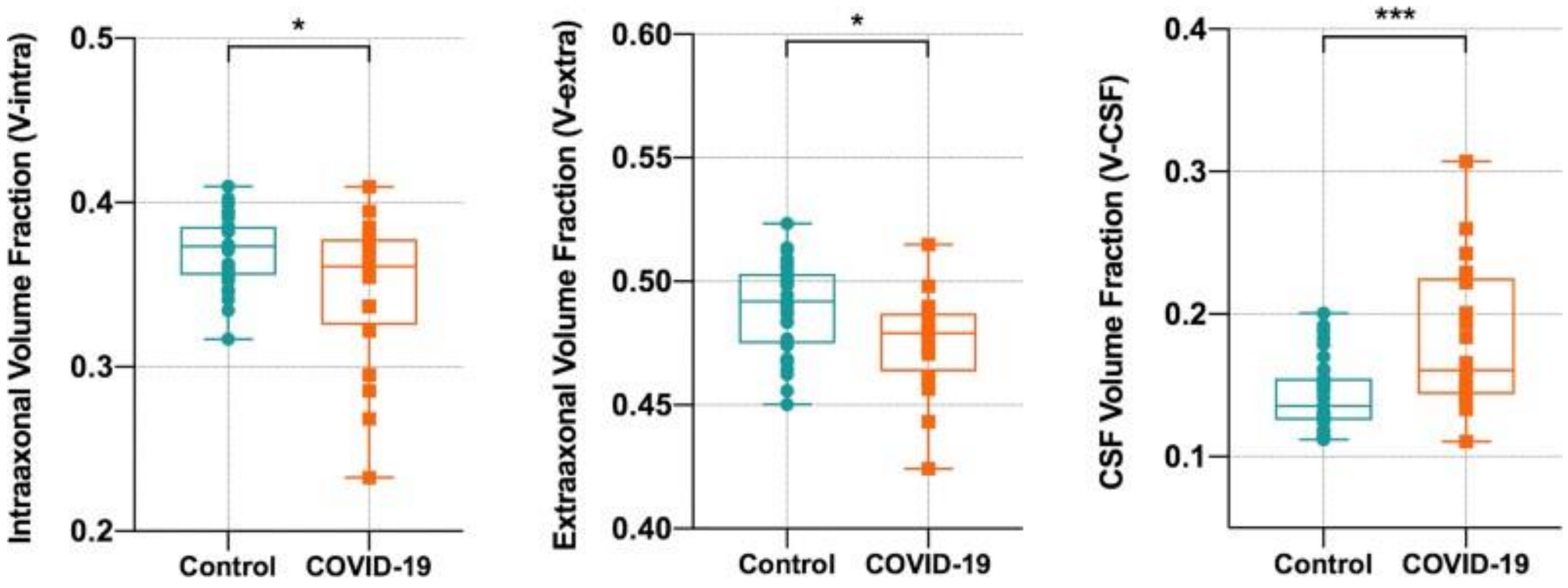
Figure 2. Hypometabolism with respect to controls in patients still presenting with hyposmia during early recovery after SARS-CoV-2 infection was highlighted in parahippocampal and fusiform gyri in both hemispheres (BA 20, 36, 37) and in the insula in the left hemisphere (BA 13). Height threshold of significance was set at $p < 0.05$ FWE-corrected at the cluster level. Regions of significant difference

Alterations in White Matter Tracts Following COVID Infection



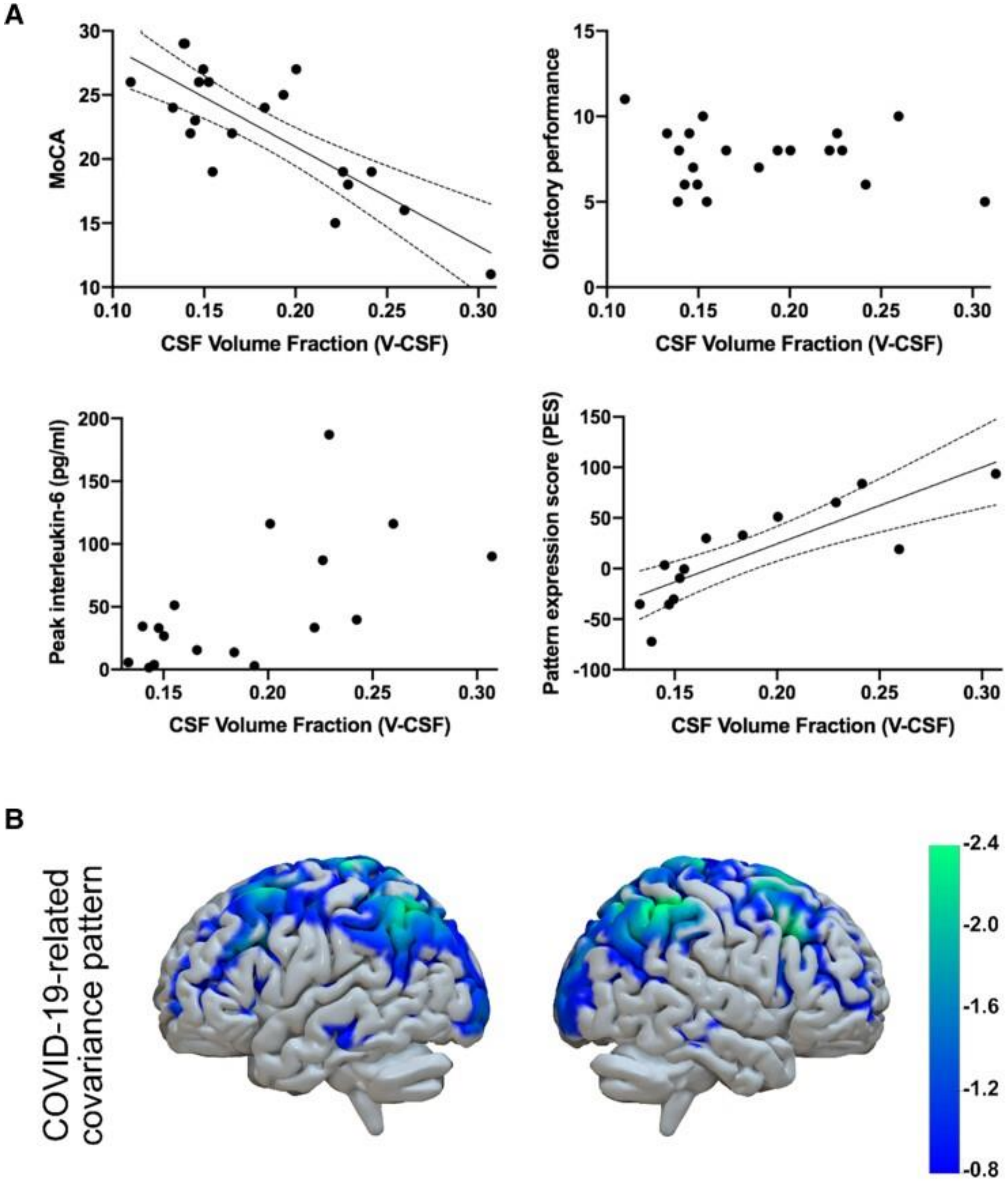
Rau et al 2022 Brain; Blue tracts show significant shift into free water fraction V-CSF in patients with Covid infection and neurological symptoms and cognitive dysfunction (N=20) 30 days post COVID compared to controls (N=35) detected by Diffusion Microscopic Imaging (DMI)

Alterations in White Matter Tracts Following COVID Infection



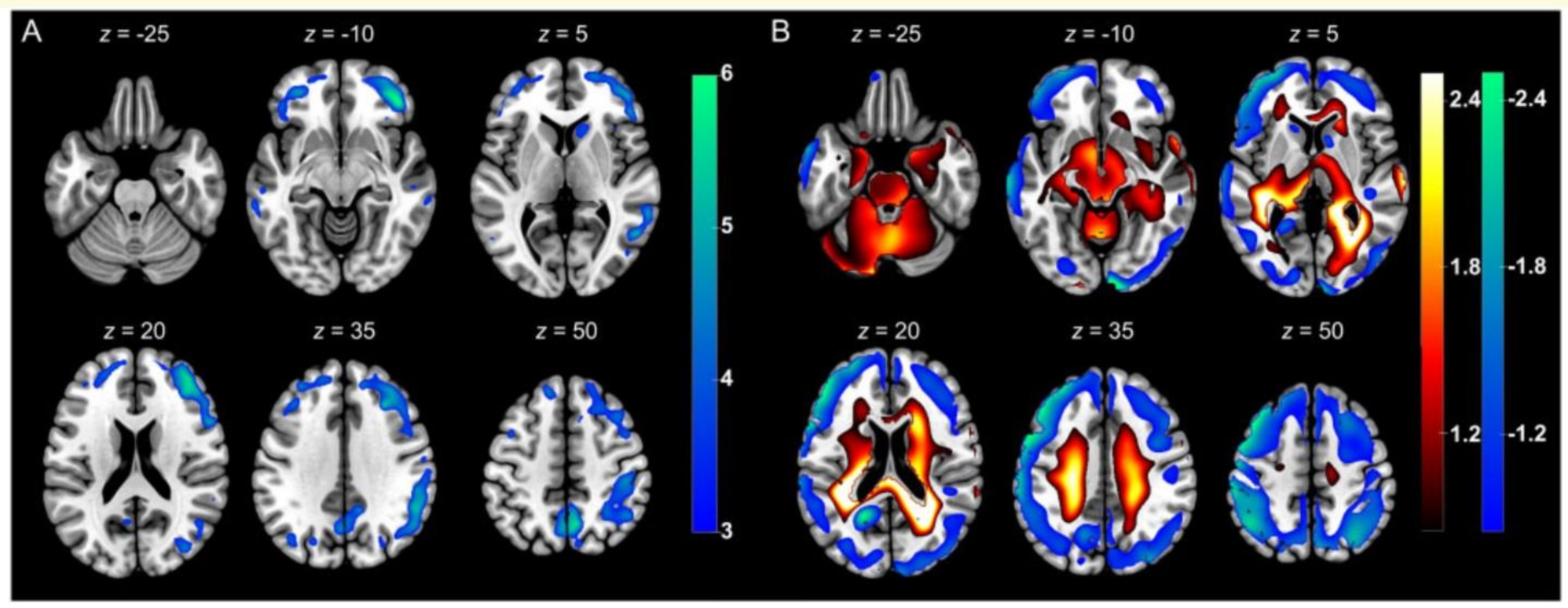
Rau et al 2022 Brain; There was a decrease in intra- and extra-axonal water content and increased cerebrospinal fluid (CSF) water content in patients with Covid infection and neurological symptoms (N=20) compared to controls (N=35) detected by Diffusion Microscopic Imaging (DMI) suggesting a shift in water content to CSF.

Alterations in White Matter Tracts Following COVID Infection



Rau et al 2022 Brain; Increased CSF water content correlates with decreased frontoparietal metabolism on positron emission tomography (PET) and [F-18]2-fluoro-2-deoxyglucose (FDG) increased interleukin 6 (inflammatory cytokine) and decreased olfactory performance in patients with COVID and neurological symptoms and cognitive impairment. 20 inpatients with neuro symptoms

Decreased Frontal and Parietal Metabolism in Subacute COVID



Hosp et al 2021: Hospitalized patients with neurological symptoms

Microglia Activation in Subacute COVID

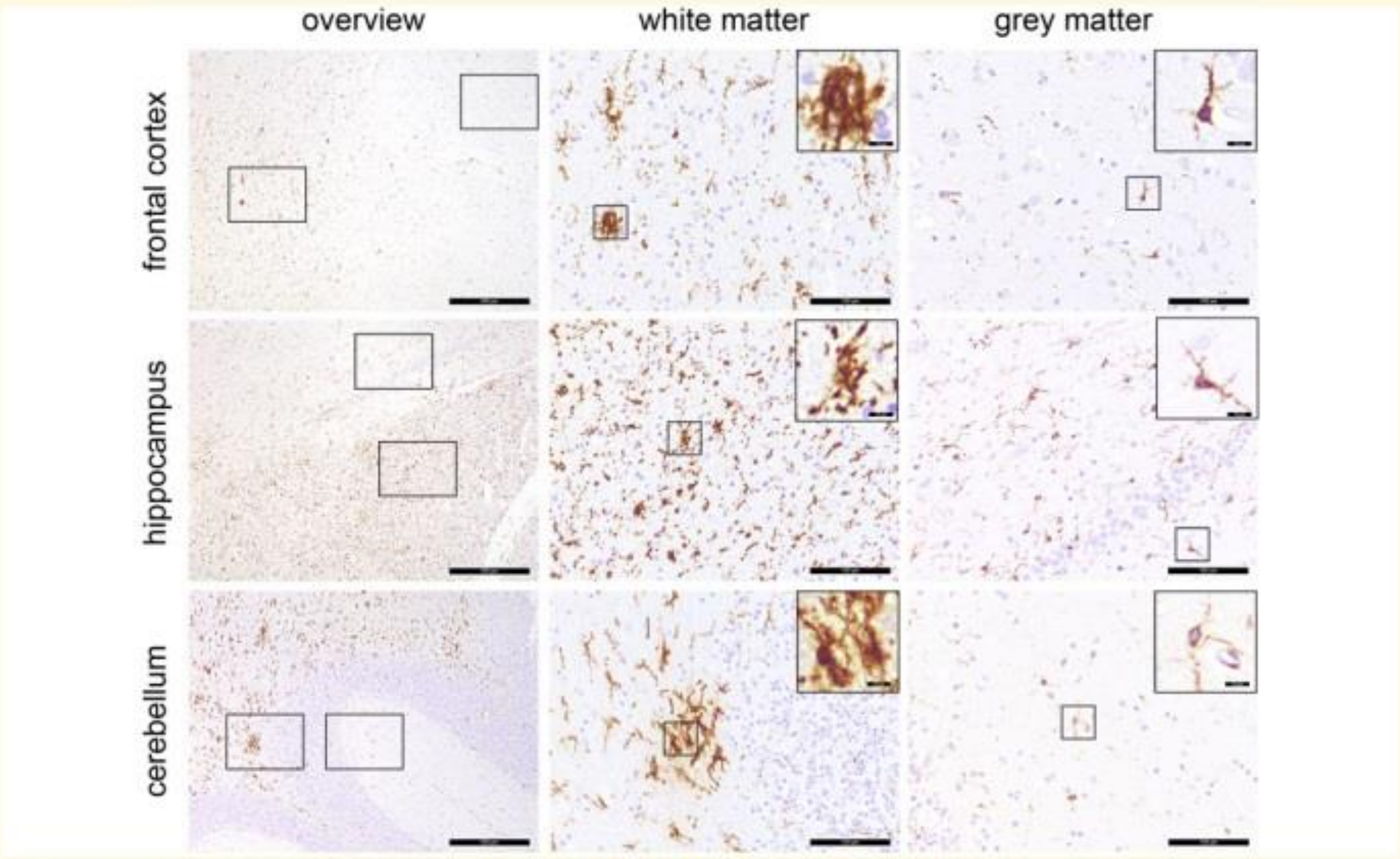
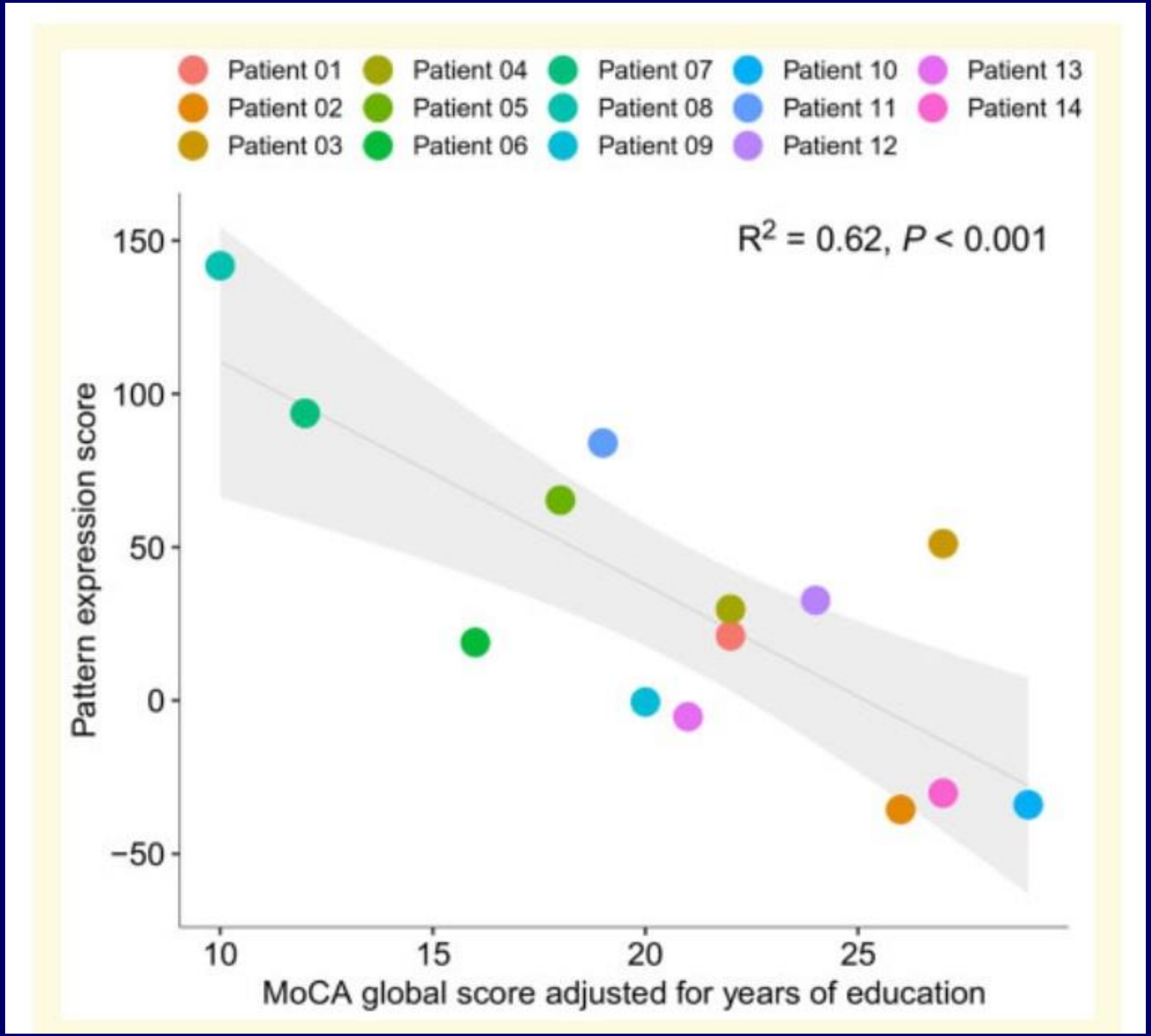


Figure 6 Distribution pattern of microglia activation. Immunohistochemical reactions for human leukocyte antigen DR isotype (brown), counterstaining with haematoxylin (blue) in different regions of the CNS. Microgliosis and formation of microglia nodules are confined to the white matter, whereas grey matter regions are largely unaffected. Scale bars = 500 µm, 100 µm and 10 µm in the *insets*, respectively.

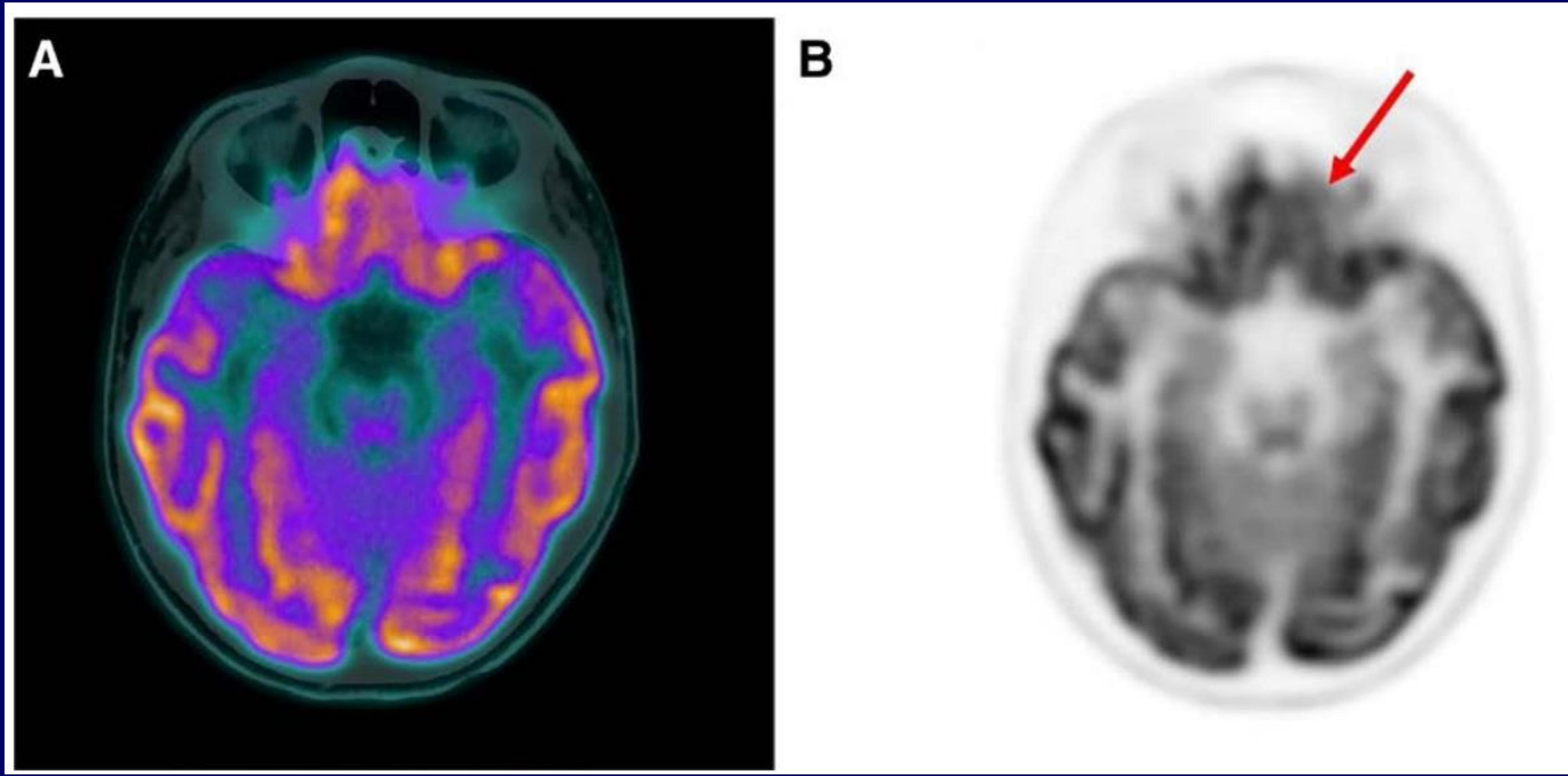
Hosp et al 2021: Hospitalized patients with neurological symptoms

Decreased Frontal and Parietal Metabolism in Subacute COVID Correlates with Cognitive Dysfunction



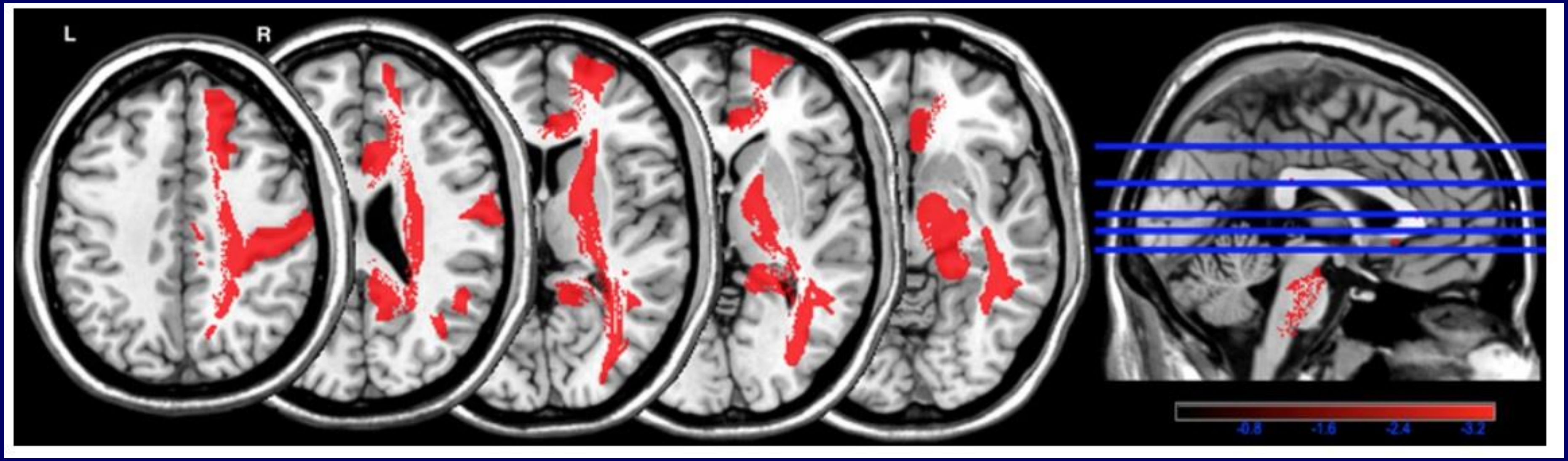
Hosp et al 2021: Hospitalized patients with neurological symptoms. MoCA=Montreal Cognitive Assessment

Decreased Orbitofrontal Metabolism in Children with Long COVID



Cocciolilo 2922: Three children with Long COVID, PET FDG of the brain

White Matter Hyperintensities on MRI Correlate with Cognitive Dysfunction on Neuropsychological Testing



Andriuta et al 2022. Long COVID patients with neurocognitive complaints

MRI Abnormalities in Frontal Cortex with COVID

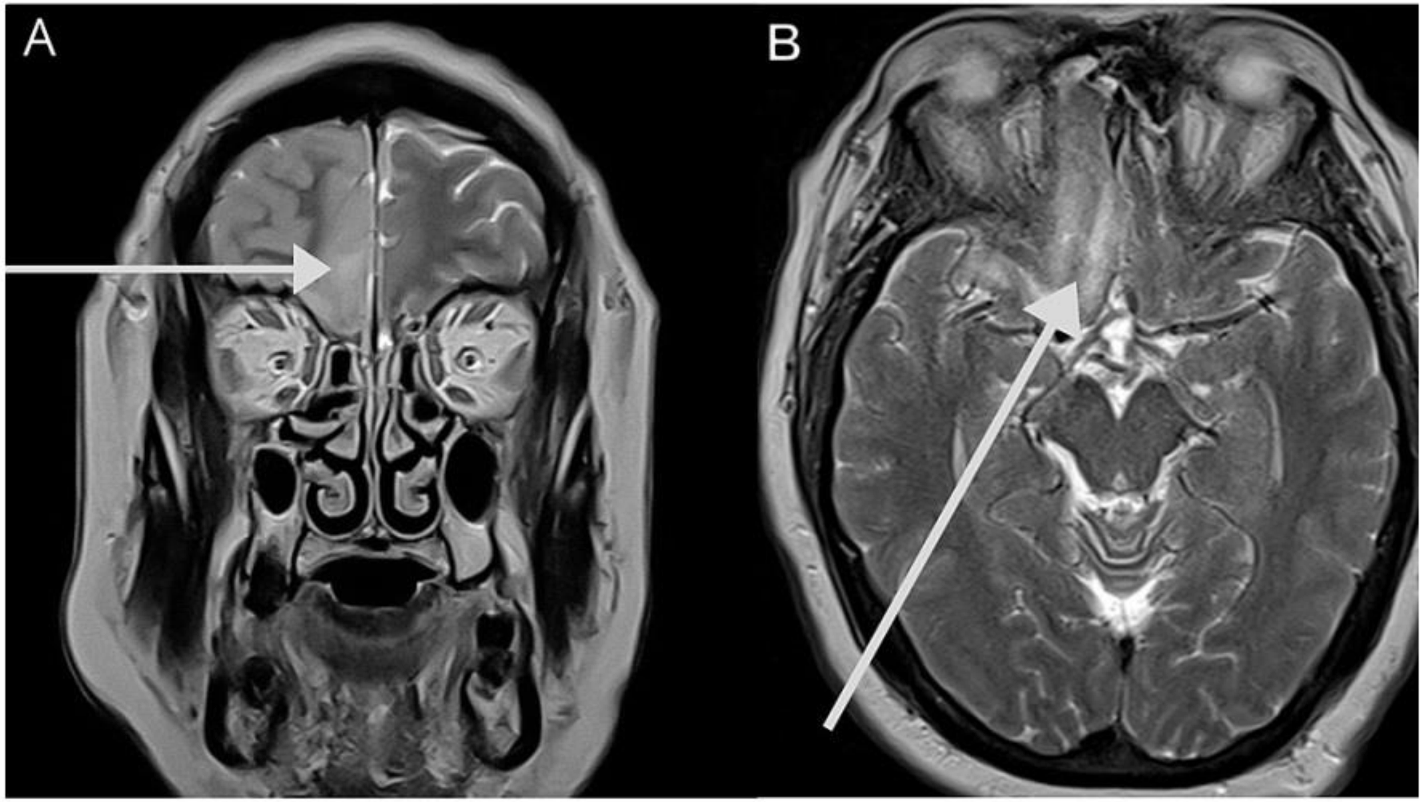


FIGURE 1: Olfactory neuropathy in a 47-year-old male patient with a stiff neck, headache, disorientation, anosmia, SARS-CoV-2 RT-PCR (+) test result, and pneumonia.

(A) Coronal T2WI shows unilateral frontal cortical thickening and decreased subarachnoid space. (B) Axial

Mendez Elizondo 2021

Olfactory Bulb Affected by COVID with Loss of Smell

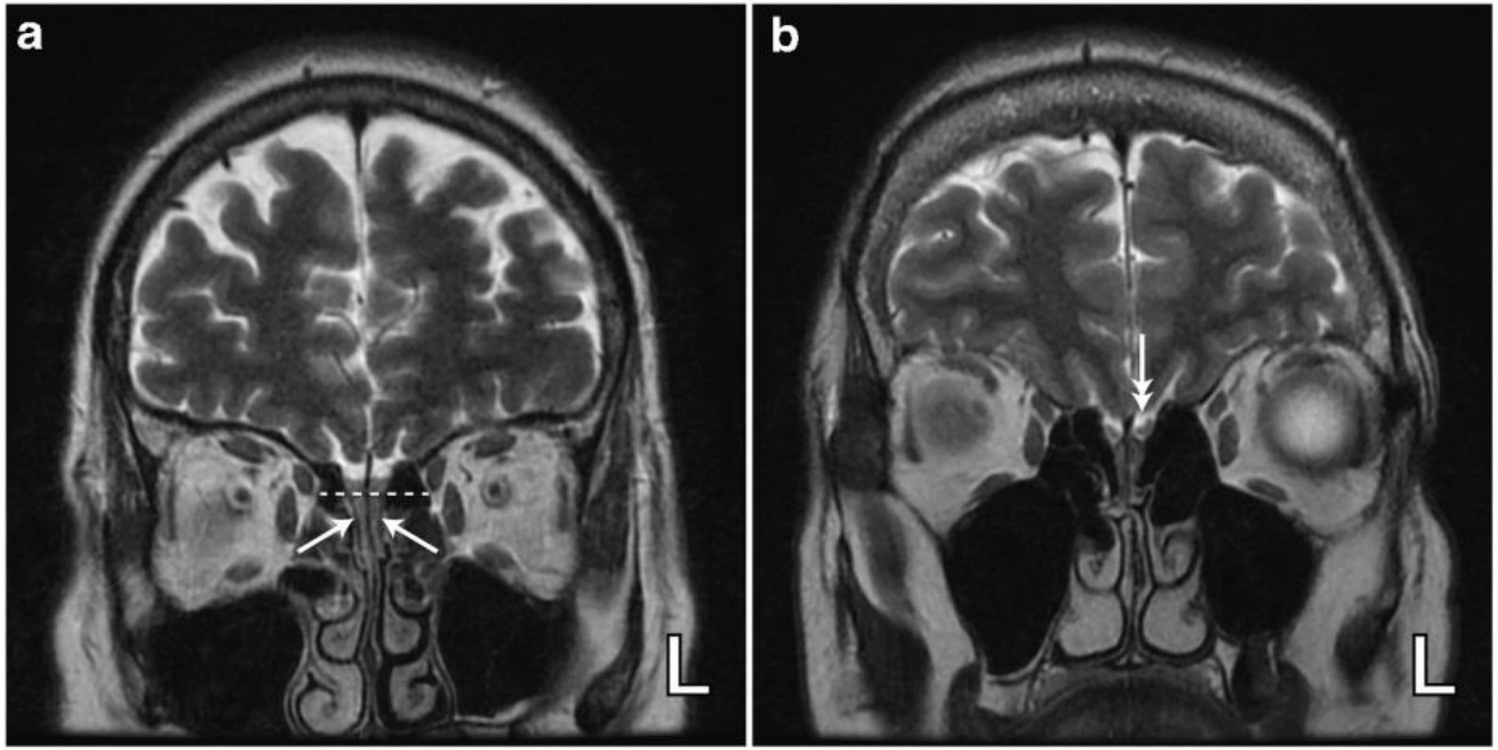
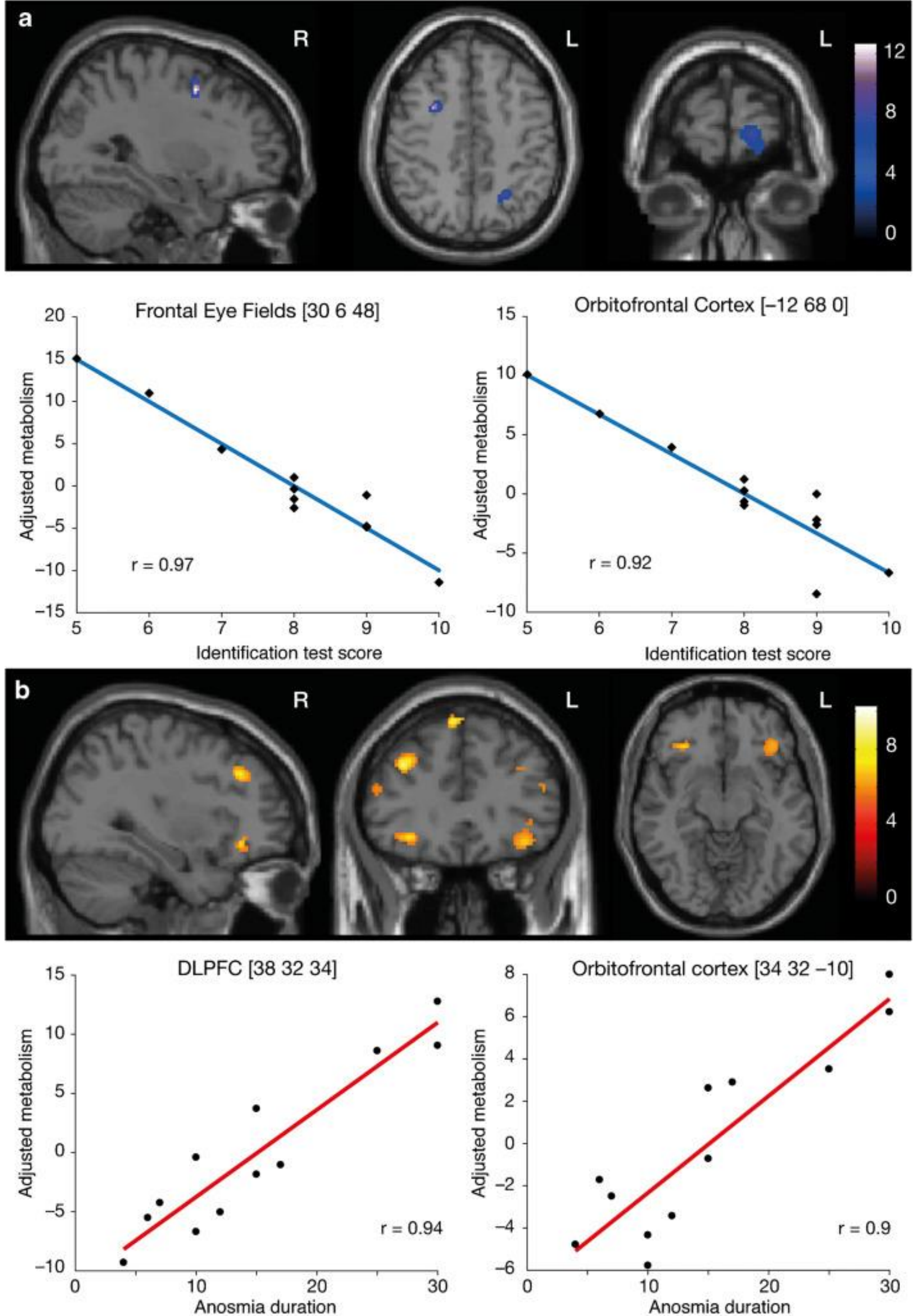


Fig. 1 Axial T2-weighted coronal images demonstrating bilateral and complete obliteration of the olfactory clefts (white single arrows) with (**a**) no associated olfactory bulb asymmetry and with (**b**) asymmetry of the olfactory bulbs (left (L) bulb relatively enlarged, white double arrow). The criblate plate is illustrated by the dotted line

Neisen et al 2021 Eur J Nucl Med Mol

Olfactory Impairment Correlates with Metabolism in Orbitofrontal Cortex and Dorsolateral Prefrontal Cortex



Neisen et al 2021 Eur J Nucl Med Mol

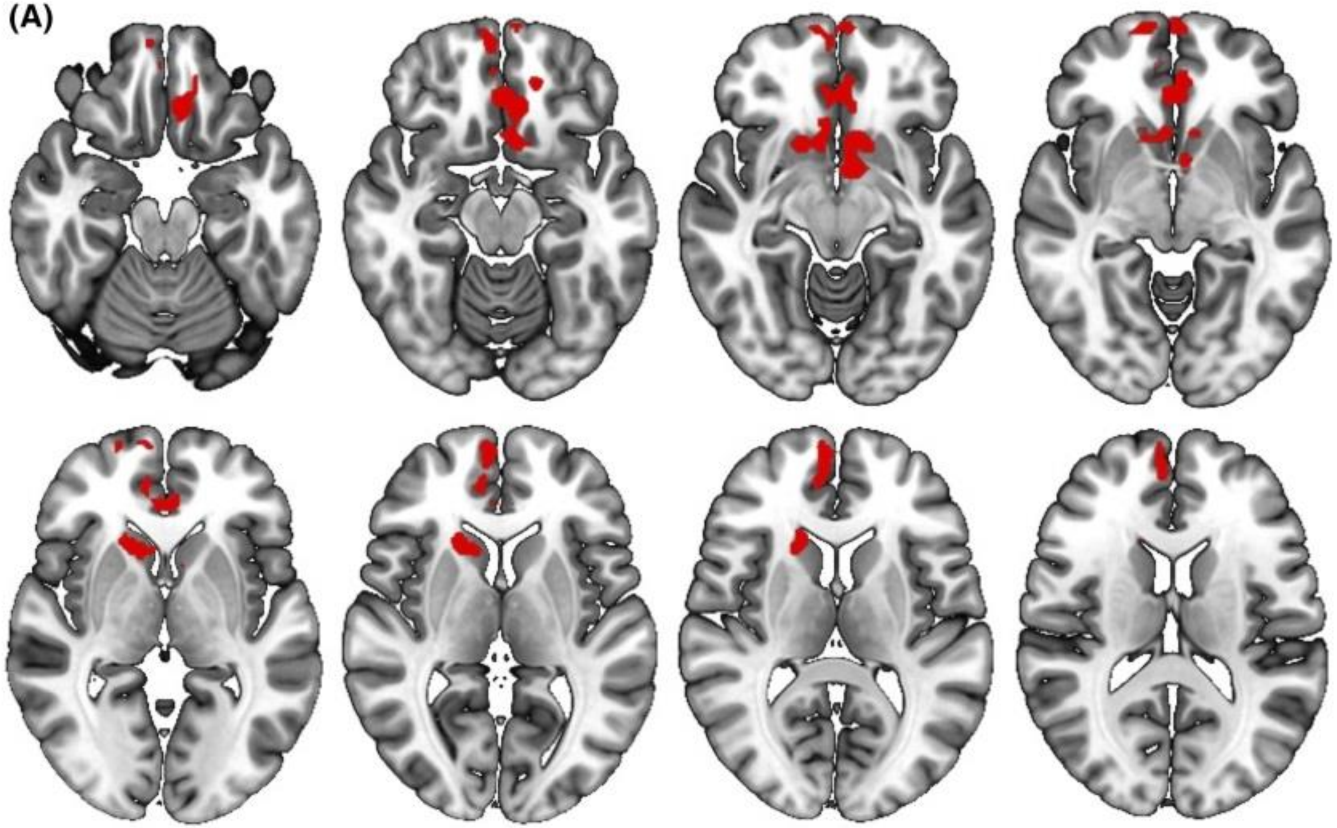
12 patients with sudden loss of smell after COVID infection

Identification Test Score=score on olfactory identification test

Anosmia= loss of smell

DLPFC=dorsolateral prefrontal cortex

Reduced Perfusion in Orbitofrontal and Medial Prefrontal Cortex and Dorsolateral Prefrontal Cortex

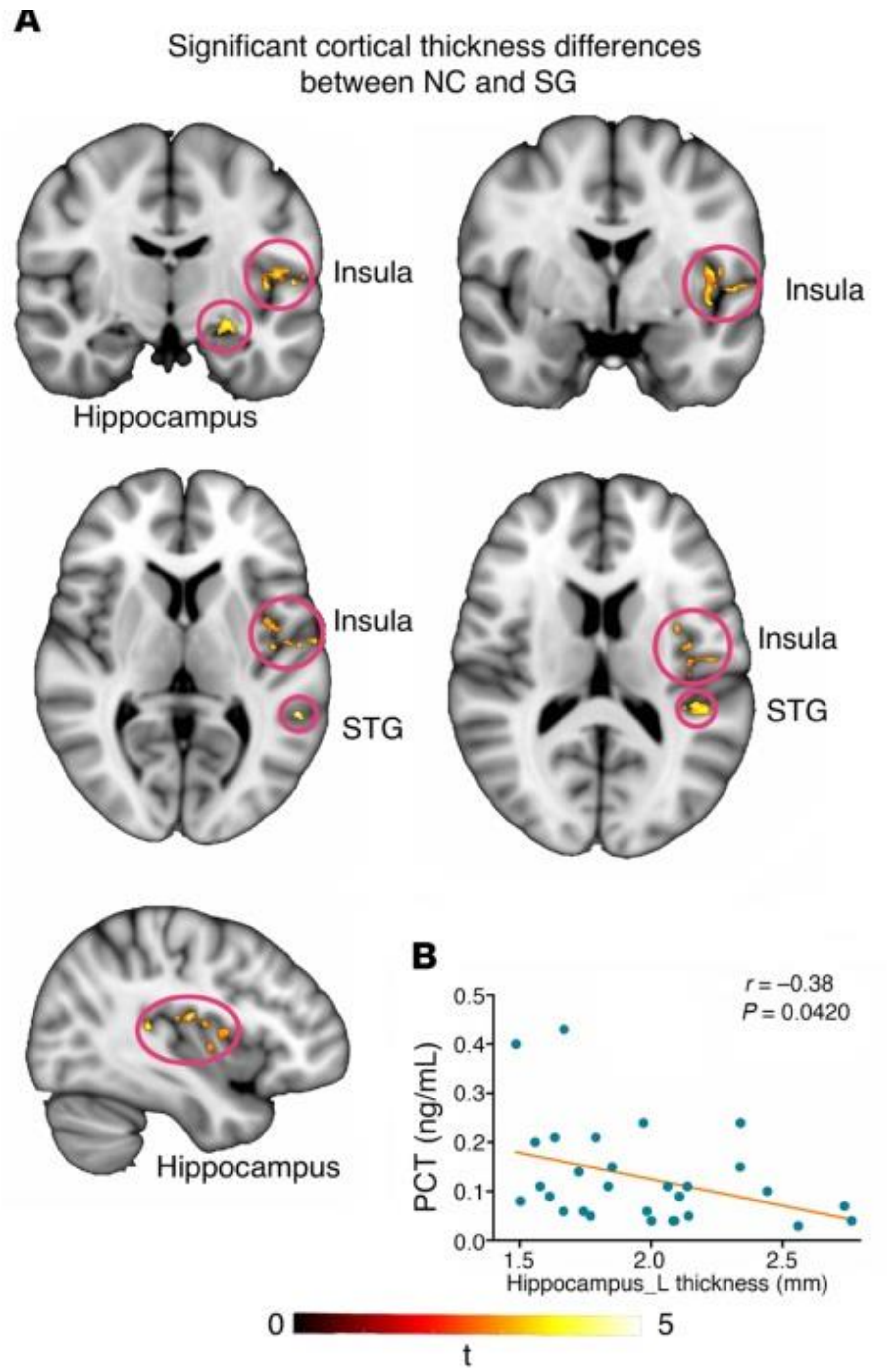


Yus et al 2022

82 patients with Long COVID at 11 months.

Areas of correlation of reduced smell measured with Brief Smell Identification Test (BSIT) and reduced perfusion on MRI

Decreased Gray Matter Cortical Thickness Post COVID



Qin et al 2021 51 Covid patients at 3 months

Decreased Gray Matter Cortical Thickness Post COVID

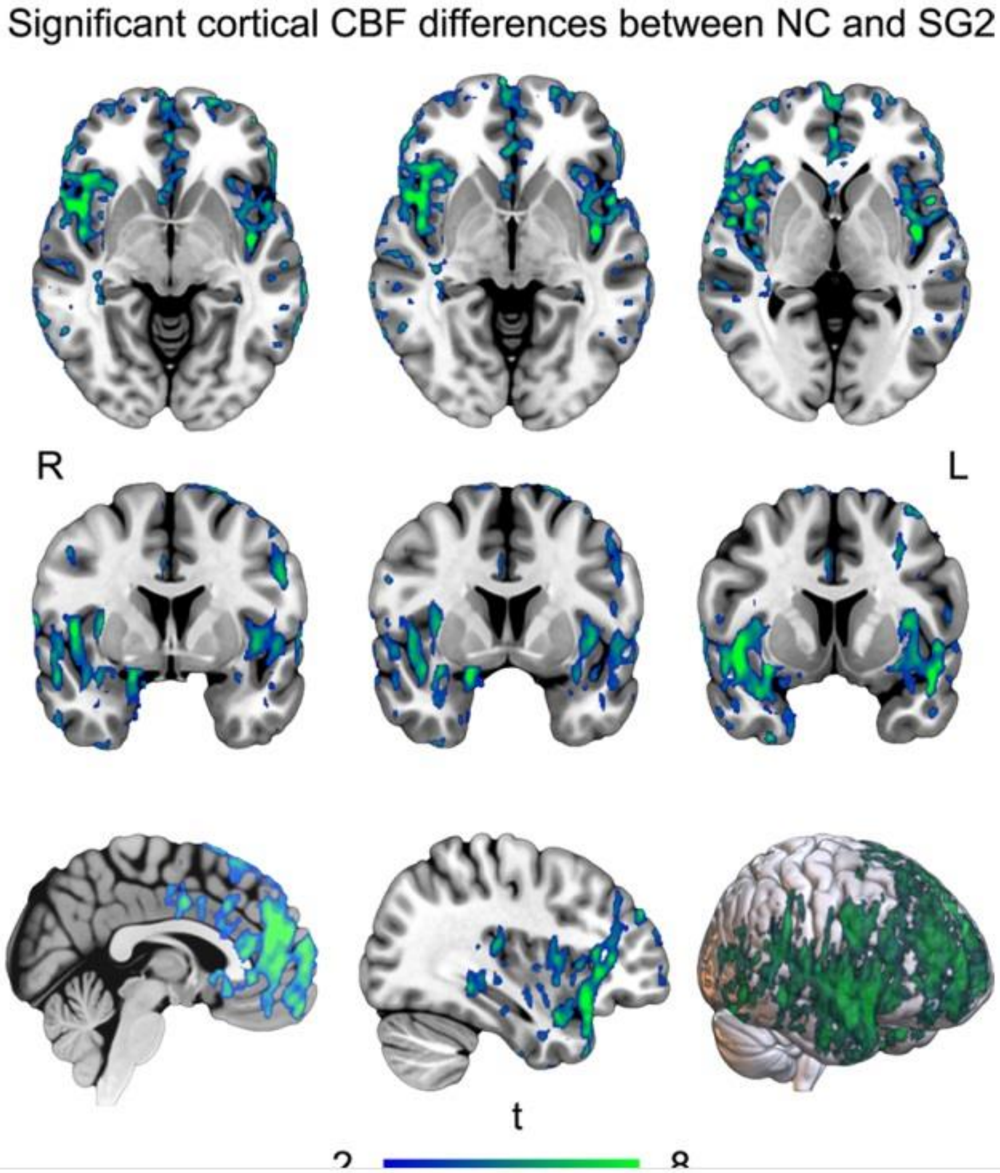
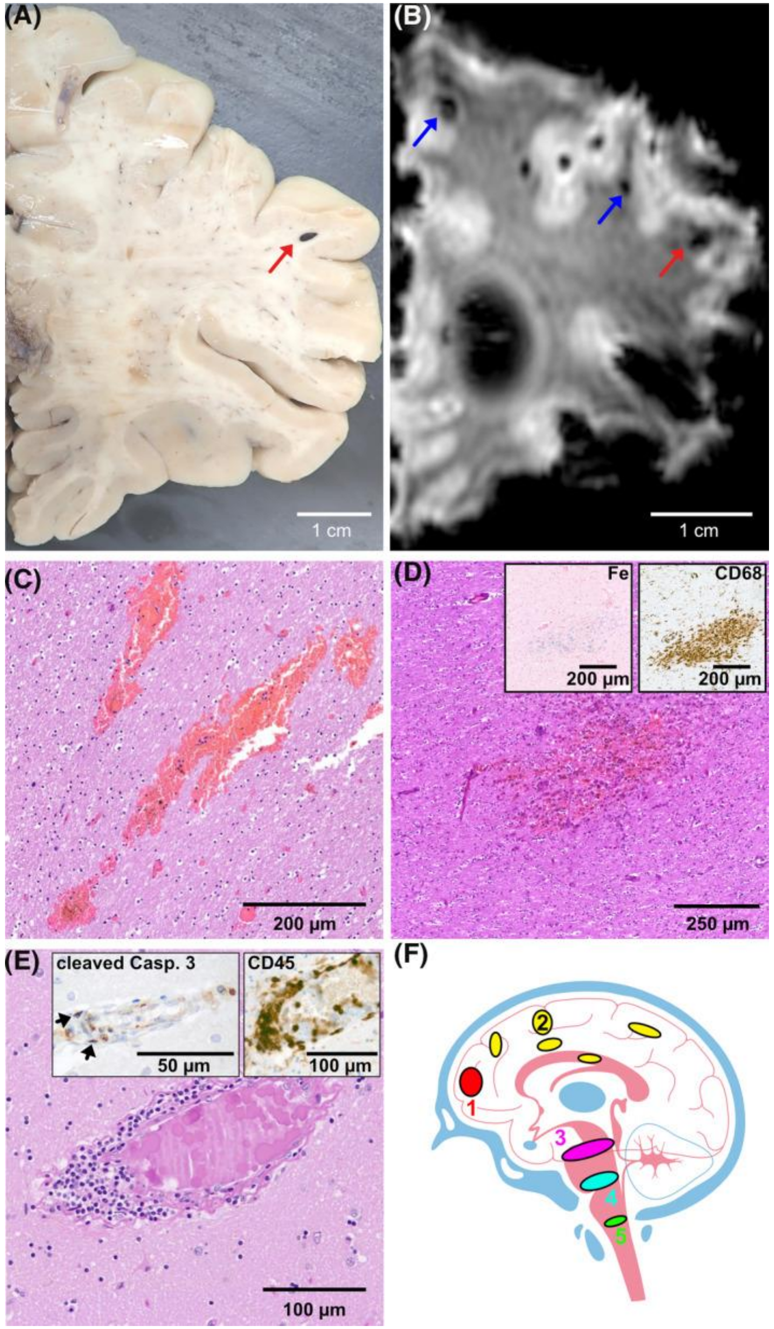


Figure 3. Cortical CBF analyses. Compared with NC
SG2 showed extensive lower CBF values in the brai
CBF, cerebral blood flow; L, left; NC, normal control;
right; SG2, severe group at 10 months after dischar

Tian et al 2022 34 Covid hospitalized patients without neurological symptoms at 10 months

COVID Infection Induces Endotheliitis and Microbleeds in the Brain



Post-mortem following death from Covid infection

Red arrows (A, B) point to microbleeds at juncture of grey and white matter

(C) Fresh hemorrhage; (D) infiltration of macrophages (CD68)

(E) Infiltration of lymphocytes (CD45) associated with elevated angiotensin

Converting enzyme-2 (ACE2) receptor in the brain vasculature

(F) areas of pathology in anterior cingulate (1)

Cortex (2) midbrain (3) pons (4), medulla (5)

Kirschenbaum et al 2020 Neuropathology and Applied Neurobiology

Increased Glia and Loss of Neurons in Brain Post COVID

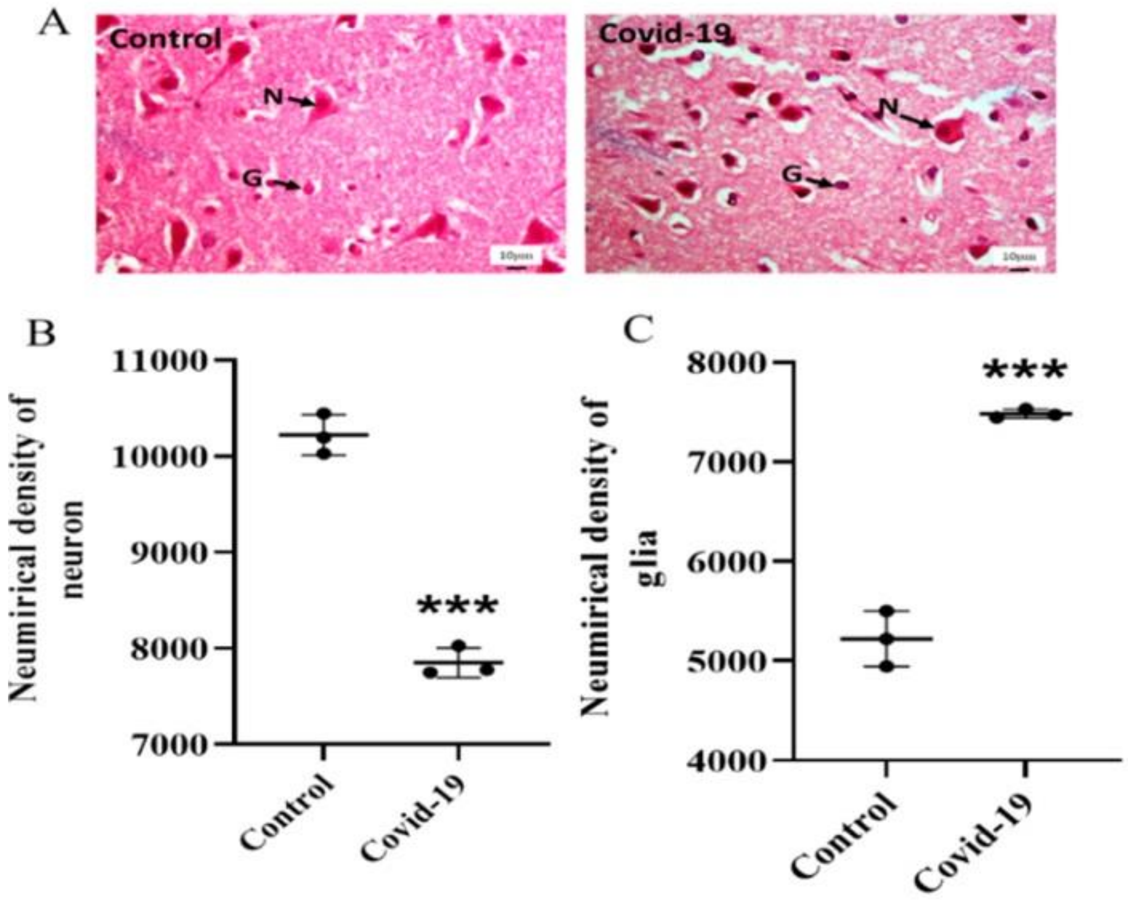


Figure 1. (A) H&E staining of the cerebral cortex. Black arrows show neurons (N) and glial cells (G) in control and COVID-19 groups. (B) The number of neurons decreased in COVID-19 patients compared to the control group (***$P < 0.001$), while the number of glial cells remarkably increased in the COVID-19 group in comparison with the

Boroujeni et al 2021 ACS Chem Neurosci

Increased Vasculitis in the Brain Post COVID

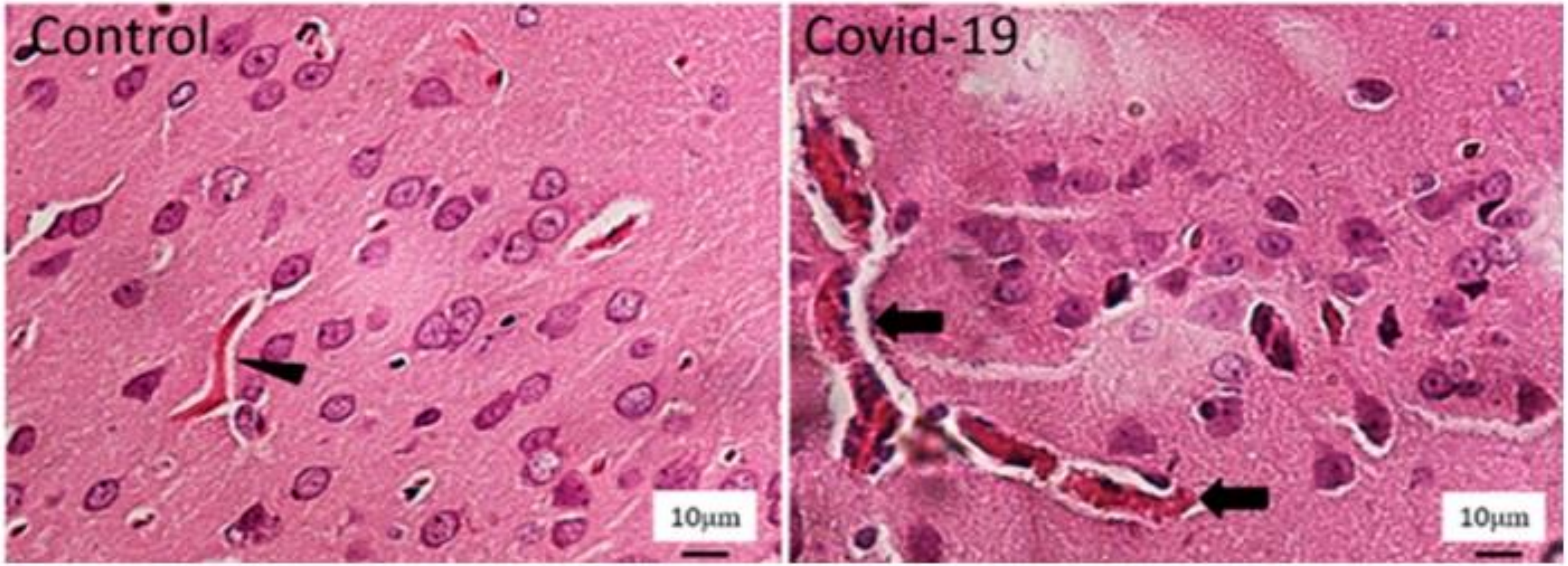


Figure 2. H&E-stained brain sections of the cerebral cortex in control and COVID-19 groups. Healthy vessel (arrowhead) and vasculitis (long arrow) are depicted.

Boroujeni et al 2021 ACS Chem Neurosci

Pathology in the Brain Post COVID

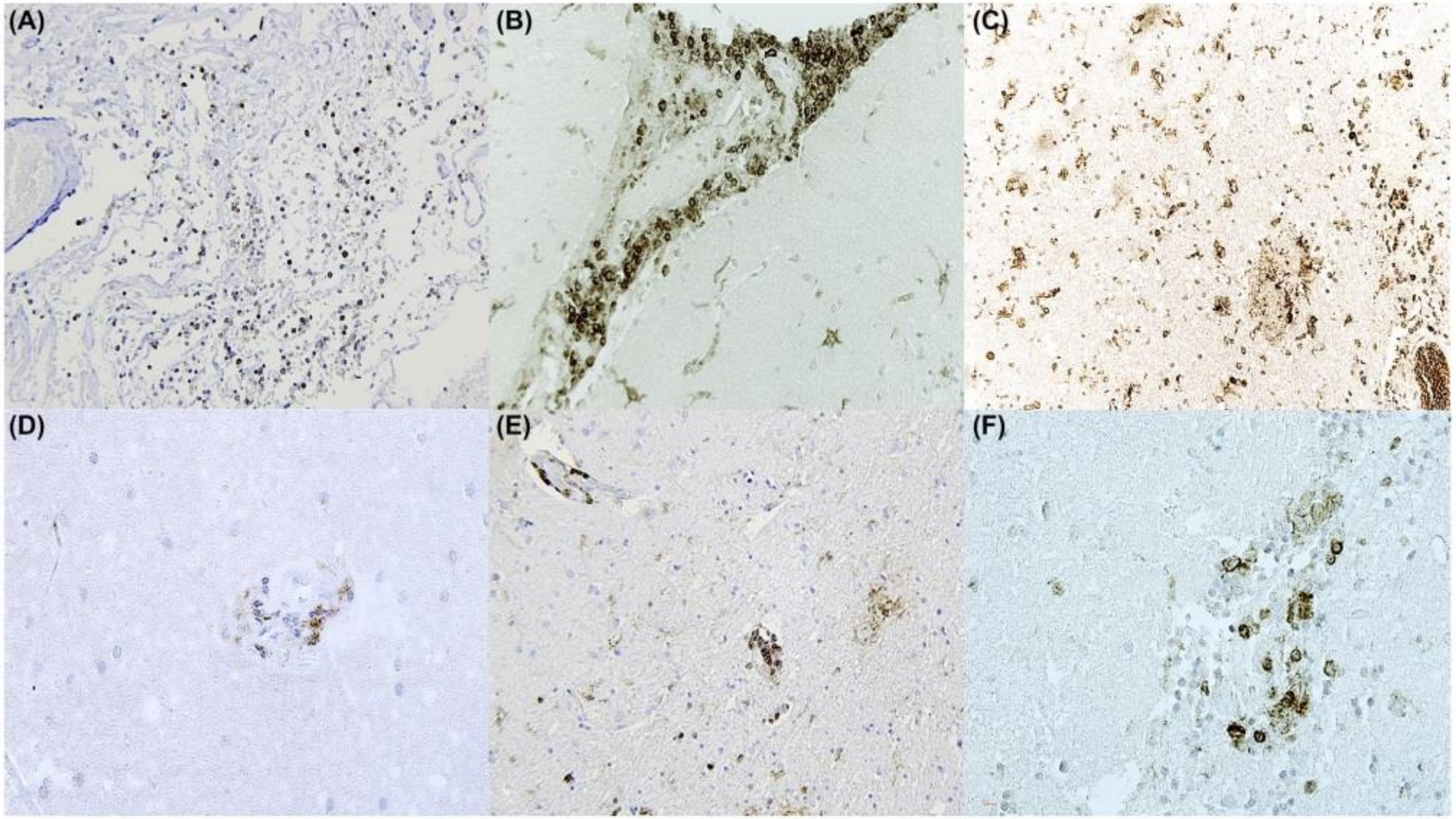


FIGURE 2 (A) Leptomeningitis with diffuse presence of CD45, also clearly evident at perivasal level (B). Microglia activation evidenced by IBA1 reaction (C). (D) Perivascular lymphocytic foci (CD4+). (E) Encephalitis with CD4 positivity and, (F) focal leptomeningeal inflammation (CD4+)

Maiese et al 2021

Inflammation in CSF Associated with COVID Encephalitis

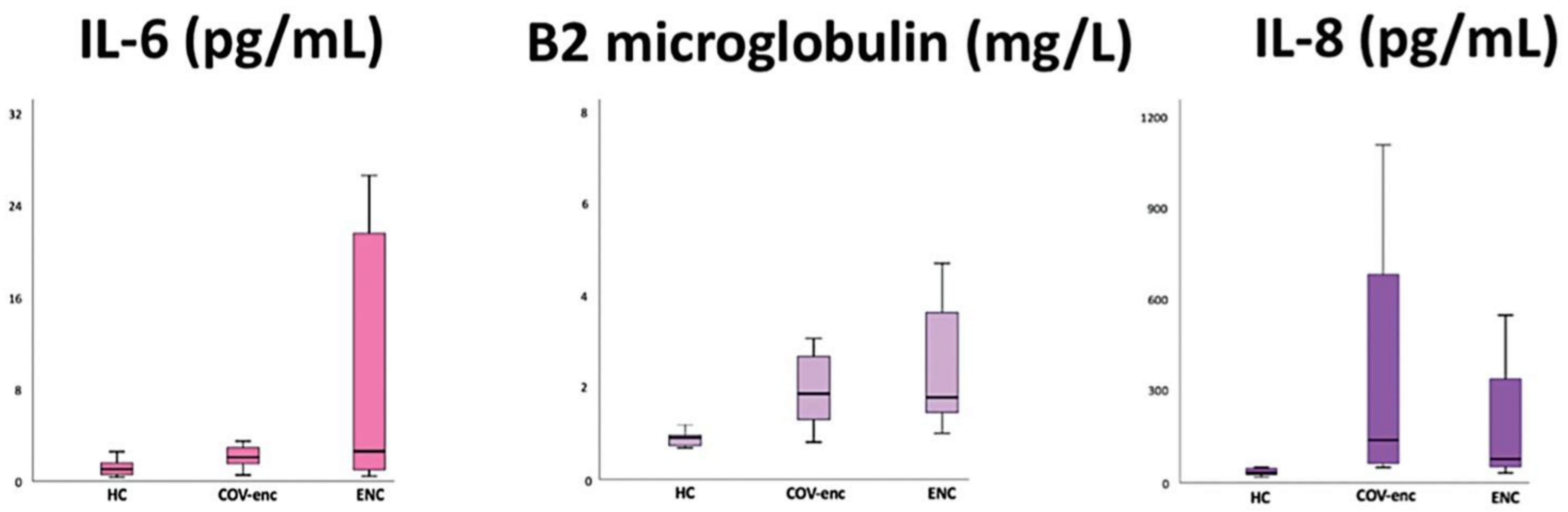
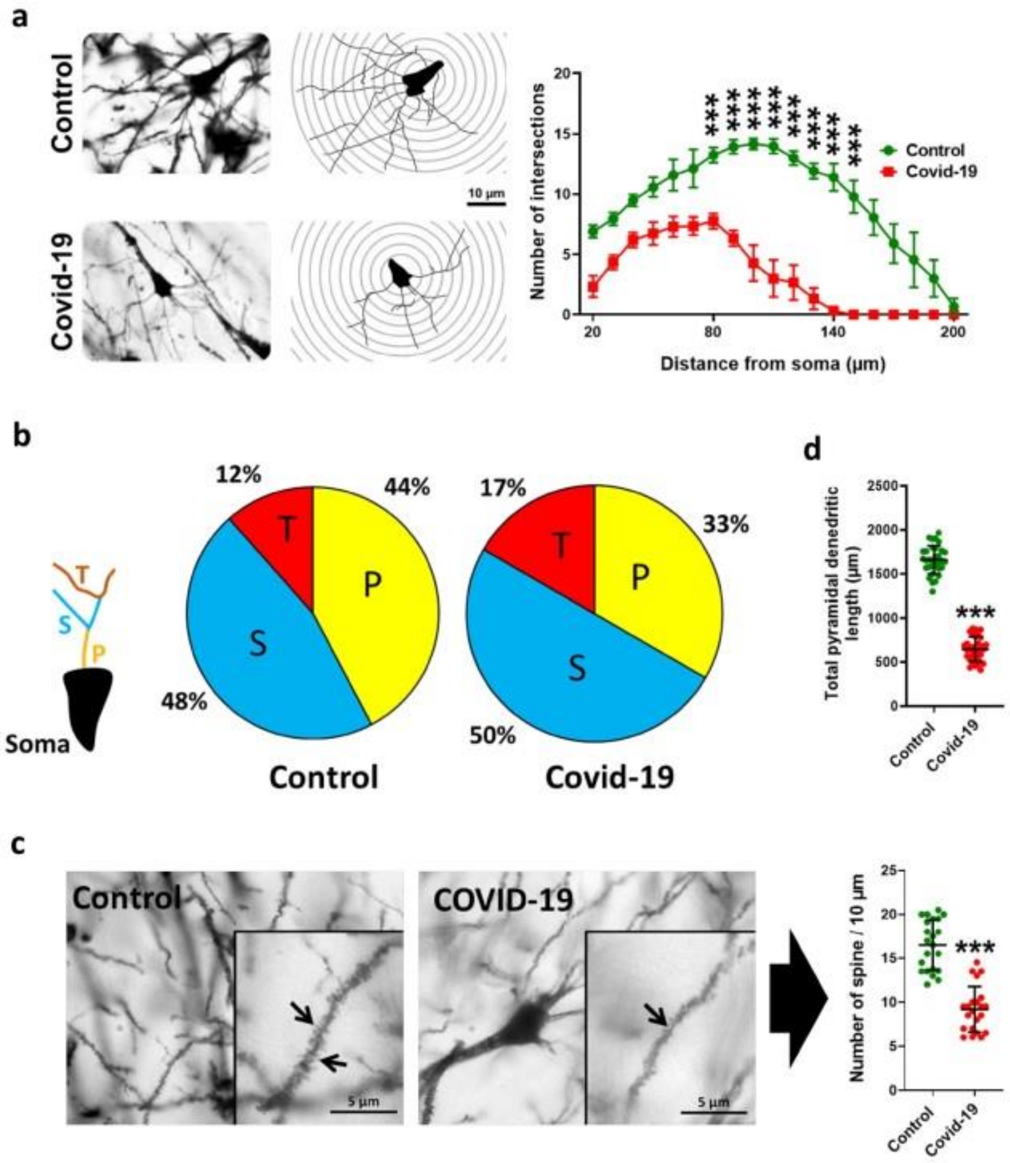


Figure 1. Differences in neuronal, glial, and inflammatory markers according to the clinical diagnosis. Boxplot indicate median and interquartile ranges. Abbreviations: COV-Enc, encephalitis cases concomitant coronavirus disease 2019 (COVID-19); CXCL13, chemokine (C-X-C motif) ligand 13; ENC, encephalitis without concomitant COVID-19; GFAP, glial fibrillary acidic protein; HC, healthy control group; IL, interleukin; NfL, neurofilament light chain; sTREM2, soluble triggering receptor expressed on myeloid cells 2; YKL-40, chitinase-3-like protein 1.

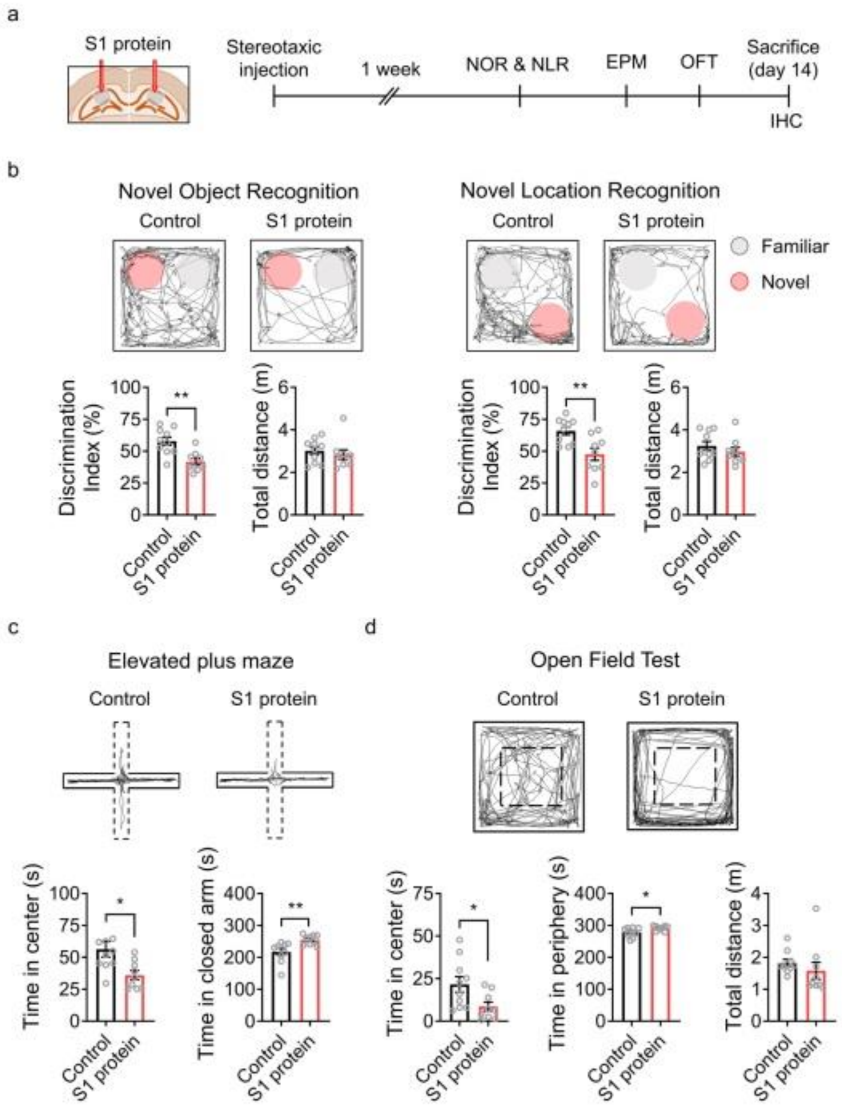
Pilotto et al 2022 13 Covid encephalitis 21 encephalitis without Covid 18 controls. CSF=cerebrospinal fluid inc. IL6 TNF alpha and biomarkers of glial activation

Decreased Branching of Hippocampal Neurons with COVID



Bayat et al 2022 Post Mortem brain of four patients who died of COVID

Effects of COVID Spike Protein on Hippocampal Neurons



Oh et al 2022 Spike protein in mouse hippocampus induces anxiety and cognitive deficits

Effects of COVID Spike Protein on Hippocampal Neurons

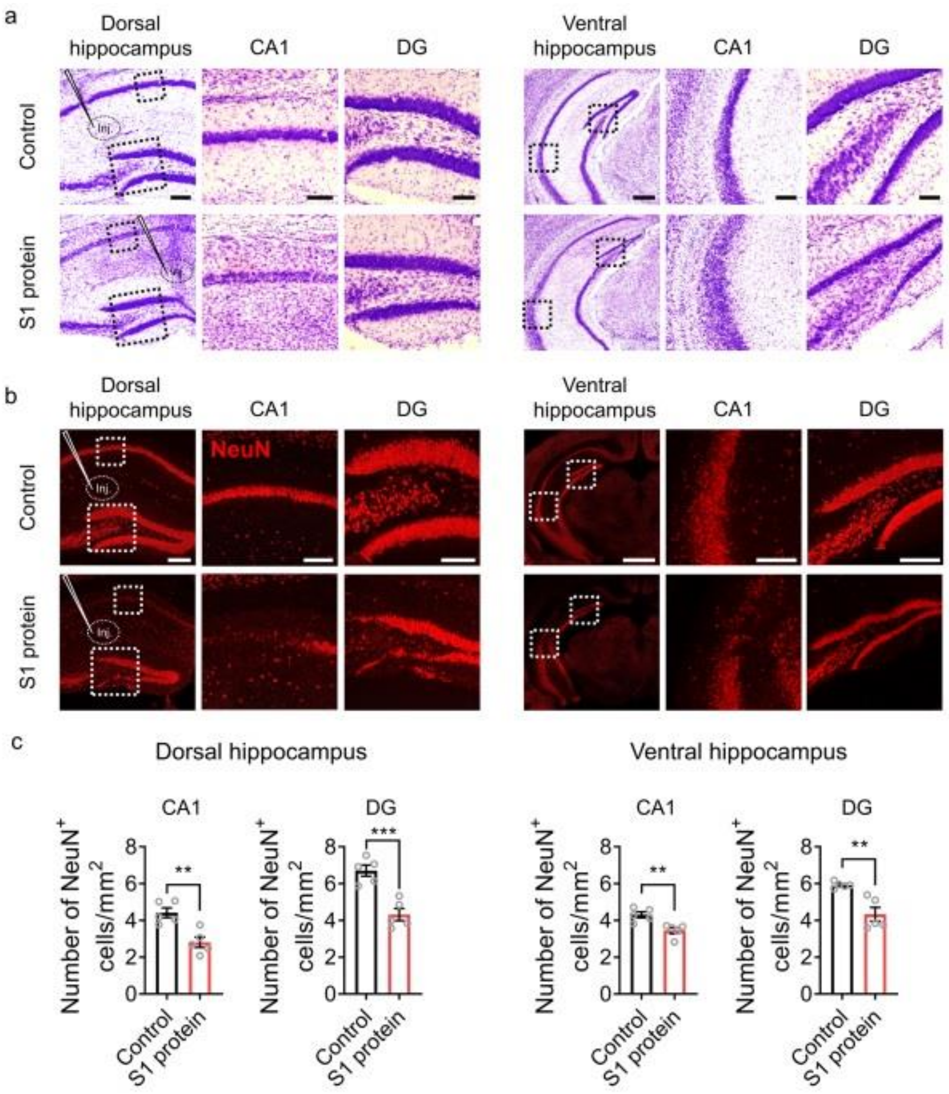


Figure 2. SARS-CoV-2 S1 protein induces hippocampal neuronal death in CA1 and DG areas. **(a-b).** Hippocampal neurons in mice injected with S1 protein (n = 5) or vehicle (Control, n = 5) were visualized by

Oh et al 2022 Spike protein in mouse hippocampus induces neuronal death

Effects of COVID Spike Protein on Hippocampal Neurons

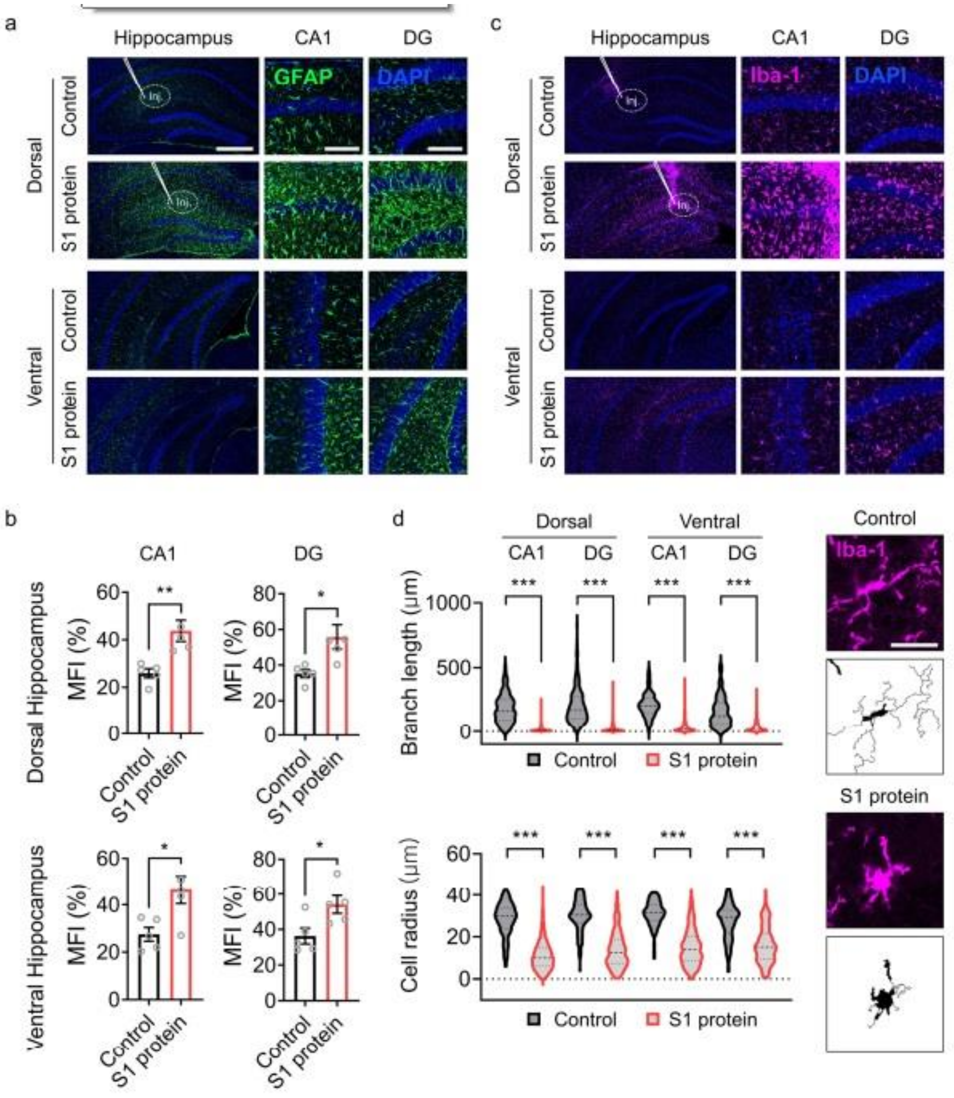
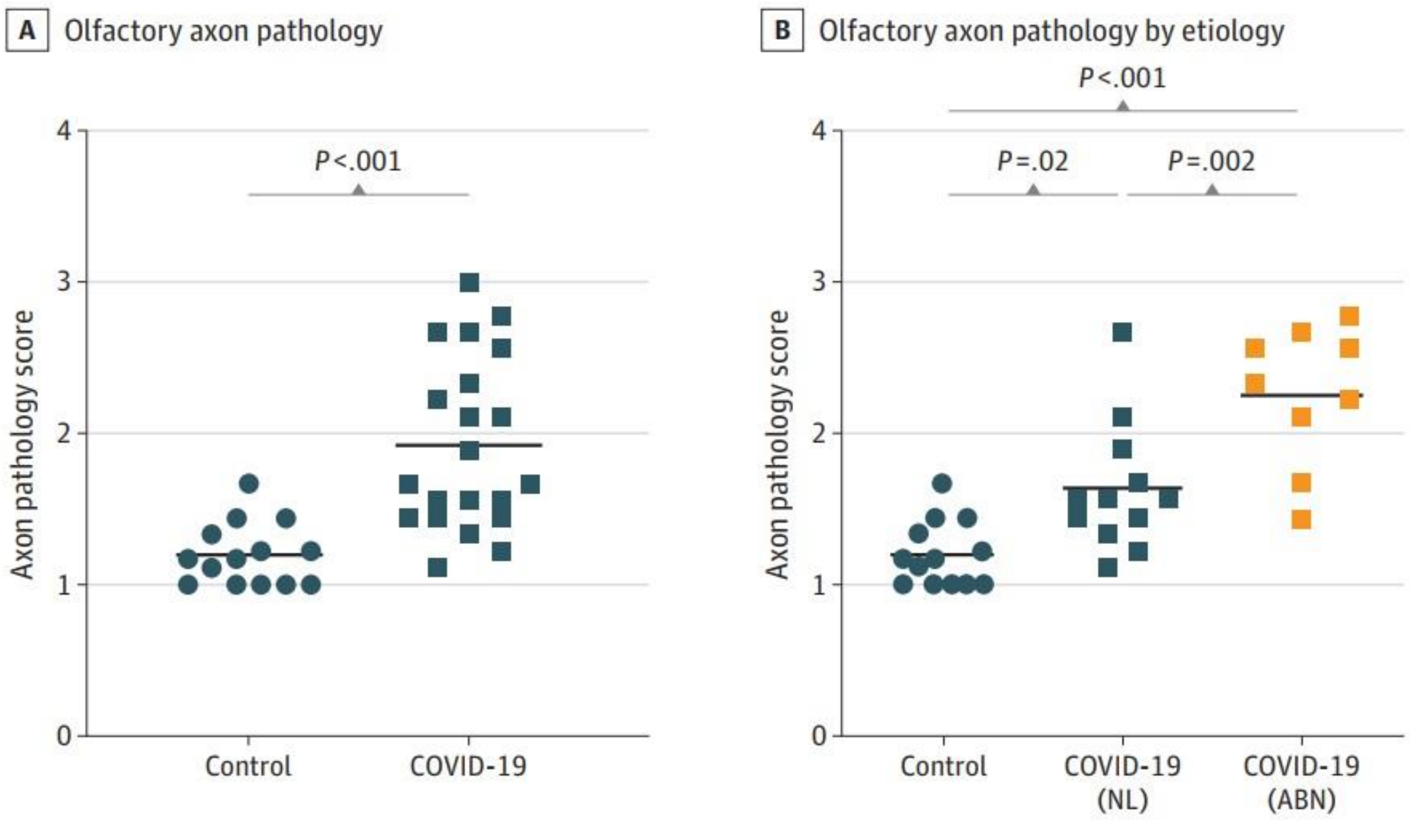


Figure 3. S1 protein induces astrocyte and microglia activation in the hippocampus. (a, c) Representative

Oh et al 2022 Spike protein in mouse hippocampus activates astrocytes and glia via interleukin 1beta

Damage to Olfactory Tissue with COVID



Ho et al 2022 Post Mortem brain of patients who died of COVID. NL=normal smell, ABN=abnormal smell

Angiotensin II and COVID

Sfera et al 2021

EC=endothelialcell

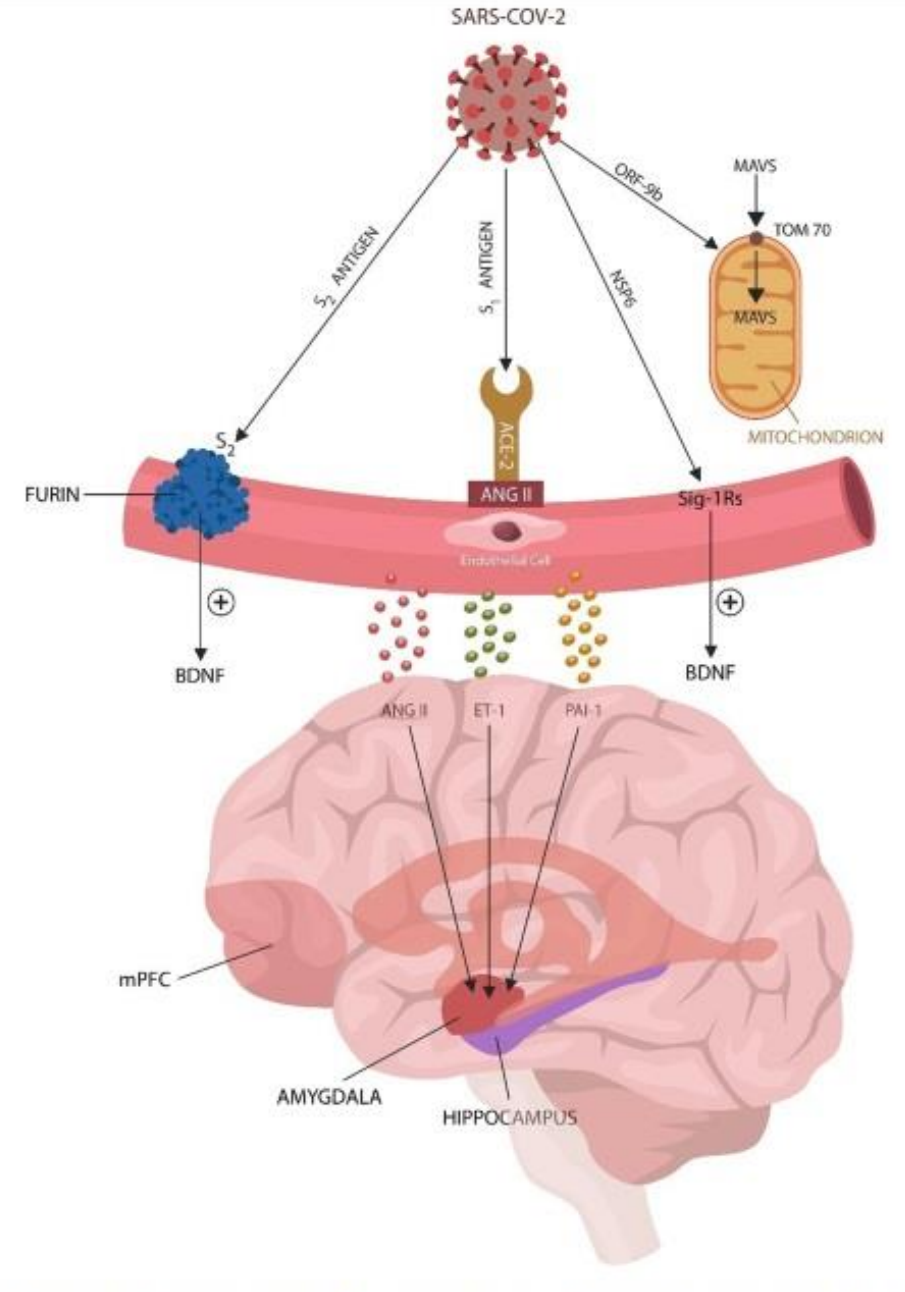
ANG II=angiotensin II

S1=spike protein

BDNF=brain derived neurotrophic factor

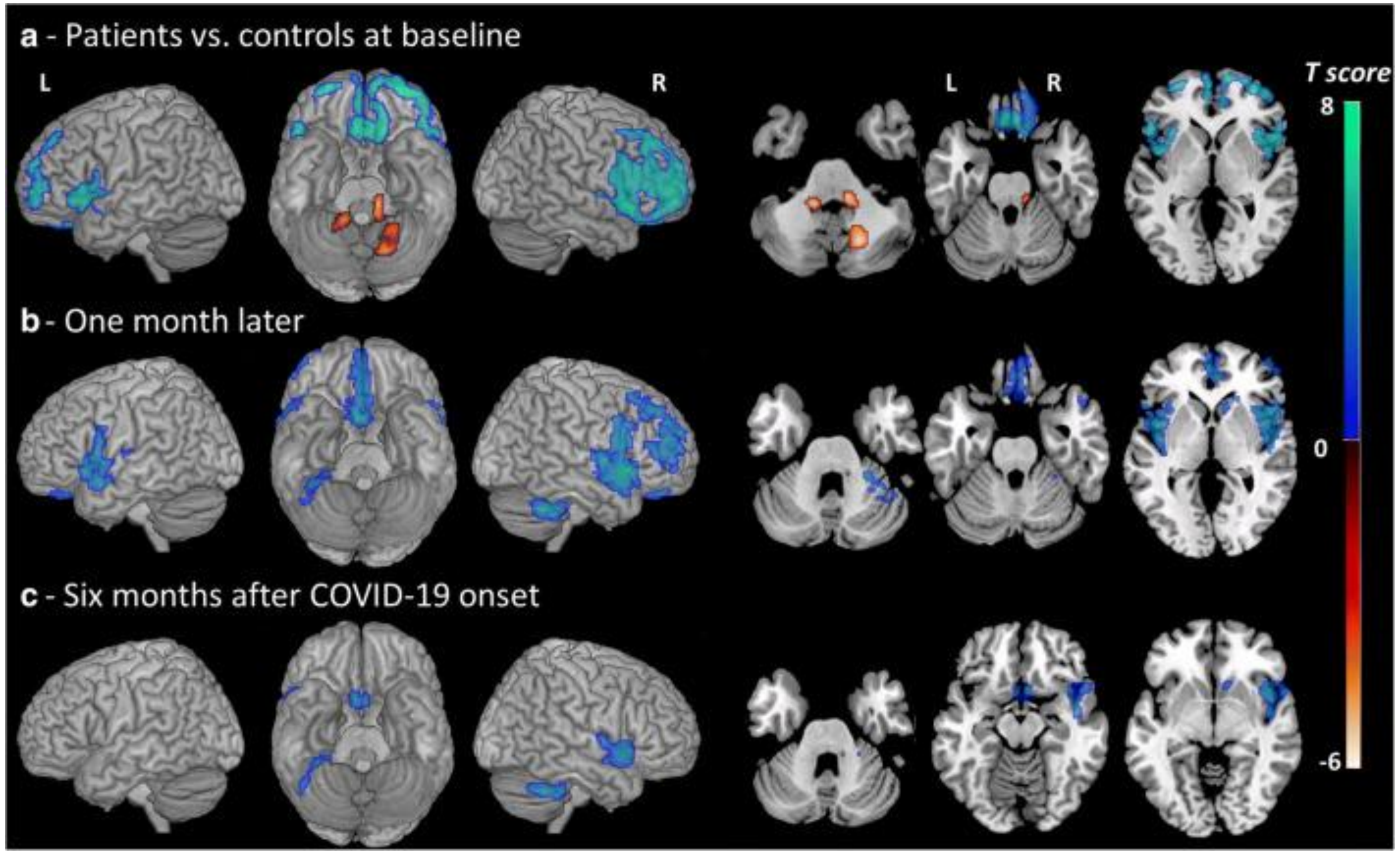
ET=endothelin 1

PAI=plasminogen activator inhibitor 1



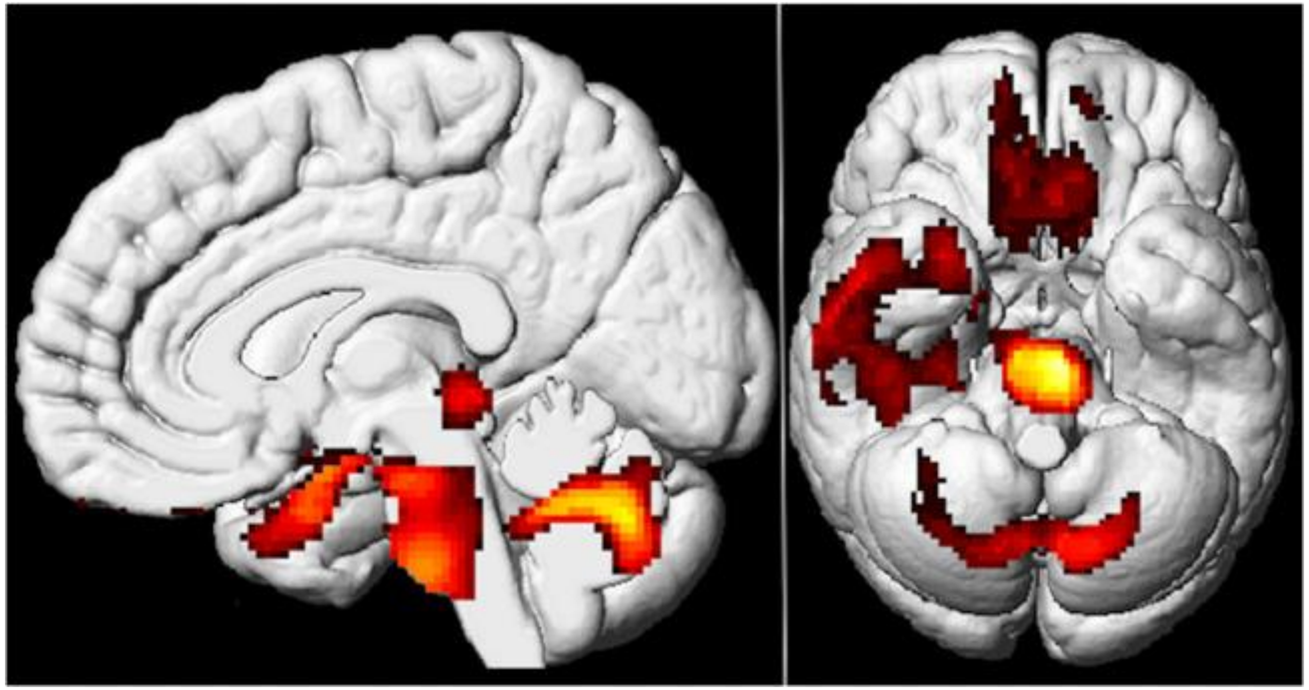
GRAPHICAL ABSTRACT 1 | Covid-19 triggers endothelial cell (EC) senescence and dysfunction, likely predisposing to PTSD by increasing microvascular permeability that enables the extravasation of stress molecules into the brain trauma-processing networks in amygdala, hippocampus and the medial prefrontal cortex. The virus upregulates host angiotensin II (ANG II) (via S1 antigen), usurps furin/plasmin (via S2 antigen), mitochondria (via ORF9b), and Sigma-1 receptors (Sig-1Rs) via NSP6. These structures, previously associated with PTSD, link the SARS-CoV-2 virus to increased susceptibility for stress related disorders. As ECs are major producers of brain derived neurotrophic factor (BDNF), a neurotrophin altered in PTSD, senescent ECs lower this molecule further, predisposing to stress related disorders.

Alterations in Brain Function with Covid



Kas et al 2001 FDG imaging with Covid showed hypometabolism at baseline in prefrontal cortex, insula, anterior cingulate and caudate. At one and six months decreases in mediofrontal, olfactory/gyrus rectus, insula, caudate and cerebellum

Alterations in Brain Metabolism with Long COVID



Guedj et al 2021 FDG decreased metabolism in 35 Long Covid patients versus 44 controls in rectal/orbital gyrus, olfactory gyrus, amygdala, hippocampus, pons, thalamus and cerebellum

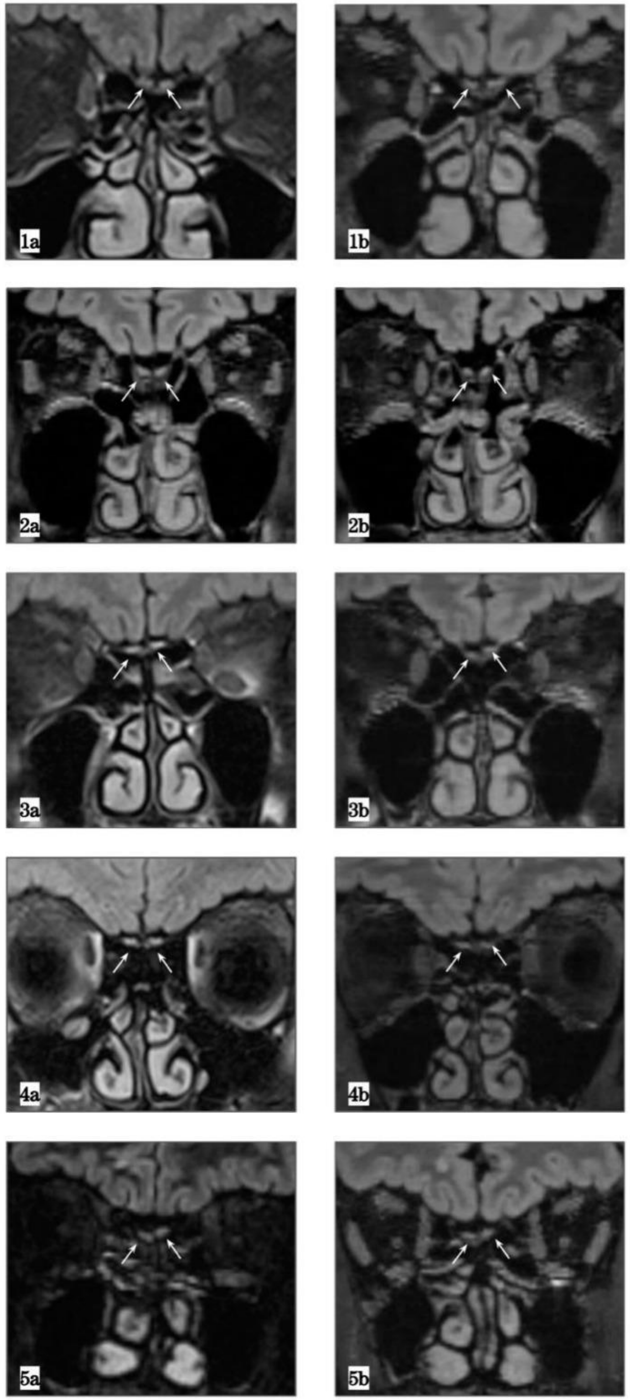
Olfactory Bulb Reduction in Long COVID

MRI showing Pre-Covid (left) and post Covid MRI scans in the same patients (right)

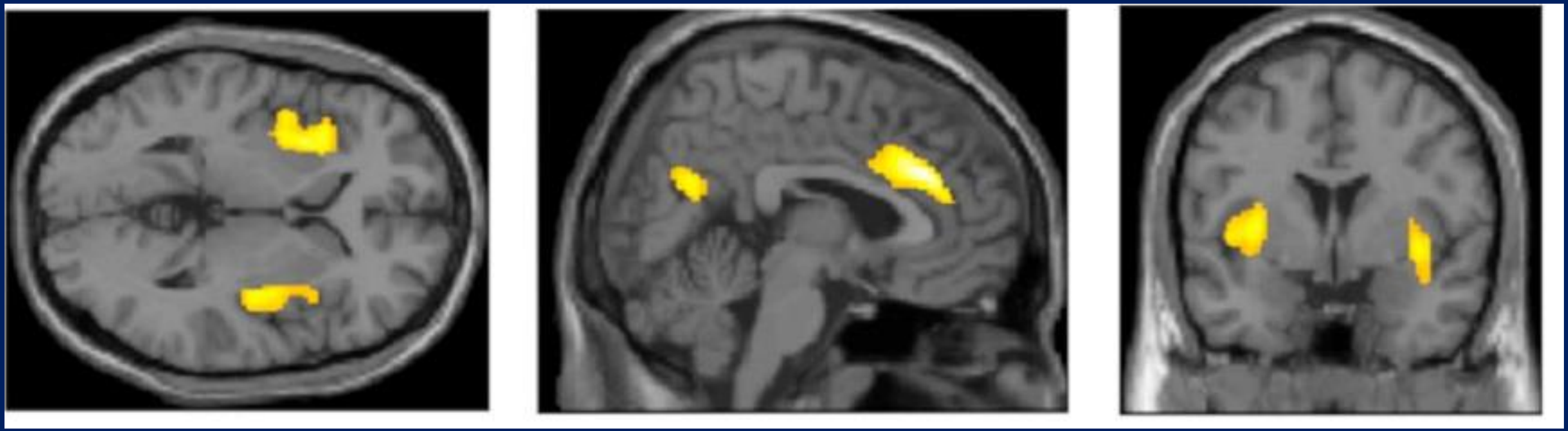
Reduction in olfactory bulb volumes with Long Covid (arrows)

Scan 5 in a normal individual without infection

Frosolini et al 2022 Brain Sciences;

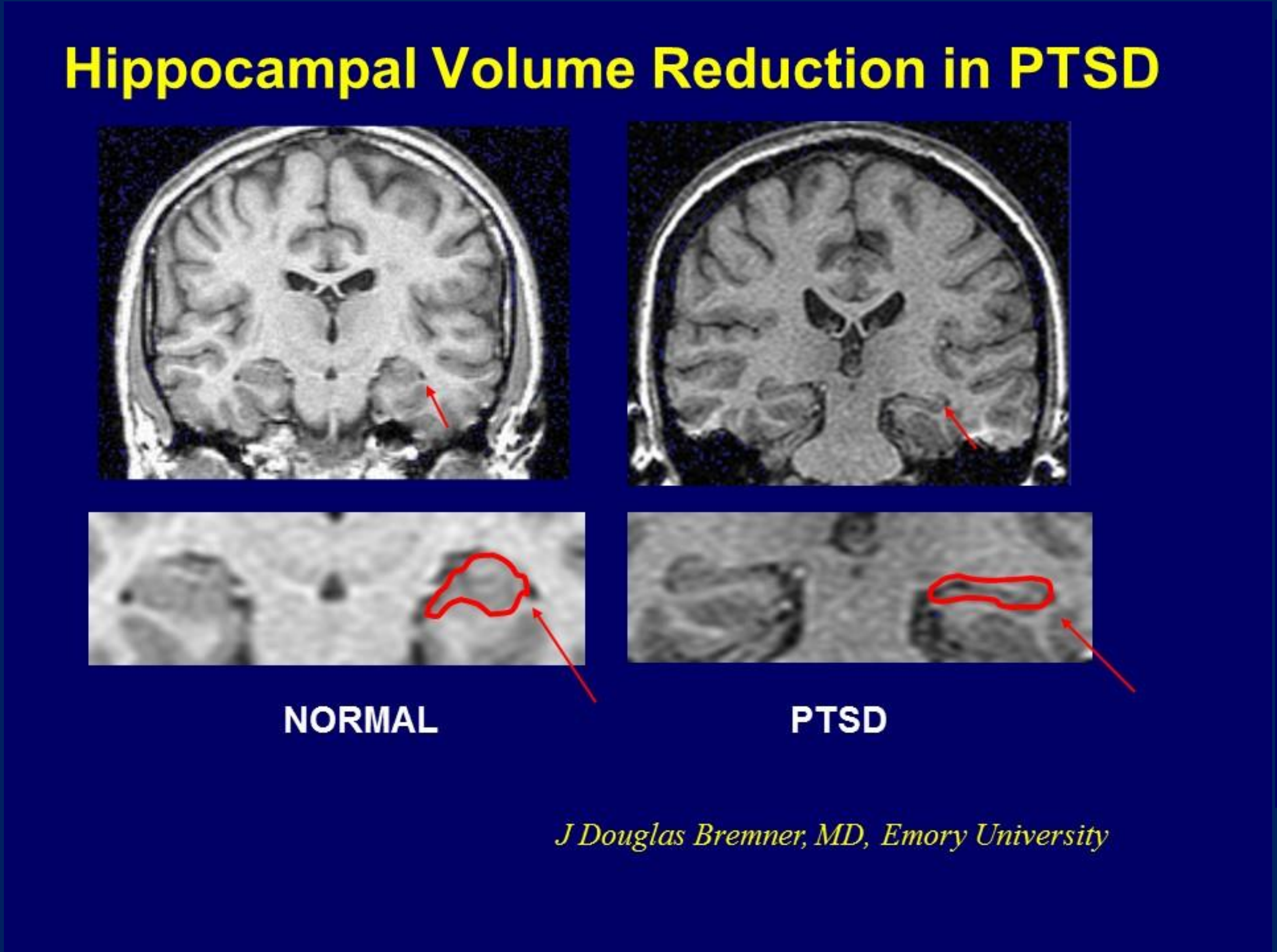


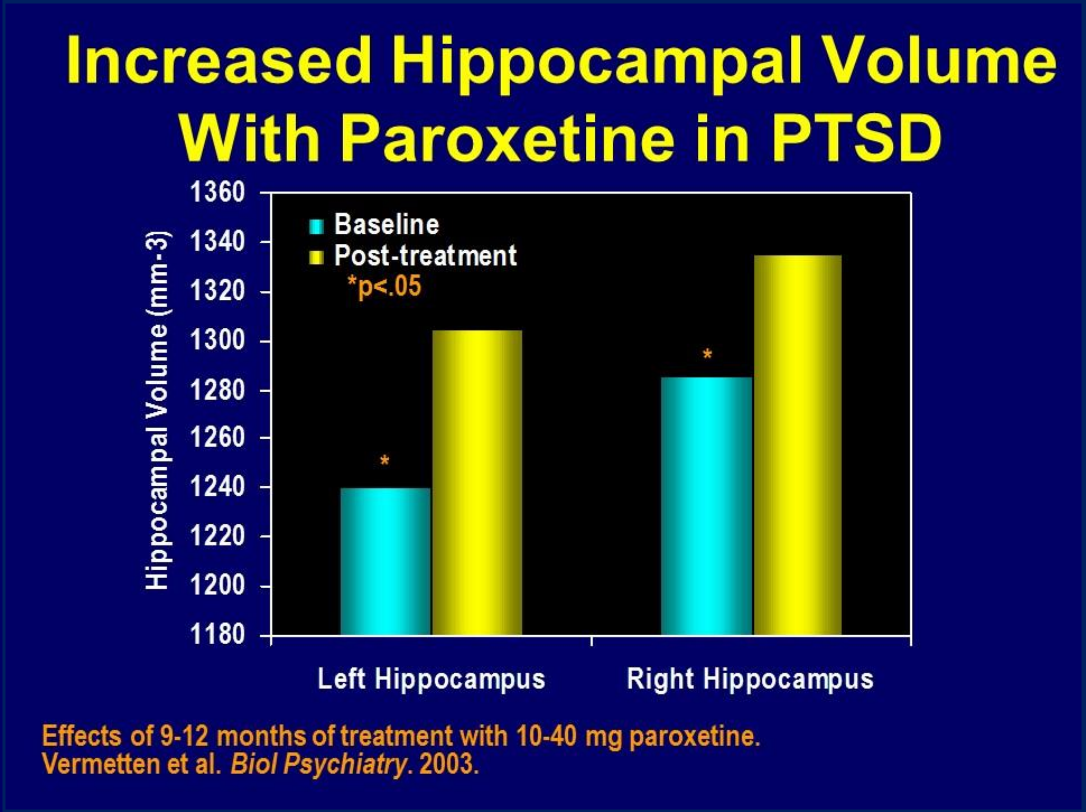
Decreased Gray Matter Volume Correlates with Increased Depressive Symptoms in Long COVID



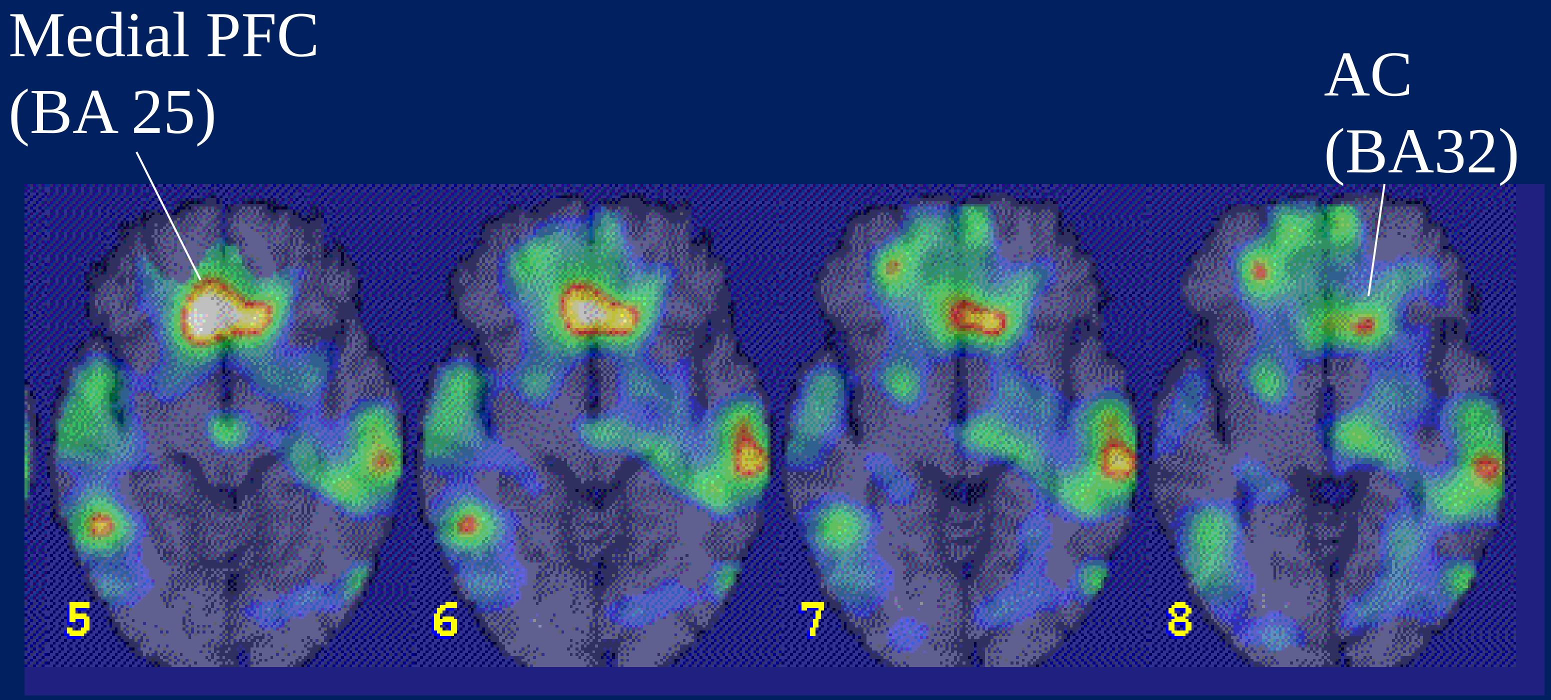
Benedetti et al 2021

Brain Circuitry of PTSD: Medial Prefrontal Cortex, Amygdala and Hippocampus





Medial Prefrontal Cortical Dysfunction with Traumatic Memories in PTSD



Decreased function in medial prefrontal cortical areas
Anterior Cingulate BA 25, BA 32 in veterans with PTSD compared to Veterans without PTSD during viewing of combat-related slides & sounds
Z score >3.00; p<.001

Antidepressants Prevent COVID Infection

Table 2 Odds ratios with 95% CIs of the unadjusted and adjusted medication models of COVID-19 infection

Medication	Unadjusted model		Adjusted model[a]		Fully adjusted model[b]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
CPZE	**1.0007 (1.0002–1.0013)**	**0.004**[c]	**1.0007 (1.0002–1.0014)**	**0.044**	**1.0007 (1.0001–1.0015)**	**0.046**[d]
Typical antipsychotic	1.765 (0.947–3.287)	0.073				
Mood stabiliser	1.016 (0.547–1.888)	0.960				
Benzodiazepine	1.986 (1.046–3.773)	0.036				
Anticholinergic	1.402 (0.757–2.598)	0.283				
Antilipidemic	0.757 (0.375–1.528)	0.438				
Antihypertensive	1.322 (0.690–2.534)	0.399				
Antibiotic	0.811 (0.05–13.19)	0.883				
Antiviral	2.489 (0.253–24.436)	0.434				
Steroid	1.097 (0.435–2.765)	0.844				
Supplement	1.916 (1.029–3.567)	0.040				
Antidepressant	**0.327 (0.153–0.698)**	**0.004**[c]	**0.357 (0.132–0.966)**	**0.042**	**0.280 (0.094–0.837)**	**0.023**[e]
SSRI/SNRI	**0.302 (0.120–0.780)**	**0.013**				
SARI	**0.064 (0.008–0.505)**	**0.009**				

Significant models are in bold. CPZE, chlorpromazine-equivalent daily dose; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SARI, serotonin-2 antagonist reuptake inhibitor.

a. Adjusted for age (categorical: 18–44 years (reference group), 45–54, 55–64, 65+); gender; ethnicity (categorical: African American (reference group), White, Other); psychiatric diagnosis; ward (categorical: 7 levels), BMI (ordinal: normal, overweight, obese).

b. Adjusted as for footnote a, plus for the presence of diabetes, hypertension, respiratory illness or heart disease.

c. Benjamini–Hochberg adjusted $P < 0.05$

d. Stepwise regression model OR = 1.0007 (1.000004–1.0014), $P = 0.049$.

Clelland et al 2022

- Effects driven by meds with serotonin reuptake properties

Cognitive Deficits Improve Over Time Post Covid

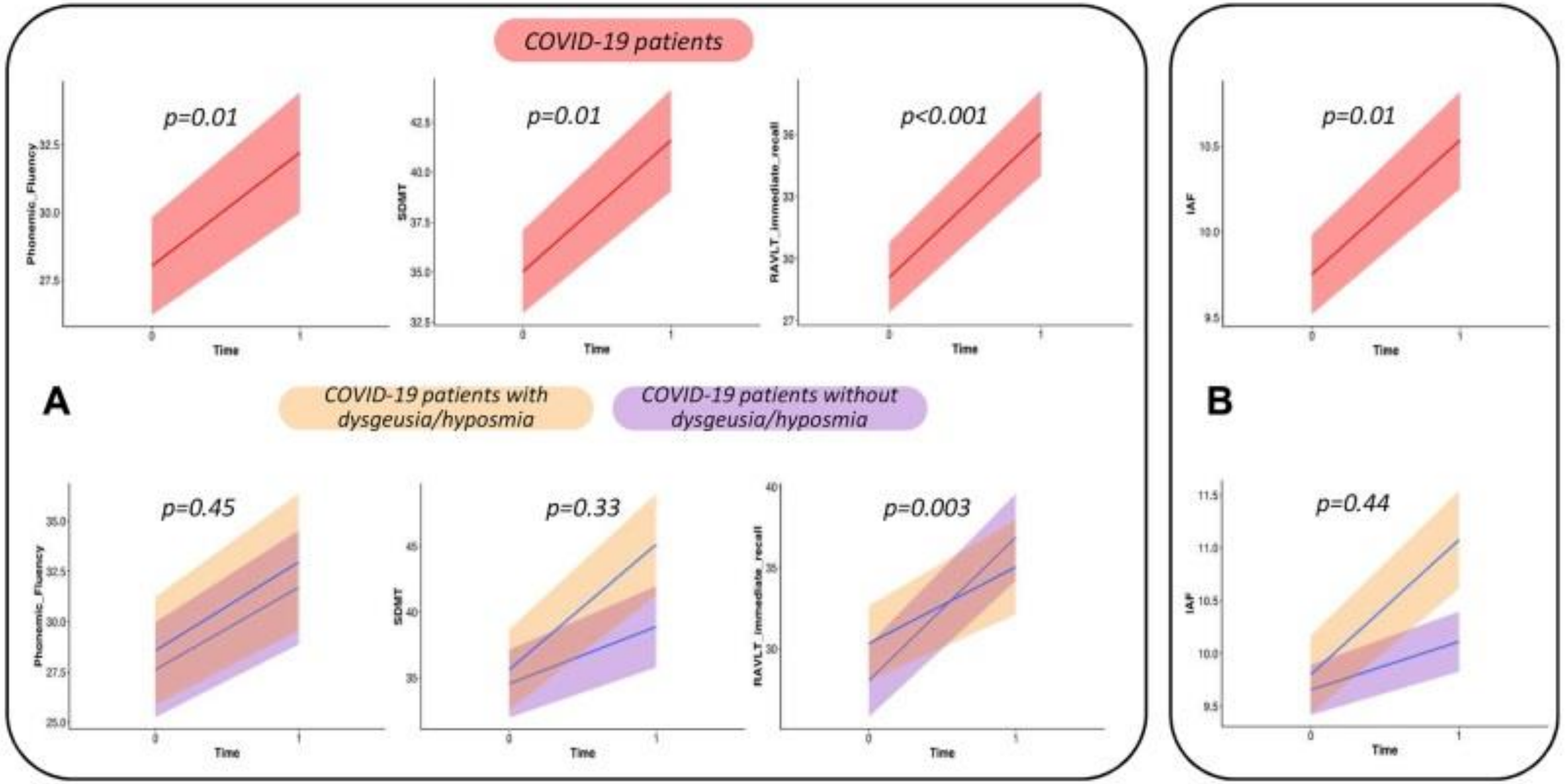
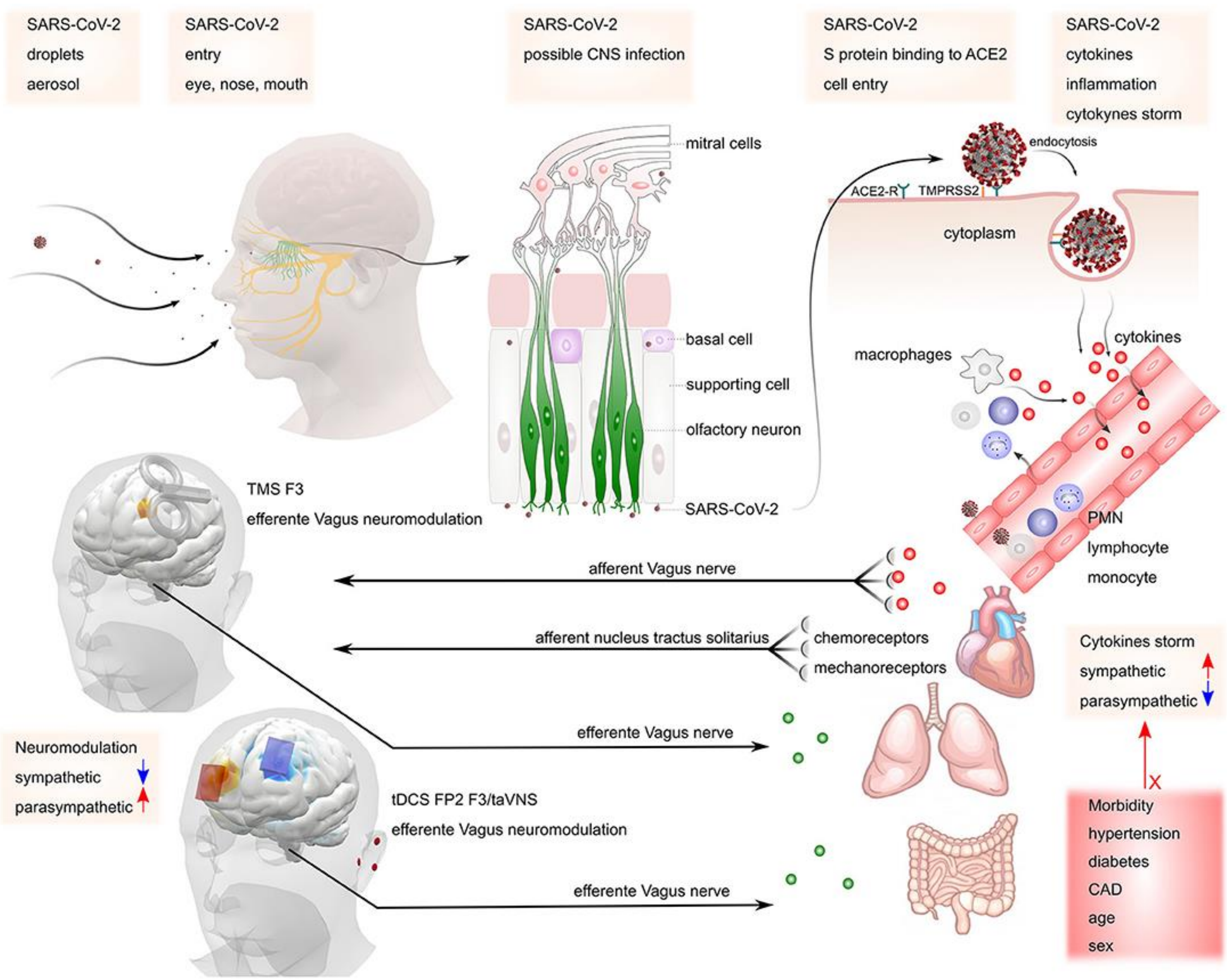


Fig. 3 Longitudinal and subgroup analyses investigating cognitive (**A**) and IAF (**B**) changes over time in COVID-19 patients. Upper row: *p* values refer to linear mixed-effect models adjusted for age, sex, education and individual follow-up duration in the whole patients' group (Bonferroni-corrected for multiple comparisons, $p < 0.05$). Lower row: *p* values refer to linear mixed-effect models adjusted for age, sex, education, individual follow-up duration, the considered variable (cognitive or EEG) at baseline and the presence of both PTSD and depression in the two subgroups of patients with/without dysgeusia/hyposmia (Bonferroni-corrected for multiple comparisons, $p < 0.05$). *IAF* individual alpha frequency, *RAVLT* Rey auditory verbal learning test, *SDMT* symbol digit modality test

Cecchetti et al 2022

- Up to one year post infection

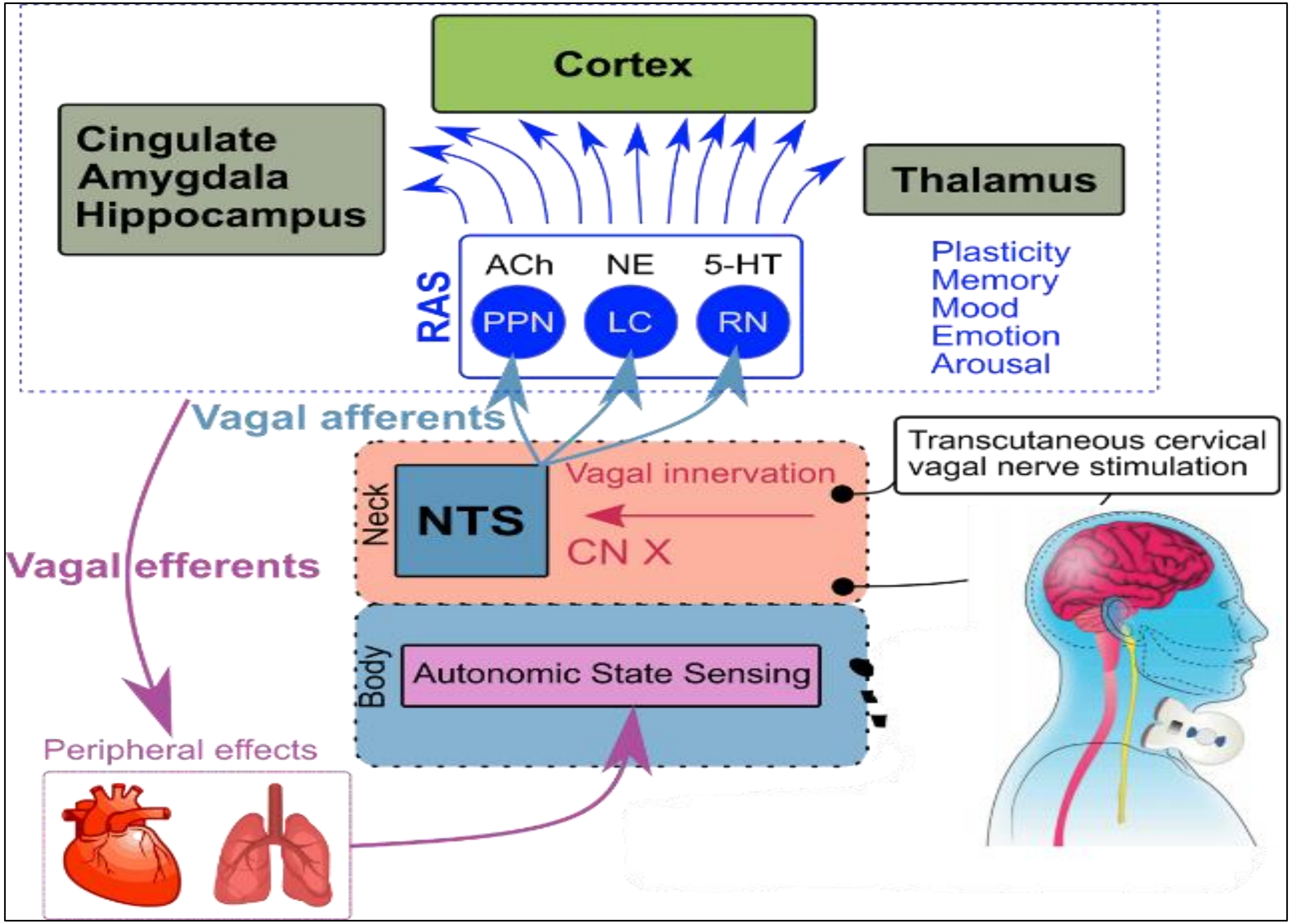
Neuromodulation for COVID and Long COVID



Baptista et al 2020 Applications of nVNS to Disorders related to Covid-19 Front. Neurol

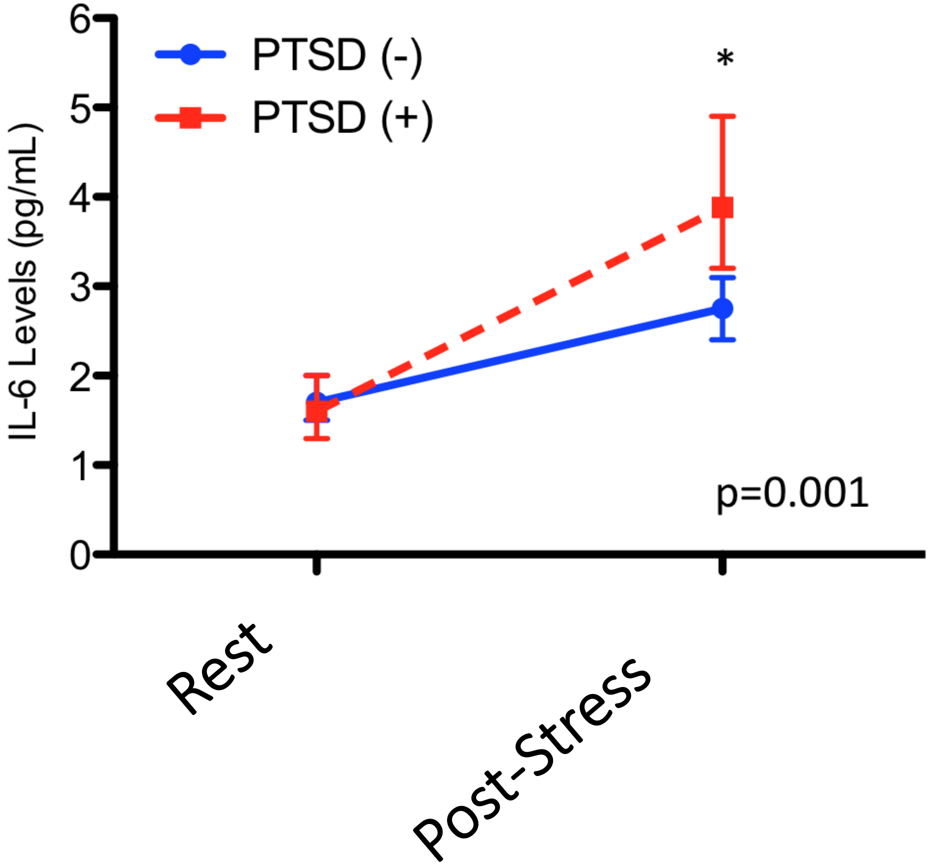
- Noninvasive Vagal Nerve Stimulation (nVNS)
- Auricular (ear) & neck (cervical) VNS
- Transcutaneous Direct Current Stimulation (tDCS)
- Reduces inflammatory (IL-6) and sympathetic responses
- Potentially blocks cytokine storm
- Opens airways and enhances breathing
- Reduces pain
- Reduces symptoms of PTSD and depression
- Promotes neural plasticity, recovery from ischemic stroke, tinnitus, heart failure
- Modulates brain areas involved in Long COVID
- Mobile and can be administered at home

Physiological Correlates of VNS

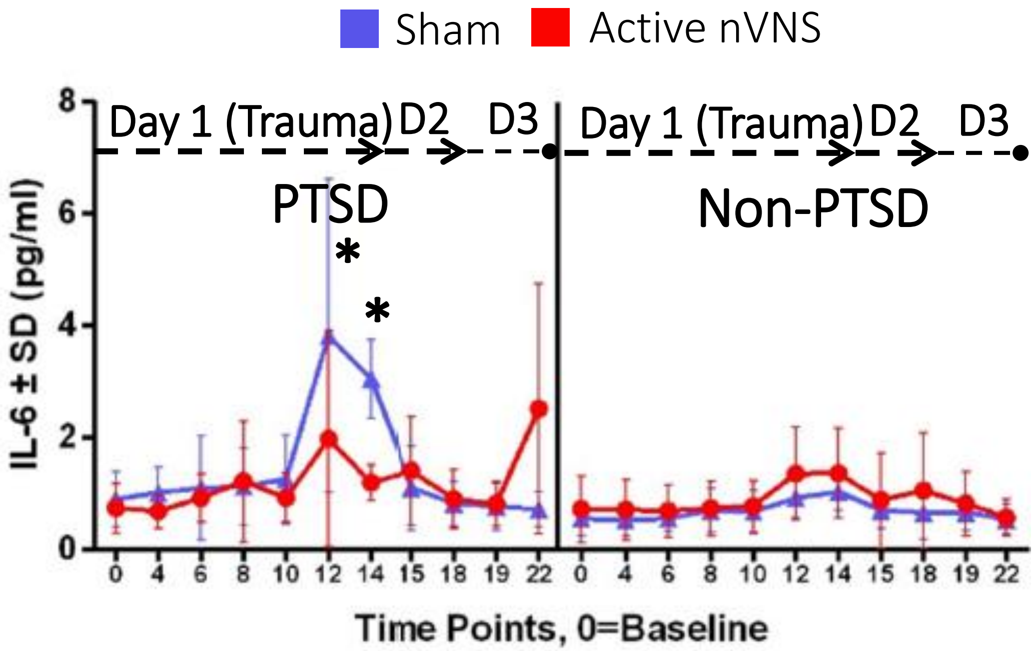


- *tcVNS activates the Nucleus Tractus Solitarius (NTS) which has projections through norepinephrine (NE), acetylcholine (Ach) and serotonin (5-HT)*
- *These pathways lead to brain areas involved in emotion including the mPFC/anterior cingulate, hippocampus, amygdala and cortex (insula).*
- *Vagal efferents project to peripheral cardiovascular, autonomic and inflammatory pathways.*

Interleukin-6 (IL-6) Increases with Mental Stress Tasks in Posttraumatic Stress Disorder (PTSD), Blocked by Vagal Nerve Stimulation

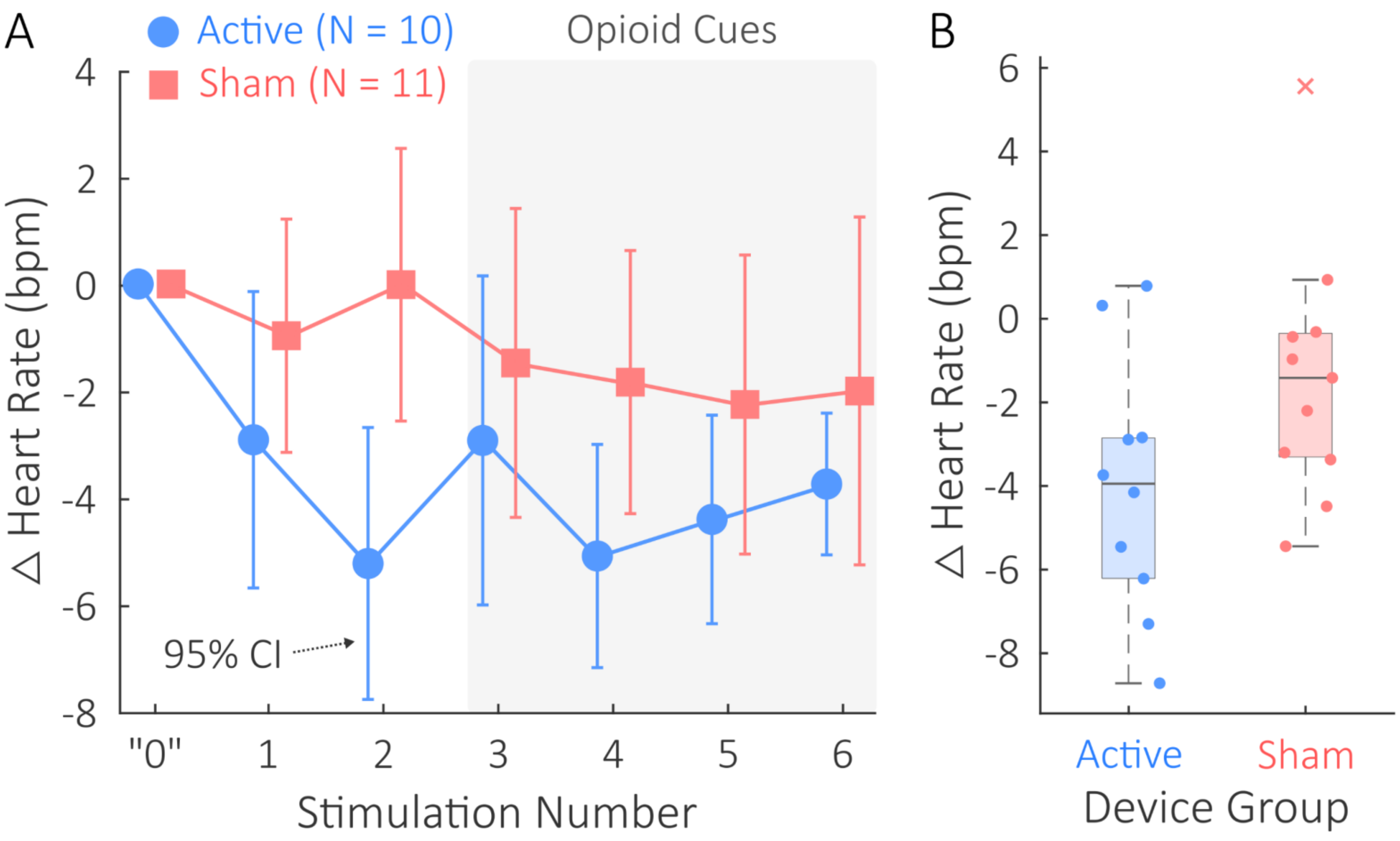


Lima et al., *Brain, Behavior, and Immunity* (2018). CHD patients with and without PTSD undergoing public speaking stress (mental stress) task



Bremner et al., *Brain, Behavior, and Immunity-Health* (2021). IL-6 response to traumatic scripts blocked by noninvasive vagal nerve stimulation (nVNS)

Reduced Heart Rate with Active VNS for Opioid Withdrawal

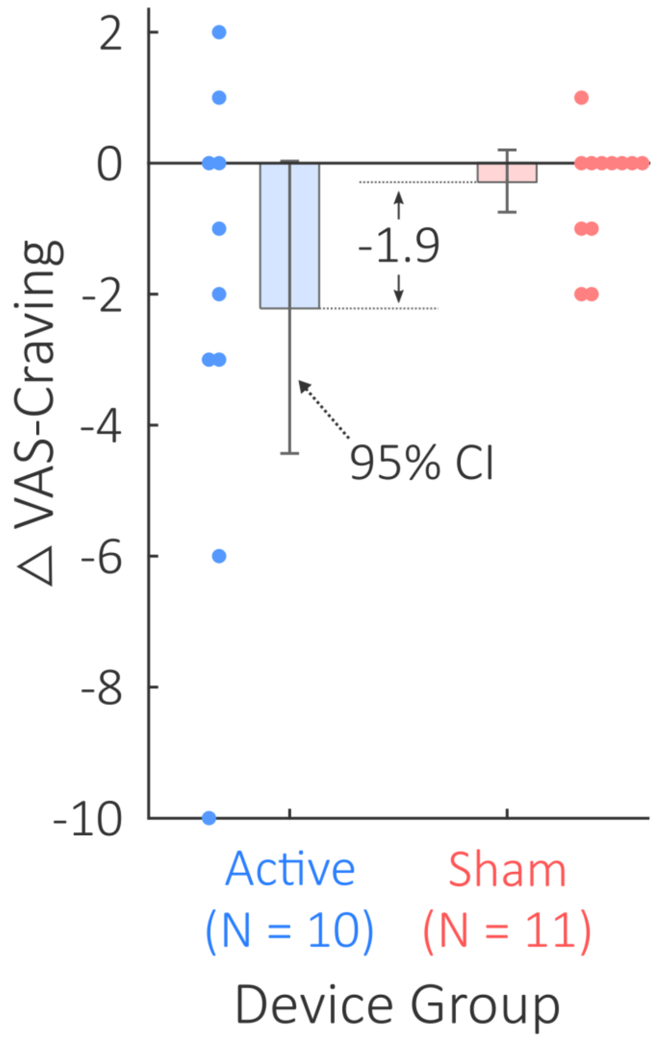


t ϵ [31, 60] for each stimulation

Georgia Institute of Technology

EMORY UNIVERSITY

Greater than 1.5 Point Reduction in Mean Craving with Active VNS

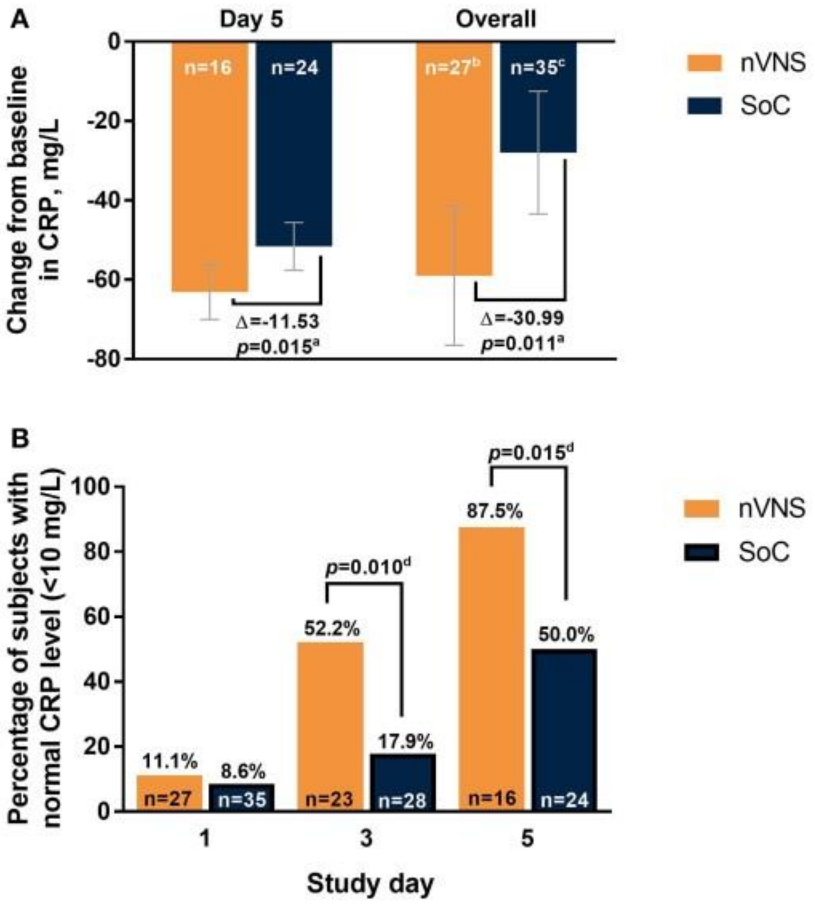


Patients with Opioid Use Disorders in acute withdrawal from opiates administered active tcVNS or sham stimulation

Georgia Institute of Technology

EMORY UNIVERSITY

Vagal Nerve Stimulation Decreases C-Reactive Protein (CRP) In Acute COVID Infections



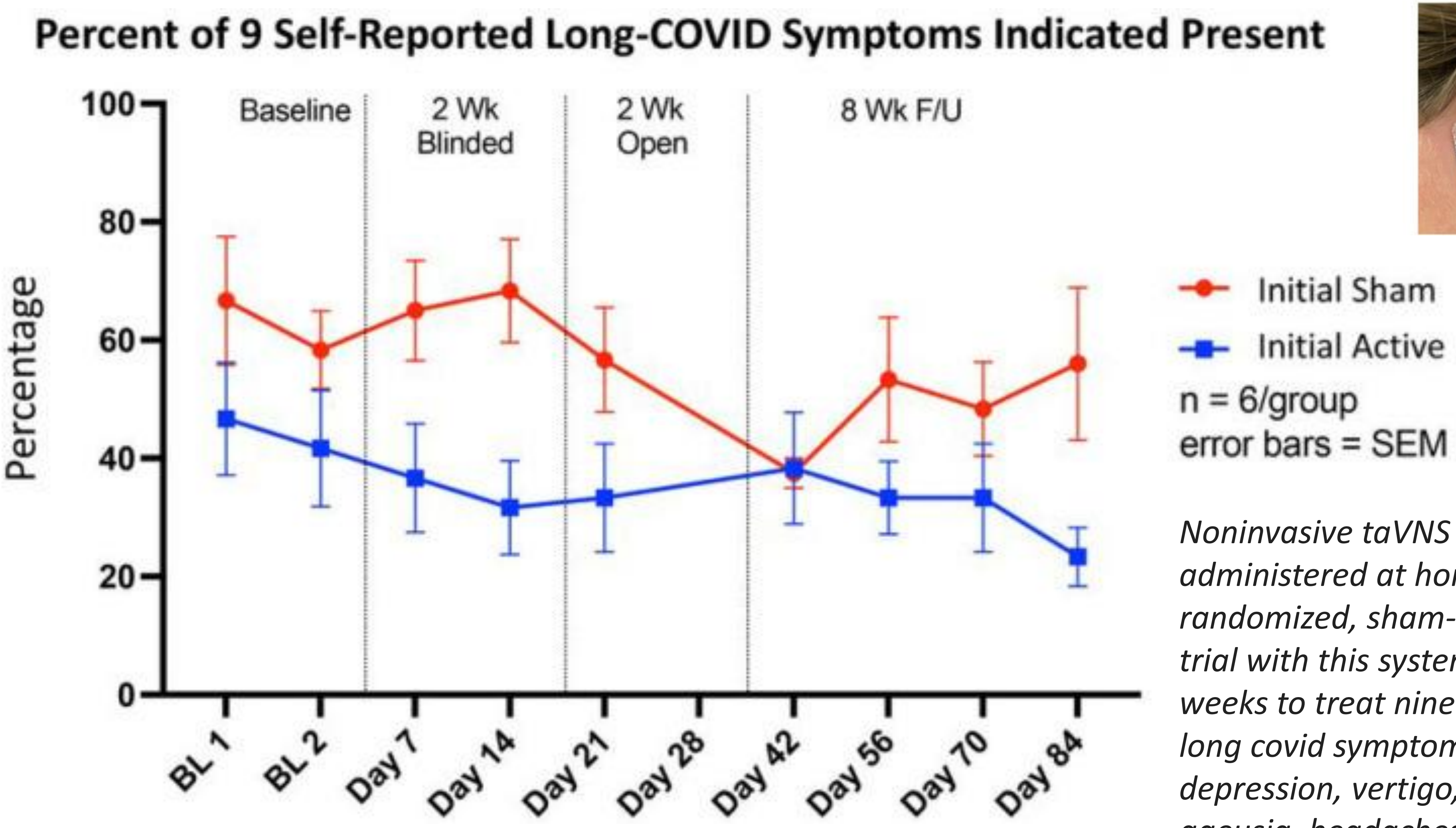
Tornero et al 2022 “SAVIOR 1” Front Neurol

Study Assessing Vagal Nerve Stimulation in Covid Respiratory Symptoms (SAVIOR 1) Tornero et al 2022 Front Neurol

Three times daily two consecutive non invasive Vagal Nerve Stimulation (nVNS) versus Standard of Care (SoC)

No change in respiratory outcomes

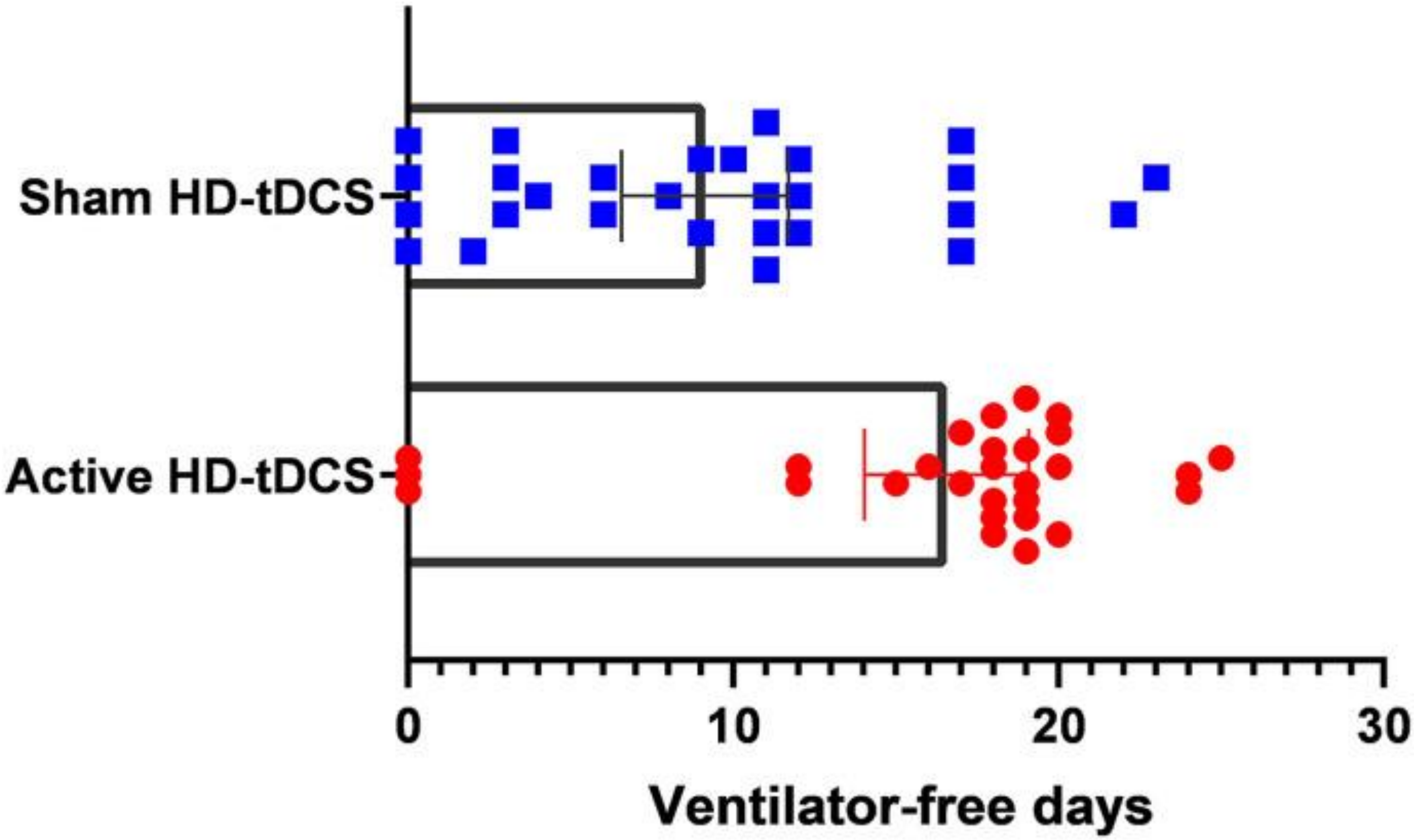
Transcutaneous Auricular Vagal Nerve Stimulation for Long COVID



Noninvasive taVNS self-administered at home (n = 13) randomized, sham-controlled, trial with this system for four weeks to treat nine predefined long covid symptoms (anxiety, depression, vertigo, anosmia, ageusia, headaches, fatigue, irritability, brain fog).

Badran et al 2022 "Pilot double blind randomized trial of taVNS for Long Covid"

Transcranial Direct Current Stimulation (tDCS) for Hospitalized COVID



Andrade et al 2022 Brain Stimulation "The HD-RECOVERY randomized clinical trial"

Significant reduction in days on ventilator in critically ill patients with COVID (N=56) with active versus sham tDCS 2x day 30 min

Reduction in organ dysfunction and delirium at one month follow up

Long COVID Brain and Mental Health Conclusions

- Long COVID mechanisms involve inflammation in the brain
- Associated with increase in anxiety and depression disorders
- Preferential effect on brain areas involved in smell (olfactory bulb, orbitofrontal cortex)
- Involves brain areas involved in emotion and memory: hippocampus, prefrontal cortex
- Neuromodulation shows promise for treatment

Long COVID/PASC

Thank you!

Hang in there!

Help is on the Way!

Researching the Effects of COVid to Effect Recovery (RECOVER)

Neuropsychiatric Subcommittee