COVID-19, Brain and Inflammation

Jordi Matias-Guiu

Department of Neurology.
Hospital Clínico San Carlos. Madrid.
Instituto de Investigación Sanitaria San Carlos (IdISSC).
Madrid, Spain

@MatiasGuiu
@iNeuroClinico

IdISSC INSTITUTO de INVESTIGACIÓN SANITARIA Hospital Clínico San Carlos

SaludMadrid Hospital Clínico San Carlos

Comunidad de Madrid

COVID-19, Brain and Inflammation

1. **Does SARS-CoV-2 actually affect the brain?**
2. **How does SARS-CoV-2 cause brain dysfunction? Does inflammation play a role?**

Does SARS-CoV-2 actually affect the brain?

Acute neurological complications

Neurological symptoms	Neurological manifestations and complications
Gustatory dysfunctions (38.5%)	Stroke (2.3%)
Olfactory dysfunctions (hyposmia/anosmia) (35.8%)	Epilepsy and seizures (0.9%)
Myalgia (19.3%)	Cerebral venous (sinus) thrombosis (0.3%)
Headache (14.7%)	
Altered mental status (9.4%) [5, 117]	

Harapan & Yoo *J Neurol* 2021

Neuropathology

Neuropathology of patients with COVID-19 in Germany: a post-mortem case series

Jakob Matschke, Marc Lütgehetmann, Christian Hagel, Jan P Sperhake, Ann Sophie Schröder, Carolin Edler, Herbert Mushumba, Antonia Fitzek, Lena Allweiss, Maura Dandri, Matthias Dottermusch, Axel Heinemann, Susanne Pfefferle, Marius Schwabenland, Daniel Sumner Magruder, Stefan Bonn, Marco Prinz, Christian Gerloff, Klaus Püschel, Susanne Krasemann, Martin Aepfelbacher, Markus Glatzel

Summary

Background Prominent clinical symptoms of COVID-19 include CNS manifestations. However, it is unclear whet

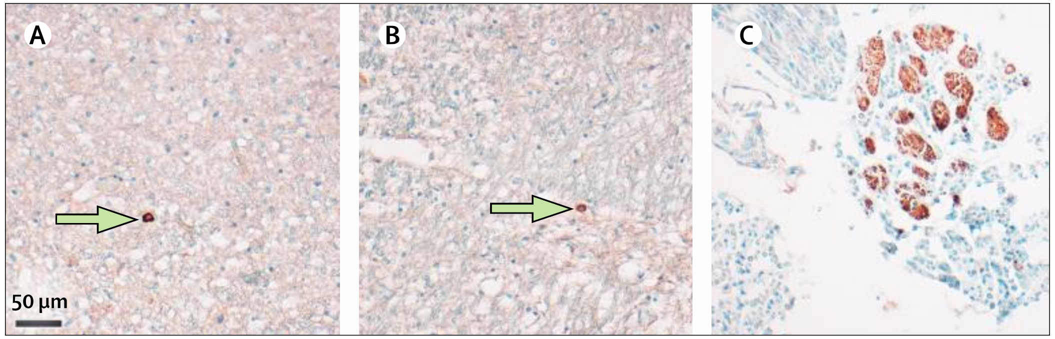
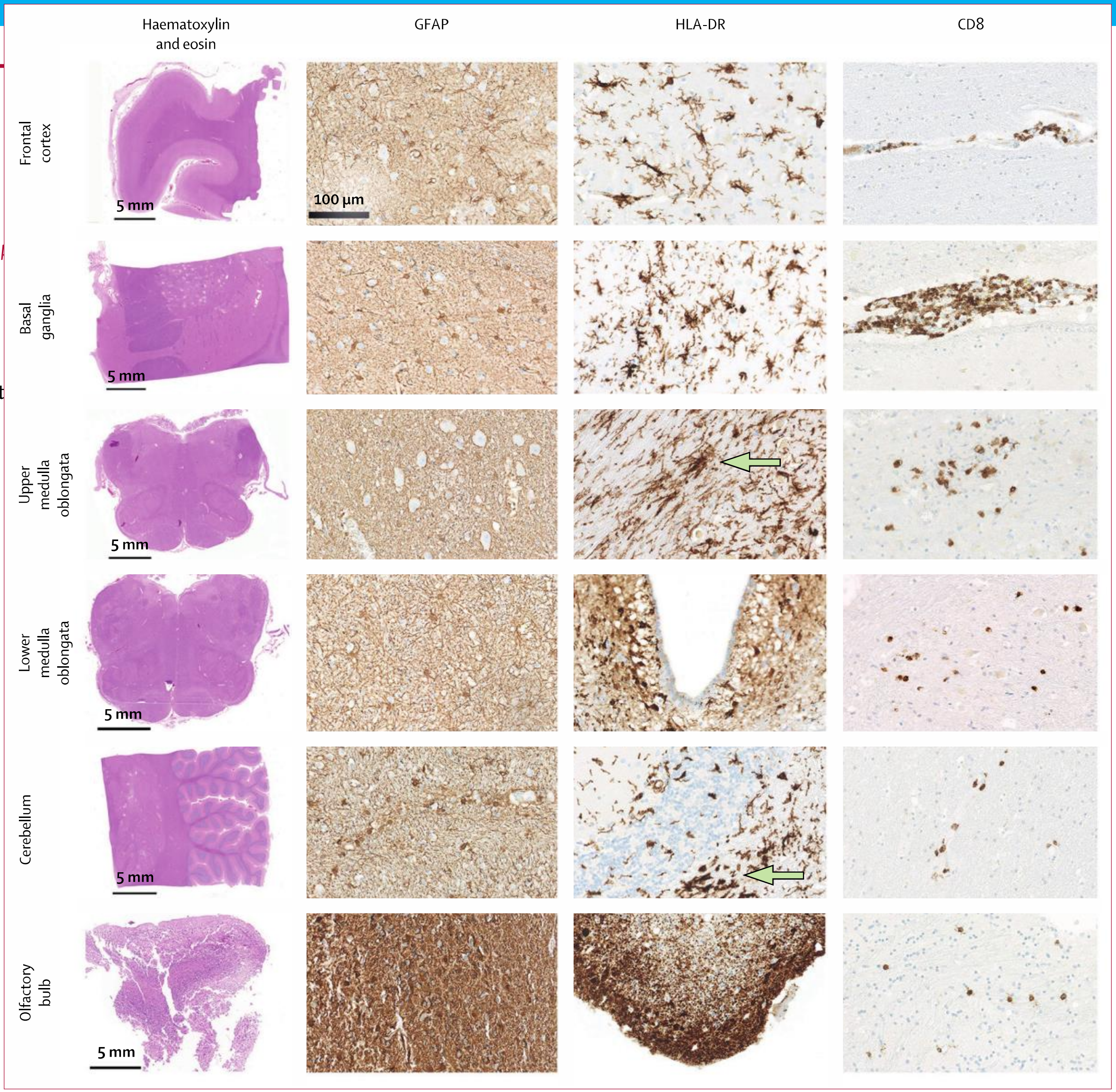
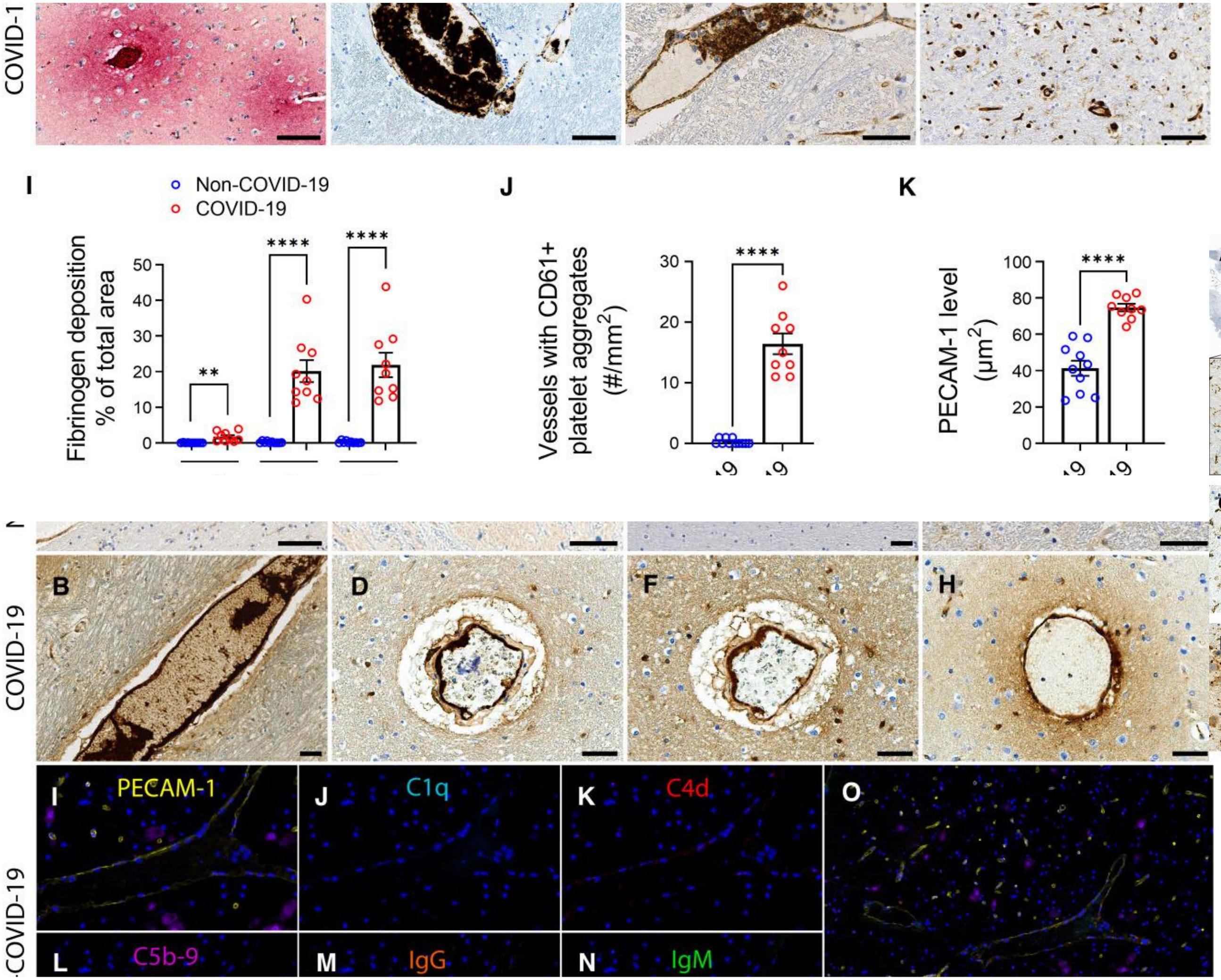


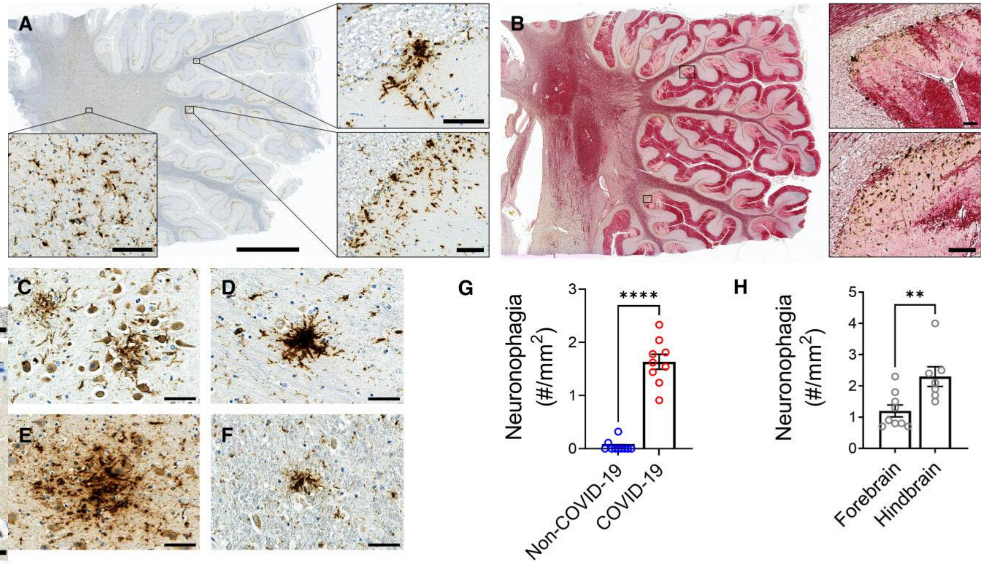
Figure 5: Distribution of SARS-CoV-2 within the CNS



Neuropathology



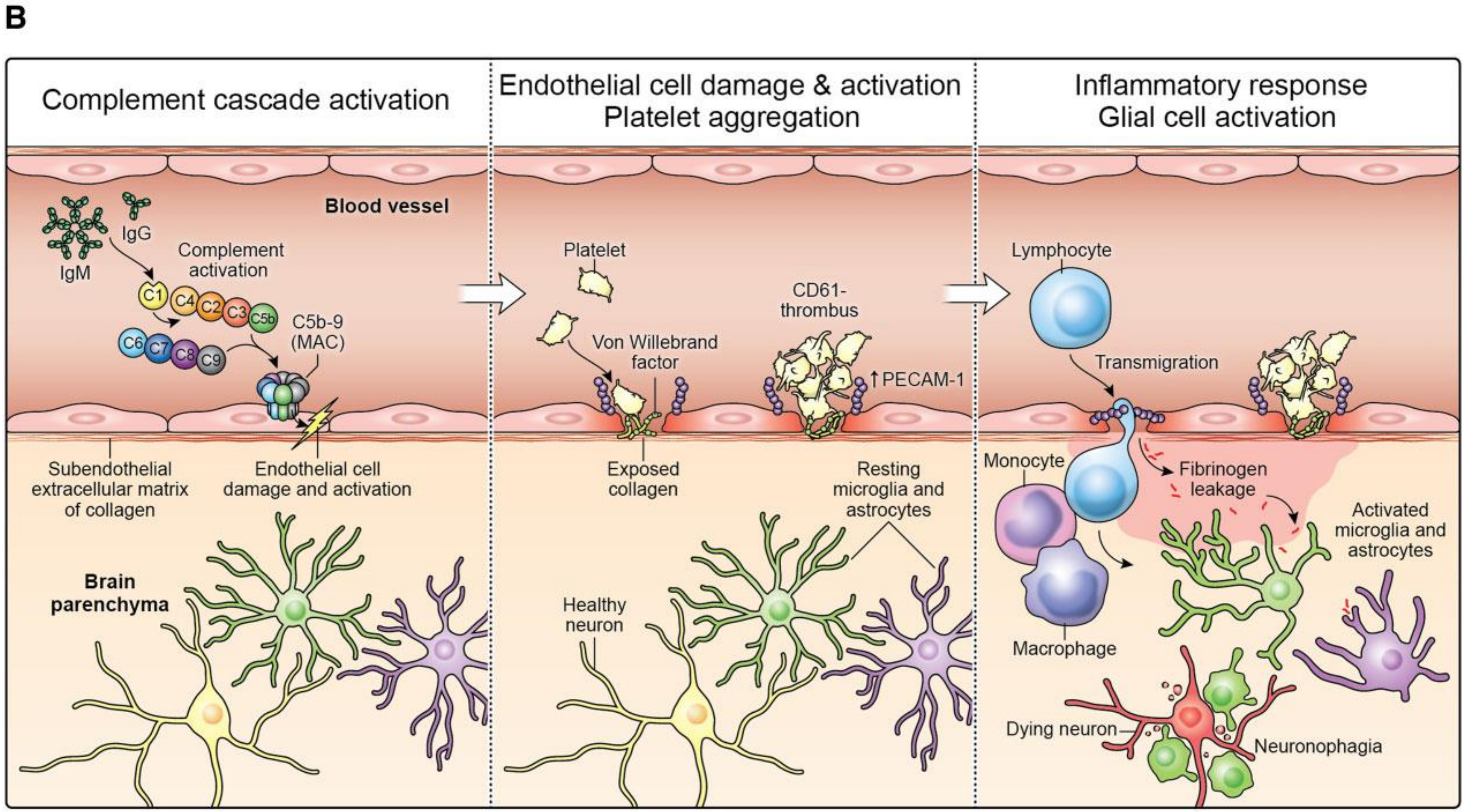
9 patients died due to COVID-19 (only one in ICU)



"All techniques failed to detect any virus in the brain, including regions where there were obvious signs of inflammation"

Lee, Perl et al. *Brain* 2022

Neuropathology



Lee, Perl et al. *Brain* 2022

Long Covid Criteria

Post COVID-19 condition occurs in individuals with **a history of probable or confirmed SARS-CoV-2** infection, **usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.** Common symptoms include **fatigue, shortness of breath, cognitive dysfunction** but also others (see Table 3 and Annex 2) which generally have an **impact on everyday functioning.** Symptoms may be **new onset,** following initial recovery from an acute COVID-19 episode, or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time. A separate definition may be applicable for children.

WHO criteria October 2021

Long COVID symptoms

General symptoms
- Tiredness or fatigue that interferes with daily life
- Post-exertional malaise
- Fever

Respiratory and heart symptoms
- Difficulty breathing or shortness of breath
- Cough
- Chest pain
- Fast-beating or pounding heart (also known as heart palpitations)

Digestive symptoms
- Diarrhea
- Stomach pain

Neurological symptoms
- Difficulty thinking or concentrating (sometimes referred to as “brain fog”)
- Headache
- Sleep problems
- Dizziness when you stand up (lightheadedness)
- Pins-and-needles feelings
- Change in smell or taste
- Depression or anxiety

Other symptoms
- Joint or muscle pain
- Rash
- Changes in menstrual cycles

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Cognitive dysfunction

Brain, Behavior, & Immunity - Health 9 (2020) 100163

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

ELSEVIER

Full Length Article

Cognitive profile following COVID-19 infection: Clinical predictors leading to neuropsychological impairment

M. Almeria [a,*], J.C. Cejudo [b], J. Sotoca [c], J. Deus [d,e,**], J. Krupinski [c]

[a] Cognition and Behavior Unit, Department of Neurology, Hospital Universitari MútuaTerrassa, Terrassa, Barcelona, Spain
[b] Cognitive Impairment and Dementia Unit, Hospital Sagrat Cor, Hermanas Hospitalarias, Martorell, Barcelona, Spain
[c] Department of Neurology, Hospital Universitari MútuaTerrassa, Terrassa, Barcelona, Spain
[d] Clinical and Health Department, Psychology Faculty, Autonomus University of Barcelona, Barcelona, Spain
[e] MRI Research Unit, Hospital del Mar, Barcelona, Spain

Received: 11 August 2021 | Revised: 27 December 2021 | Accepted: 5 January 2022

DOI: 10.1002/brb3.2508

Brain and Behavior Open Access WILEY

ORIGINAL ARTICLE

Neuropsychological deficits in patients with cognitive complaints after COVID-19

Carmen García-Sánchez[1] | Marco Calabria[2] | Nicholas Grunden[3] | Catalina Pons[4] | Juan Antonio Arroyo[5] | Beatriz Gómez-Anson[6] | Alberto Lleó[7] | Daniel Alcolea[7] | Roberto Belvís[8] | Noemí Morollón[8] | Isabel Mur[9] | Virginia Pomar[9] | Pere Domingo[9]

ANNALS of Clinical and Translational Neurology

Open Access

ANA AMERICAN NEUROLOGICAL ASSOCIATION INNOVATORS IN DISCOVERY, EDUCATION, AND CARE

RESEARCH ARTICLE

Persistent neurologic symptoms and cognitive dysfunction in non-hospitalized Covid-19 "long haulers"

Edith L. Graham, Jeffrey R. Clark, Zachary S. Orban, Patrick H. Lim, April L. Szymanski, Carolyn Taylor, Rebecca M. DiBiase, Dan Tong Jia, Roumen Balabanov, Sam U. Ho, Ayush Batra, Eric M. Liotta & Igor J. Koralnik

Davee Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

PLOS ONE

Cognitive function in non-hospitalized patients 8–13 months after acute COVID-19 infection: A cohort study in Norway

Knut Stavem[1,2,3]*, Gunnar Einvik[1,3], Birgitte Tholin[3,4], Waleed Ghanima[3,4], Erik Hessen[5,6], Christofer Lundqvist[3,5]

Cognitive dysfunction

OXFORD
UNIVERSITY PRESS

Archives of Clinical Neuropsychology 00 (2022) 1–9

Archives of CLINICAL NEUROPSYCHOLOGY

Neurocognitive Profiles in Patients With Persisting Cognitive Symptoms Associated With COVID-19

Kamini Krishnan[1,2,*], Ashley K. Miller[1], Katherine Reiter[1,2] and Aaron Bonner-Jackson[1,2]

[1] *Department of Neurology, Cleveland Clinic, Cleveland, OH, USA*
[2] *Lou Ruvo Center for Brain Health, Cleveland Clinic, Cleveland, OH, USA*

*Corresponding author at: 9500 Euclid Avenue, P 57, Cleveland, OH 44195, USA. Tel.: 216-445-1637; fax: 216-444-4525.
E-mail address: krishnk3@ccf.org (K. Krishnan)

Accepted 10 January 2022

CORTEX 152 (2022) 77–97

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Journal homepage: www.elsevier.com/locate/cortex

Review

COVID-19 associated cognitive impairment: A systematic review

Check for updates

José W.L. Tavares-Júnior [a,], Ana C.C. de Souza [b], José W.P. Borges [c], Danilo N. Oliveira [a], José I. Siqueira-Neto [a], Manoel A. Sobreira-Neto [a] and Pedro Braga-Neto [d]*

Journal of Neurology
https://doi.org/10.1007/s00415-022-11077-z

ORIGINAL COMMUNICATION

Check for updates

Long-term cognitive impairments following COVID-19: a possible impact of hypoxia

Thibaut Dondaine[1,4] · Florine Ruthmann[1] · Fanny Vuotto[2] · Louise Carton[1,4] · Patrick Gelé[1] · Karine Faure[2,3] · Dominique Deplanque[1,4] · Régis Bordet[1,4]

Frontiers in Aging Neuroscience

TYPE Original Research
PUBLISHED 20 October 2022
DOI 10.3389/fnagi.2022.1029842

Neuropsychological impairment in post-COVID condition individuals with and without cognitive complaints

Mar Ariza[1,2,3], Neus Cano[1,3], Bàrbara Segura[1,2,4,5], Ana Adan[2,6], Núria Bargalló[4,7,8], Xavier Caldú[2,6,9], Anna Campabadal[1,2,4], Maria Angeles Jurado[2,6,9], Maria Mataró[2,6,9], Roser Pueyo[2,6,9], Roser Sala-Llonch[2,4,10,11], Cristian Barrué[12], Javier Bejar[12], Claudio Ulises Cortés[12], NAUTILUS-Project Collaborative Group, Carme Junqué[1,2,4,5] and Maite Garolera[3,13*]

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Cognitive dysfunction

Journal of Psychiatric Research 150 (2022) 40–46

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

ELSEVIER

Check for updates

Cognitive dysfunction associated with COVID-19: A comprehensive neuropsychological study

Cristina Delgado-Alonso [a], Maria Valles-Salgado [a], Alfonso Delgado-Álvarez [a], Miguel Yus [b], Natividad Gómez-Ruiz [b], Manuela Jorquera [b], Carmen Polidura [b], María José Gil [a], Alberto Marcos [a], Jorge Matías-Guiu [a], Jordi A. Matías-Guiu [a,*]

3 days of cognitive assessment: standard paper-and-pencil battery and computerized battery

MRI

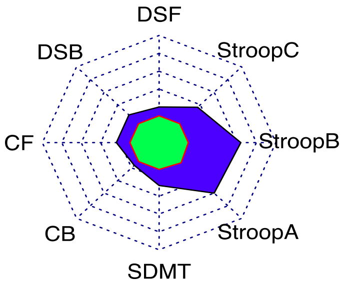
2 control groups:
-National normative data
-Matched healthy control group

Table 1
Main demographic and clinical characteristics during the acute phase.

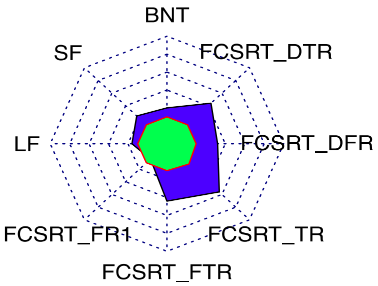
Demographics	Age	51.06 ± 11.65	
	Sex (% women)	37 (74%)	
	Years of education	13.58 ± 4.01	
	Handedness	100% Right	
	Arterial hypertension	14 (28%)	
	Diabetes mellitus	8 (16%)	
	Dyslipidemia	16 (32%)	
	Tobacco smoking	4 (16%)	
COVID history	Time from diagnosis of COVID-19 to assessment (months)	9.42 ± 3.54	
	Anosmia or ageusia	36 (72%)	
	Headache	42 (84%)	
	Confusion	23 (46%)	
	Hospitalization	18 (36%)	
	Days of hospitalization	19.06 ± 15.53	
	ICU	5 (10%)	
	Ventilatory assistance	4 (8%)	
MRI findings	Fazekas scale	Grade 0	47 (94%)
		Grade 1	3 (6%)
		Grade 2-3	0 (0%)
	Presence of microbleeds	2 (4%)	

Cognitive dysfunction

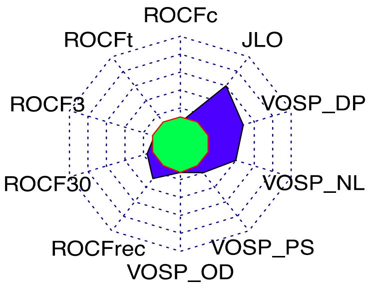
Attention



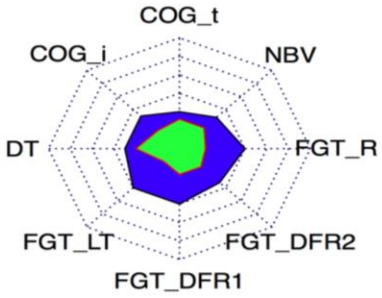
Language, verbal fluency and verbal memory



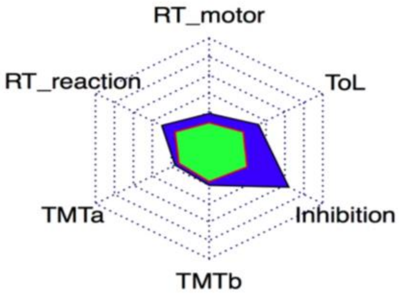
Visuospatial and visuoperceptive function



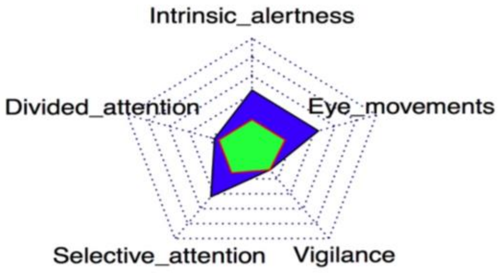
COGBAT (I)



COGBAT (II)



WAF



Cognitive dysfunction

Psychiatry Research 319 (2023) 115006

Contents lists available at ScienceDirect

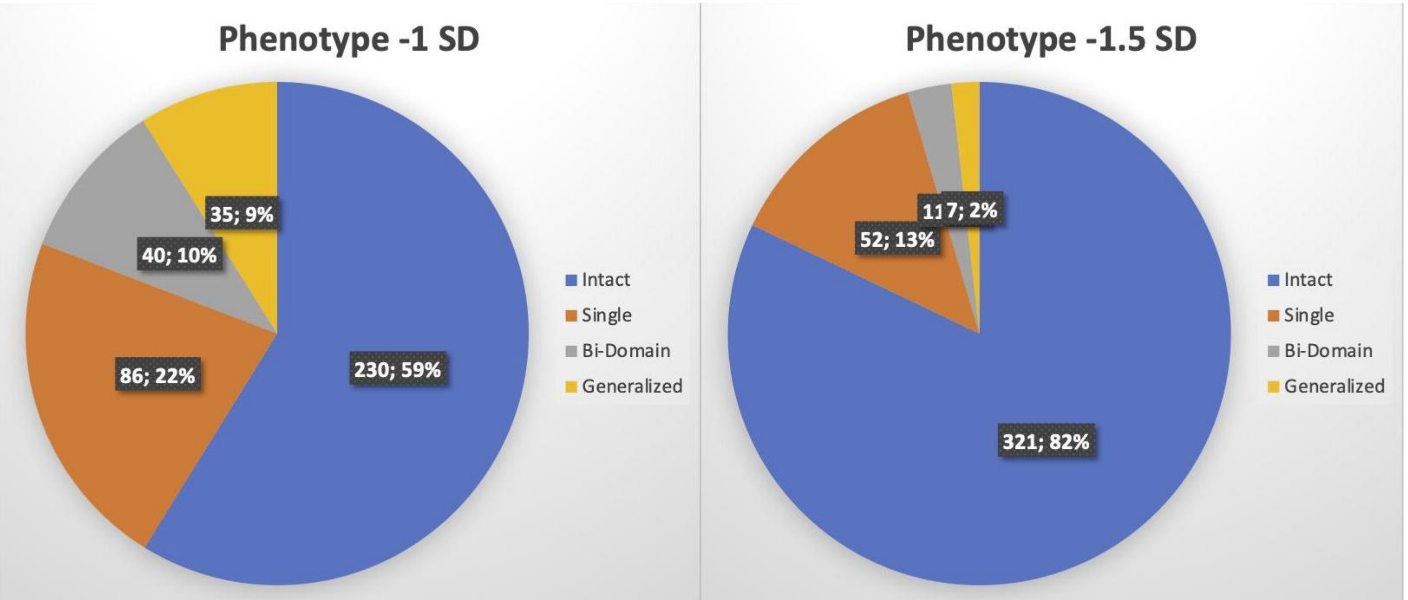
Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

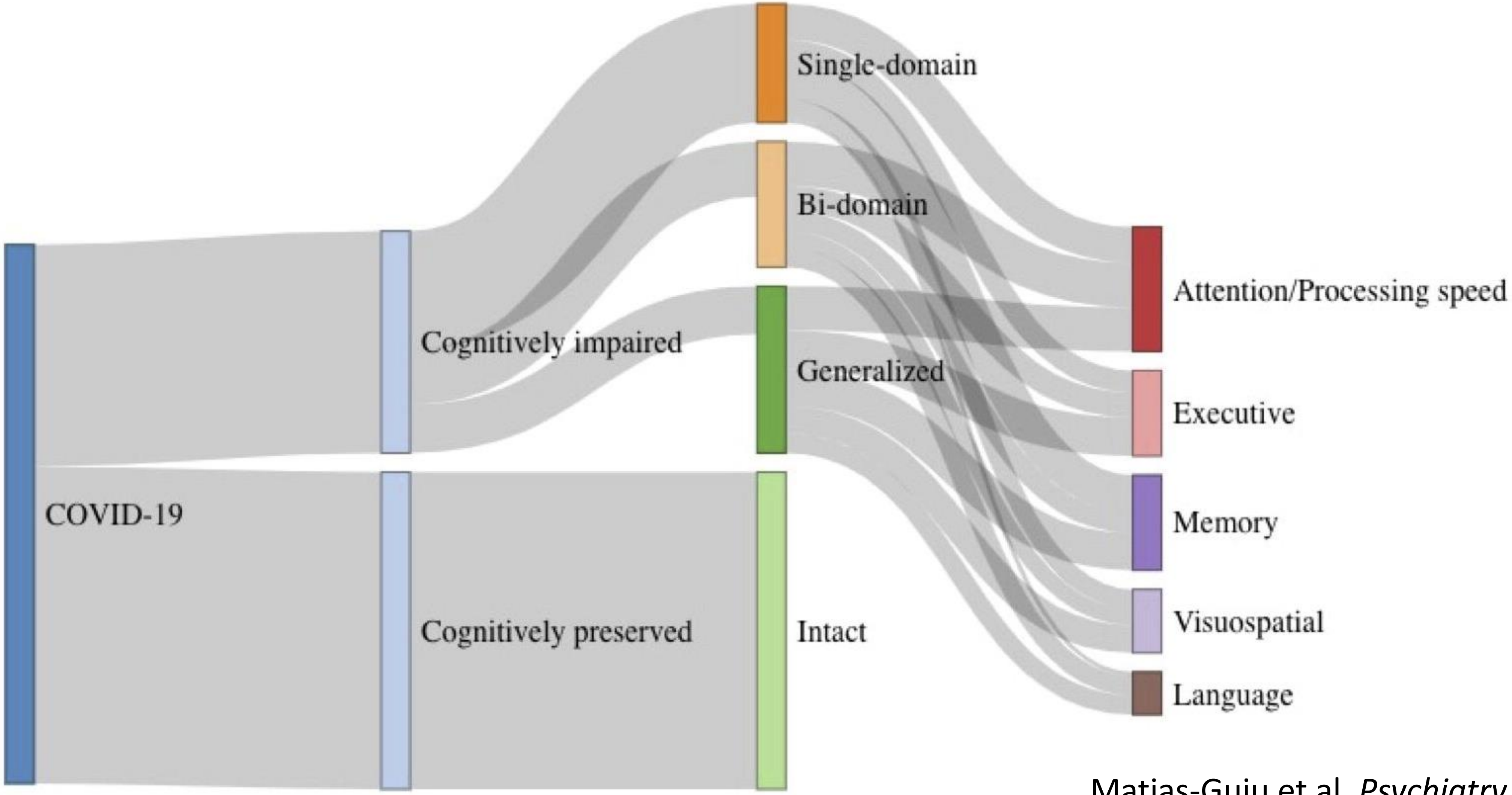
Development of criteria for cognitive dysfunction in post-COVID syndrome: the IC-CoDi-COVID approach

Jordi A Matias-Guiu [a,*], Elena Herrera [b], María González-Nosti [b], Kamini Krishnan [c], Cristina Delgado-Alonso [a], María Díez-Cirarda [a], Miguel Yus [d], Álvaro Martínez-Petit [e], Josué Pagán [e,f], Jorge Matías-Guiu [a], José Luis Ayala [f,g], Robyn Busch [c], Bruce P Hermann [h]

404 patients
145 controls



Cognitive dysfunction



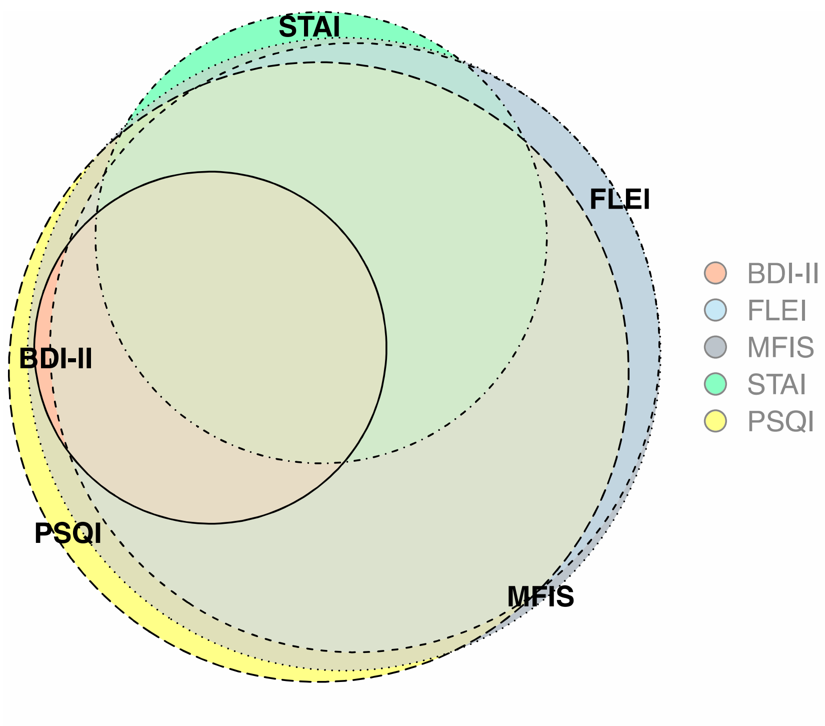
Matias-Guiu et al. *Psychiatry Res* 2023

Received: 24 February 2023 | Accepted: 17 September 2023
DOI: 10.1111/ene.16084
european journal of neurology

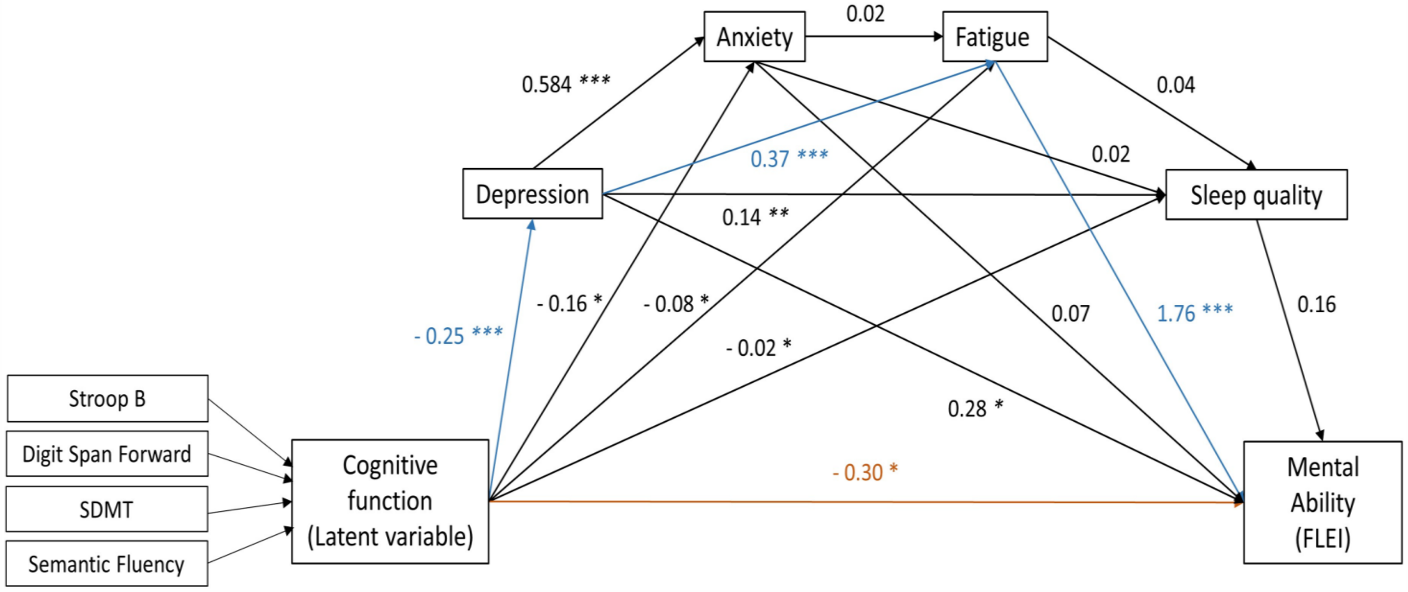
ORIGINAL ARTICLE

Unraveling brain fog in post-COVID syndrome: Relationship between subjective cognitive complaints and cognitive function, fatigue, and neuropsychiatric symptoms

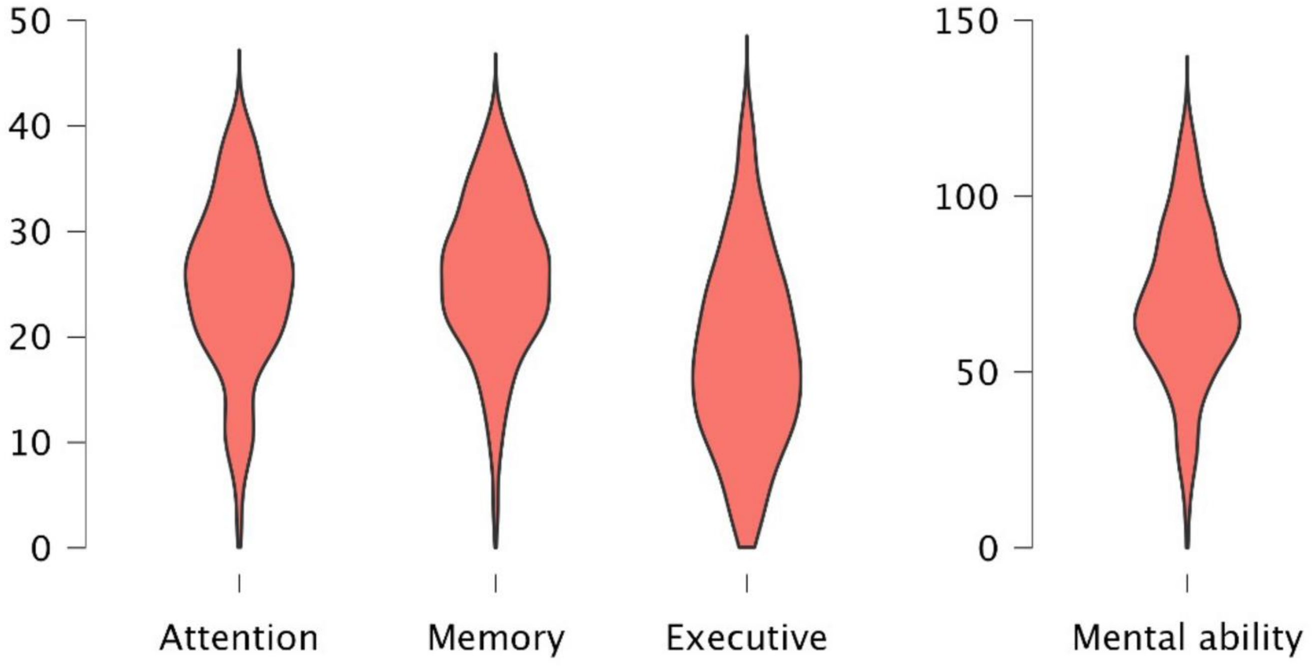
Cristina Delgado-Alonso[1] | María Díez-Cirarda[1] | Josué Pagán[2,3] | Carlos Pérez-Izquierdo[4] | Silvia Oliver-Mas[1] | Lucía Fernández-Romero[1] | Álvaro Martínez-Petit[2,3] | María Valles-Salgado[1] | María José Gil-Moreno[1] | Miguel Yus[5] | Jorge Matías-Guiu[1] | José Luis Ayala[6] | Jordi A. Matias-Guiu[1]



BDI-II: depression
FLEI: subjective cognition
MFIS: fatigue
PSQI: sleep quality
STAI: anxiety



FLEI (subjective cognition)



Higher scores mean more symptoms (worst cognition)

Delgado-Alonso et al. *Eur J Neurol* 2023

TABLE 1 Sample description and associations of the main clinical and demographic factors with the FLEI scale.

	Sample description	Associations with FLEI scale			
	$N = 170$	FLEI–mental ability	FLEI–attention	FLEI–memory	FLEI–executive function
Age, years	49.37 ± 10.95 years	0.032 (0.683)	−0.095 (0.218)	0.075 (0.333)	0.104 (0.179)
Sex: women	125 (73.09%)	−1.865 (0.064)	−1.813 (0.072)	−2.948 **(0.004)**	−0.674 (0.502)
Years of education	14.87 ± 3.59	0.018 (0.818)	0.036 (0.645)	−0.010 (0.895)	0.021 (0.786)
Arterial hypertension	39 (22.94%)	−0.194 (0.846)	0.673 (0.502)	−0.543 (0.588)	−0.650 (0.517)
Diabetes mellitus	20 (11.76%)	0.021 (0.983)	0.212 (0.832)	−0.015 (0.988)	−0.125 (0.901)
Dyslipidemia	47 (27.64%)	1.014 (0.312)	1.577 (0.117)	0.255 (0.799)	0.928 (0.355)
Tobacco smoking	26 (15.29%)	−0.093 (0.926)	−0.328 (0.743)	0.716 (0.475)	−0.527 (0.599)
Months from symptom onset to assessment	14.50 ± 6.91	0.037 (0.631)	0.030 (0.698)	0.037 (0.633)	0.036 (0.642)
Olfactory or gustatory symptoms during the acute infection	113 (66.40%)	1.758 (0.081)	1.559 (0.121)	1.999 **(0.047)**	1.377 (0.170)
Headache during the acute infection	135 (78.41%)	−2.067 **(0.040)**	−2.326 **(0.021)**	−1.952 (0.058)	−1.171 (0.243)
Hospitalization	45 (26.47%)	−0.595 (0.401)	−0.680 (0.497)	−0.586 (0.559)	−1.023 (0.308)
Intensive care unit admission	12 (7.05%)	−2.024 **(0.045)**	−1.523 (0.130)	−1.469 (0.144)	−2.52 **(0.013)**
Ventilatory assistance	15 (8.82%)	−1.600 (0.112)	−1.204 (0.230)	−1.116 (0.266)	−2.039 **(0.044)**

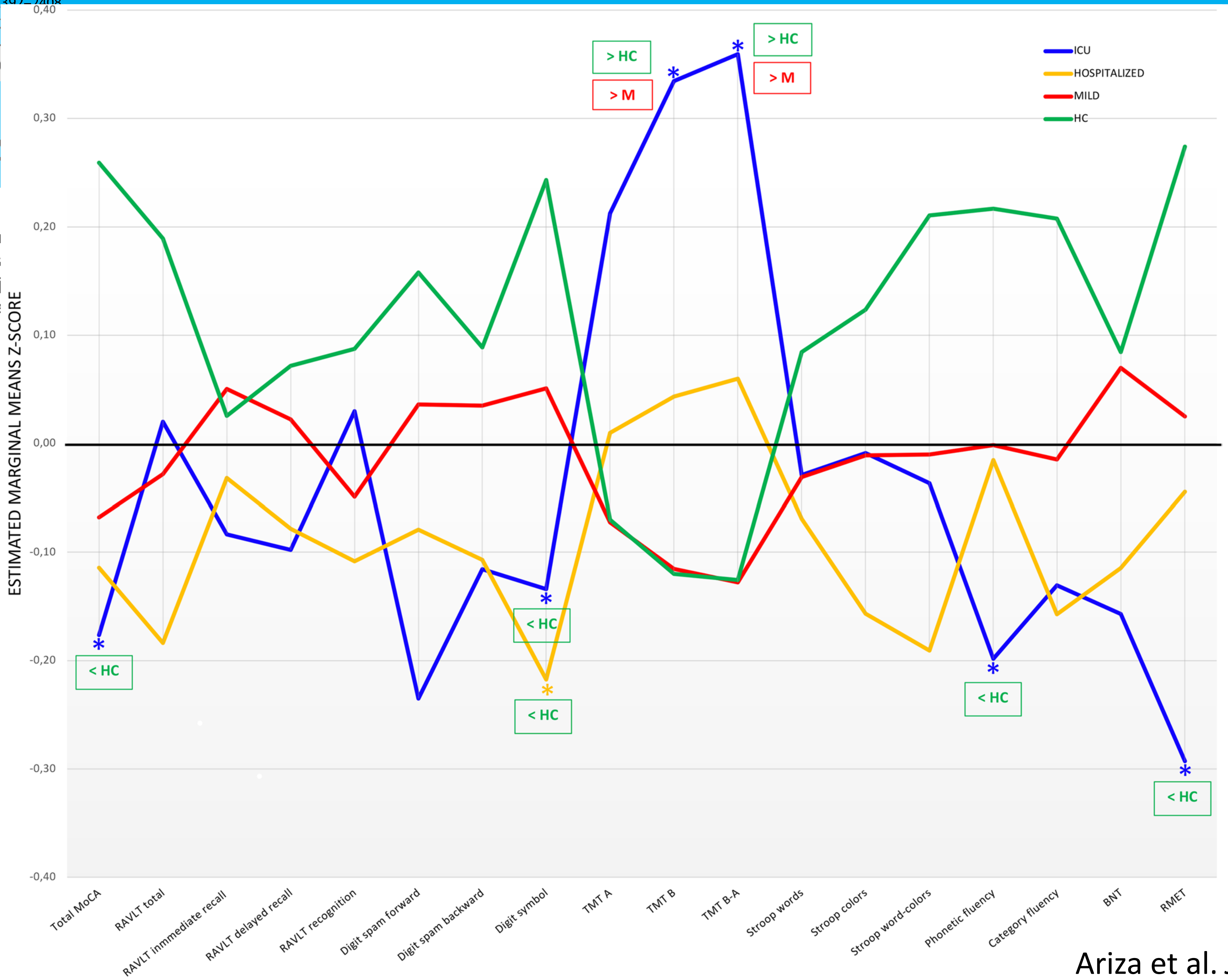
Delgado-Alonso et al. *Eur J Neurol* 2023

Journal of Neurology (2023) 270:2392–2408
https://doi.org/10.1007/s00415-0

ORIGINAL COMMUNICA

COVID-19 severit
with post-COVID

Mar Ariza[1,2,3] · Neus Can
Anna Campabadal[1,2,4] · M
Cristian Barrué · Javier Bej
Maite Garolera[3,13] · Carme



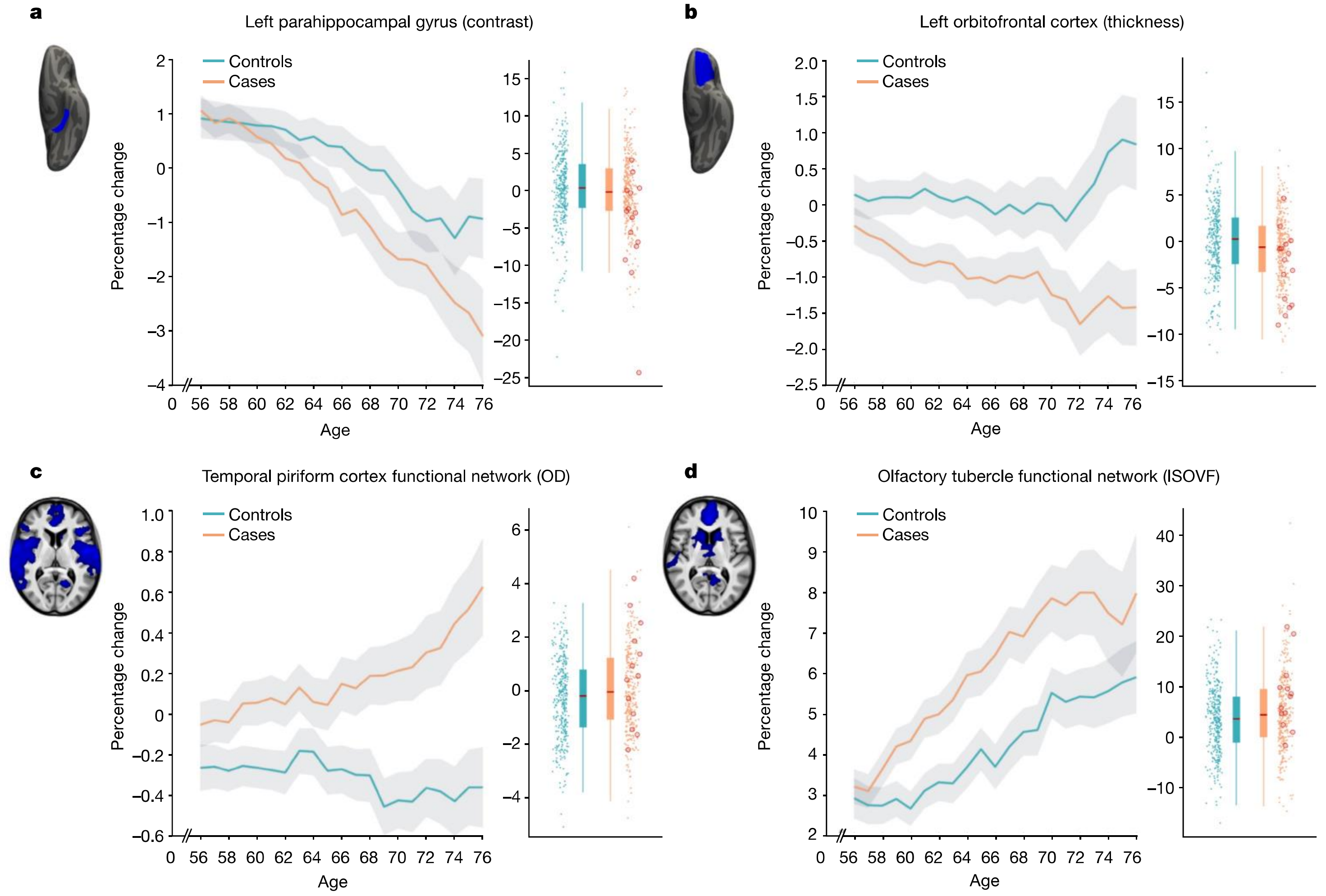
Ariza et al. *J Neurol* 2023

Article

SARS-CoV-2 is associated with changes in brain structure in UK Biobank

https://doi.org/10.1038/s41586-022-04569-5
Received: 19 August 2021
Accepted: 21 February 2022
Published online: 7 March 2022

Gwenaëlle Douaud[1✉], Soojin Lee[1], Fidel Alfaro-Almagro[1], Christoph Arthofer[1], Chaoyue Wang[1], Paul McCarthy[1], Frederik Lange[1], Jesper L. R. Andersson[1], Ludovica Griffanti[1,2], Eugene Duff[1,3], Saad Jbabdi[1], Bernd Taschler[1], Peter Keating[4], Anderson M. Winkler[5], Rory Collins[6], Paul M. Matthews[7], Naomi Allen[6], Karla L. Miller[1], Thomas E. Nichols[8] & Stephen M. Smith[1]

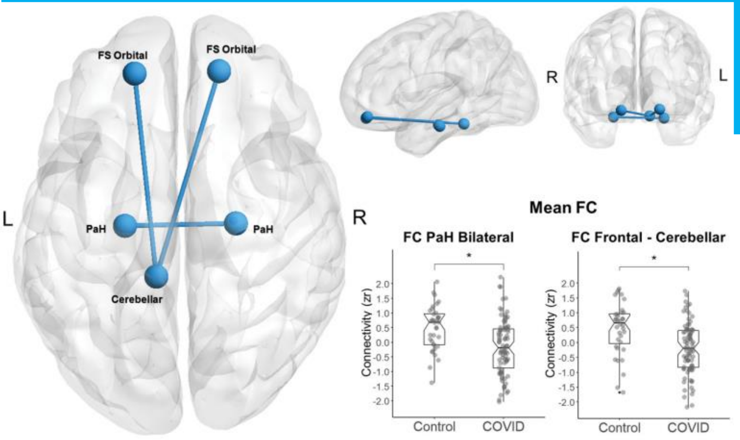


- **Longitudinal changes in 394 patients infected by SARS-CoV-2 vs 388 controls.**
- **Volume loss in gray matter in parahippocampal gyrus, orbitofrontal cortex and insula.**

Doaud et al. *Nature* 2022

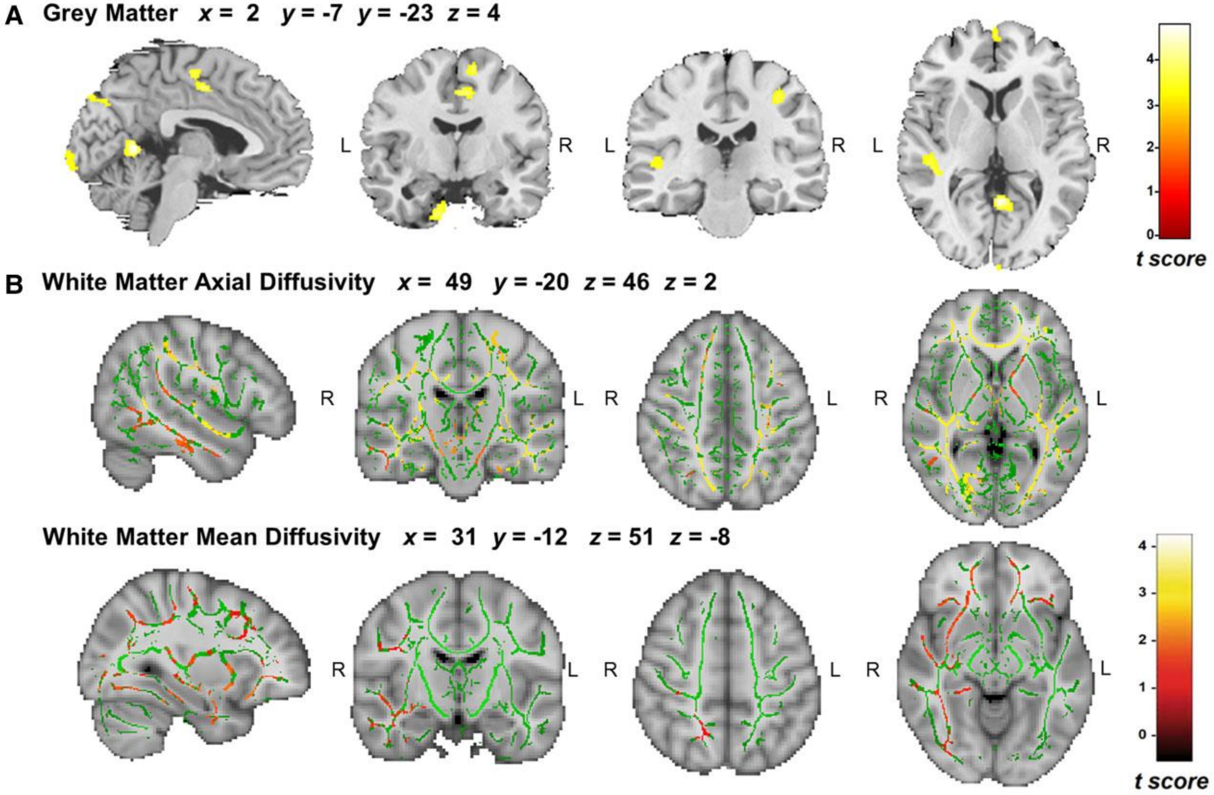
https://doi.org/10.1093/brain/awac384 BRAIN 2022: 00; 1–11 | 1

BRAIN
ORIGINAL ARTICLE



Multimodal neuroimaging in post-COVID syndrome and correlation with cognition

María Díez-Cirarda,[1] Miguel Yus,[2] Natividad Gómez-Ruiz,[2] Carmen Polidura,[2] Lidia Gil-Martínez,[2] Cristina Delgado-Alonso,[1] Manuela Jorquera,[2] Ulises Gómez-Pinedo,[1] Jorge Matias-Guiu,[1] Juan Arrazola[2] and Jordi A. Matias-Guiu[1]



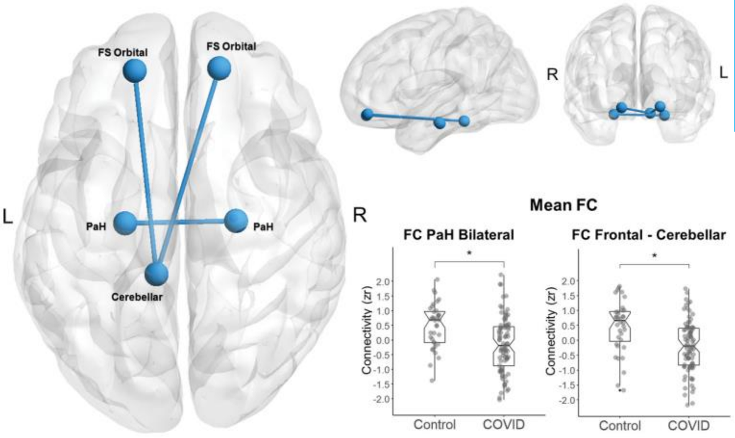
https://doi.org/10.1093/brain/awac384 BRAIN 2022: 00; 1–11 | 1

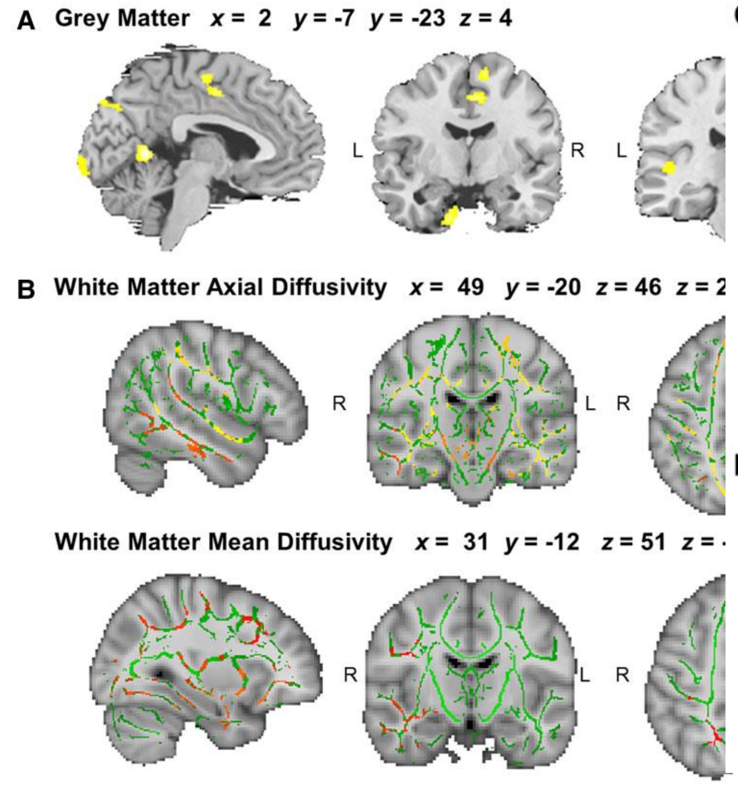
BRAIN

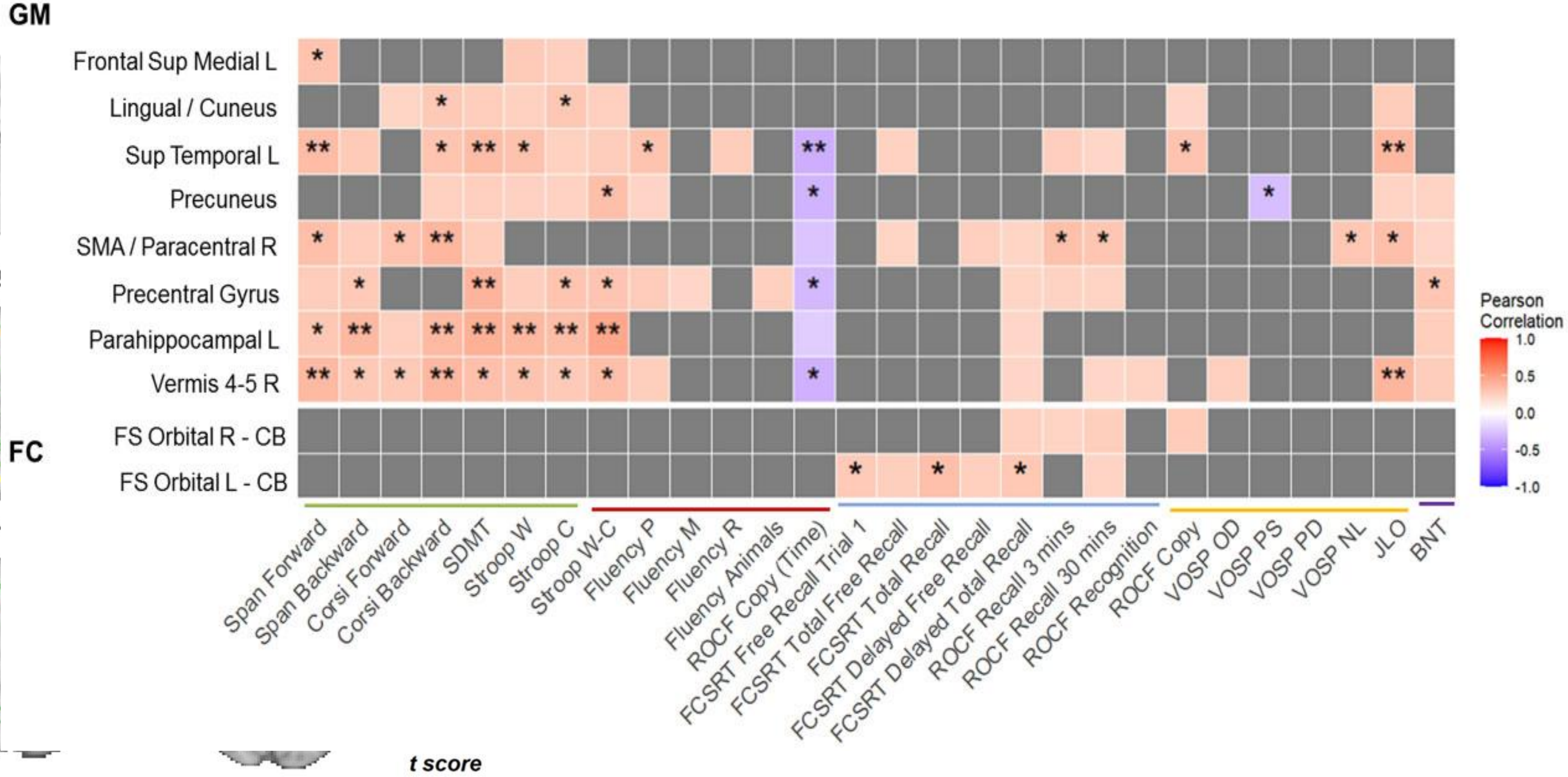
ORIGINAL ARTICLE

Multimodal neuroimaging in post-COVID syndrome and correlation with cognition

María Díez-Cirarda,[1] Miguel Yus,[2] Natividad Gómez-Ruiz,[2] Carmen Polidura,[2] Lidia Gil-Martínez,[2] Cristina Delgado-Alonso,[1] Manuela Jorquera,[2] Ulises Gómez-Pinedo,[1] Jorge Matias-Guiu,[1] Juan Arrazola[2] and Jordi A. Matias-Guiu[1]





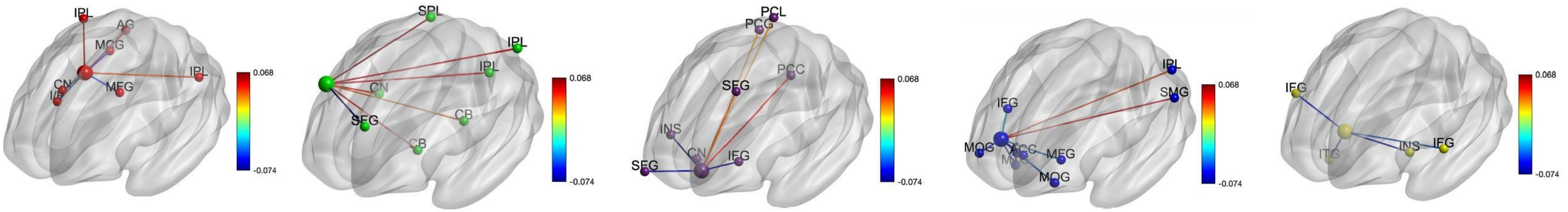


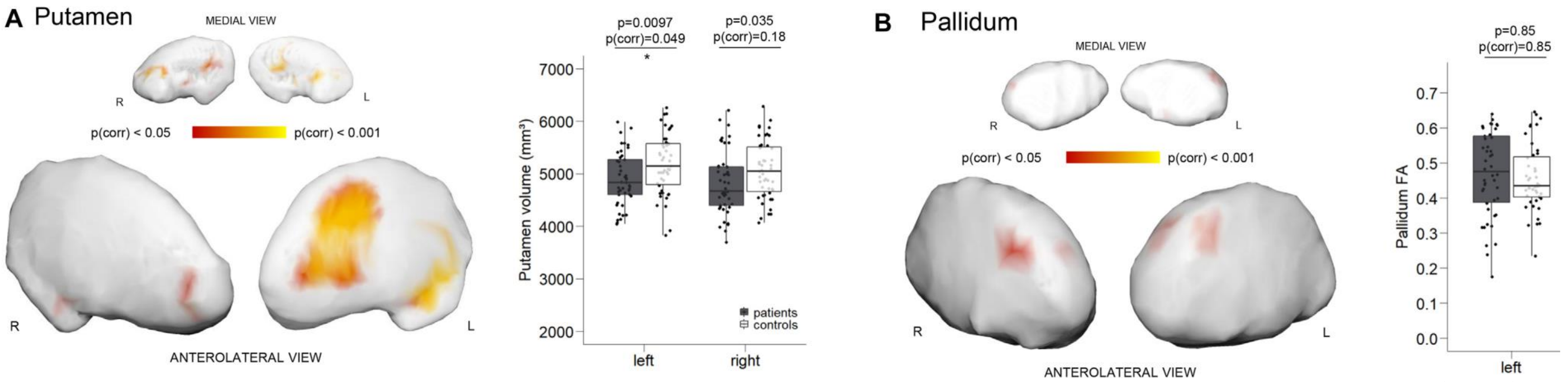
Neural basis of fatigue?

"Fatigue network"

Wiley et al. *Sci Rep* 2020

SEED dACC **SEED DLPFC** **SEED vmPFC** **SEED Insula** **SEED Striate**





Heine et al. *EClinicalMedicine* 2023

ARTICLE

Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19

Nelly Kanberg, MD, Nicholas J. Ashton, PhD, Lars-Magnus Andersson, MD, PhD, Aylin Yilmaz, MD, PhD, Magnus Lindh, MD, PhD, Staffan Nilsson, PhD, Richard W. Price, MD, PhD, Kaj Blennow, MD, PhD, Henrik Zetterberg, MD, PhD, and Magnus Gisslén, MD, PhD

Correspondence
Dr. Gisslén
magnus.gisslen@infect.gu.se

Neurology® 2020;95:e1754-e1759. doi:10.1212/WNL.0000000000010111

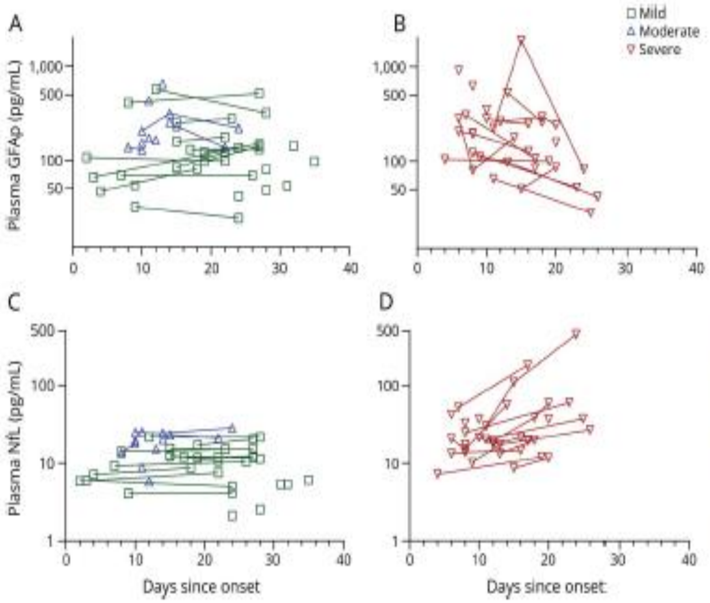
Blood biomarkers: *GFAP, Neurofilament*

Abstract

Objective
To test the hypothesis that coronavirus disease 2019 (COVID-19) has an impact on the CNS by measuring plasma biomarkers of CNS injury.

Results
The patients with severe COVID-19 had higher plasma concentrations of GFAp ($p = 0.001$) and NfL ($p < 0.001$) than controls, while GFAp was also increased in patients with moderate disease ($p = 0.03$). In patients with severe disease, an early peak in plasma GFAp decreased on follow-up ($p < 0.01$), while NfL showed a sustained increase from first to last follow-up ($p < 0.01$), perhaps reflecting a sequence of early astrocytic response and more delayed axonal injury.

Conclusion
We show neurochemical evidence of neuronal injury and glial activation in patients with moderate and severe COVID-19. Further studies are needed to clarify the frequency and nature of COVID-19–related CNS damage and its relation to both clinically defined CNS events such as hypoxic and ischemic events and mechanisms more closely linked to systemic severe acute respiratory syndrome coronavirus 2 infection and consequent immune activation, as well as to evaluate the clinical utility of monitoring plasma NfL and GFAp in the management of this group of patients.



Plasma glial fibrillary acidic protein (GFAp) and neurofilament light chain protein (NfL) concentrations in patients with mild (green squares), moderate (blue triangles), and severe (red triangles) coronavirus disease 2019 (COVID-19). Lines connect multiple sampling in individual patients. (A and C) No significant changes from initial to last follow-up were found in mild or moderate disease. (B and D) In contrast, a significant decrease in plasma GFAp ($p = 0.004$) and increase in plasma NfL ($p = 0.002$) were found in severe COVID-19.

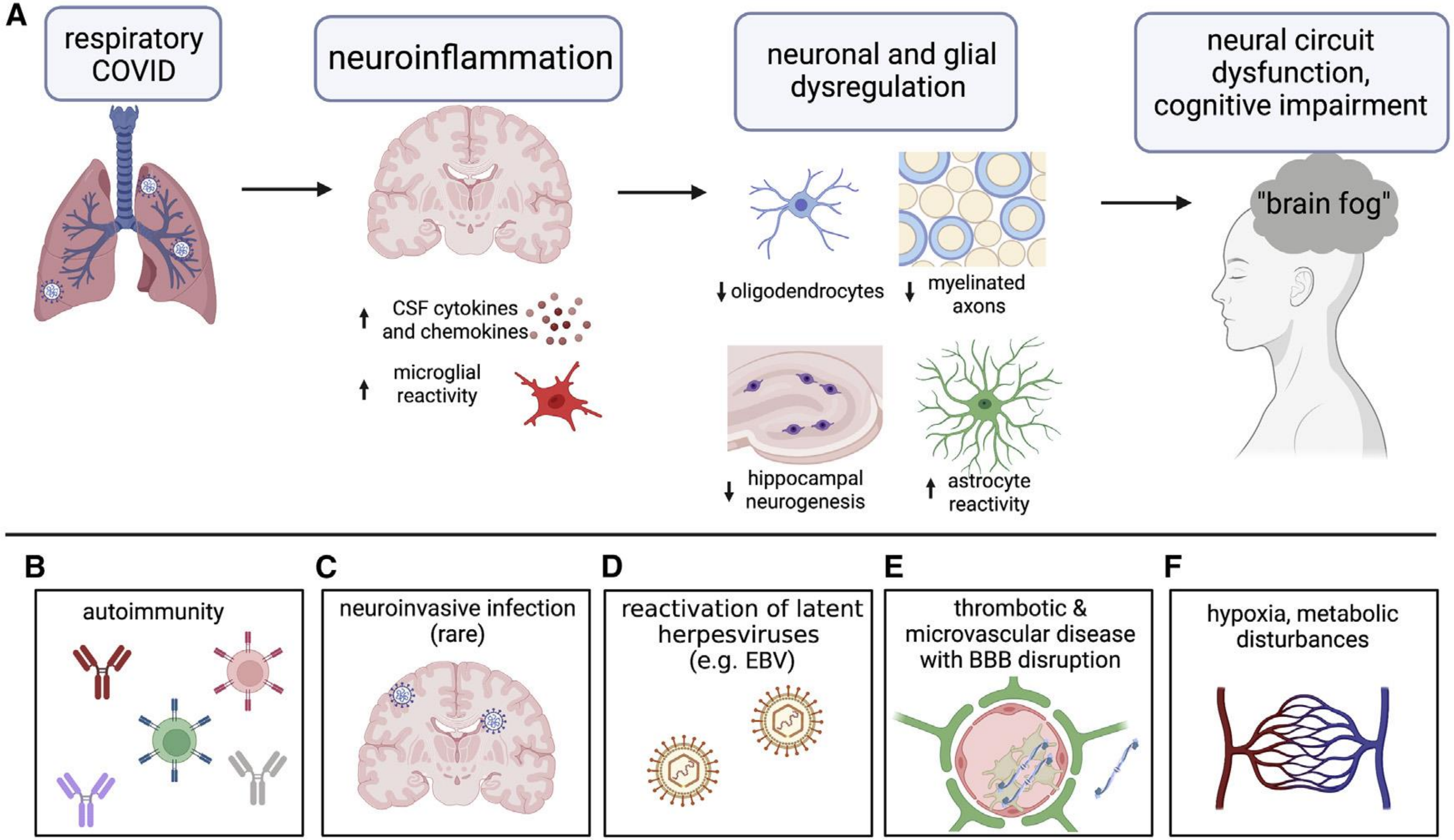
Summary – SARS-CoV-2 & Brain

- Cognitive complaints are among the most common symptoms in the post-Covid condition.
- Cognitive symptoms result from objective cognitive deficits and/or fatigue.
- Cognitive dysfunction is primarily characterized by attention/processing speed, episodic memory, and executive function deficits.
- Neuroimaging evidence supports structural and functional brain changes in patients with post-Covid condition, which are associated with cognitive functioning.
- While fatigue has a complex pathophysiology, there is also evidence of neurological involvement in its mechanism.

How does SARS-CoV-2 cause brain dysfunction? Does inflammation play a role?

Immune dysregulation in Long COVID?

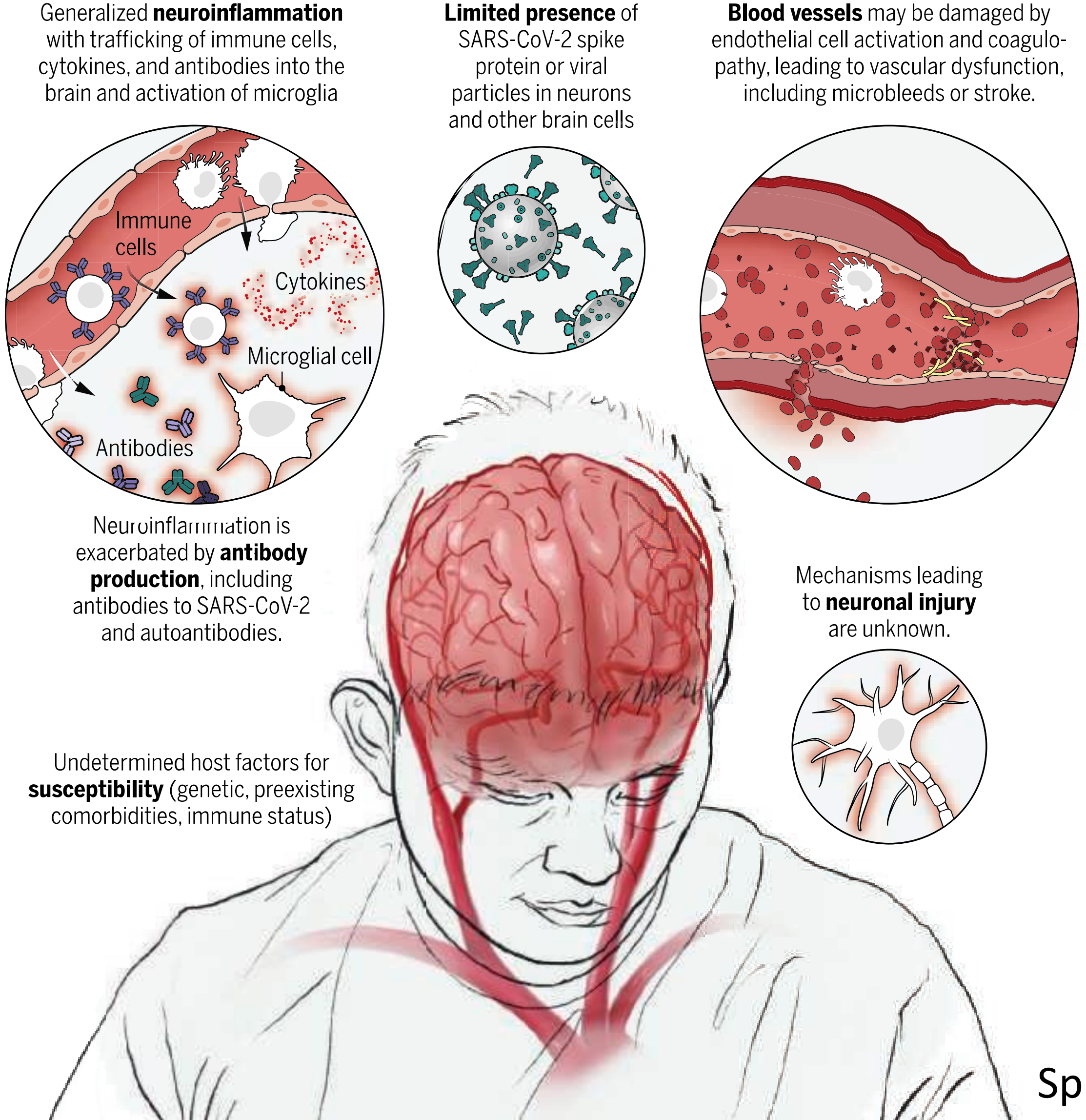
- Demographic characteristics of Long Covid patients
  - 70-80% of women
  - Age 30-60
- Not just sequelae because
  - Not particularly related to the severity of the acute phase
  - Chronicity, lack of clear improvement in a significant proportion of cases
- Common symptoms with other autoimmune diseases
  - Chronic fatigue, joint and muscle pain, brain fog, joint pain, …
- Higher risk of autoimmune disorders (Lim et al. JAMA Netw Open 2023)



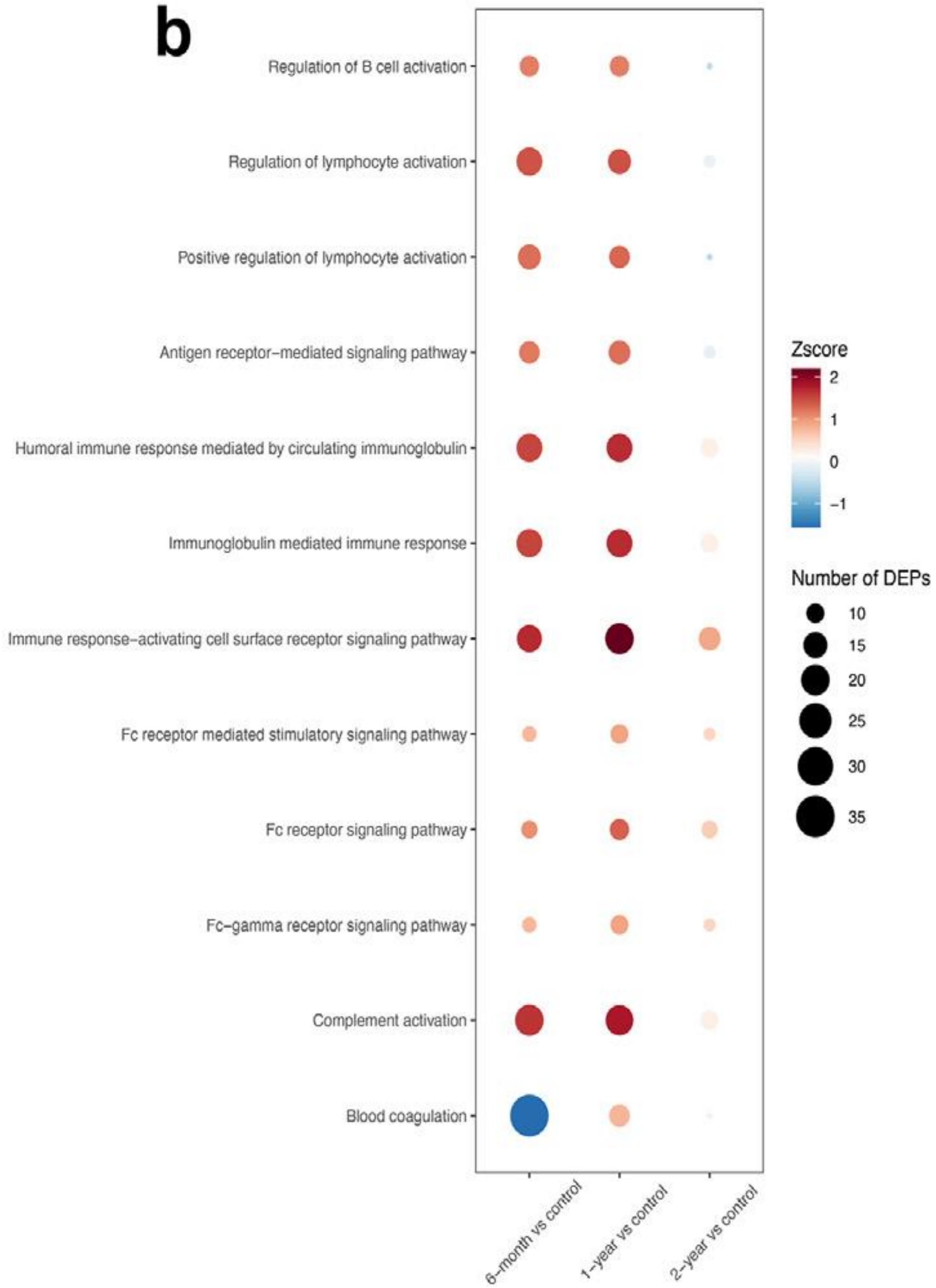
Monje & Iwasaki. *Neuron* 2022

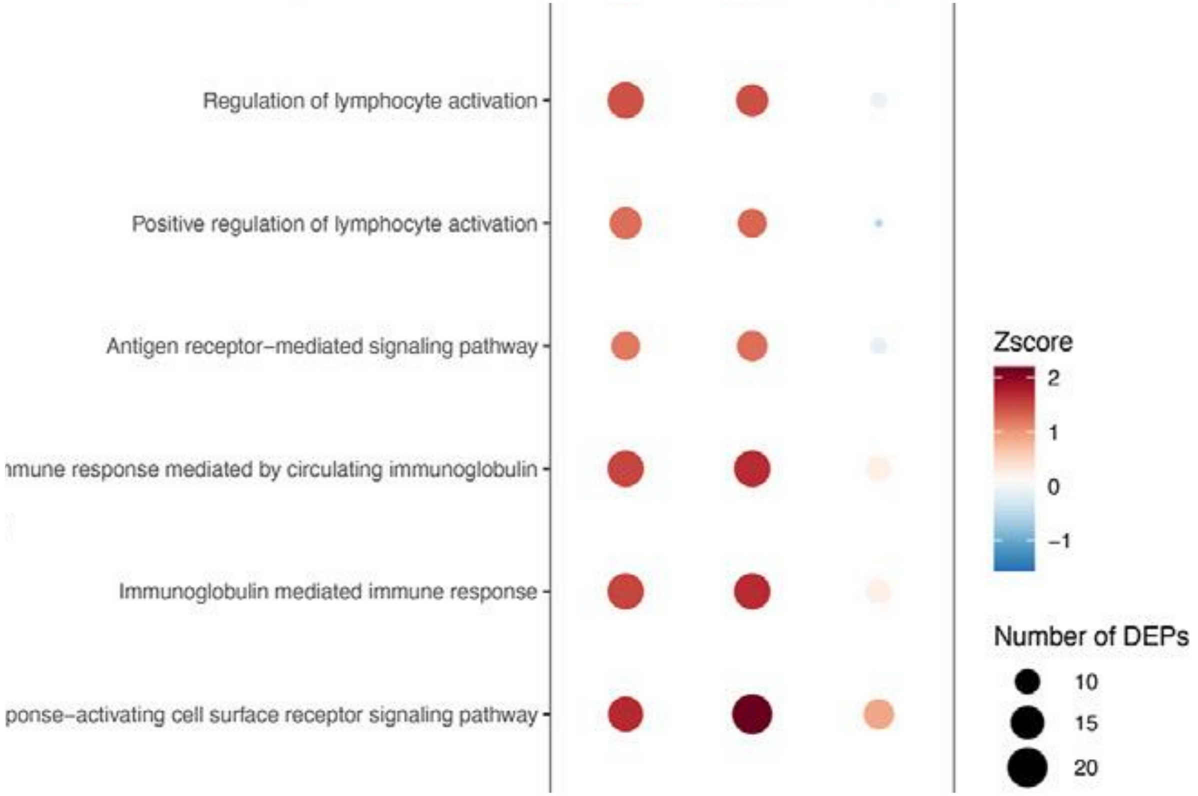
Putative neuropathogenic effects of SARS-CoV-2

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to neuropsychiatric effects during acute COVID-19, including confusion, stroke, and neuromuscular disorders. These may arise from neuroinflammation, coagulopathy, neuronal injury, and possibly viral infection in the central nervous system. Causes of Long Covid symptoms affecting the nervous system may result from the emergence and persistence of these mechanisms.

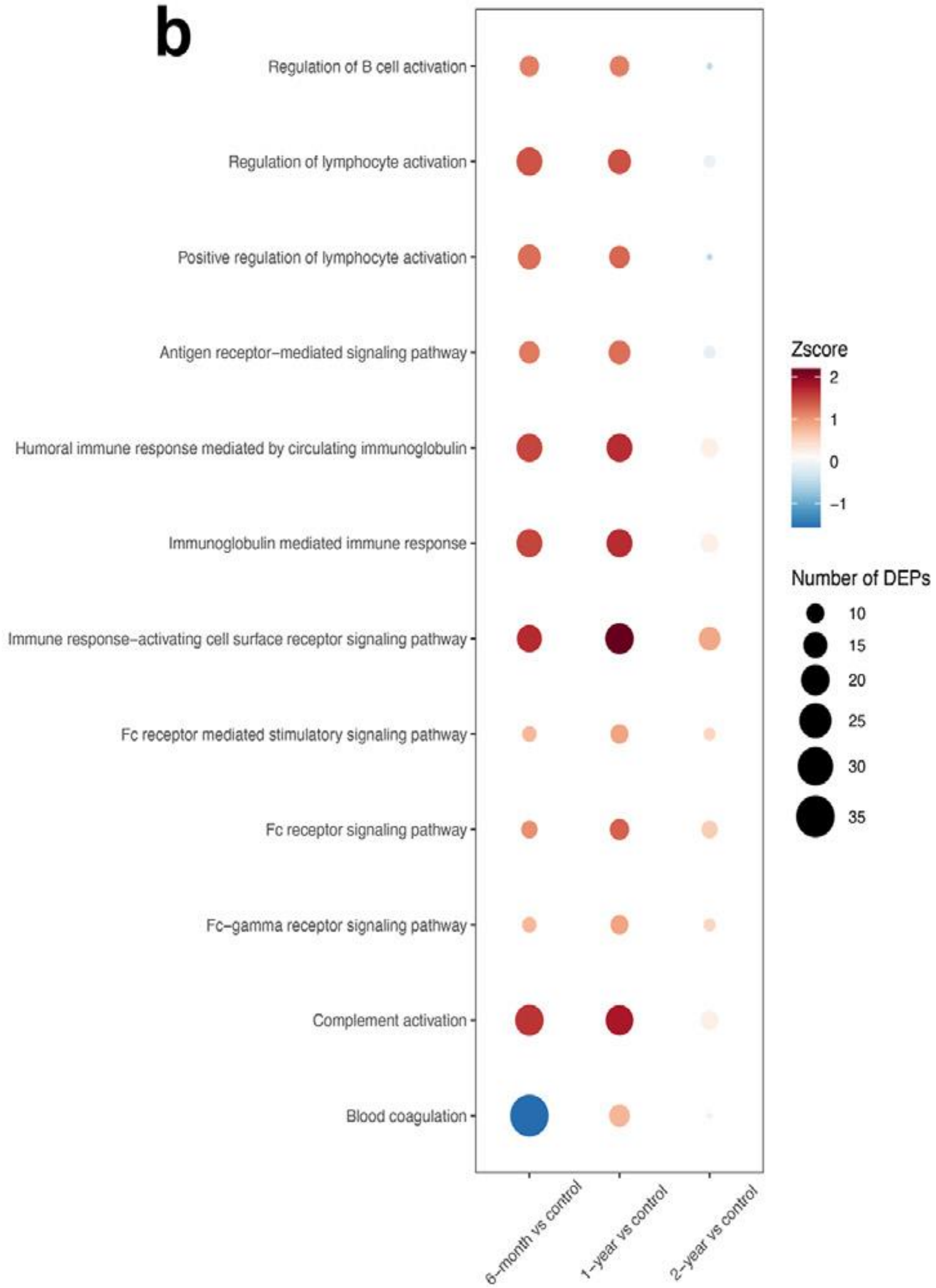


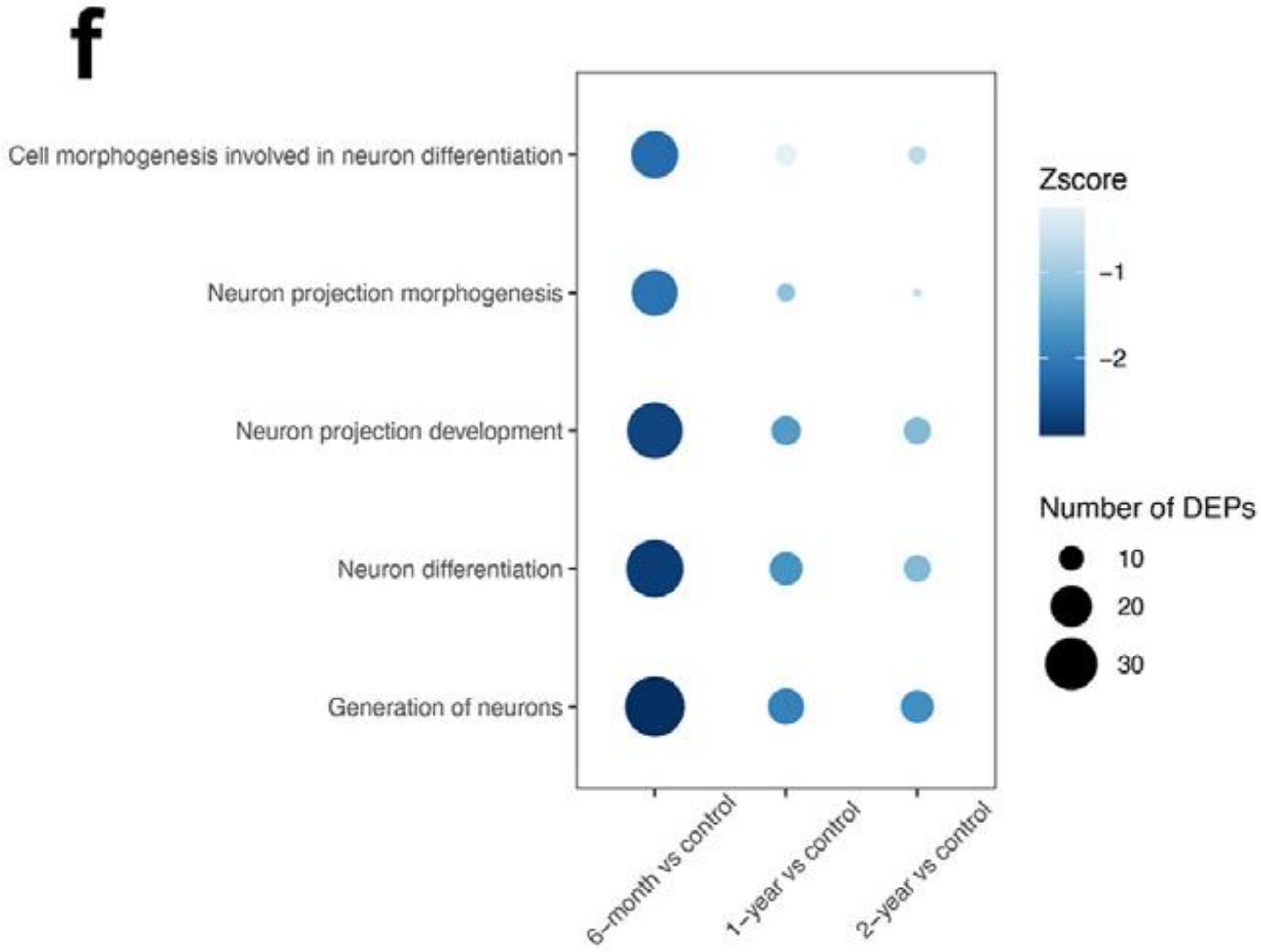
Spudich & Nath. *Science* 2022





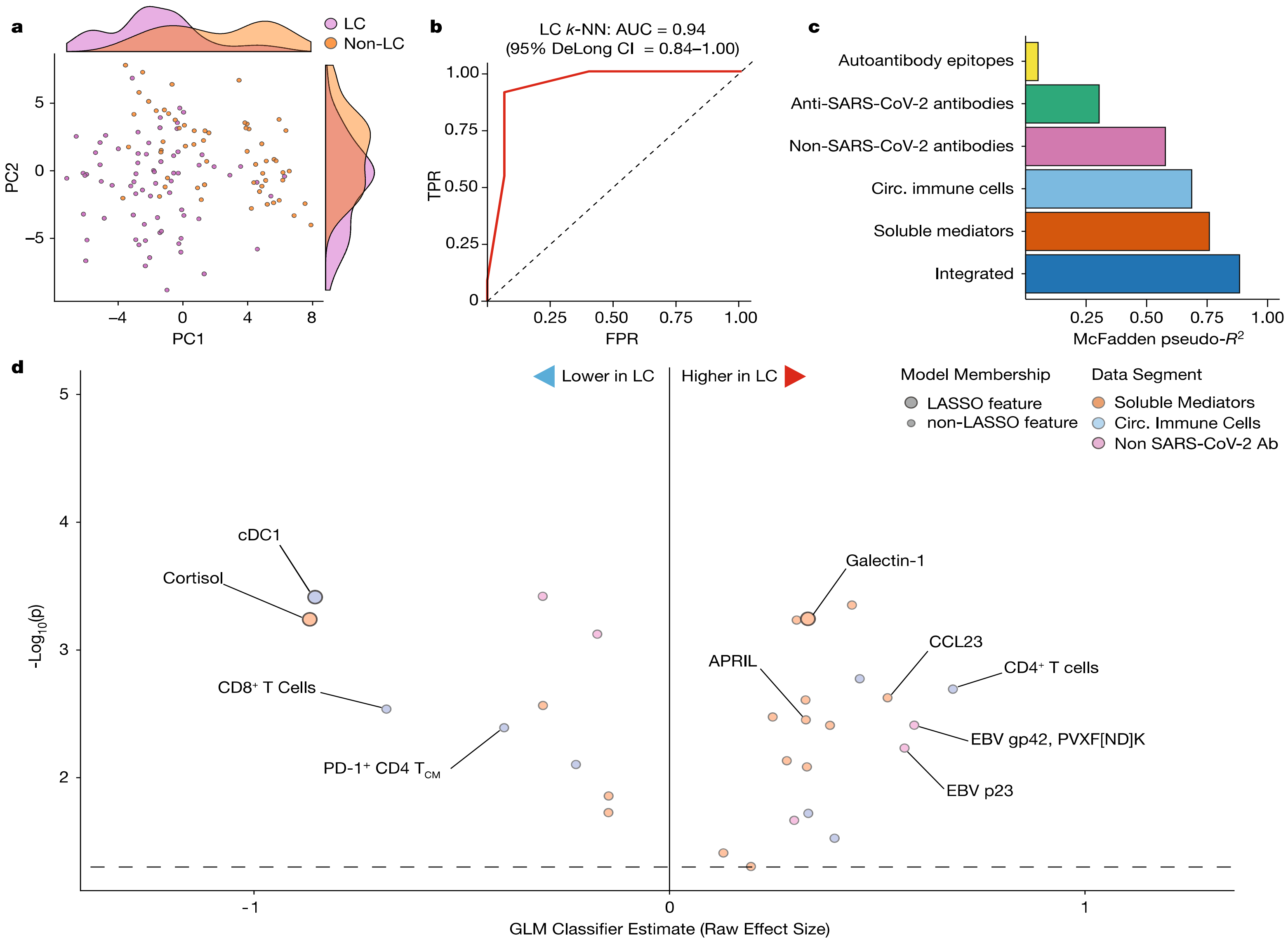
Gu et al. *EBioMedicine* 2023





Gu et al. *EBioMedicine* 2023

Immune dysregulation in Long COVID?

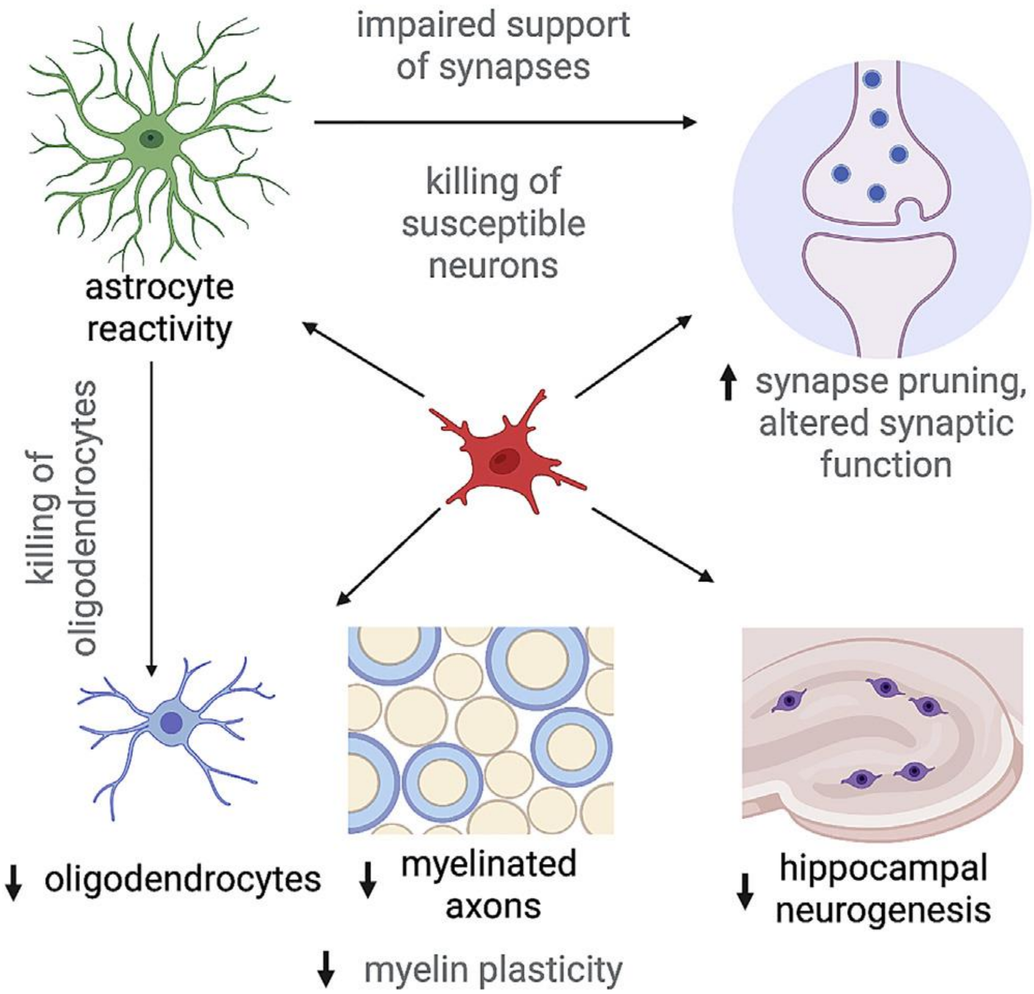


Klein et al. *Nature* 2023

Why immune dysregulation?

- Viral persistence
- Reactivation of latent viruses (e.g. Epstein-Barr)
- Bacteriophage-like actions of SARS-CoV-2 (by gut bacteria)
- Chronic inflammation and immune dysregulation (cytokine storm, lymphopenia)
- Generation of autoimmunity
- Mast cell activation

- Tissue damage (infection, hypoxia)
- Coagulation disorders



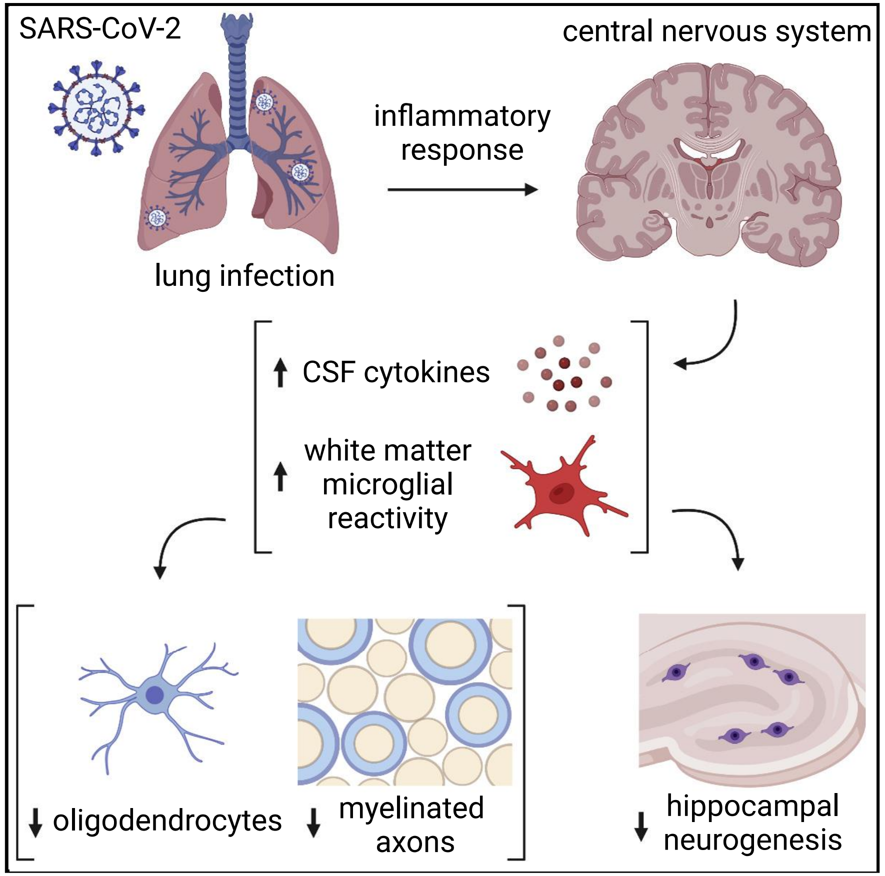
Monje & Iwasaki. *Neuron* 2022

Experimental studies

Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation

Cell

Graphical abstract



Authors

Anthony Fernández-Castañeda, Peiwen Lu, Anna C. Geraghty, ..., Avindra Nath, Akiko Iwasaki, Michelle Monje

Correspondence

akiko.iwasaki@yale.edu (A.I.), mmonje@stanford.edu (M.M.)

In brief

Mild respiratory COVID causes neuroinflammation and multi-lineage cellular dysregulation in the central nervous system, a phenomenon mirroring cancer-therapy-related cognitive impairment.

Mice after mild SARS-COV-2 infection:

-Hippocampal neurogenesis impairment

-Reduction of oligodendrocytes and myelin

-Prominent inflammation

- Role of CCL11

"We find here that even mild respiratory COVID can induce prominent elevation of multiple cytokines and chemokines together with lasting reactivity of white matter microglia in subcortical and hippocampal regions".

Fernandez-Castañeda et al. Cell 2022

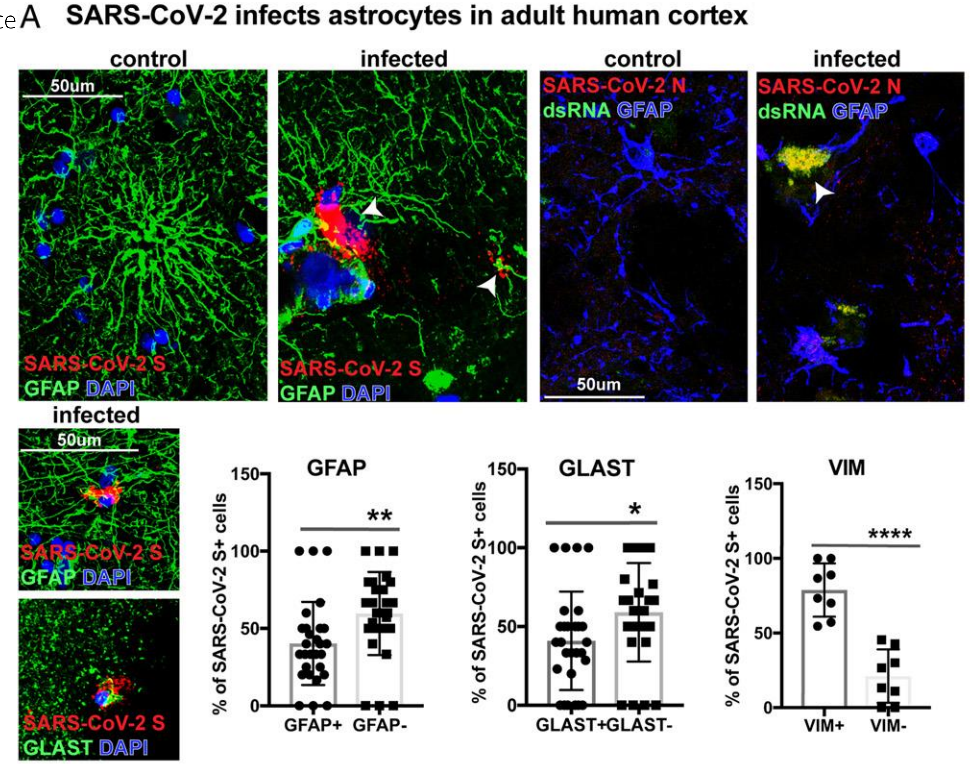
Experimental studies

PNAS RESEARCH ARTICLE | DEVELOPMENTAL BIOLOGY OPEN ACCESS

Tropism of SARS-CoV-2 for human cortical astrocytes

Madeline G. Andrews[a,b,c,1], Tanzila Mukhtar[a,b,1], Ugomma C. Eze[a,b], Camille R. Simoneau[d,e,f], Jayden Ross[a,g], Neelroop Parikshak[a,b], Shaohui Wang[a,b], Li Zhou[a,b], Mark Koontz[h], Dmitry Velmeshev[a,b], Clara-Vita Siebert[a,b], Kaila M. Gemenes[a,b], Takako Tabata[d,e], Yonatan Perez[a,b], Li Wang[a,b], Mohammed A. Mostajo-Radji[a,b], Martina de Majo[h], Kevin C. Donohue[g], David Shin[a,g], Jahan Salma[i], Alex A. Pollen[a,b], Tomasz J. Nowakowski[a,g], Erik Ullian[h], G. Renuka Kumar[d,e], Ethan A. Winkler[j], Elizabeth E. Crouch[b,k], Melanie Ott[d,e], and Arnold R. Kriegstein[a,b,2]

Edited by Lawrence Goldstein, Sanford Consortium for Regenerative Medicine, La Jolla, CA; received December 8, 2021; acce

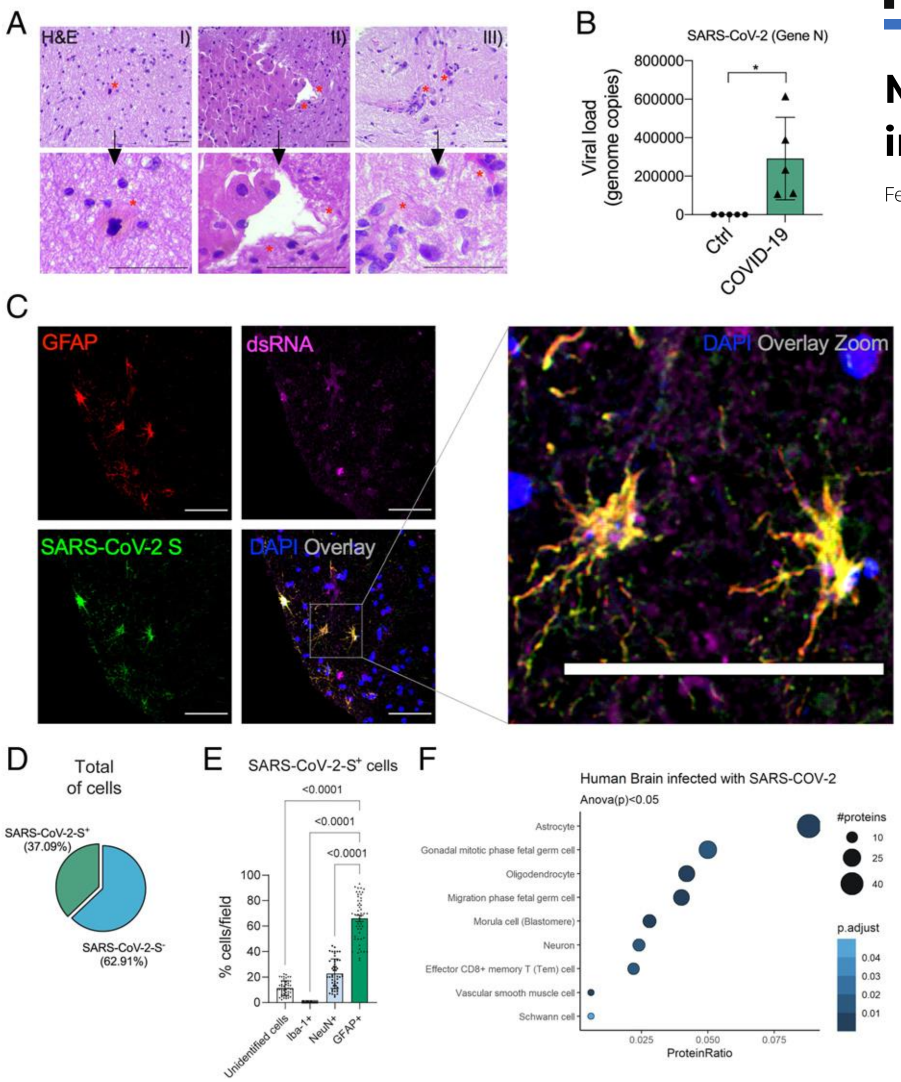


Study in brain organoids and human brain tissue

Direct (infection) and indirect involvement of astrocytes → neuronal loss

Andrews et al. *PNAS* 2022

Experimental studies



PNAS RESEARCH ARTICLE | NEUROSCIENCE OPEN ACCESS

Morphological, cellular, and molecular basis of brain infection in COVID-19 patients

Fernanda Crunfl[a,1], Victor C. Carregari[a,1], Flavio P. Veras[b,1], Lucas S. Silva[a], Mateus Henrique Nogueira[a],

Brain tissue of patients dead due to COVID-19, in vitro models

SARS-CoV-2 is detected in some patients, mainly involving astrocytes → metabolic changes, glutamatergic neurotransmission reduction

Experimental studies

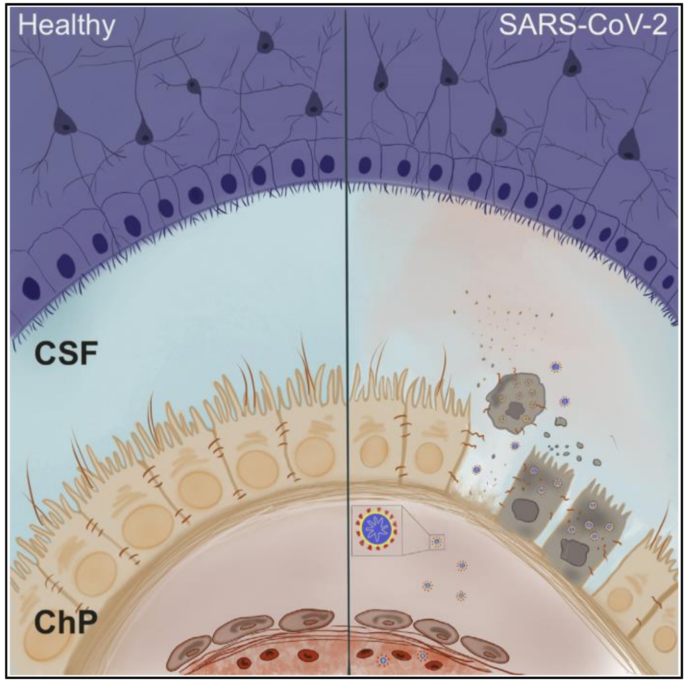
Cell Stem Cell

CellPress OPEN ACCESS

Short Article

SARS-CoV-2 Infects the Brain Choroid Plexus and Disrupts the Blood-CSF Barrier in Human Brain Organoids

Laura Pellegrini,[1] Anna Albecka,[1] Donna L. Mallery,[1] Max J. Kellner,[1] David Paul,[1] Andrew P. Carter,[1] Leo C. James,[1] and Madeline A. Lancaster[1,2,*]



Article

Dysregulation of brain and choroid plexus cell types in severe COVID-19

https://doi.org/10.1038/s41586-021-03710-0

Received: 20 October 2020

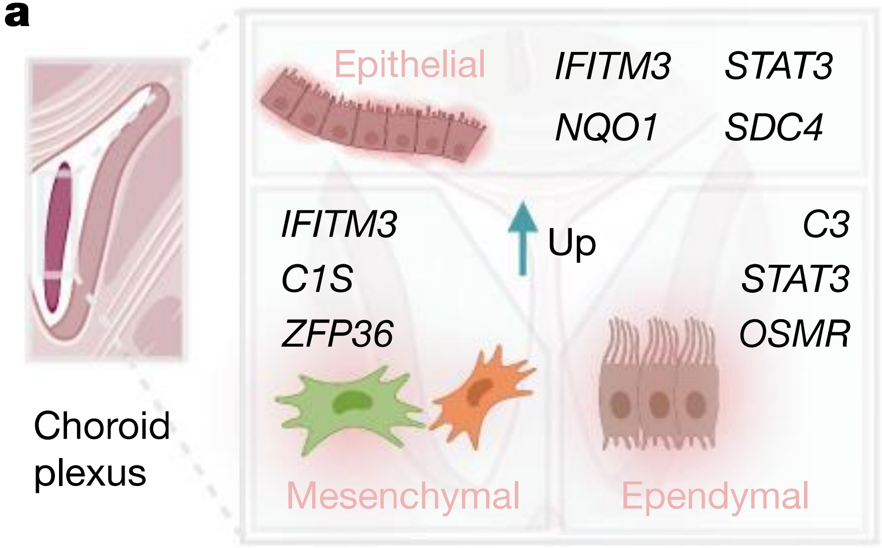
Accepted: 7 June 2021

Published online: 21 June 2021

Check for updates

Andrew C. Yang[1,2,3,11], Fabian Kern[4,11], Patricia M. Losada[3], Maayan R. Agam[3], Christina A. Maat[3], Georges P. Schmartz[4], Tobias Fehlmann[4], Julian A. Stein[5], Nicholas Schaum[3], Davis P. Lee[3], Kruti Calcuttawala[3], Ryan T. Vest[3], Daniela Berdnik[3], Nannan Lu[3], Oliver Hahn[3], David Gate[3], M. Windy McNerney[6], Divya Channappa[3], Inma Cobos[3,7], Nicole Ludwig[8], Walter J. Schulz-Schaeffer[5], Andreas Keller[3,4,12] ✉ & Tony Wyss-Coray[2,3,9,10,12] ✉

a



Viral persistence?

Table 1 | Identification of SARS-CoV-2 RNA and protein after COVID-19

	RNA	Protein	PASC symptoms	Location
Tissue (biopsy)				
Goh et al.[39]	√	S, N	√	Appendix, skin and breast tissues 163 and 426d after COVID-19
Zollner et al.[38]	√	N	√	Gut mucosa/epithelium tissue ~7 months after COVID-19
deMelo et al.[27]	√	N	√	Olfactory neuroepithelium tissue 110–196d after COVID-19
Gaebler et al.[33]	√	N	No	Intestinal tissue ~4 months after COVID-19
Cheung et al.[114]	√	S, N	NM	Colon, appendix, ileum, hemorrhoid, liver, gallbladder and lymph nodes 9–180d after COVID-19
Hany et al.[29]	NM	N	NM	Gastric and gallbladder tissues 274–380d after COVID-19
Miura et al.[30]	√	N	No	Adenoid tonsil, adenoid tissue, nasal cytobrush and nasal wash from children with no documented COVID-19 or upper airway infection in the month before collection
Xu et al.[37]	√	NM	No	Child adenoid and tonsil tissue up to 303d after COVID-19
Peluso et al.[24]	√	NM	√	Colorectal lamina propria tissue 158–676 d after COVID-19
Yao et al.[25]	√	S,N	√	Fungiform papillae tongue tissue 6–63 weeks after COVID-19
Tissue (autopsy)				
Stein et al.[31]	√	N	NM	Dozens of human body and brain tissue types at least 31d and up to 230d after COVID-19
Roden et al.[32]	√	NM	NM	Lung tissue up to 174d after COVID-19
Rendiero et al.[26]	NM	S	NM	Lung tissue up to 359d after COVID-19
Stool				
Natarajan et al.[115]	√	NM	√	Stool up to 230d after COVID-19
Yonker et al.[84]	√	S, N	√	RNA in stool of children with MIS-C 13–62d after COVID-19, S and N protein in plasma
Jin et al.[116]	√	S	NM	Neonatal stool in infants born to mothers whose COVID-19 symptoms resolved more than 10 weeks before delivery
Blood				
Schultheiß et al.[40]	NM	S1	√	Plasma at a median time of 8 months after COVID-19
Swank et al.[41]	NM	S, S1, N	√	Plasma up to 12 months after COVID-19
Peluso et al.[44]	NM	S1, N	√	Plasma neuron-derived EVs 35–84d after COVID-19
Peluso et al.[42]	NM	S1, S, N	√	Plasma up to 16 months after COVID-19
Craddock et al.[45]	√	S	√	Spike linked to EVs in samples obtained at least 8–12 weeks (up to 1 year) after COVID-19
Tejerina et al.[117]	√	NM	√	Plasma at a median time of 55d after COVID-19 (also found in stool/urine at the same median time point)

√, identified; No, not present; NM, not measured; S and S1, spike protein.

Proal et al. *Nat Immunol* 2023

EBioMedicine
Published by THE LANCET

Check for updates

Hippocampal subfield abnormalities and biomarkers of pathologic brain changes: from SARS-CoV-2 acute infection to post-COVID syndrome

Maria Díez-Cirarda,[a,**] Miguel Yus-Fuertes,[b] Rafael Sanchez-Sanchez,[c] Javier J. Gonzalez-Rosa,[d,e] Gabriel Gonzalez-Escamilla,[f] Lidia Gil-Martínez,[b] Cristina Delgado-Alonso,[a] Maria Jose Gil-Moreno,[a] Maria Valles-Salgado,[a] Fatima Cano-Cano,[d] Denise Ojeda-Hernandez,[a] Natividad Gomez-Ruiz,[b] Silvia Oliver-Mas,[a] María Soledad Benito-Martín,[a] Manuela Jorquera,[b] Sarah de la Fuente,[a] Carmen Polidura,[b] Belén Selma-Calvo,[a] Juan Arrazola,[b] Jorge Matias-Guiu,[a] Ulises Gomez-Pinedo,[a,g] and Jordi A. Matias-Guiu[a,g,*]

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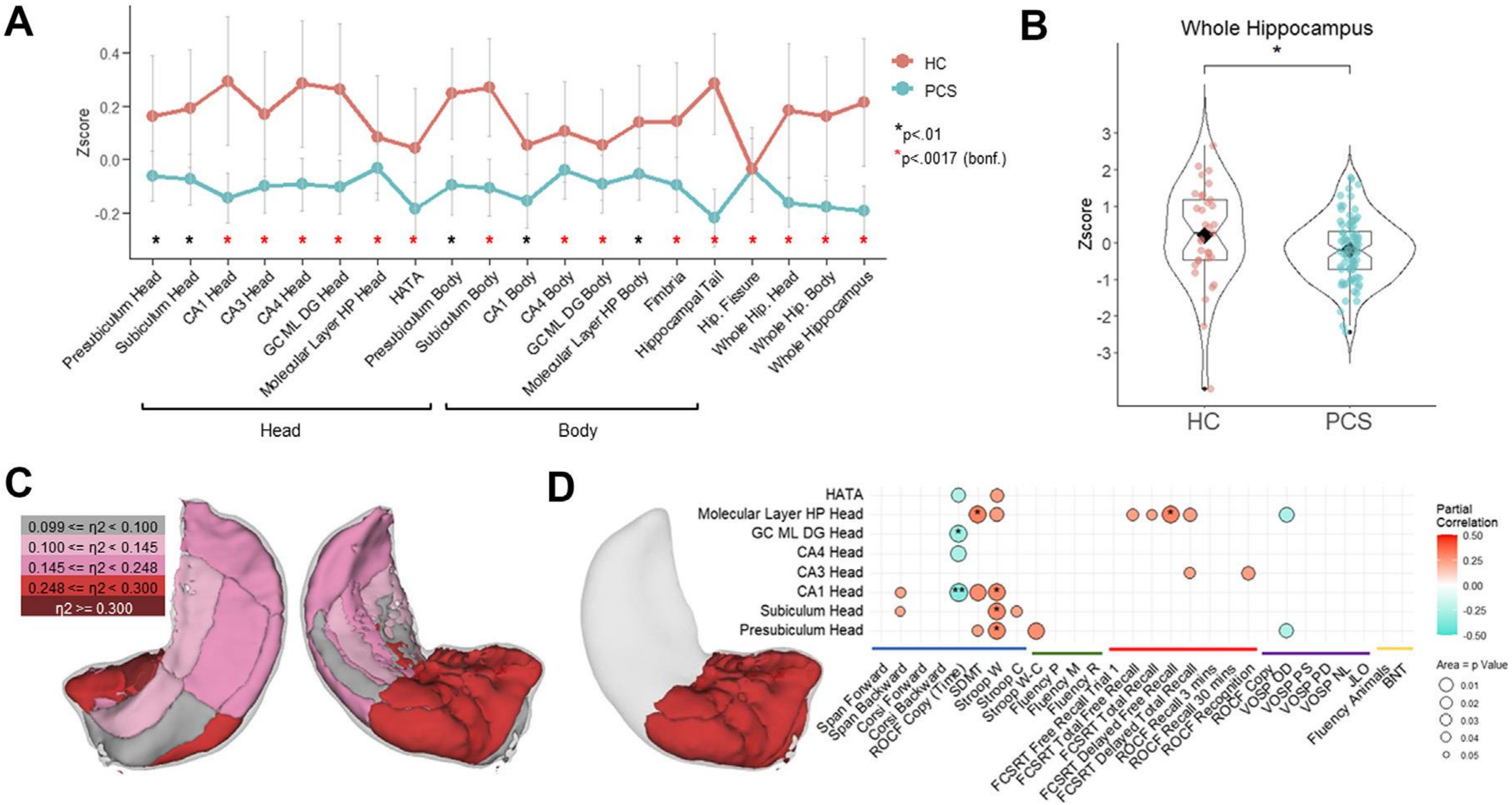
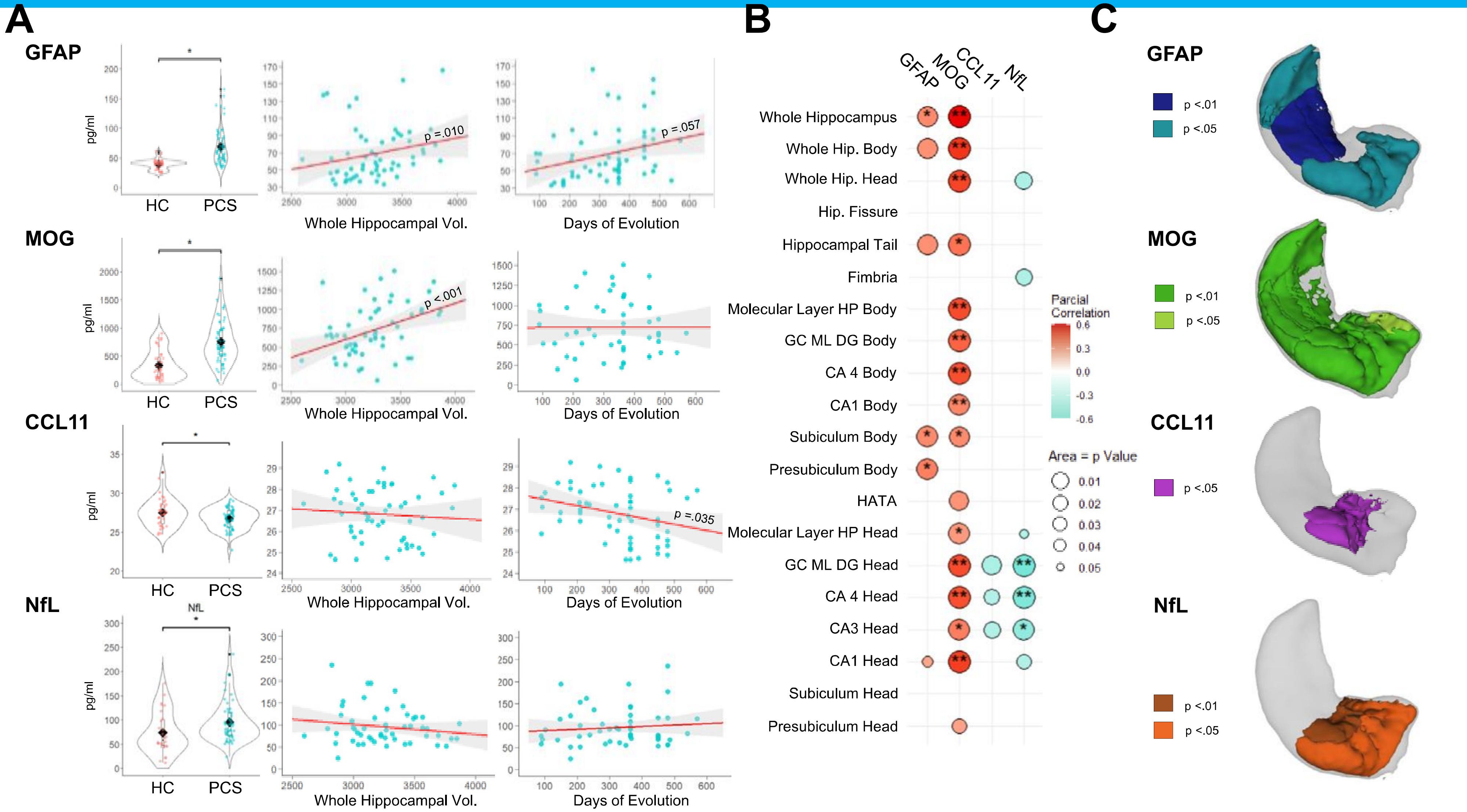
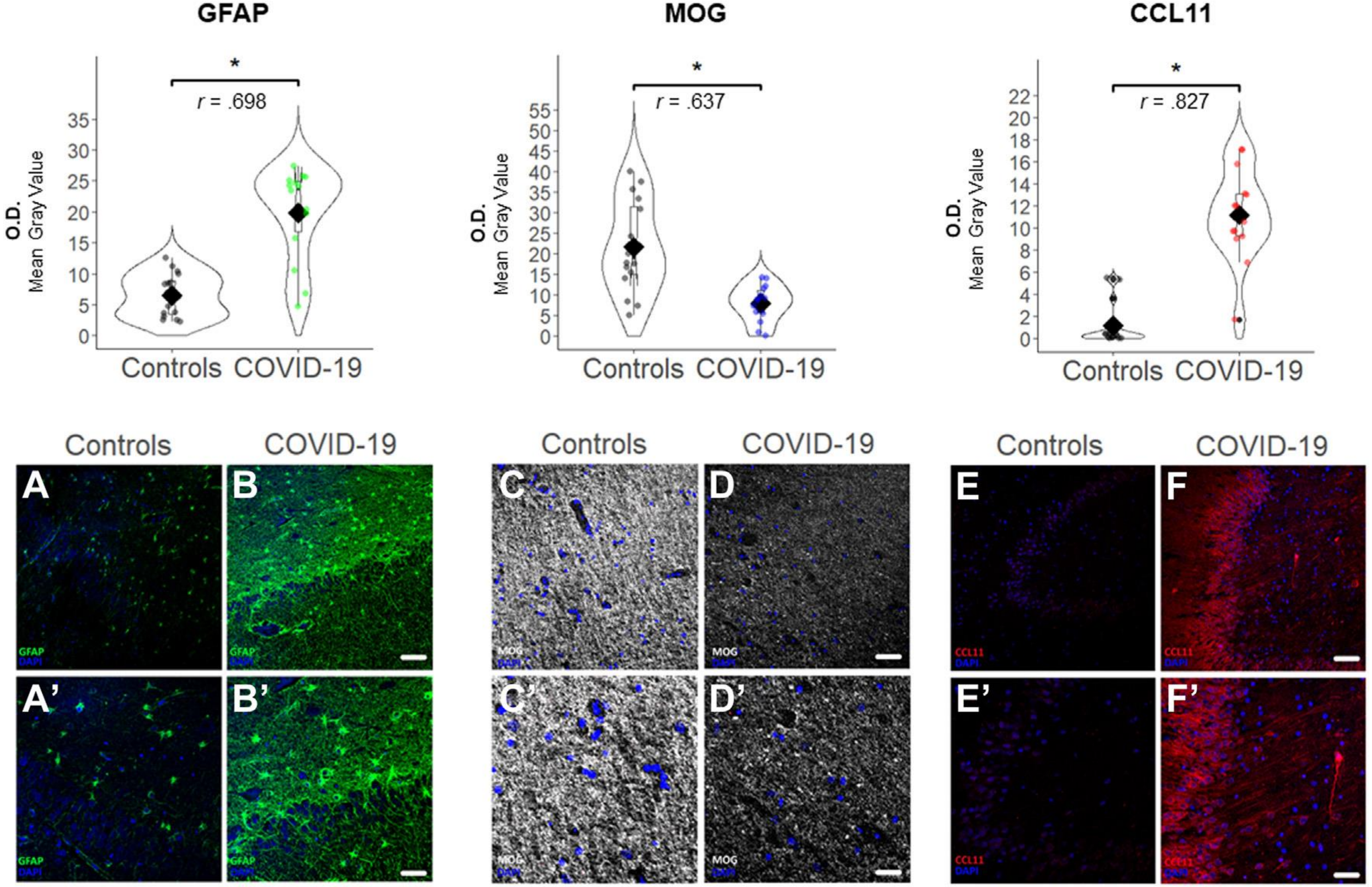


A
Zscore
0.4
0.2
0.0
-0.2
HC
PCS
*p<.01
*p<.0017 (bonf.)
Presubiculum Head
Subiculum Head
CA1 Head
CA3 Head
CA4 Head
GC ML DG Head
Molecular Layer HP Head
HATA
Presubiculum Body
Subiculum Body
CA1 Body
CA4 Body
GC ML DG Body
Molecular Layer HP Body
Fimbria
Hippocampal Tail
Hip. Fissure
Whole Hip. Head
Whole Hip. Body
Whole Hippocampus
Head
Body
B
Whole Hippocampus
Zscore
HC
PCS
C
0.099 <= η2 < 0.100
0.100 <= η2 < 0.145
0.145 <= η2 < 0.248
0.248 <= η2 < 0.300
η2 >= 0.300
D
HATA
Molecular Layer HP Head
GC ML DG Head
CA4 Head
CA3 Head
CA1 Head
Subiculum Head
Presubiculum Head
Span Forward
Span Backward
Corsi Forward
Corsi Backward
ROCF Copy (Time)
SDMT
Stroop W
Stroop C
Stroop W-C
Fluency P
Fluency M
Fluency R
FCSRT Free Recall Trial 1
FCSRT Total Free Recall
FCSRT Total Recall
FCSRT Delayed Free Recall
FCSRT Delayed Total Recall
ROCF Recall 3 mins
ROCF Recall 30 mins
ROCF Recognition
ROCF Copy
VOSP OD
VOSP PS
VOSP PD
VOSP NL
JLO
Fluency Animals
BNT
Partial Correlation
0.50
0.25
0.00
-0.25
-0.50
Area = p Value
0.01
0.02
0.03
0.04
0.05



A
GFAP
MOG
CCL11
NfL
pg/ml
HC
PCS
Whole Hippocampal Vol.
Days of Evolution
p =.010
p =.057
p <.001
p =.035
B
GFAP
MOG
CCL11
NfL
Whole Hippocampus
Whole Hip. Body
Whole Hip. Head
Hip. Fissure
Hippocampal Tail
Fimbria
Molecular Layer HP Body
GC ML DG Body
CA 4 Body
CA1 Body
Subiculum Body
Presubiculum Body
HATA
Molecular Layer HP Head
GC ML DG Head
CA 4 Head
CA3 Head
CA1 Head
Subiculum Head
Presubiculum Head
Parcial Correlation
Area = p Value
C
p <.01
p <.05


GFAP
MOG
CCL11
*
r = .698
r = .637
r = .827
O.D.
Mean Gray Value
Controls
COVID-19
Controls
COVID-19
A
B
C
D
E
F
A'
B'
C'
D'
E'
F'
GFAP
DAPI
MOG
DAPI
CCL11
DAPI

Summary – SARS-CoV2 & Inflammation

- SARS-CoV-2 may affect the central nervous system in different ways, including:
  - Neuroinflammation derived from the immune response to the virus in the respiratory system.
  - Autoimmune response
  - Direct infection of the brain by the virus (rare)
  - Reactivation of latent herpesvirus
  - Vascular and thrombotic events, blood-brain barrier disruption
  - Hypoxia due to lung and multi-system failure
- Neuroinflammation seems to have a central role in several of these mechanisms.

Conclusions – Take home messages

- Post COVID condition is a novel and heterogeneous syndrome, in which brain dysfunction plays an important role in the pathophysiology.
- There are several mechanisms described, not mutually exclusive.
- Cognitive symptoms have a neurobiological basis, although the interplay with fatigue (cognitive fatigue) and neuropsychiatric symptoms is complex and should be elucidated individually.
- Neuroinflammation seems key in the pathophysiology.
- Evidence in Long COVID contributes to the knowledge about the interaction between systemic or extra-brain disorders and brain function.
- Further investigation is urgently needed to better understand the effects of COVID-19 in brain and inflammation.

Thank you so much for your attention!

Jordi Matías-Guiu
Department of Neurology.
Hospital Clínico San Carlos. Madrid.
Instituto de Investigación Sanitaria San Carlos (IdISSC). Madrid

@MatiasGuiu
@iNeuroClinico
jordi.matias-guiu@salud.madrid.org

Hospital Clínico San Carlos
SaludMadrid

IdISSC INSTITUTO de INVESTIGACIÓN SANITARIA Hospital Clínico San Carlos

COVID-19, Brain and Inflammation

Jordi Matías-Guiu
Department of Neurology.
Hospital Clínico San Carlos. Madrid.
Instituto de Investigación Sanitaria San Carlos (IdISSC). Madrid

@MatiasGuiu
@iNeuroClinico
jordi.matias-guiu@salud.madrid.org

Hospital Clínico San Carlos SaludMadrid

IdISSC INSTITUTO de INVESTIGACIÓN SANITARIA Hospital Clínico San Carlos