ACUTE AND POST-ACUTE COVID-19 RELATED COGNITIVE IMPAIRMENT: ENDOTHELIAL DYSFUNCTION, INFLAMMATION AND NEURODEGENERATION

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DISCLOSURES

- NIH/NIA R01AG077422 (mPI: Frontera, Ge, Wisniewski) "Alzheimer's Disease Related Biomarkers following SARS-CoV-2 Infection" Role: PI

- NIH/NCATS UL1TR001445 (PI: Frontera) "Study of Cognitive and Functional Outcomes in Patients with or without Convalescent Plasma during COVID-19 Hospitalization (SCAFOLD-COVID)" Role: PI

- NIH/NHLBI grant 1OT2HL161847-01 (mPI: Katz, Horwitz, Troxel). "RECOVER: Post-Acute Sequelae of SARS-CoV-2 Infection Initiative: NYU Langone Health Clinical Science Core". Role: Co-Investigator

- NIH/NINDS grant 3U24NS11384401S1 (mPIs: Troxel, Petkova). "EPICCNet COVID databank, NeuroCOVID databank and biobank". Role: Co-Investigator

- NIH/NIA grant 3P30AG066512-01, (PI: Wisniewski). "Identification of Plasma Biomarkers in Older COVID-19 Symptomatic Adults with and without AD that Predispose to More Severe Disease and Neurological Symptoms" Role: Co-Investigator
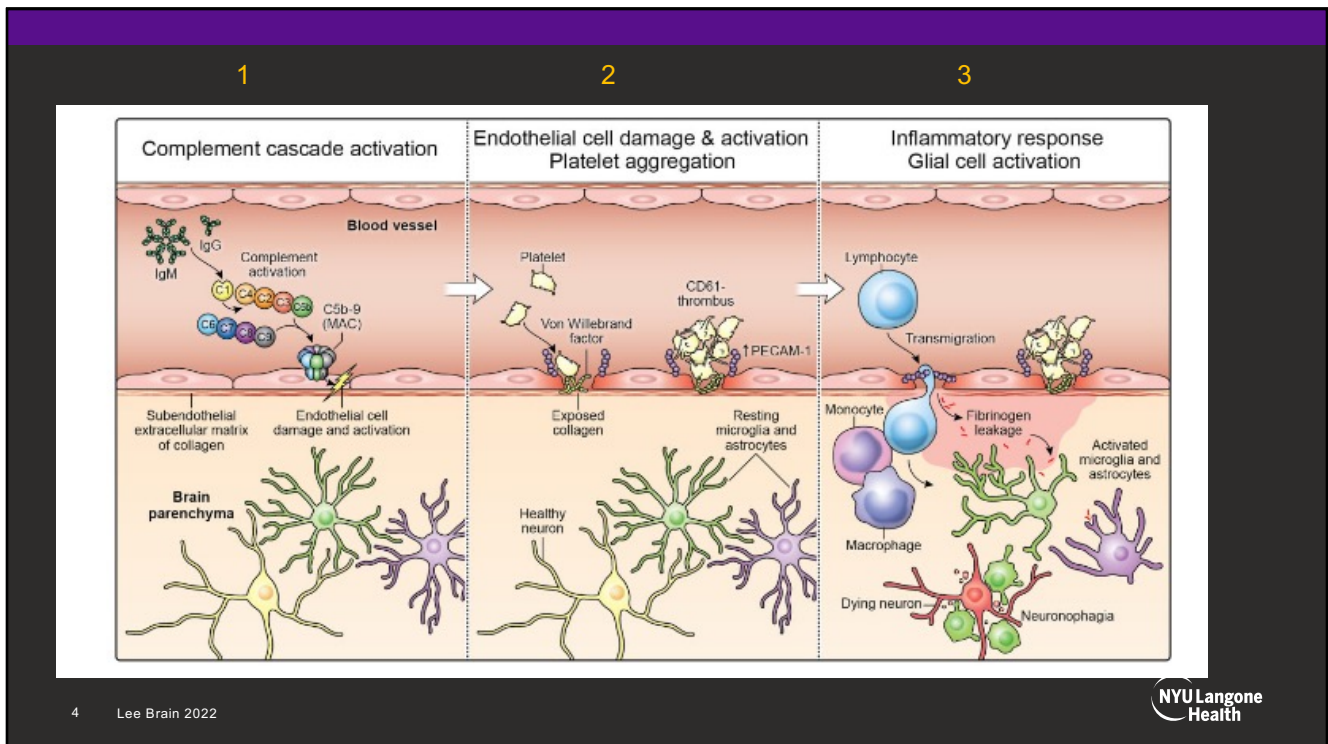
- WHO Brain Health COVID-19 Task Force Member

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MECHANISMS OF ACUTE NEURO INJURY WITH SARS-COV-2
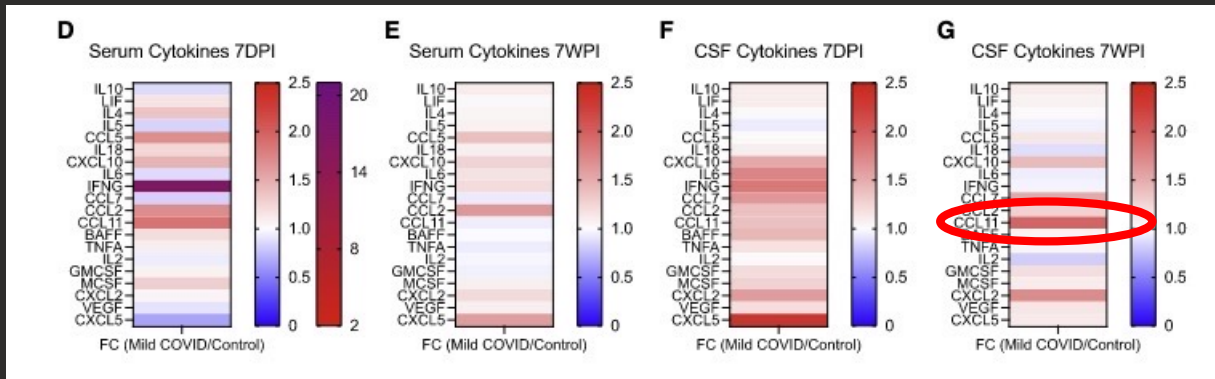
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Lee Brain 2022

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1. Inflammation: Cytokine and Chemokine Elevations in CSF and blood at 7 days and 7 weeks in Mice with mild COVID

CCL 11 recruits eosinophils and related to allergic reactions BUT also affects microglia and is elevated in neurodegenerative disorders (Nazarinia Acta Neurol Belgica 2022)
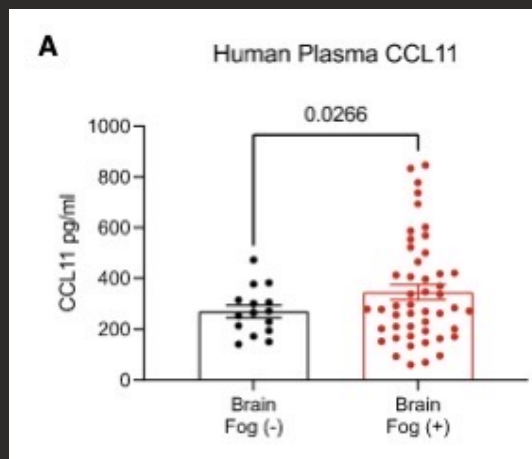
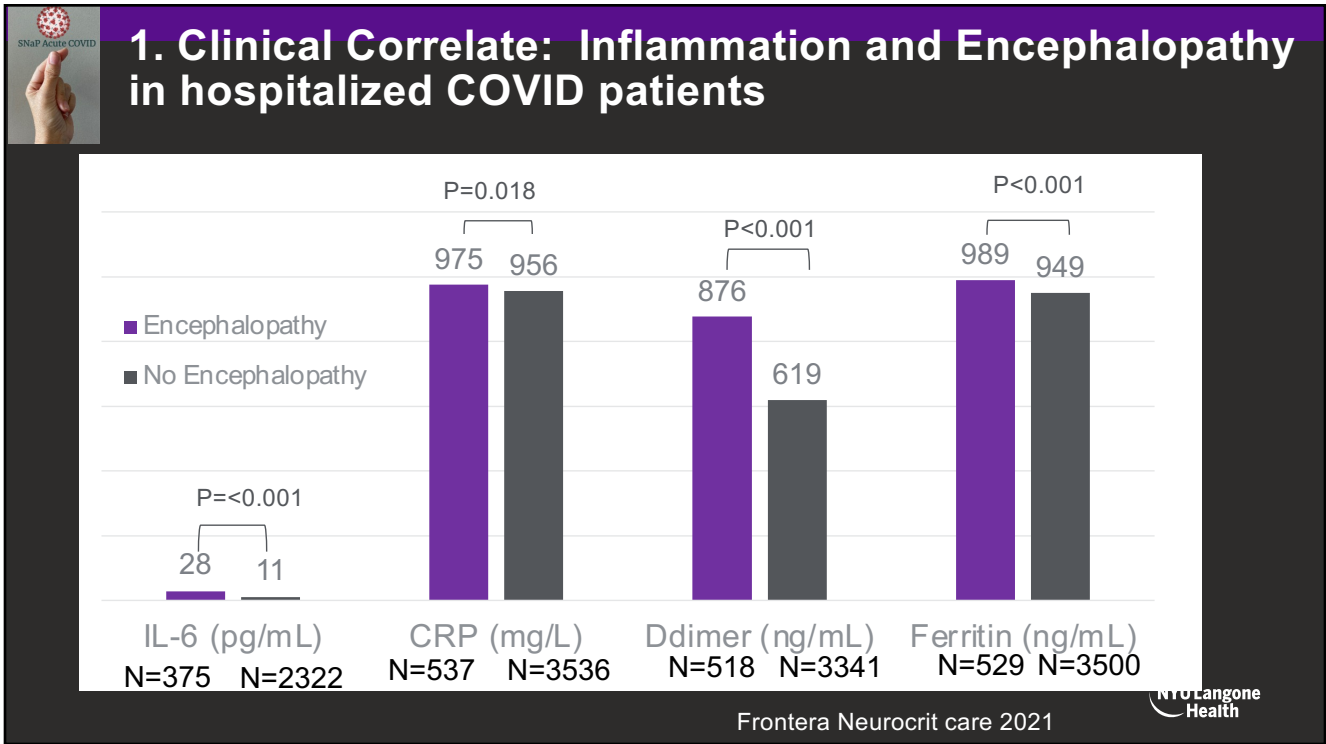Fernandez-Castaneda Cell 2022

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1. Clinical Correlate: Elevated CCL11 in COVID Patients with Brain fog

6 Fernandez-Castaneda Cell 2022

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1. Clinical Correlate: Inflammation and Encephalopathy in hospitalized COVID patients

Frontera Neurocrit care 2021

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2. Acute Microvascular Injury, BBB disruption in humans

Green=fibrinogen staining
In parenchyma of olfactory bulb (B)
And pons (D)

B1 shows fibrinogen staining in parenchyma
B2 show thinning of basal lamina (arrow)

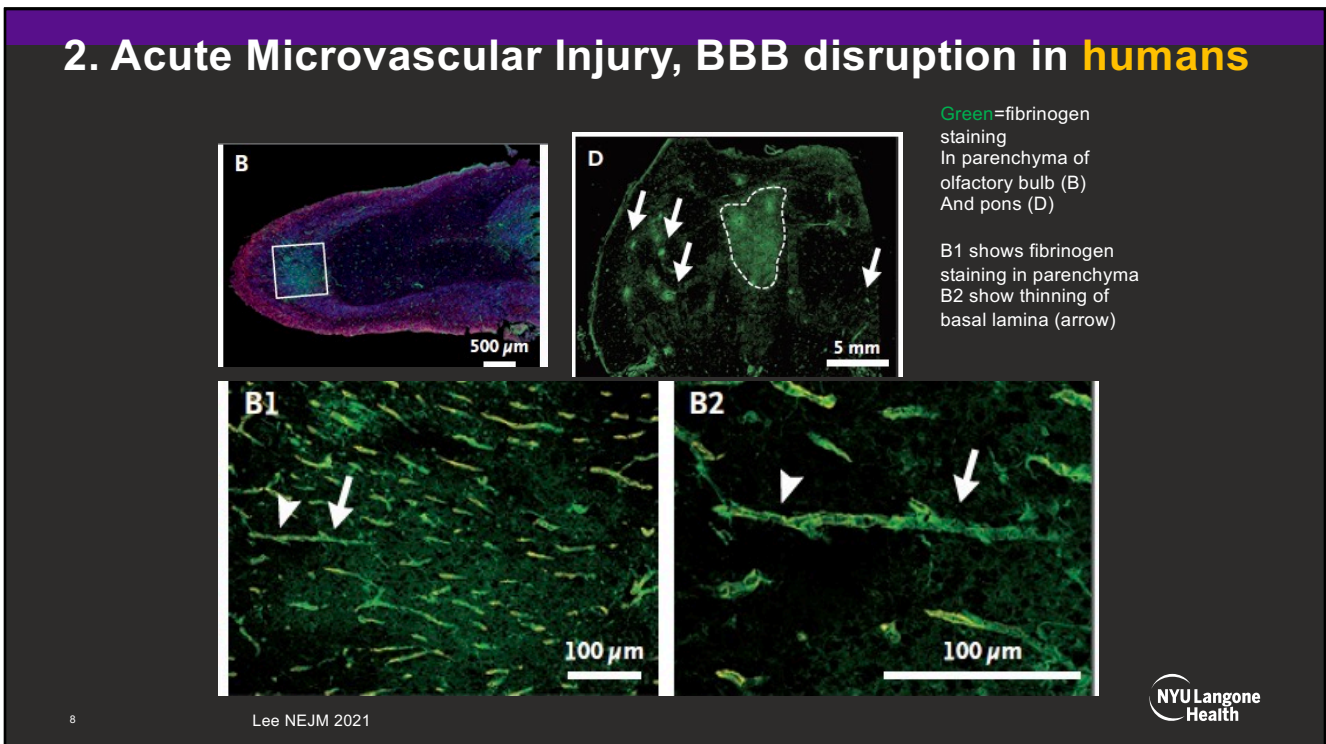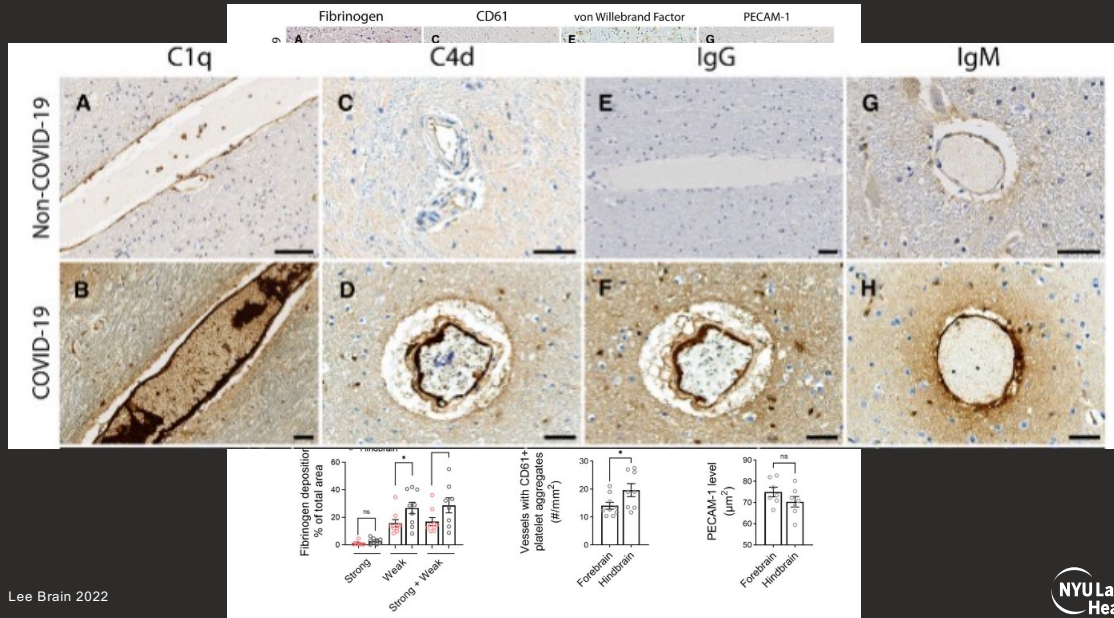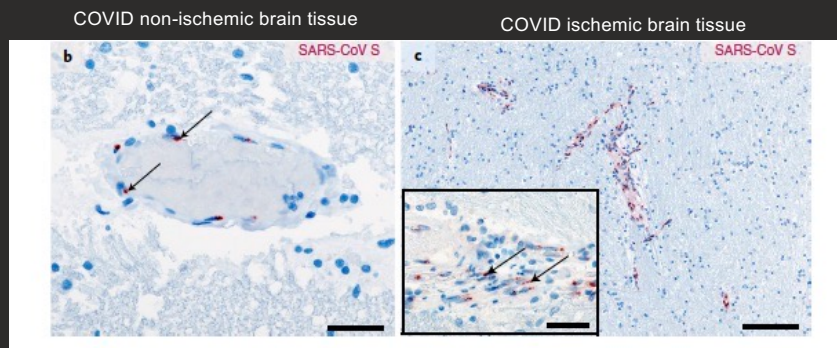Lee NEJM 2021

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2. Microthrombi and Microvascular injury, Complement deposition in cerebral endothelial cells in *humans*

Lee Brain 2022

2. Brown staining = SARS-COV2 S protein in endothelial cells in *humans*

COVID non-ischemic brain tissue   COVID ischemic brain tissue

Meinhardt Nature Neuroscience 2020

2. Cerebral Microvascular Injury and BBB disruption in **humans**
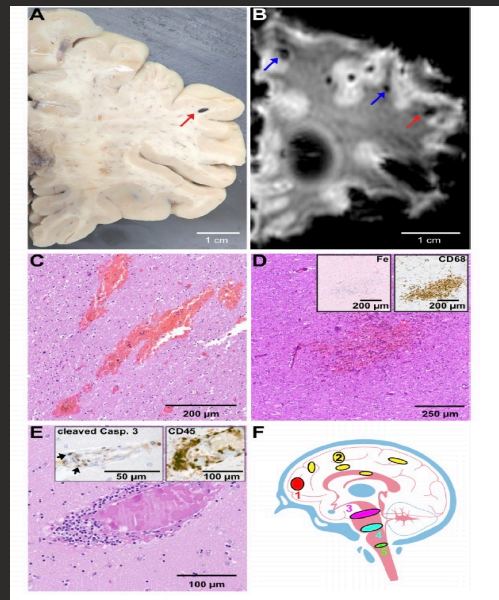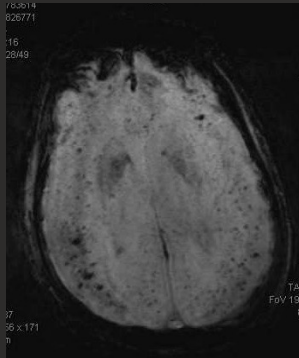
11

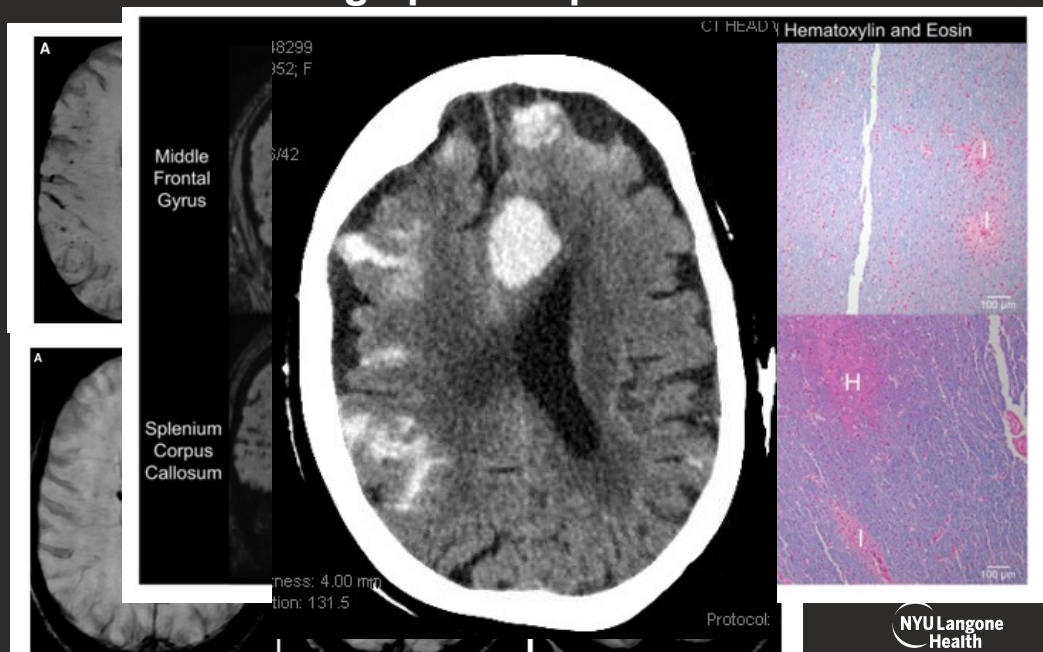Kirschenbaum Neuropathol Appl Neurobiol 2020

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2. Unusual microhemorrhage pattern post COVID

APOEε4 increases risk of cerebral microhemorrhages and post COVID cognitive abnormalities (Kurki Acta Neuropath Comm 2021)

Fitsiori J Neuroimaging 2020, Conklin J Neurol Sci 2021

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2. Hypoxia and Hemorrhagic Conversion of Ischemic strokes

N=41 post-mortem brains

100% with hypoxic brain injury
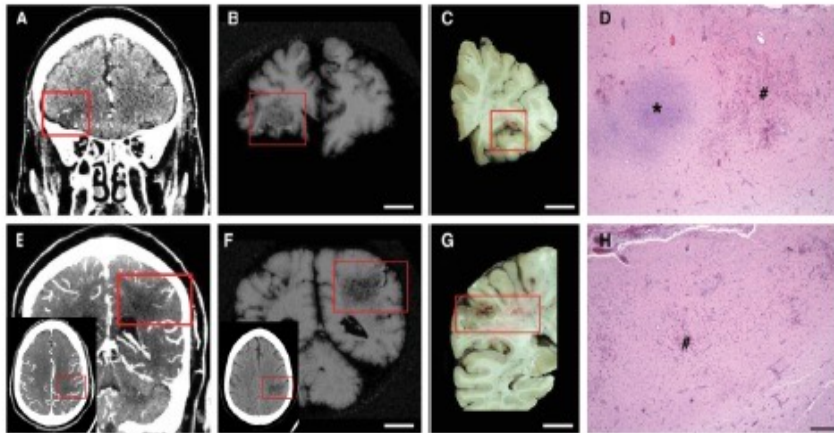
Figure 2. Acute, focal hemorrhagic infarcts in COVID-19 patients.
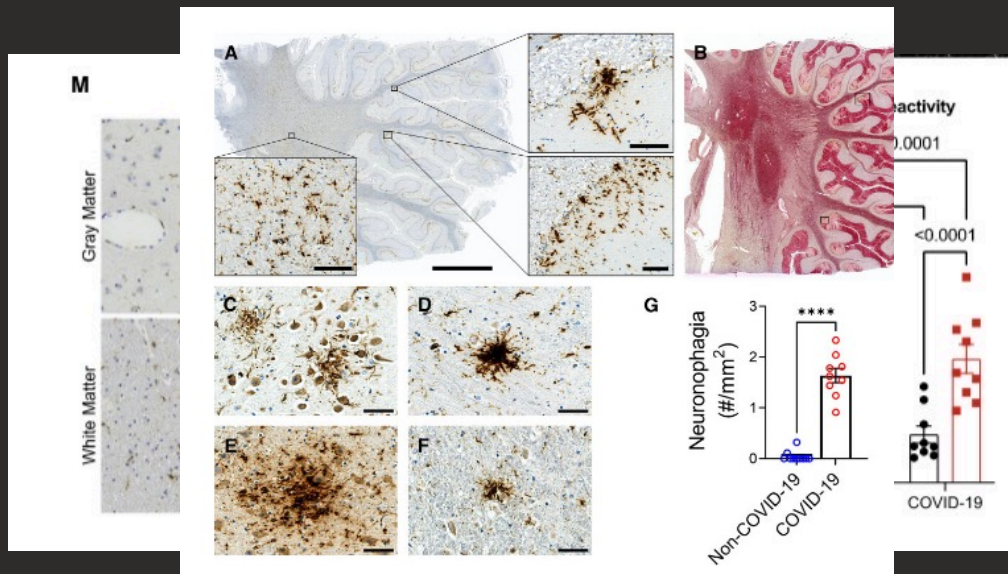
Thakur Brain 2021

13

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3. Microglial Activation in mild and severe COVID in humans

14   Fernandez-Castaneda Cell 2022 and Lee Brain 2022

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LINK BETWEEN INFECTION, INFLAMMATION AND ALZHEIMER'S

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Viral hypothesis of Alzheimer's Disease

HSV, EBV, CMV induce amyloid and tau formation in cell culture and mouse models (Devanand Curr Neruol Neurosci Rep 2018, Carter Neurochem Int 2011)

HSV1 detected in AD brains more than controls, HSV1 DNA co-localizes with amyloid plaques (Wozniak PLOSOne 2011)

Amyloid beta may have anti-microbial function (Eimer Neuron 2018)

MCI and dementia correlate with HSV, CMV, HHV6 reactivation (Warren-Gash Sci Rep 2019)

HSV1 associated with 2.5x increased risk of dementia and anti-herpetic meds reduce risk 9-fold (Tzeng Neurotherapeutics 2018)

Ongoing VALAD trial of valacyclovir in HSV + people with mild AD (PI Devanand, NCT 03282916)

16   Created in BioRender

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Systemic Inflammation and Alzheimer's Disease Pathology
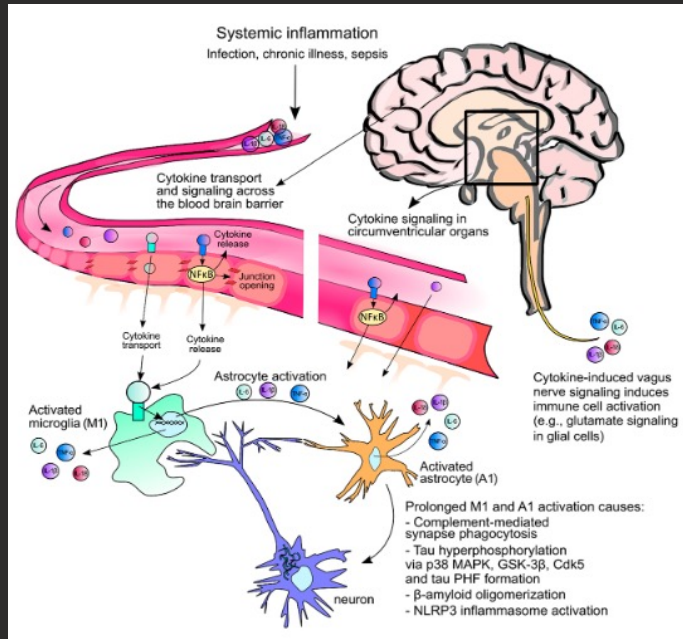
Walker ACS Chem Neurosci 2019

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Neurodegeneration due to Hypoxia, BBB disruption, inflammation

Figure 1. SARS-CoV-2 related hypoxia and hyperinflammation lead to blood brain barrier (BBB) disruption, microglial activation, increased Amyloidβ production and decreased breakdown, and increased neurofibrillary tangle (NFT) formation
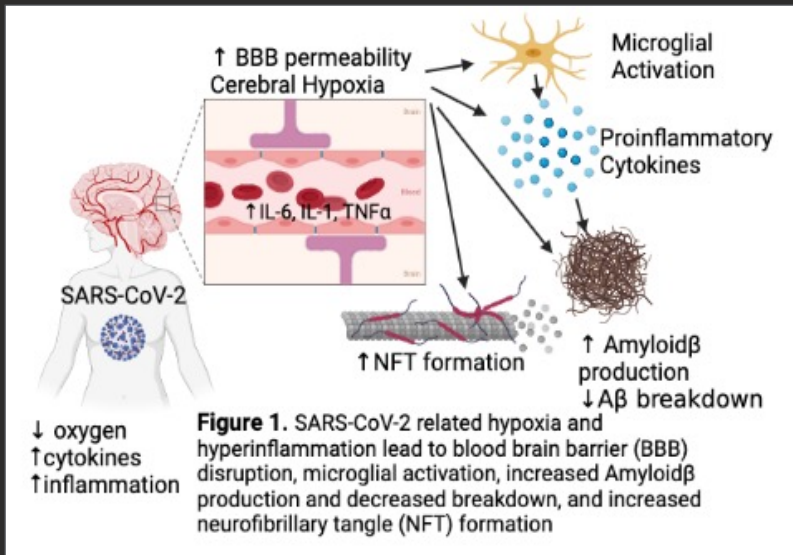
HYPOXIA

- ↓ amyloid precursor protein cleavage by ADAM10 ⟹ ↑ amyloid

- HIF-1a increases in β-secretase (BACE1) and ɣ-secretase ⟹ ↑ amyloid

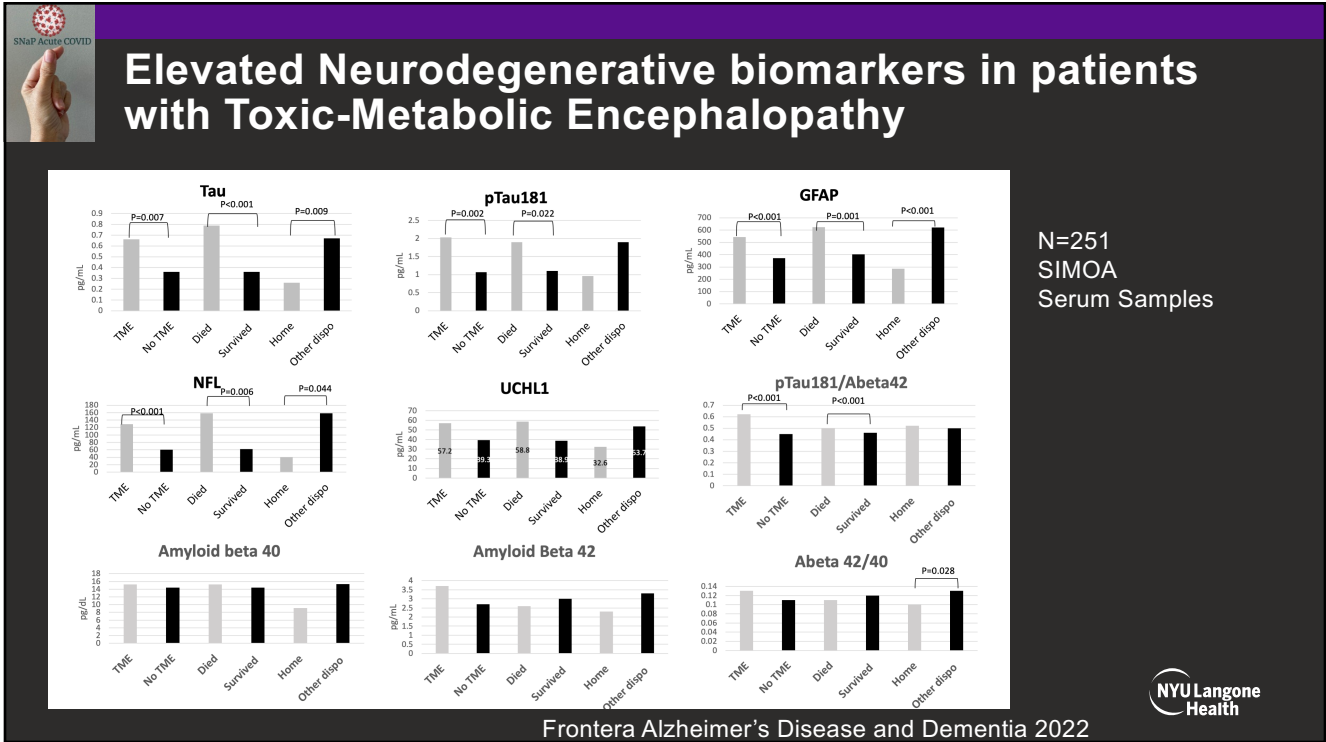- ↓ metalloprotease (neprilysin) ⟹ ↓ β-amyloid breakdown

Shi Brain Res 2000, Webster Brain Res Mol 2004, Sun Proc Natl Acad Sci 2006, Kerridge Front Neurosci 2015
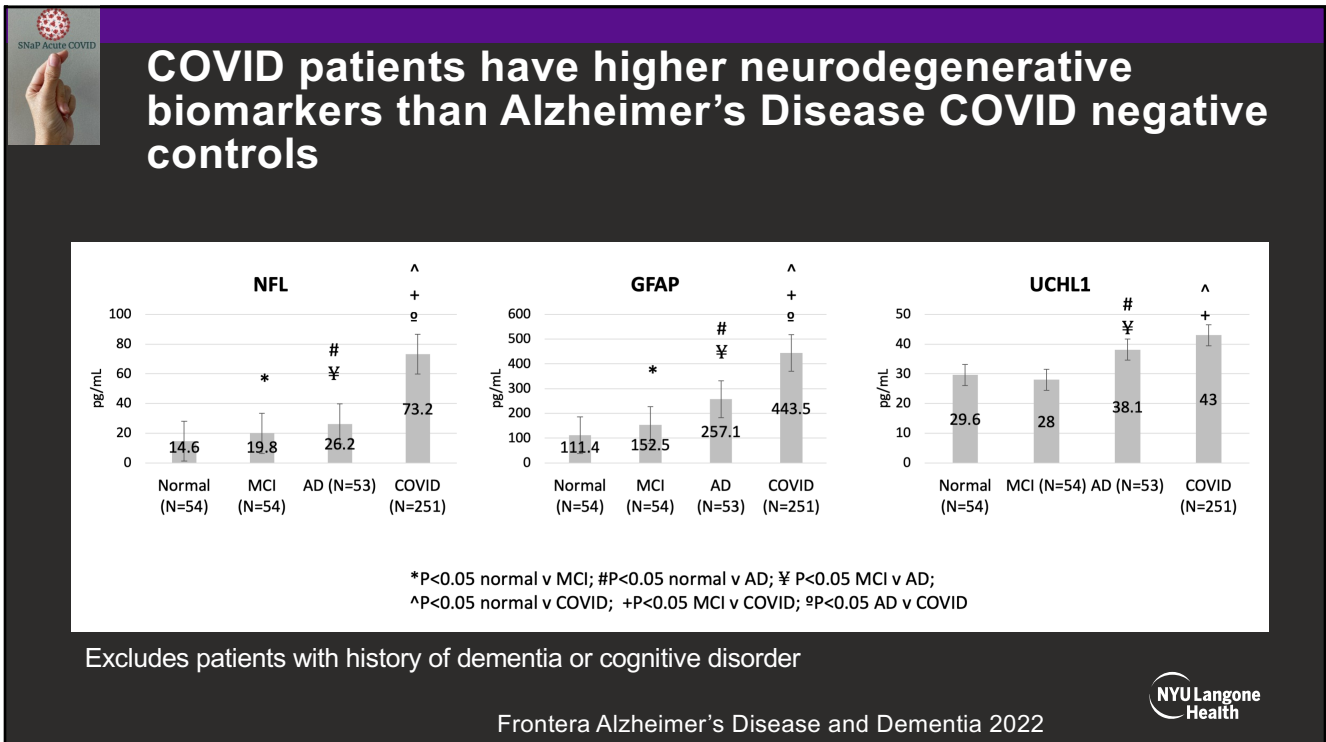
18   Frontera 2021

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Elevated Neurodegenerative biomarkers in patients with Toxic-Metabolic Encephalopathy

N=251
SIMOA
Serum Samples

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COVID patients have higher neurodegenerative biomarkers than Alzheimer's Disease COVID negative controls

*P<0.05 normal v MCI; #P<0.05 normal v AD; ¥ P<0.05 MCI v AD;
^P<0.05 normal v COVID; +P<0.05 MCI v COVID; ºP<0.05 AD v COVID

Excludes patients with history of dementia or cognitive disorder

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SNaP Acute COVID

		p-tau181			UCHL1		Aβ42
	Tau N = 241	N = 157	NfL N = 246	GFAP N = 246	N = 246	Aβ 40 N = 146	N = 120
Demographics							
Age	0.213 (0.09–0.33)	0.367 (0.22–0.50)	0.273 (0.15–0.39)	0.435 (0.32–0.54)	0.084 (−0.04–0.21)	0.294 (0.13–0.44)	0.14 (−0.04–0.31)
Male sex	0.024 (−0.10–0.15)	0.068 (−0.09–0.22)	0.031 (−0.09–0.16)	0.058 (−0.07–0.18)	0.124 (0.00–0.25)	0.044 (−0.12–0.21)	0.079 (−0.10–0.25)
Race (White vs. other)	0.149 (0.02–0.27)	0.147 (−0.01–0.30)	0.058 (−0.07–0.18)	0.129 (0.00–0.25)	0.061 (−0.06–0.18)	0.096 (−0.07–0.25)	0.104 (−0.08–0.28)
Severity of COVID-19 illness							
Intubation	0.232 (0.11–0.35)	0.054 (−0.10–0.21)	0.276 (0.15–0.39)	0.108 (−0.02–0.23)	0.186 (0.06–0.30)	0.005 (−0.16–0.17)	0.021 (−0.16–0.20)
Worse SOFA score	0.345 (0.23–0.45)	0.261 (0.11–0.40)	0.461 (0.35–0.56)	0.25 (0.13–0.37)	0.313 (0.19–0.42)	0.13 (−0.03–0.29)	0.138 (−0.04–0.31)
Lowest O$_2$ saturation	0.138 (0.01–0.26)	0.039 (−0.12–0.19)	0.176 (0.056–0.30)	0.117 (−0.01–0.24)	0.126 (0.00–0.25)	0.079 (−0.08–0.24)	0.033 (−0.15–0.21)
Lowest mean arterial blood pressure	0.312 (0.19–0.42)	0.256 (0.10–0.40)	0.385 (0.27–0.49)	0.178 (0.05–0.30)	0.271 (0.15–0.39)	0.075 (−0.09–0.23)	0.065 (−0.12–0.24)
Hypoxic ischemic brain injury	0.177 (0.05–0.30)	0.264 (0.11–0.41)	0.206 (0.08–0.32)	0.133 (0.01–0.25)	0.125 (0.00–0.25)	0.044 (−0.12–0.21)	0.034 (−0.15–0.21)
Ventilator days	0.215 (0.09–0.33)	0.279 (0.12–0.42)	0.085 (−0.04–0.21)	0.141 (0.02–0.26)	0.099 (−0.03–0.22)	0.586 (0.46–0.69)	0.352 (0.18–0.50)
LOS	0.135 (0.01–0.26)	0.046 (−0.11–0.20)	0.291 (0.17–0.40)	0.101 (−0.02–0.22)	0.193 (0.07–0.31)	0.046 (−0.12–0.21)	0.009 (−0.17–0.19)
Inflammatory Markers							
Admission IL-6	−0.031 (−0.16–0.10)	0.026 (−0.13–0.18)	0.069 (−0.06–0.19)	0.003 (−0.12–0.13)	0.038 (−0.09–0.16)	0.144 (−0.02–0.30)	0.022 (−0.16–0.20)
Admission CRP	0.006 (−0.12–0.13)	−0.017 (−0.17–0.14)	0.044 (−0.08–0.17)	−0.059 (−0.18–0.07)	0.003 (−0.12–0.13)	−0.096 (−0.25–0.07)	0.056 (−0.12–0.23)
Admission ferritin	−0.015 (−0.14–0.11)	0.026 (−0.13–0.18)	0.023 (−0.10–0.15)	−0.005 (−0.13–0.12)	0.002 (−0.12–0.13)	0.113 (−0.05–0.27)	0.02 (−0.16–0.20)
Admission D-dimer	−0.022 (−0.15–0.10)	0.188 (0.03–0.34)	0.167 (0.04–0.29)	0.139 (0.01–0.26)	0.035 (−0.09–0.16)	−0.026 (−0.19–0.14)	−0.074 (−0.25–0.11)

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SNaP Acute COVID

Neurodegenerative biomarkers and 6- and 12-month outcomes

	Tau	Ptau181	NFL	GFAP	UCHL1
6-mo tMoCA	0.276	0.131	0.010	−0.016	0.152
6-mo mRS	0.191	**0.562**	**0.385**	**0.336**	0.101
6-mo Barthel	−0.026	−0.413	**−0.580**	**−0.481**	−0.327
6-mo Anxiety	−0.200	0.113	0.212	0.214	−0.050
6-mo Depression	−0.113	0.422	0.091	**0.397**	0.057
6-mo Fatigue	−0.011	0.328	0.182	0.330	0.252
6-mo Sleep	−0.251	−0.124	−0.050	0.041	−0.020

	Tau	Ptau181	NFL	GFAP	UCHL1
12-mo tMoCA	0.171	0.027	−0.112	−0.392	−0.066
12-mo mRS	−0.167	0.005	0.320	0.330	**0.467**
12-mo Barthel	−0.060	−0.247	**−0.565**	**−0.604**	**−0.565**
12-mo Anxiety	−0.222	−0.162	−0.212	−0.114	−0.181
12-mo Depression	−0.159	0.290	0.047	0.003	−0.082
12-mo Fatigue	−0.225	0.245	−0.018	0.221	0.024
12-mo Sleep	**−0.465**	0.192	0.064	0.041	0.175

Excludes patients with h/o cognitive impairment

NFL significantly associated with 12 month mRS 4-6 after adjusting for age, sex, ventilator status:

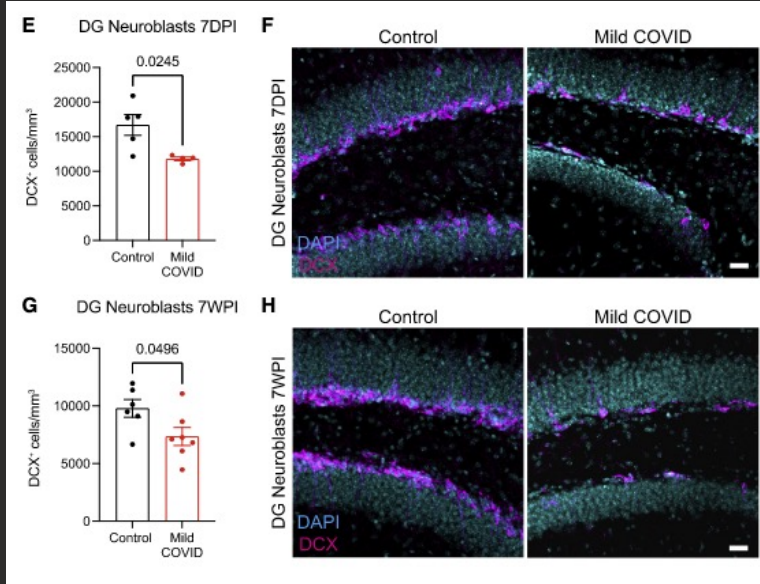aOR 1.012 (1.00-1.023) P=0.045

22   Frontera unpublished

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Decreased hippocampal neurogenesis at 7 days and 7 weeks in Mice with mild COVID

7 days post COVID

7 weeks post COVID

23   Fernandez-Castaneda Cell 2022

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Brain Atrophy- Neurodegeneration, De-afferentation in humans?

N=501 COVID (15 hospitalized)
N=384 control
Imaged pre and post-COVID (avg 141 d apart)
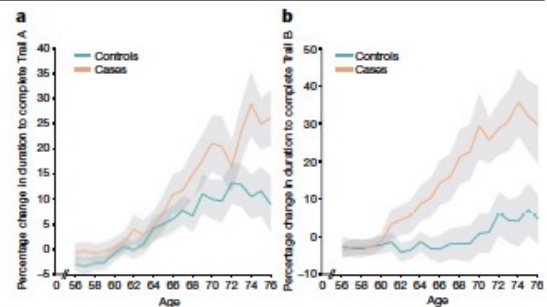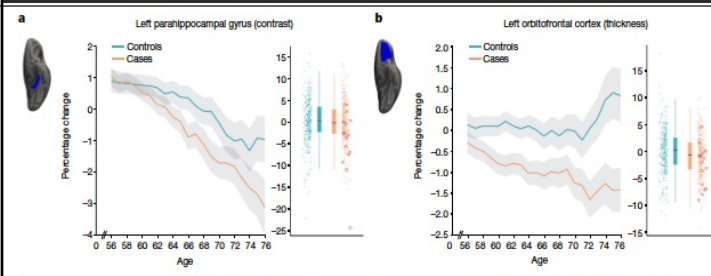Percent change in controls and COVID modest: 0.2%-2%

Fig. 3 | Significant longitudinal differences in cognition. a, b, The percentage longitudinal change for SARS-CoV-2-positive cases and controls in the duration to complete trails A (a) and B (b) of the UK Biobank Trail Making Test. The absolute baseline (used to convert longitudinal change into percentage change) was estimated across the 785 participants. These curves were created using a ten-year sliding window across cases and controls (s.e. values are shown in grey).
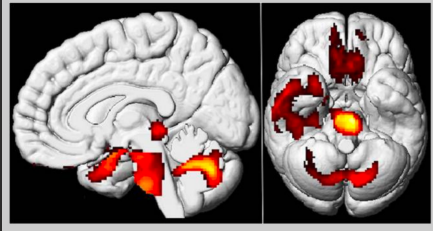
Issue: no data on clinical correlates with anosmia
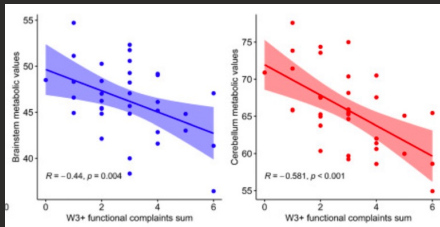
24   Douaud Nature 2022

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Brain hypometabolism correlates with symptoms in **humans**

N=45 participants with persistent symptoms for median of 3 months (range 26-155 days) after onset acute COVID-19 → regional hypometabolism on ^{18}F- FDG PET compared to 44 healthy controls.
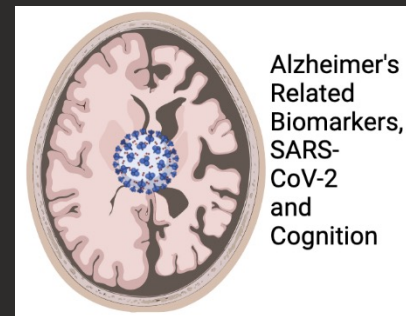

PET metabolism inversely associated with symptoms (memory loss, pain, anosmia)

Guedj et al, *European J Nucl Med & Molecular Imaging,* 2021

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Ongoing Studies

ADULT COHORT

PEDS COHORT

RECOVER
Researching COVID to Enhance Recovery
An Initiative Funded by the National Institutes of Health

AUTOPSY COHORT

ELECTRONIC HEALTH RECORD STUDY

COVID-19 NEURO DATABANK/ BIOBANK

Alzheimer's Related Biomarkers, SARS-CoV-2 and Cognition

26   https://recovercovid.org/

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Summary

- Hyperinflammation and Hypoxia during acute COVID-19 lead to:
    - endothelial injury, microthrombi, microhemorrhages
    - Leaky Blood Brain Barrier
    - Microglial activation> Astrocyte activation> Neuronophagia
- Downstream increased amyloid plaque and NFT formation may occur as in other infectious models of AD
- Clinical correlates of encephalopathy, "brain fog" with elevated cyto/chemokines
- Radiographic correlates of atrophy, hypometabolism with neuropsych testing
- Stay tuned!

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OUR FANTASTIC RESIDENTS/FELLOWS:

Shashank Agarwal, MD;
Andres Andino, MD;
Kristie Bauman, MD;
Samuel Baskharoun, MD;
Lena Bell, MD;
Stephen Berger, MD;
Dhristie Bhagat, MD
Matthew Bokhari, MD;
Steven Bondi, MD;
Levi Dygert, MD
Taolin Fang, MD;
Brent Flusty, DO;
Benjamin Fuchs, MD;
Andre Granger, MD;
Daniel Gratch, MD;
Jennifer Horng, MD;
Ruben Jauregui, MD;
Yuan Ji, MD;
Penina Krieger, MPhil;
Alexandra Kvernland, MD
Susan Liu, DO;
Chai Medicherla, MD
Patricio Millar-Vernetti, MD;
Nicole Morgan, MD;
Anlys Oivera, MD, PhD;
Mirza Omari, MD;
Palak Patel, MD;
Jonathan Rosenthal, MD
Thomas Snyder, MD;
Rebecca Stainman, MD;
Daniel Talmasov, MD;
Betsy Thomas, MD;
Eduard Valdes, MD;
Dixon Yang, MD;
Yingrong Zhu, MD

Thank You Team!
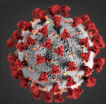
OUR AMAZING ATTENDINGS:

Nada Abou-Fayssal MD;
Laura Balcer, MD, MSCE;
Alexander Chervinsky, PhD;
Barry M. Czeisler, MD;
Adam de Havenon, MD;
Daniel Friedman, MD;
David Friedman, MD;
Steven Galetta, MD
Yulin Ge, PhD
Lindsey Gurin, MD;
Josef Gutman, MD;
Manisha Holmes, MD;
Koto Ishida, MD;
Ethan Kahn, DO;
Ethan Koch, MD;
Rebecca Lalchan, DO;
Ariane Lewis, MD;
Kaitlyn Lillemoe, MD;
Jessica Lin, MD;
Aaron S. Lord, MD;
Kara Melmed, MD;
Dimitris Placantonakis, MD;
Sakinah Sabadia, MD;
Sujata Thawani, MD;
Jose Torres, MD;
Thomas Wisniewski, MD;
Shadi Yaghi, MD;
Ting Zhou, MD

NIH/NINDS NEUROCOVID DATA/BIO BANK :
Andrea Troxel, PhD;
Eva Petkova, PhD;
Sharon Meropol, MD

NIH RECOVER:
Stu Katz, MD;
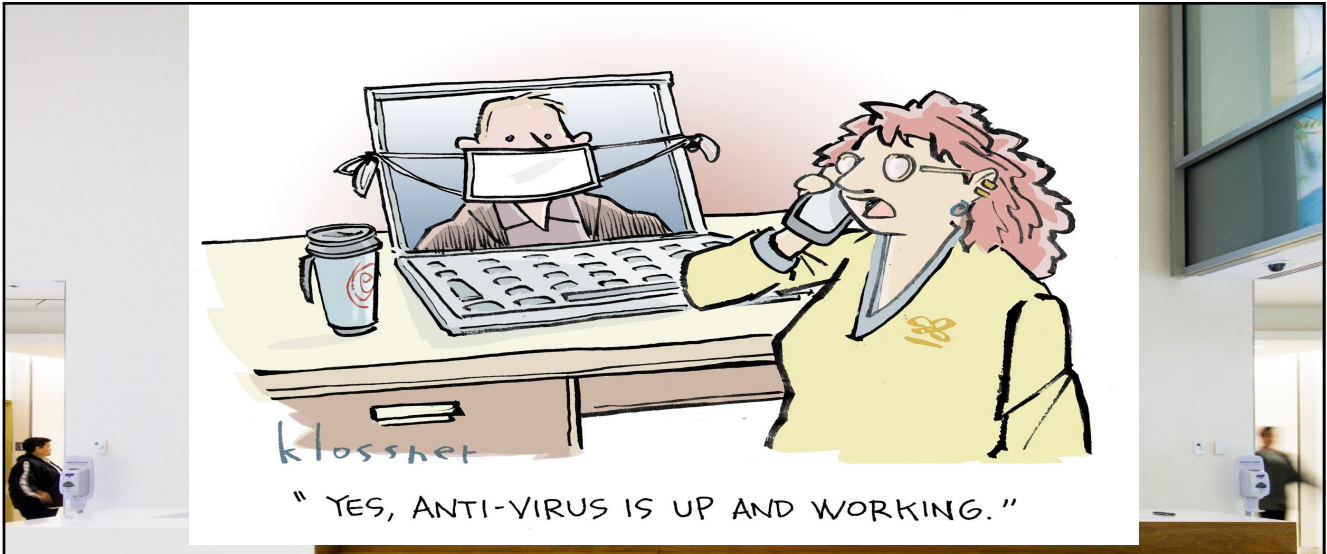Leora Horwitz, MD;
Andrea Troxel, ScD

WHO Collaborators:
Brain Health Group;
Global COVID-19 Neuro Research Coalition

Research Coordinators and MCIT support:
Joshua Huang, MSc
Lisena Hasanaj
Erica Scher, RN, MPH

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"YES, ANTI-VIRUS IS UP AND WORKING."

THANK YOU

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