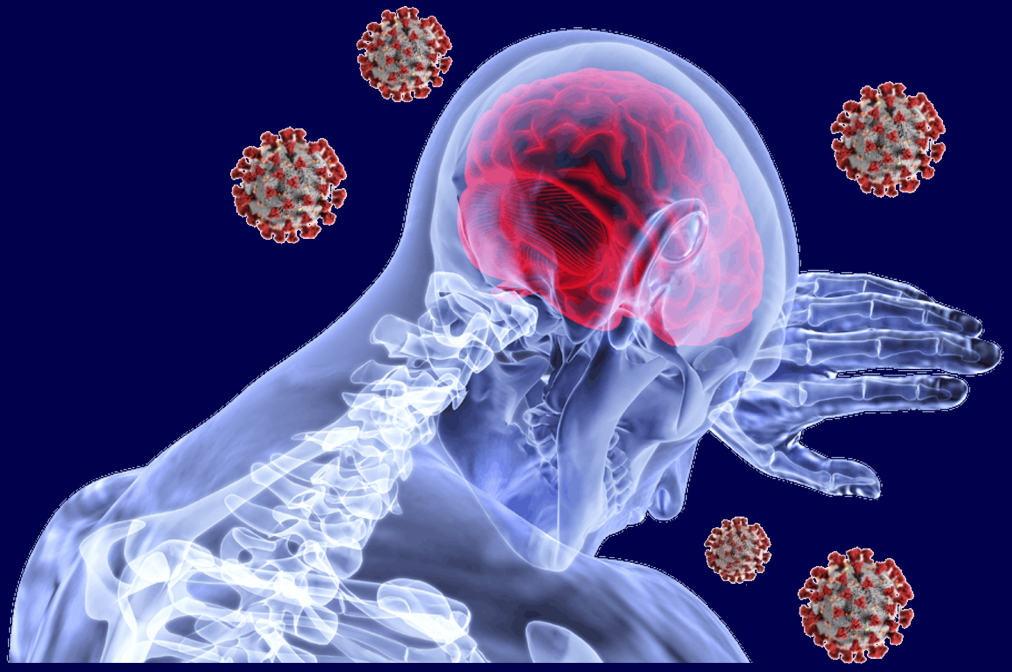
‘Brain Fog’ and cognitive impairment: pathogenesis and clinical presentations



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Definition: Brain Fog

- Brain fog is a colloquial term for a common complaint among patients with Post-acute Covid-19.

- It is an umbrella term used to describe the constellation of cognitive function impairment such as confusion, short-term memory loss, dizziness, and inability to concentrate.

Krishnan et al., *J Health Serv Psychol*, 2022
Garg et al., *Int J Gen Med*, 2021

Lived experience of ‘brain fog’

- 50 participants’ own descriptions of their symptoms
- Five focus groups of 60–90-minute duration were held via Zoom
- An accessible and well-known shorthand to disclose their wide-ranging cognitive difficulties to others

Callan et al, *BMJ Open*, 2022

Brain fog symptoms

Difficulty with the ability to:

- think and reason
- concentrate,
- remember things,
- process information,
- learn, speak, and understand
- often related to specific domains of cognitive function— particularly, executive function, attention, memory and language, with most describing difficulties across all of these domains

Prevalence of Brain Fog

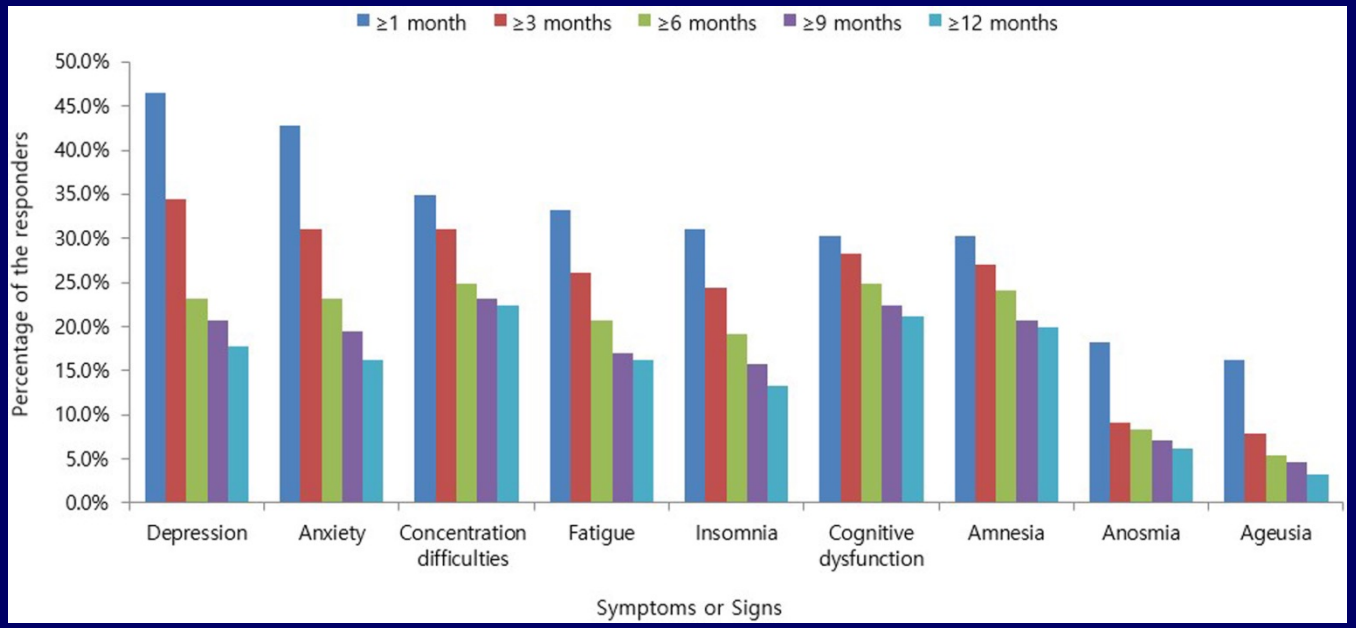
	Brain fog, $N = 194$	No brain fog, $N = 2502$	p, df
Sex (female: male)	102: 92 (ratio: 1.11)	1120: 1382 (ratio: 0.81)	0.036, 1
Age (mean ± SD), years	42 ± 8	41 ± 9	0.109
Length of hospital stay (mean ± SD), days	6·9 ± 4.9	6·4 ± 6.1	0.221
Respiratory problems at the onset	180 (93%)	2195 (88%)	0.038, 1
Neurological problems at the onset	40 (21%)	486 (19%)	0.707, 1
Gastrointestinal problems at the onset	27 (14%)	405 (16%)	0.417, 1
Pre-existing chronic medical problems	56 (29%)	652 (26%)	0.398, 1
ICU admission[a]	28 (14%)	200 (8%)	0.004, 1

Abbreviations: *df*, degree of freedom; ICU, intensive care unit; SD, standard deviation.
[a]Nine missing values.

- Cohort study from Fars, Southern Iran
- Telephonic follow-up post 3 months
- 194 of 2696 (7.2%) developed Brain Fog

Asadi-Pooya et al., *J Med Virol*, 2021

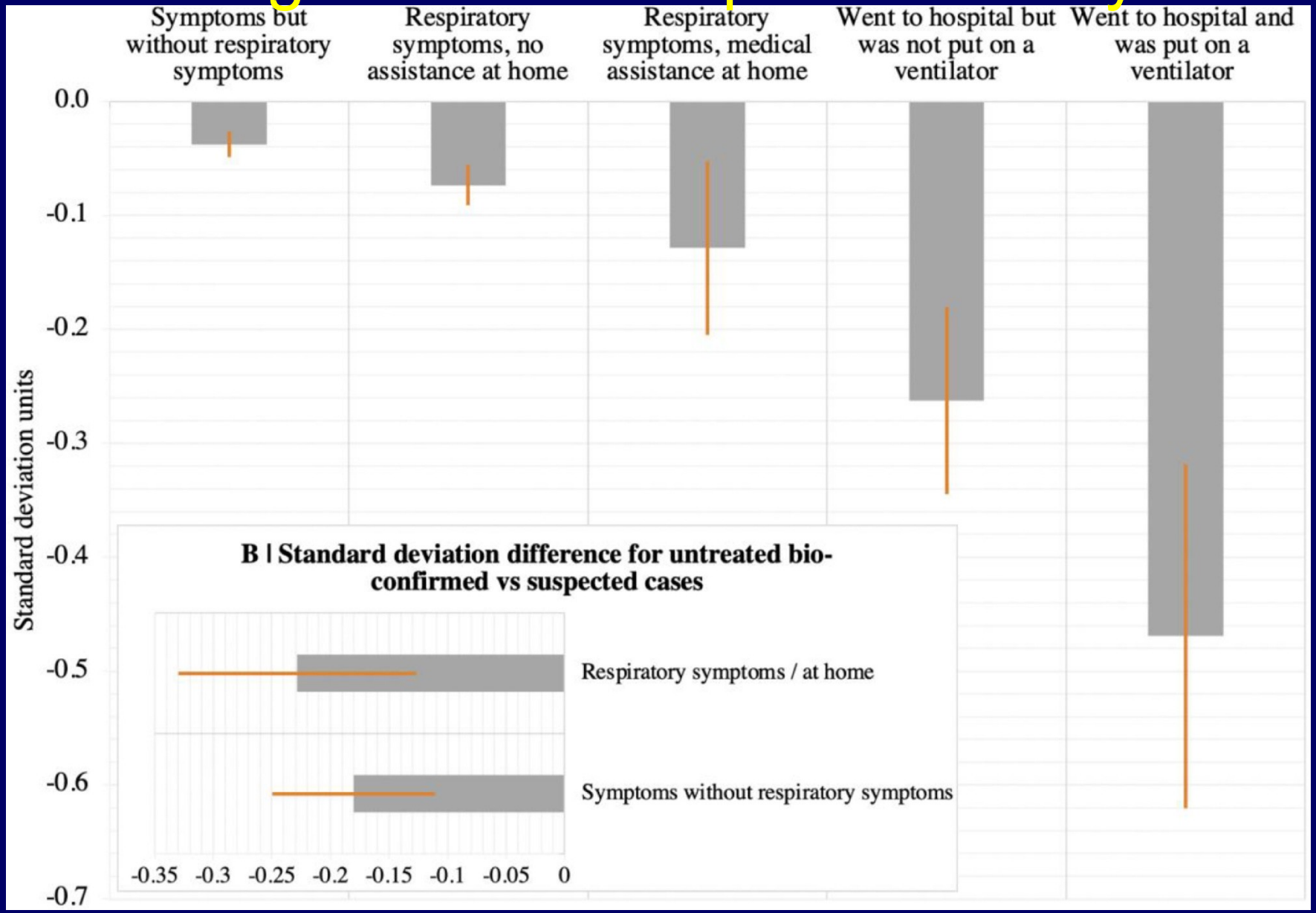
Prevalence of Brain Fog



Duration of key persistent symptoms or signs after acute COVID-19 infection
Online survey from South Korea of 241 participants

Kim et al., *BMC Infect Dis*, 2022

Great British Intelligence Test: Cognitive deficits post recovery



Possible mechanisms

N -	Neuronal degeneration, Neuro-genesis impaired Bulfamante, *J Neurol*, 2021; Solomon et al., N Engl J Med, 2020
C	Coagulopathy, Cellular apoptosis Ramakrishnan, *Front Immunol*, 2021
O	Oxygen deprivation (hypoxic-ischaemic), Oxidative stress Solomon et al., N Engl J Med, 2020
V	Vasculopathy, Viral invasion? Zubair, *JAMA Neurol*, 2020
I	Inflammation, Immune dysregulation Bodin, *Nat Med*, 2021; Matschke, *Lancet Neurol*, 2020
D	Dysautonomia, Disturbed metabolism Tsivgoulis et al., *Eur J Neurol*, 2021; Tsivgoulis et al., *J Neurol Neurosurg Psychiatry*, 2021

Stefanou et al., *Ther Adv Chronic Dis*, 2022

PET-CT studies

Hypometabolism in ACE2-rich brain areas:

- Orbital gyrus
- Amygdala
- Hippocampus
- Hypothalamus-thalamus
- Brain stem

?autoimmunity

Gut and brain

- Prolonged SARS-COV2 shedding in GIT post-infection
- 7/14 (50%) intestinal biopsies: SARS-COV2 nucleic acids and protein persisting at 4 months
- More studies required to elucidate link

Gaebler et al. Nature 2021:591: 639–644

Are neurological manifestation a result of direct invasion of CNS by the virus?

Direct invasion of CNS by COVID-19 virus are rare

Cerebrospinal Fluid Analysis Post–COVID-19 Is Not Suggestive of Persistent Central Nervous System Infection

Finja Schweitzer, PhD,[1†] Yasemin Goereci, MD,[1†] Christiana Franke, MD,[2] Steffi Silling, PhD,[3] Fabian Bösl, MD,[2] Franziska Maier, PhD,[4] Eva Heger, PhD,[3] Birgit Deiman, PhD,[5,6,7] Harald Prüss, MD,[2,8] Oezguer A. Onur, MD,[1,9] Florian Klein, MD,[3,10,11] Gereon R. Fink, MD,[1,9] Veronica Di Cristanziano, MD,[3†] and Clemens Warnke, MD[1†]

This study was undertaken to assess whether SARS-CoV-2 causes a persistent central nervous system infection. SARS-CoV-2–specific antibody index and SARS-CoV-2 RNA were studied in cerebrospinal fluid following COVID-19. Cerebrospinal fluid was assessed between days 1 and 30 (n = 12), between days 31 and 90 (n = 8), or later than 90 days (post–COVID-19, n = 20) after COVID-19 diagnosis. SARS-CoV-2 RNA was absent in all patients, and in none of the 20 patients with post–COVID-19 syndrome were intrathecally produced anti–SARS-CoV-2 antibodies detected. The absence of evidence of SARS-CoV-2 in cerebrospinal fluid argues against a persistent central nervous system infection as a cause of neurological or neuropsychiatric post–COVID-19 syndrome.

ANN NEUROL 2022;91:150–157

SARS-CoV-2 RNA absent in all patients
Schweitzer et al., *Ann Neurol*, 2022

Jarius *et al. Journal of Neuroinflammation* 2022, **19**(1):19
https://doi.org/10.1186/s12974-021-02339-0

Journal of Neuroinflammation

RESEARCH Open Access

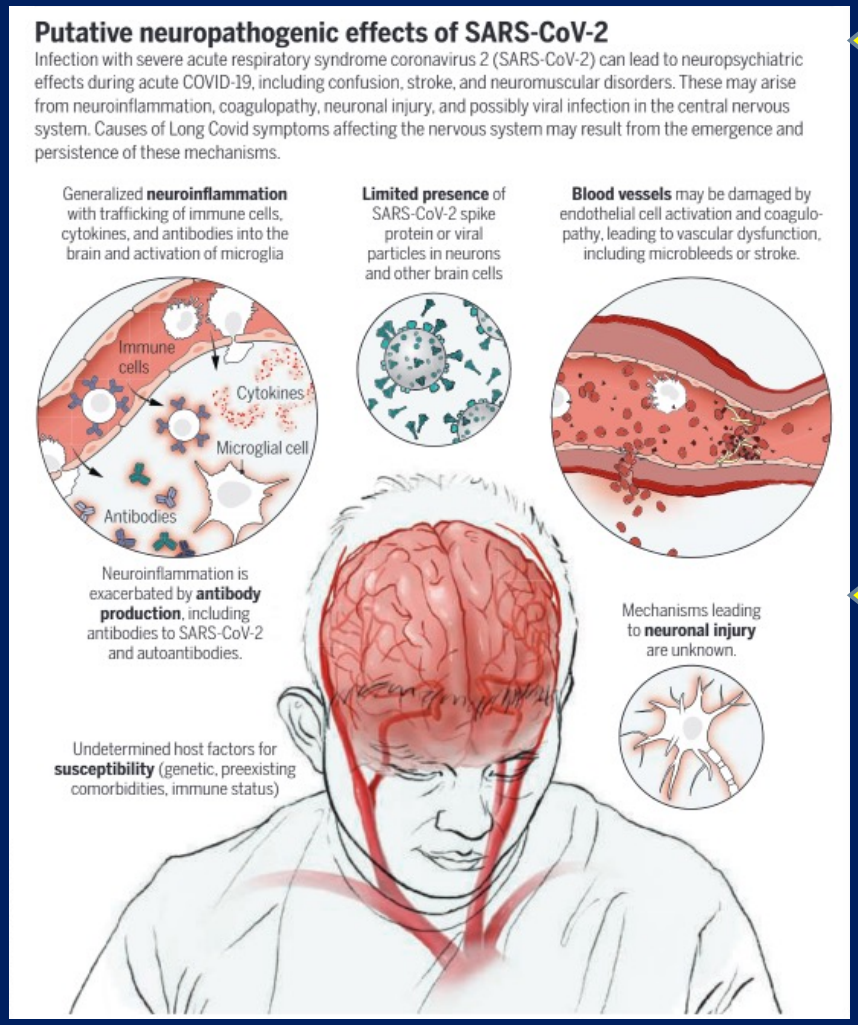
Cerebrospinal fluid findings in COVID-19: a multicenter study of 150 lumbar punctures in 127 patients

Sven Jarius[1*], Florence Pache[2], Peter Körtvelyessy[2,3], Ilijas Jelčić[4], Mark Stettner[5], Diego Franciotta[6], Emanuela Keller[7], Bernhard Neumann[8,9], Marius Ringelstein[10,11], Makbule Senel[12], Axel Regeniter[13], Rea Kalantzis[2], Jan F. Willms[14], Achim Berthele[15], Markus Busch[16], Marco Capobianco[17], Amanda Eisele[18], Ina Reichen[4], Rick Dersch[19], Sebastian Rauer[19], Katharina Sandner[20], Ilya Ayzenberg[21,22], Catharina C. Gross[23], Harald Hegen[24], Michael Khalil[25], Ingo Kleiter[21], Thorsten Lenhard[26], Jürgen Haas[1], Orhan Aktas[10], Klemens Angstwurm[8], Christoph Kleinschnitz[5], Jan Lewerenz[12], Hayrettin Tumani[12,27], Friedemann Paul[28], Martin Stangel[29†], Klemens Ruprecht[2†], and Brigitte Wildemann[1†]; in cooperation with the German Society for Cerebrospinal Fluid Diagnostics and Clinical Neurochemistry

SARS-CoV-2 RNA absent in all 76 patients, where tested
SARS-CoV-2-IgG-antibody index (AI) found in 2 of 19 patients, where tested

Jarius et al., *J Neuroinflammation*, 2022

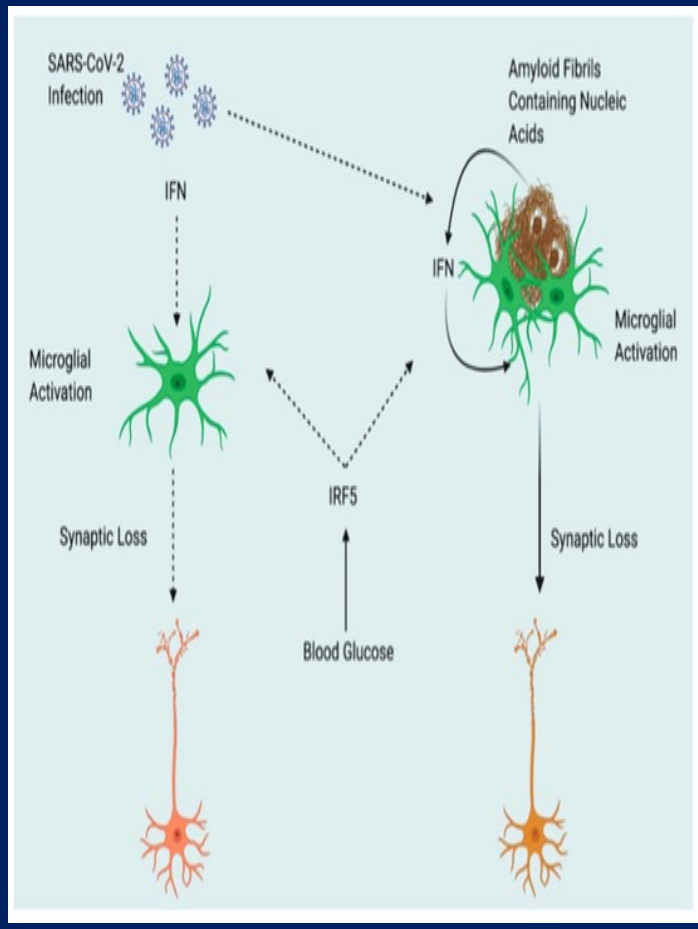
Possible mechanism



Neuro-inflammation

Damage to small vessels of the brain

Neuronal injury via Amyloid Fibrils & Microglial activation



Serena Spudich & Avindra Nath, *Science*, 2022

Hardan et al., *Medicina*, 2021

Large Genetic studies implicate same gene for COVID-19 severity and Alzheimer's Disease (AD)

- GWAS of 2,244 critically ill (208 ICUs form UK) vs 5 times population controls → OAS1 locus: Pairo-Castineira et al., *Nature*, 2021
- Has a protective haplotype of ~75 kilobases derived from Neanderthals: Zeberg & Pääbo, *Proc Natl Acad Sci USA*, 2021
- OAS1 variant, rs1131454 associated with AD, 1313 sporadic AD vs 1234 controls: Magusali et al., *Brain*, 2021
- Human induced pluripotent stem cell-derived microglia with lowered OAS1 expression, shows exaggerated production of TNF-α with IFN-γ stimulation: Magusali et al., *Brain*, 2021

Thank you