Unraveling Long COVID: Blood brain barrier disruption and neuropsychiatric symptoms.

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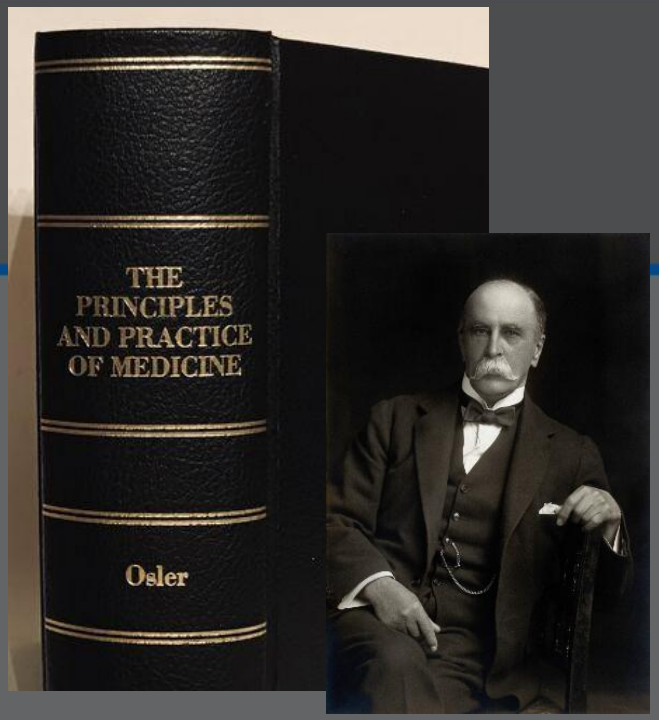
Department of Physical Medicine and Rehabilitation



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MEDICINE

XII. NEURASTHENIA.

Definition.—A condition of weakness or exhaustion of the nervous system.

In the cerebral form the symptoms are chiefly connected with an inability to perform the ordinary mental work. Thus a row of figures cannot be correctly added, the dictation or the writing of a few letters is a source of the greatest worry, the transaction of petty details in business is a painful effort, and there is loss of power of fixed attention.

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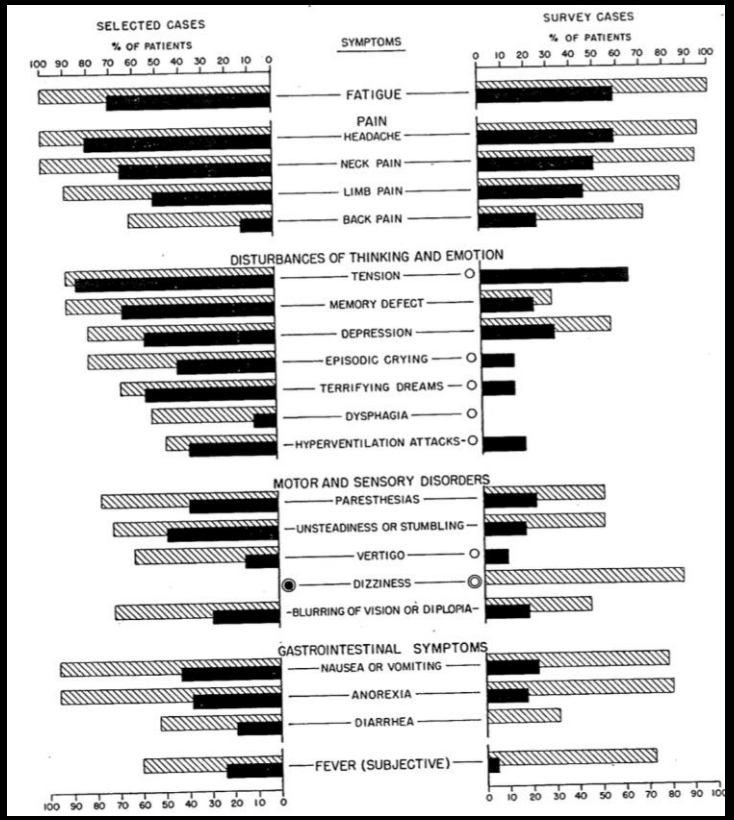
356 THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 22, 1957

EPIDEMIC NEUROMYASTHENIA*

An Outbreak in Punta Gorda, Florida

David C. Poskanzer, M.D.,† Donald A. Henderson, M.D.,‡ E. Charles Kunkle, M.D.,§ Seymour S. Kalter, Ph.D.,¶ Walter B. Clement, M.D.,‖ and James O. Bond, M.D., M.P.H.**



An outbreak of encephalomyelitis in the Royal Free Hospital Group, London, in 1955

NIGEL DEAN COMPSTON
M.A., M.D., F.R.C.P.

Royal Free Hospital, London

Original Contributions

A Cluster of Patients With a Chronic Mononucleosis-like Syndrome

Is Epstein-Barr Virus the Cause?

Gary P. Holmes, MD; Jonathan E. Kaplan, MD; John A. Stewart, MD; Barbara Hunt, RN; Paul F. Pinsky, MPH; Lawrence B. Schonberger, MD

2024 NASEM LONG COVID DEFINITION

Long COVID is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.

1. Attribution to Infection

No laboratory confirmation or other proof of initial SARS-CoV-2 infection required.

Can follow SARS-CoV-2 infections of any severity, including asymptomatic.

2. Onset and Duration

Must be present for at least 3 months.

Can be continuous from or delayed in onset following acute SARS-CoV-2 infection.

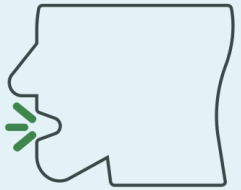
3. Symptoms

More than 200 symptoms and conditions possible, including exacerbation of pre-existing conditions.

Can affect one or more organ systems.

Can range from mild to severe and resolve over a period of months or persist for months or years.

No symptoms or conditions included in the definition are required or exclusionary.



4. Equity

Can affect children and adults, regardless of health, disability, or socioeconomic status, age, sex, gender, sexual orientation, race, ethnicity, or geographic location.

5. Functional Impairment

Can have profound emotional and physical impact and affect ability to work, attend school, take care of family, and practice self care.

Ely EW, Brown LM, Fineberg HV. Long COVID defined. N. Engl.J. Med. 2024; 391: 1746–1753.

JAMA | Original Investigation

Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection

Tanayott Thaweethai, PhD; Sarah E. Jolley, MD, MS; Elizabeth W. Karlson, MD, MS; Emily B. Levitan, ScD; Bruce Levy, MD; Grace A. McComsey, MD; Lisa McCorkell, MPP; Girish N. Nadkarni, MD, MPH; Sairam Parthasarathy, MD; Upinder Singh, MD; Tiffany A. Walker, MD; Caitlin A. Selvaggi, MS; Daniel J. Shinnick, MS; Carolin C. M. Schulte, PhD; Rachel Atchley-Challenner, PhD; RECOVER Consortium Authors; Leora I. Horwitz, MD; Andrea S. Foulkes, ScD; for the RECOVER Consortium

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Table 2. Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

- 9,764 Participants
- PASC Prevalence -10%
- 4 PASC subgroups
- Higher PASC in
  - Unvaccinated
  - Reinfected
- 12 Symptoms differentiating infected vs uninfected were identified using LASSO

Putting the PASC Score to the Test

- 130 LC patients followed by JH LC clinics, with neuropsychiatric symptoms
- 60 SARS-CoV-2-infected fully recovered
  - Long COVID Screener
- LC cohort had
  - Mean age of 47.2 yr
  - 72% Female
  - 79% White
  - 77% More than 16 yr of education
- Controls matched for demographics and time since index infection

Post-COVID infection onset of:

[ ] Limited ability to participate in pre-illness routine activities such as work, school, social life, and/or personal life, for > 6 months

[ ] New or definite onset of worsening fatigue post COVID

[ ] Symptoms worsen after physical, mental, or emotional effort that would not have caused a

Dysautonomia Screen

[ ] **Orthostatic intolerance:** Are you able to tolerate standing for prolonged periods (in line at the grocery store, showering)?

[ ] **Vasomotor symptoms** Experiencing changes in skin (color, flushing, goose bumps)?

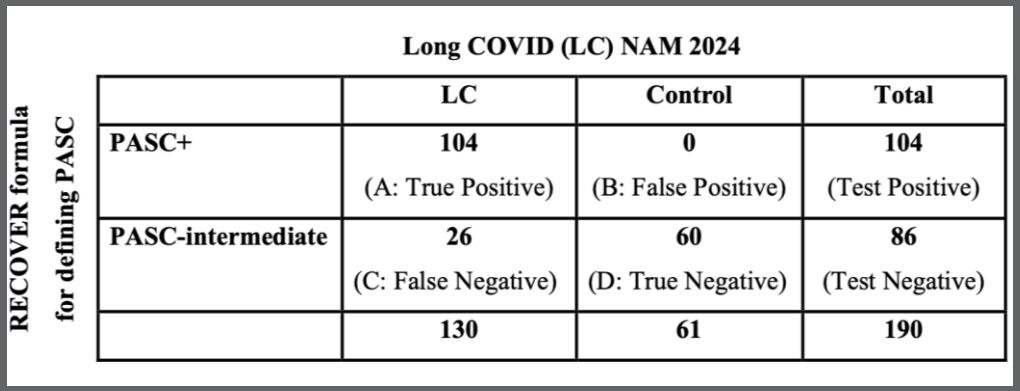
[ ] **Secretomotor symptoms:** Any changes in the way you sweat and produce saliva or tears?

[ ] **Gastrointestinal symptoms:** Have you experienced early satiety, nausea, vomiting, diarrhea,

MCAS symptoms ROS:

Yes / No	Skin/facial flushing
Yes / No	Hives
Yes / No	Rashes
Yes / No	Sun sensitivity (itching, rashes, burning more easily)
Yes / No	Swelling of lips, tongue, or eyelids
Yes / No	Eczema
Yes / No	Changes in skin/dermatographia?
Yes / No	Foods triggering abdominal pain and diarrhea (cheese, tuna, red wine, leftovers)?

Putting the PASC Score to the Test (Results)



Long COVID (LC) NAM 2024

RECOVER formula for defining PASC

	LC	Control	Total
PASC+	104 (A: True Positive)	0 (B: False Positive)	104 (Test Positive)
PASC-intermediate	26 (C: False Negative)	60 (D: True Negative)	86 (Test Negative)
	130	61	190

PASC score Demonstrated:

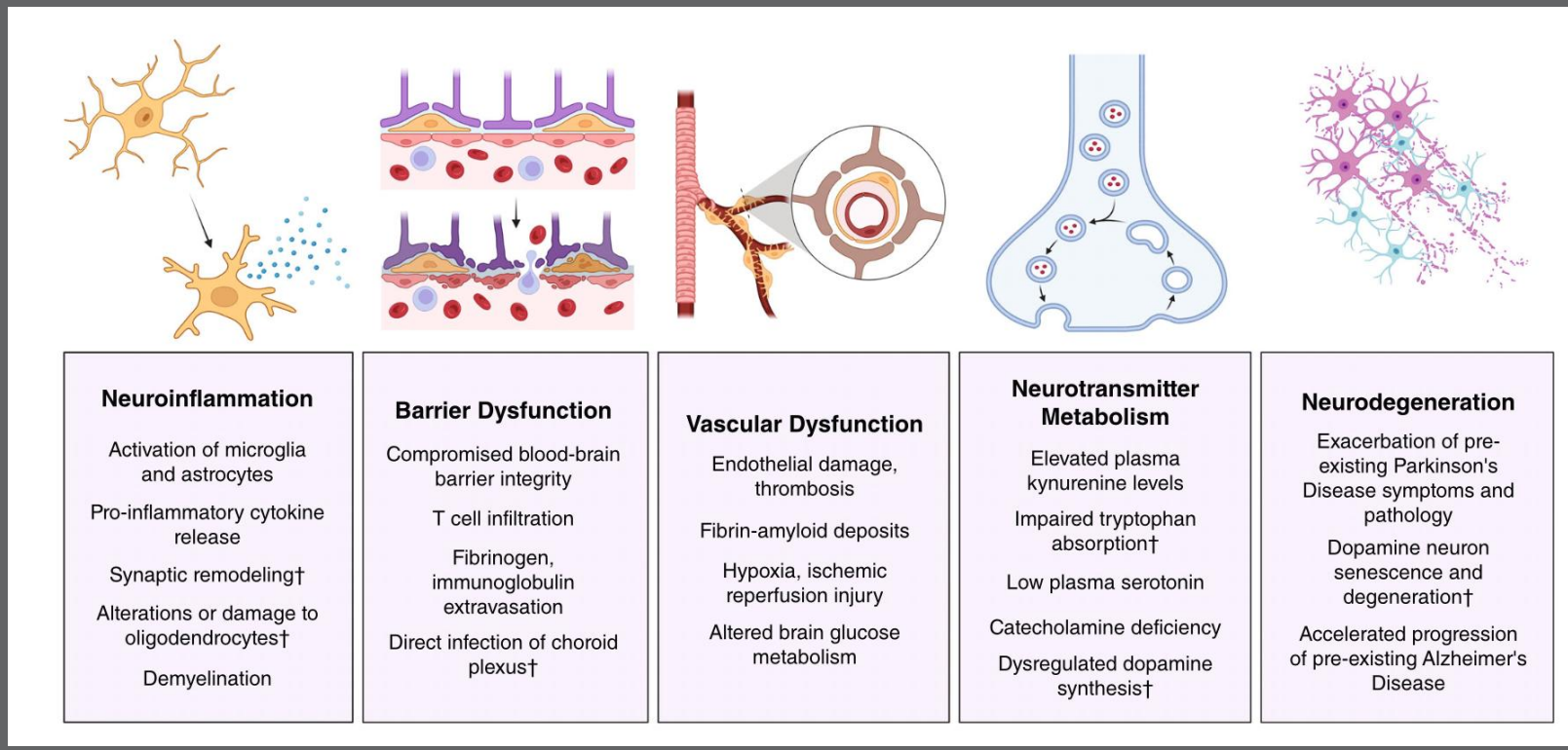
- 100% Specificity
- 80% Sensitivity
- PPV = 100%
- NPV = 70%

Evaluation of the performance of triplets of symptoms:

Loss of smell/taste + **Post-exertional malaise** + **Lack of sexual desire or capacity**

- 94% sensitivity, 92% specificity
- PPV = 96%, NPV = 87%, F1 score of 0.949.

Proposed mechanisms of Neuro-long COVID



Neuroinflammation	Barrier Dysfunction	Vascular Dysfunction	Neurotransmitter Metabolism	Neurodegeneration
Activation of microglia and astrocytes	Compromised blood-brain barrier integrity	Endothelial damage, thrombosis	Elevated plasma kynurenine levels	Exacerbation of pre-existing Parkinson's Disease symptoms and pathology
Pro-inflammatory cytokine release	T cell infiltration	Fibrin-amyloid deposits	Impaired tryptophan absorption†	Dopamine neuron senescence and degeneration†
Synaptic remodeling†	Fibrinogen, immunoglobulin extravasation	Hypoxia, ischemic reperfusion injury	Low plasma serotonin	Accelerated progression of pre-existing Alzheimer's Disease
Alterations or damage to oligodendrocytes†	Direct infection of choroid plexus†	Altered brain glucose metabolism	Catecholamine deficiency	
Demyelination			Dysregulated dopamine synthesis†	

Moen, J. K., Baker, C. A., & Iwasaki, A. (2025). Neuroimmune pathophysiology of long COVID. *Psychiatry and Clinical Neurosciences*.

Proposed mechanisms of Neuro-long COVID

Persistent viral antigen, inflammation, and tissue damage.

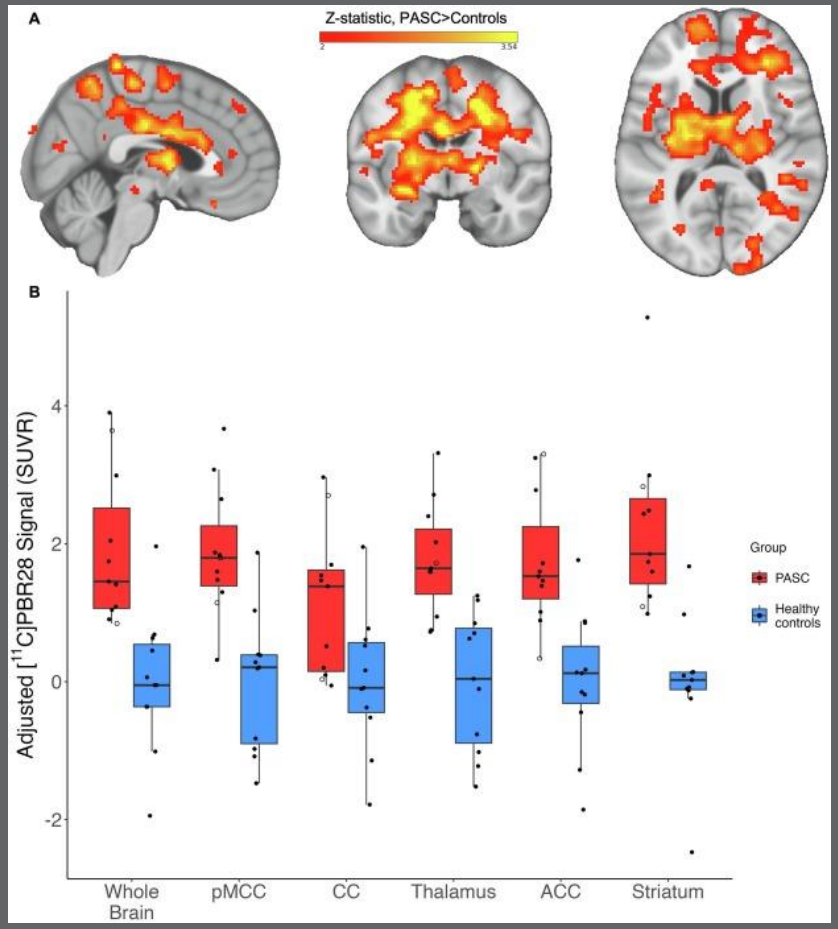
- Peluso et al – T cell activation in tissues
- Rong et al – Persistent spike protein in skull and meninges.
- Chaudhary et al - genetic polymorphisms in the immune system

Autoimmunity

- *Seibert et al - Severity of neuro-LC symptoms correlates with auto-Ab targeting vasoregulatory and autonomic receptors*
- *Chen & Wüst et al- IgG from pwLC induces symptomatology in mice.*

Neuroinflammation

- VanElzakker et al - PET with radioligand for TSPO showing upregulation in pw LC (glial activation)



Peluso et al 2024. *Science translational medicine*
Rong et al. 2024. Cell Host Microbe.
Spatola et al 2024 *Preprint*
VanElzakker MB et al. 2024. Brain Behav. Immun

Proposed mechanisms of Neuro-long COVID

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Neurotransmitter dysfunction

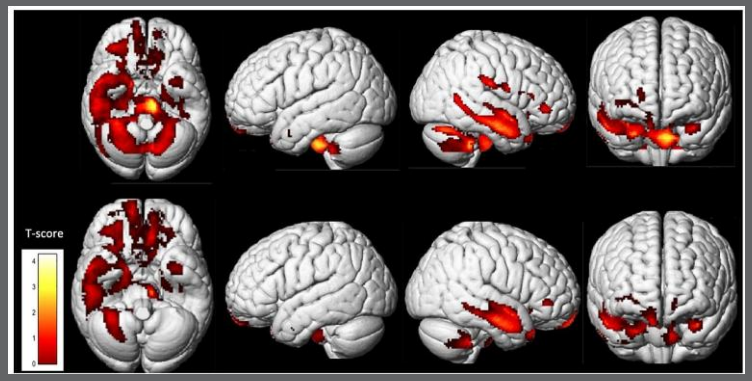
- *Bizjak et al - Elevated levels of kynurenine, blood and saliva*
- *Wong et al - Low serum serotonin*
- *Goldstein et al - Catecholamine deficiency in CSF at 1yr post-infection*

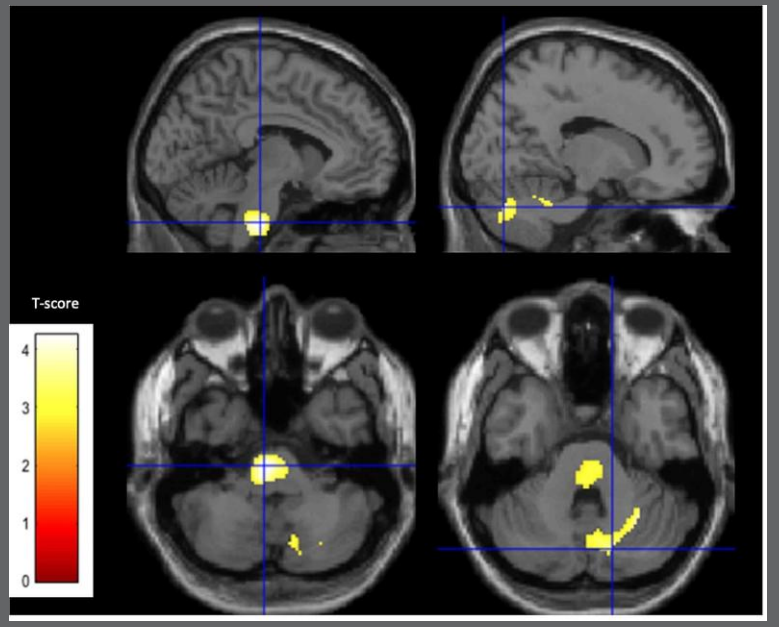
Endothelial damage and Neurovascular coupling

- Horowitz et al - Hypometabolism in the cortex, brainstem and cerebellum of pwLC

BBB Dysfunction

- Chaganti et al – BBB disruption at 3- and 12-months post-infection (LC=14, HC=10)
- Invasive MRI techniques





Bizjak Daetal. 2022. Frontiers Immunology
Goldstein et al 2024. Neurology
Chaganti, J. et al. 2024. Frontiers Neurology
Gupta, A. et al. 2024. Brain Imaging and Behavior
Reas, E.T. et al. 2025. Imaging Neuroscience
Horowitz et al. 2024 Eur. J. Nucl. Med. Mol. Imaging

Blood-Brain barrier disruption in long COVID and cognitive correlates: A cross-sectional MRI study

Leah H. Rubin [a,b,c,d,1,*], Wen Shi [e,f,1], Alba Azola [g,h,1], Aparna Bhattacharyya [a], Raha M. Dastgheyb [a], Jiani Wu [e,f], Christina Della Penna [a], Hannah Parker [a], Isabel Santiuste [a], Ana Ehrenspeck [b], Jennifer M. Coughlin [a,b], Tracy D. Vannorsdall [b], Hanzhang Lu [e,f,1,*], Rebecca Veenhuis [a,c,1,**]

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Objectives

- Investigate BBB permeability in LC patients using WEPCAST MRI.
- Compare the LC group to the SARS-CoV-2-infected recovered controls.
- Correlate BBB disruption with cognitive function
  - Multidomain cognitive battery
- We hypothesized that greater permeability in those with LC would be associated with poorer cognitive function.

Water-extraction-with-phase-contrast-arterial-spin-tagging (WEPCAST) MRI

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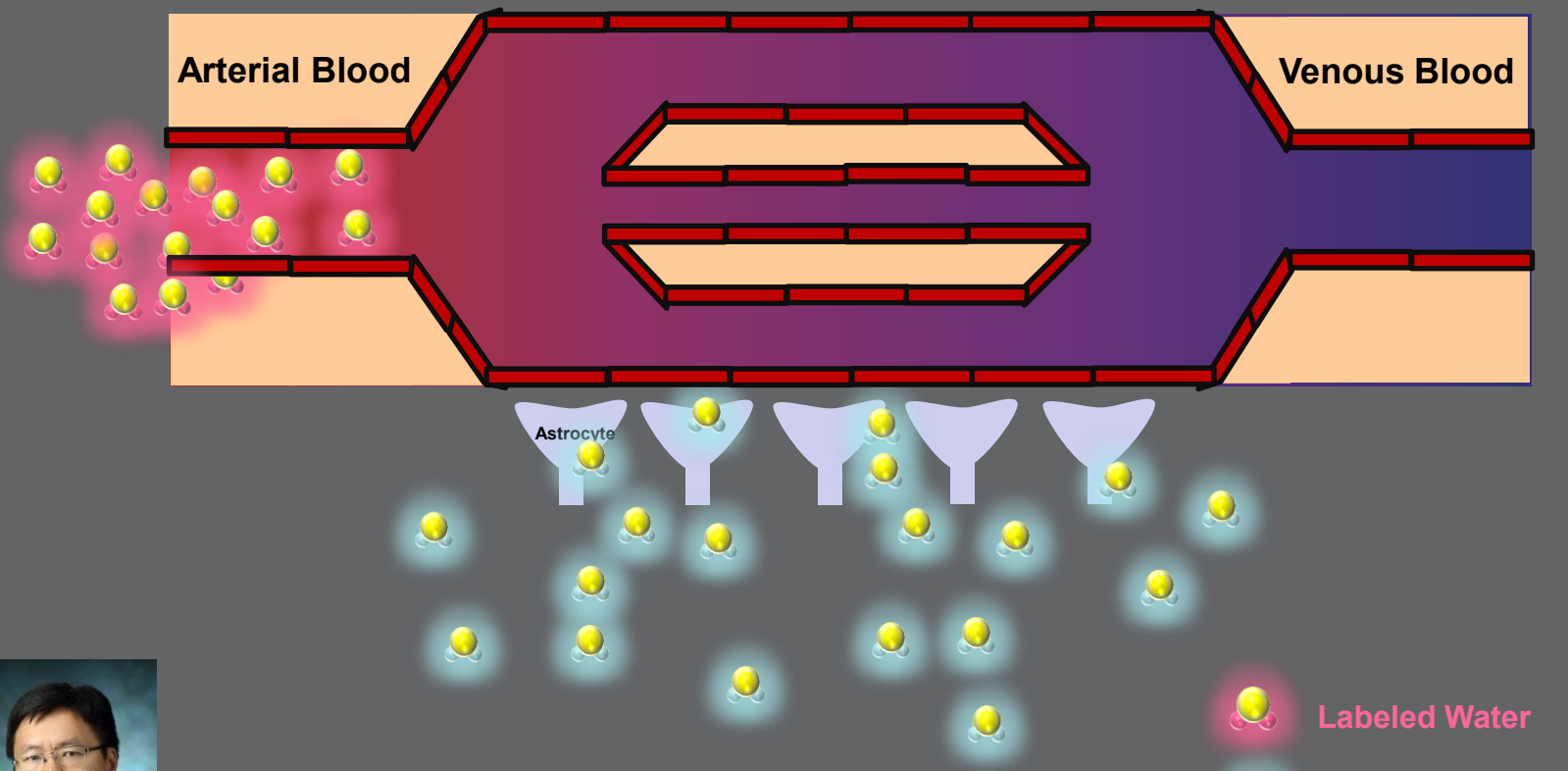

Dr. Hanzang Lu

Lin Z, *et al*. Magn. Res. Med. 2018

Water-extraction-with-phase-contrast-arterial-spin-tagging (WEPCAST) MRI

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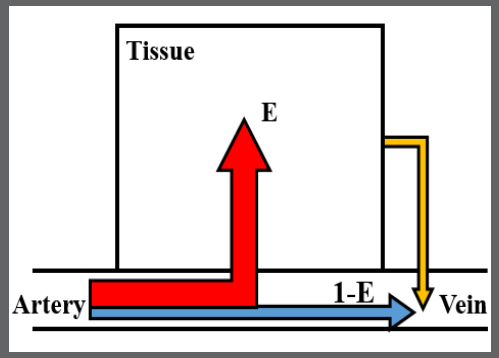

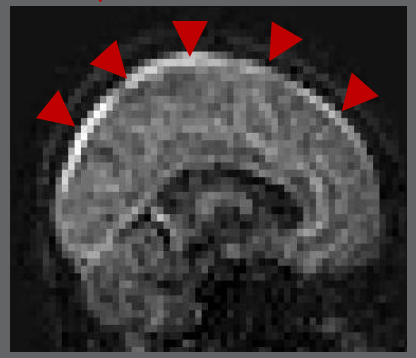

Permeability Surface-Area Product (PS)

per unit mass of tissue

$$PS = -\ln(1 - E) \times f$$

cerebral blood flow

Dr. Hanzang Lu

Lin Z, *et al*. Magn. Res. Med. 2018

Results

	Long COVID (LC)	Controls	P
N	97	31	
Age	47 yr (SD = 13)	39 yr (SD = 13)	0.003
Female	76%	55%	0.04
Education	17 yr	18 yr	0.02
Index infection	34.6 mo (SD =11.6)	30.1 mo (SD =13.7)	
Hospitalized for Acute COVID	15%	0%	0.02
Vaccination Status	96%	97%	0.99
PASC Score +	78%	1%	<0.001

- **LC group higher rates of**
  - MDD, PTSD & panic disorders
  - Childhood trauma
    - Emotional abuse & neglect
  - Autoimmune disease
  - Asthma
  - Hypertension

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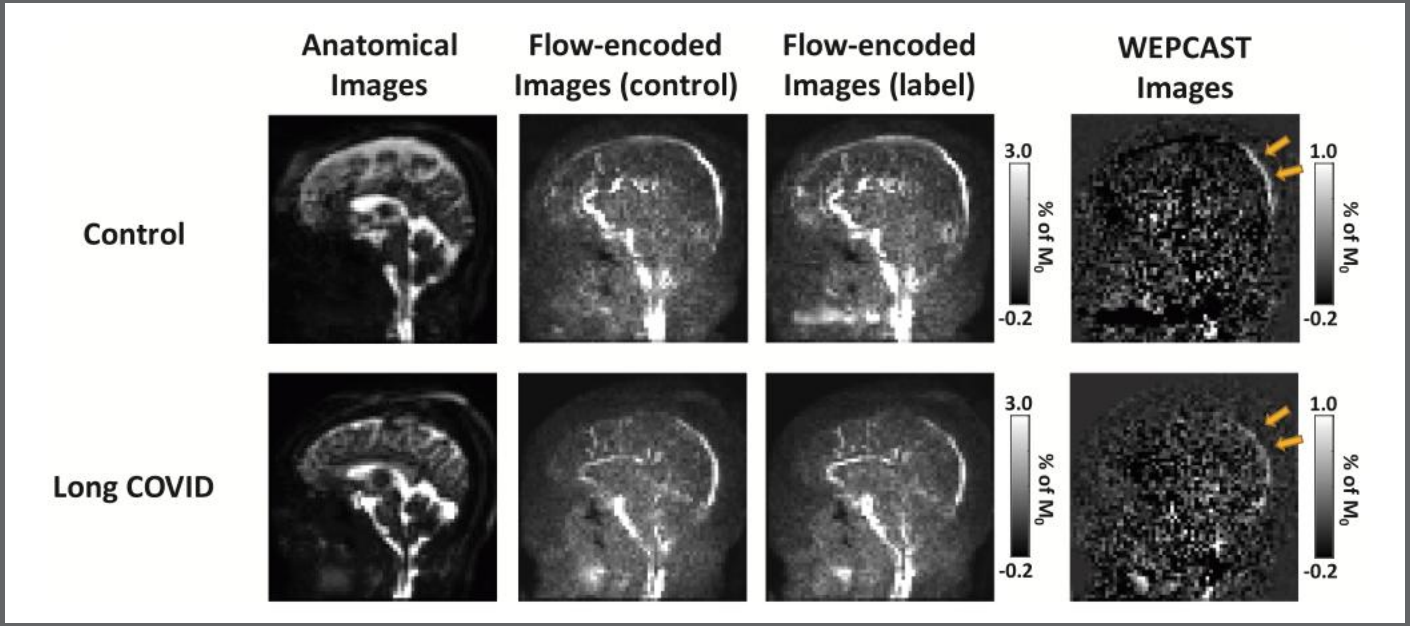
  - Hypertension

Results

- **Disability**: 45% of LC participants

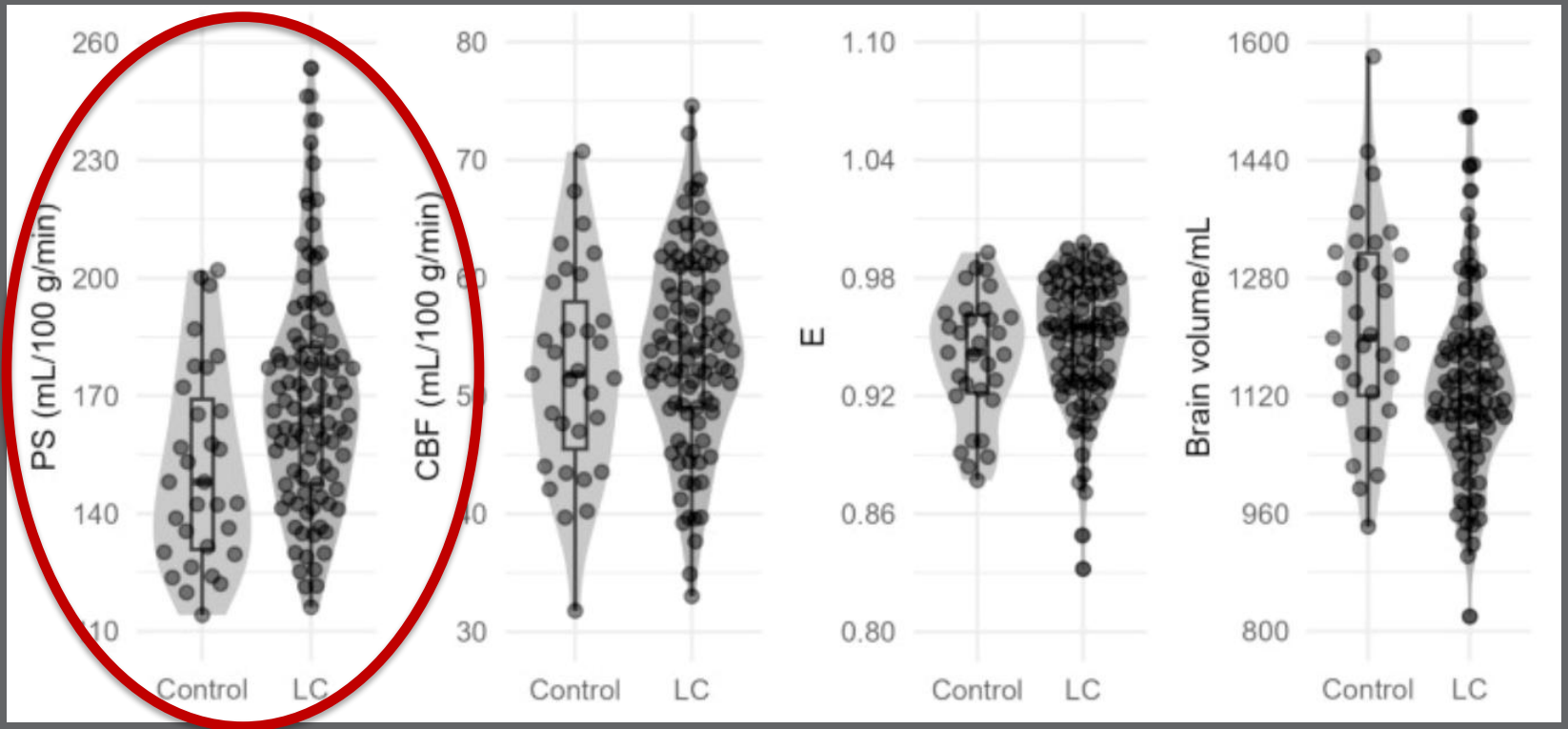
- Of those with disability:
  - 81% had difficulty concentrating, remembering, or making decisions
  - 73% had serious difficulty walking or climbing stairs
  - 73% had difficulty performing errands alone
  - 45% had difficulty dressing or bathing

Results



Rubin, L. H., Shi, W., Azola, A., Bhattacharyya, A., Dastgheyb, R. M., Wu, J., ... & Veenhuis, R. (2025). Blood-Brain barrier disruption in long COVID and cognitive correlates: A cross-sectional MRI study. *Brain, Behavior, and Immunity*.

Results



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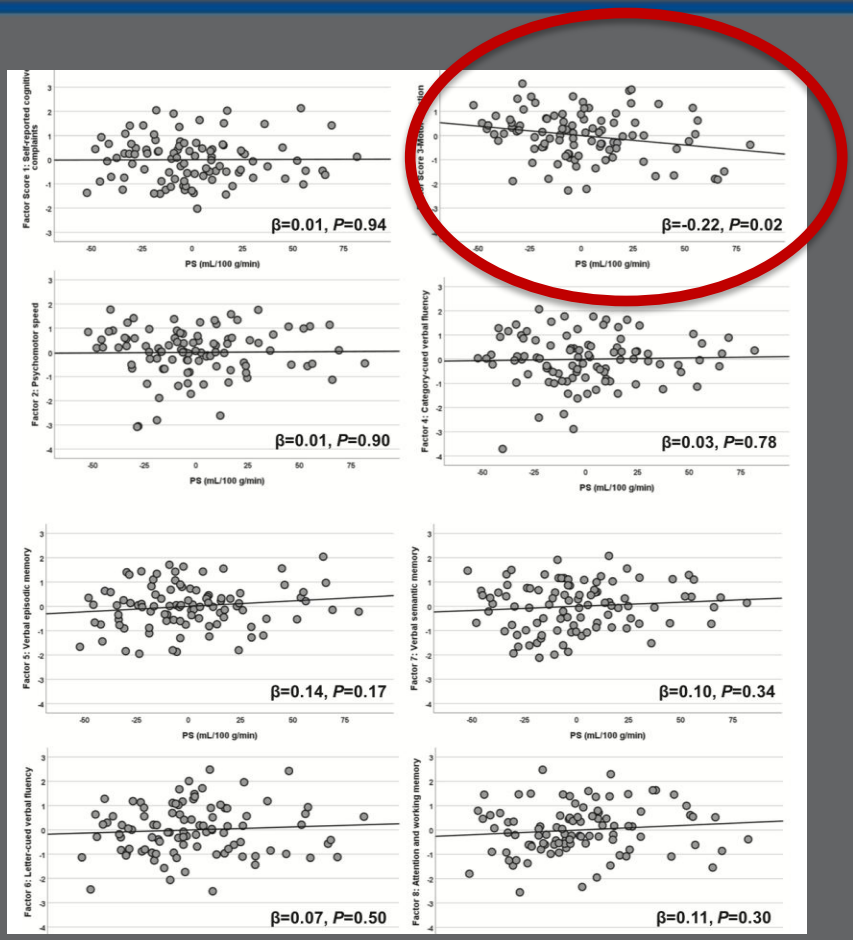
Results

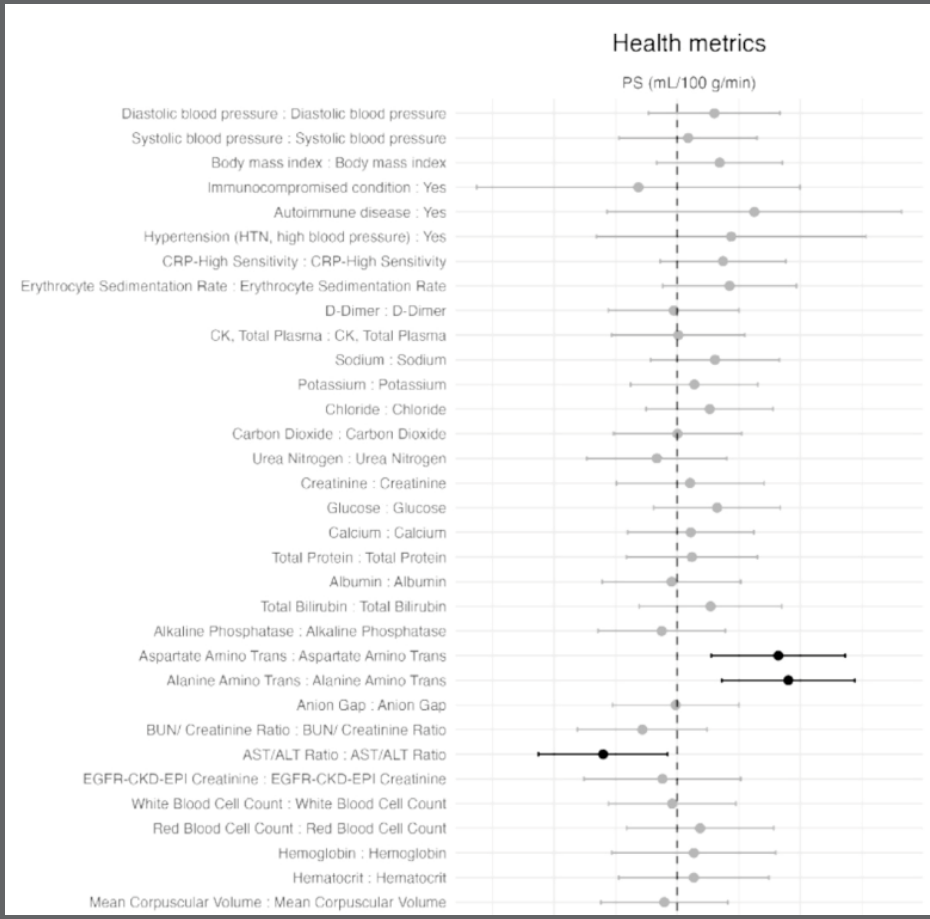
PS is significantly higher in LC group vs. controls

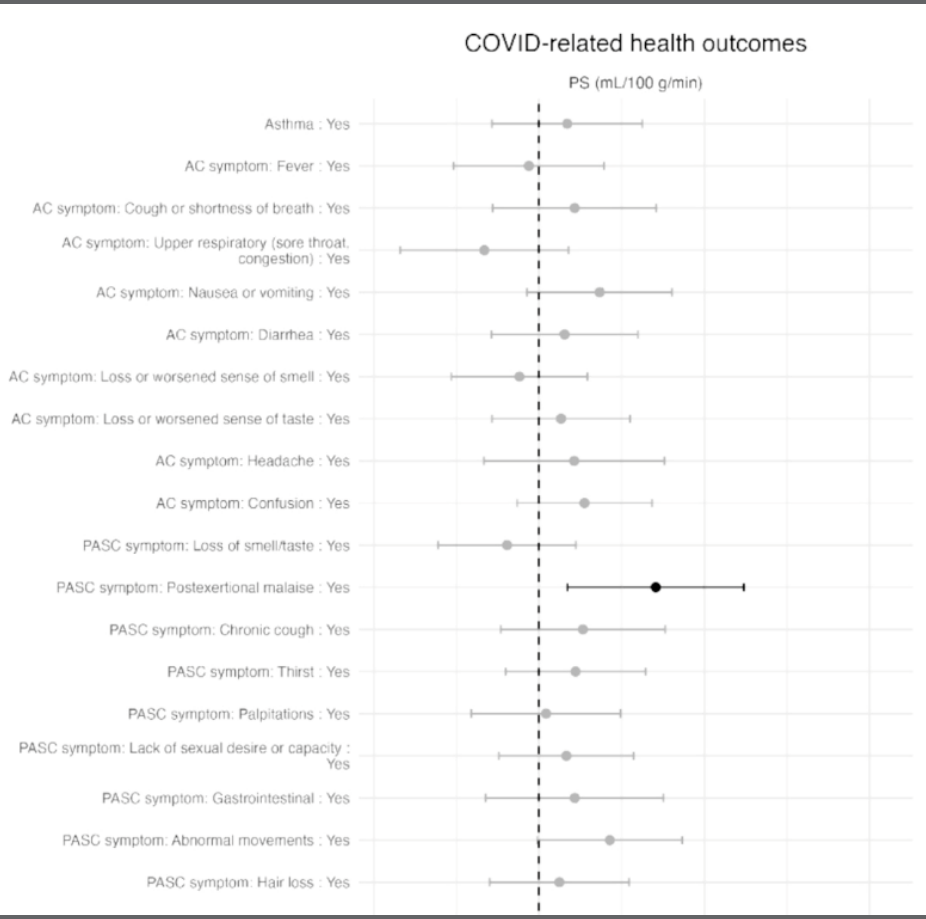
- Adjusting for age and sex (P = 0.003).
- COVID-19 hospitalization (B = 16.47, P = 0.009)
  - Acute symptoms (nausea, loss/altered taste, confusion) (P = 0.035)

- **Within LC Group**:
  - Higher PS correlated with poorer motor function (P=0.02)
    - After adjusting for age, sex, race, and education.
  - No associations between PS and other cognitive domains.



Results


Health metrics
PS (mL/100 g/min)
Diastolic blood pressure : Diastolic blood pressure
Systolic blood pressure : Systolic blood pressure
Body mass index : Body mass index
Immunocompromised condition : Yes
Autoimmune disease : Yes
Hypertension (HTN, high blood pressure) : Yes
CRP-High Sensitivity : CRP-High Sensitivity
Erythrocyte Sedimentation Rate : Erythrocyte Sedimentation Rate
D-Dimer : D-Dimer
CK, Total Plasma : CK, Total Plasma
Sodium : Sodium
Potassium : Potassium
Chloride : Chloride
Carbon Dioxide : Carbon Dioxide
Urea Nitrogen : Urea Nitrogen
Creatinine : Creatinine
Glucose : Glucose
Calcium : Calcium
Total Protein : Total Protein
Albumin : Albumin
Total Bilirubin : Total Bilirubin
Alkaline Phosphatase : Alkaline Phosphatase
Aspartate Amino Trans : Aspartate Amino Trans
Alanine Amino Trans : Alanine Amino Trans
Anion Gap : Anion Gap
BUN/ Creatinine Ratio : BUN/ Creatinine Ratio
AST/ALT Ratio : AST/ALT Ratio
EGFR-CKD-EPI Creatinine : EGFR-CKD-EPI Creatinine
White Blood Cell Count : White Blood Cell Count
Red Blood Cell Count : Red Blood Cell Count
Hemoglobin : Hemoglobin
Hematocrit : Hematocrit
Mean Corpuscular Volume : Mean Corpuscular Volume


COVID-related health outcomes
PS (mL/100 g/min)
Asthma : Yes
AC symptom: Fever : Yes
AC symptom: Cough or shortness of breath : Yes
AC symptom: Upper respiratory (sore throat, congestion) : Yes
AC symptom: Nausea or vomiting : Yes
AC symptom: Diarrhea : Yes
AC symptom: Loss or worsened sense of smell : Yes
AC symptom: Loss or worsened sense of taste : Yes
AC symptom: Headache : Yes
AC symptom: Confusion : Yes
PASC symptom: Loss of smell/taste : Yes
PASC symptom: Postexertional malaise : Yes
PASC symptom: Chronic cough : Yes
PASC symptom: Thirst : Yes
PASC symptom: Palpitations : Yes
PASC symptom: Lack of sexual desire or capacity : Yes
PASC symptom: Gastrointestinal : Yes
PASC symptom: Abnormal movements : Yes
PASC symptom: Hair loss : Yes

Conclusion & Implications

- Study supports BBB involvement in Long COVID.
- Motor function may be more sensitive to BBB breakdown.
- WEPCAST MRI is a promising, non-invasive method for future LC diagnostics.
- Supports use of BBB permeability as a potential LC biomarker.

Study Limitations

- Cross-sectional design limits causality inference.
- Global (not regional) BBB measurements via WEPCAST.
- Sample size limits subgroup analysis.
- Convenience sampling may limit generalizability.

Next Steps

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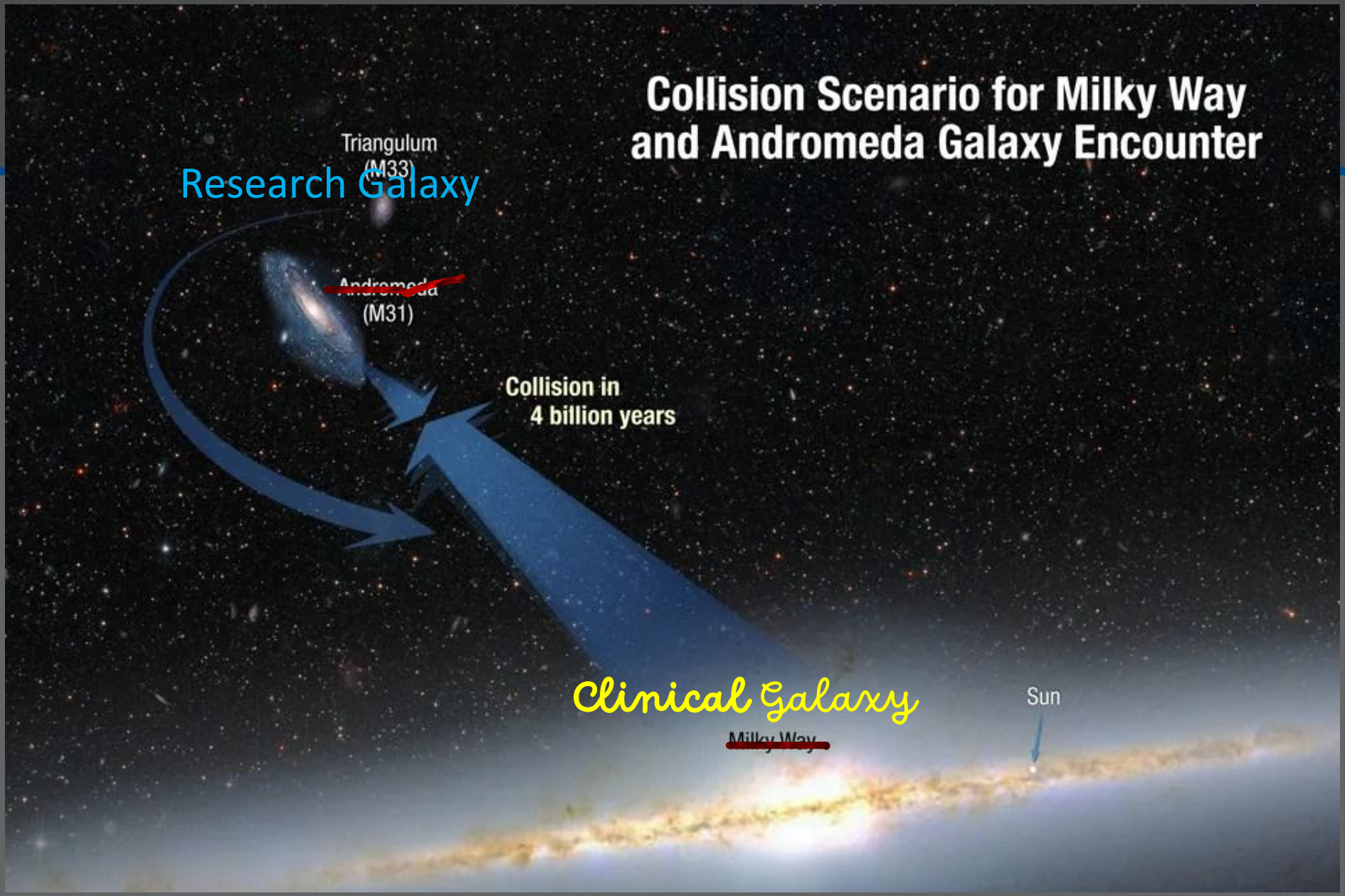
- Analysis of blood samples for immune signatures
- Adding pre-pandemic ME/CFS cohort
- Refine the WEPCAST technique to allow for the assessment of regional disruption of the BBB


Collision Scenario for Milky Way and Andromeda Galaxy Encounter
Triangulum (M33)
Research Galaxy
(M31)
Collision in 4 billion years
Clinical Galaxy
Sun

JHU-UTSW Brain Health Program (BHP)

co-directors: Leah H. Rubin, PhD, MPH & Jennifer M. Coughlin, MD

Data Science and Mathematical Modeling (DSMM)

Co-directors: Yanxun Xu, PhD & Raha M. Dastgheyb, PhD

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Trainees:
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- K Ridgeway, PhD
- Wei Jin, PhD
- Lang Lang, PhD candidate
- Jonathan Xi-Yao Ye, BS candidate
- Wenxuan Lu, PhD candidate
- Avery Ye, BS candidate
- Cesar Higgins Tejera, PhD
- Aparna Bhattacharyya, PhD
- Eero Korpela, PhD student
- Sehee Park, PhD student
- Wenxuan Lu, PhD student

Molecular and Translational Immunology (MTI)

Director: Rebecca Veenhuis, PhD

Team:
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- Katherine Haas, BS
- Hayley Romero, BS
- Lily Pohlenz, BS
- Jordin Dixson, BS

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- Edna Ferreira, PhD candidate
- Mimi Zipparo, PhD candidate
- James Wang, ScM candidate

Clinical and Translational Research (CARE)

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Trainees:
- Rebecca Easter, PhD
- Julia Denniss, MD, Neurology resident

Coordinators by Study:

JHU CAHN-Clinical Outcomes Core Cohort:
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- Ariadni Xydia, BS

CHARTER PLUS: JHU site
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- Hanniel Uwadia, BA
- Akaia Davis, BA candidate

BRAIN
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- Hannah Parker, BA
- Thordar Han, BS
- Emily Lu, BA
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- Madeline Brooks, PhD Candidate

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- Holly Schultz, MS
- Sofia Karras, BA
- Hannah Parker, BA
- Oluwatoyosi Fowowe, BS candidate

COCAINE-BRAIN
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- Katelyn Jenkins, BS
- Riley Ricci, BA

IMPACT
- Olivia Fox, BS
- Erika Guo, BA
- Natalie Smith, BS candidate

https://www.hopkinsmedicine.org/neurology-neurosurgery/specialty-areas/brain-health-program

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THANK YOU!

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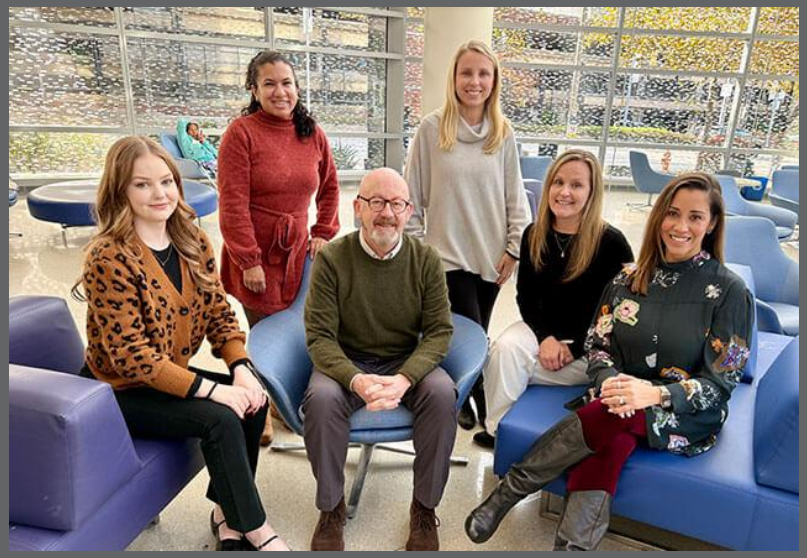
- Grants from Solve ME/CFS Initiative
- Sunshine Natural Wellbeing Foundation
- Boies Family and Allison Caldwell endowed Funds
- **Rowe's Research Runners**--Emily Steffensmeier
- Many, many families and patients



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