

Neurobiological changes associated with reduced neurocognitive performance: A systematic review on post-COVID sequelae in adults

Cambios neurobiológicos se asocian a desempeños neurocognitivos reducidos: una revisión sistemática sobre secuelas post-COVID en adultos

Gabriel M. Sepúlveda¹, Camilo Arévalo-Romero², Josefina Mattoli-Sánchez³,
Daniel Rojas-Líbano⁴

Correspondencia:

Daniel Rojas-Líbano

daniel.rojasli@mail.udp.cl

RECIBIDO: MAYO 2025 | PUBLICADO: AGOSTO 2025

Abstract

Background: Recent estimates suggest that at least 65 million individuals worldwide have experienced post-COVID sequelae, with neurocognitive impairments among the most prevalent. **Aim:** To synthesize results about neurobiological findings associated with neurocognitive difficulties in post-COVID adult patients, as reported in the scientific literature. **Methods:** A systematic review was conducted according to PRISMA guidelines using Web of Science, PubMed, and Scopus databases. Twenty-six scientific articles meeting the inclusion criteria were analyzed. Vote counting based on statistical significance was employed as a synthesis method. **Results:** In most of the included articles with significant results [87.5%; n =14] alterations of at least one neurocognitive domain in post-COVID patients are described. In 15 of 16 studies describing significant associations, neuropathological changes are confirmed among patients. Most [94%] studies reporting associations found a statistical significance between diminished neurocognitive performances and neurobiology. Particularly notable is the association between lower performance in global cognition and neuropathological findings in brain anatomy (e.g. atrophy, tissue damage, ischemia). **Conclusions:** The analysis presented in this review offers relevant background to inform policy decisions regarding the neurocognitive sequelae of COVID-19 and supports clinical decision-making for professionals caring for patients with this profile.

Keywords: Post-COVID sequelae; neurocognitive domains; neuropsychological performance; neuropathological findings, Coronavirus.

Resumen

Contexto: Estimaciones recientes sugieren que al menos 65 millones de personas en todo el mundo han padecido secuelas post-COVID y las afectaciones neurocognitivas se encuentran entre las más prevalentes. **Propósito:** Sintetizar los resultados acerca de hallazgos neurobiológicos asociados a dificultades neurocognitivas en pacientes adultos post-COVID, según lo reportado por la literatura científica. **Métodos:** Una revisión sistemática se desarrolló de acuerdo a las orientaciones PRISMA, empleando las bases de datos Web of Science, Pubmed y Scopus. Veintiséis artículos científicos que cumplieron con los criterios de inclusión fueron analizados. Un conteo de votos basado en la significancia estadística se usó como método de síntesis. **Resultados:** En la mayoría de los artículos incluidos [87.5%; n =14] se describieron alteraciones en al menos un dominio neurocognitivo en pacientes post-COVID. En 15 de 16 estudios que describen asociaciones significativas, se confirmaron cambios neuropatológicos en los pacientes. La mayoría [94%] de los estudios que reportan asociaciones, encontraron una relación estadísticamente significativa entre desempeños neurocognitivos disminuidos y cambios neurobiológicos. Particularmente destacada es la asociación entre desempeños disminuidos en la cognición global y hallazgos neuropatológicos en la anatomía cerebral (p.e. atrofia, daño tisular, isquemia). **Conclusiones:** El análisis presentado en esta revisión ofrece antecedentes relevantes tanto para informar a las políticas a cargo de abordar las secuelas neurocognitivas del COVID-19 como a la toma de decisiones clínica de profesionales al cuidado de pacientes con este perfil.

Palabras clave: Secuelas post-COVID; dominios neurocognitivos; rendimiento neuropsicológico; hallazgos neuropatológicos; Coronavirus.

¹ Programa de Doctorado en Psicología, Facultad de Psicología, Universidad Diego Portales. Santiago, Chile.

² Centro de Estudios en Neurociencia Humana y Neuropsicología, Facultad de Psicología, Universidad Diego Portales. Santiago, Chile; Instituto de Neurociencias e Investigación, Santiago, Chile.

³ Centro de Estudios en Neurociencia Humana y Neuropsicología, Facultad de Psicología, Universidad Diego Portales. Santiago, Chile; Programa de Pregrado en Psicología, Facultad de Psicología, Universidad Diego Portales. Santiago, Chile.

⁴ Centro de Estudios en Neurociencia Humana y Neuropsicología, Facultad de Psicología, Universidad Diego Portales. Santiago, Chile



Este es un artículo publicado en acceso abierto (Open Access), bajo licencia de Creative Commons Attribution, que permite el uso, distribución y reproducción en cualquier medio, sin restricciones, siempre que el trabajo original sea correctamente citado.

1. INTRODUCTION

As of July 2025, 778 million people have become infected with Coronavirus Disease 2019 (COVID-19), and more than 7 million deaths have occurred due to the disease (World Health Organization, 2025). According to some estimates, a minimum of 65 million individuals worldwide have been affected by post-COVID sequelae, with more than 200 symptoms identified, impacting virtually every organ system (Davis et al., 2023).

In the present work, post-COVID sequelae will be understood as all symptom presentations occurring due to and after the acute phase of COVID-19 infection. There is some degree of consensus about the acute phase of COVID-19 encompassing the first four weeks following infection (Nalbandian et al., 2021; NICE, 2020). Post-COVID sequelae will thus be considered as symptoms occurring after this period, with an indefinite duration and potentially chronic course in some cases. These sequelae consist of persistent post-infection multisystem conditions, commonly including symptoms such as fatigue, breathlessness, and cognitive impairment (The Lancet, 2023).

In an umbrella review, Nittas and coworkers (2022) estimated that the prevalence of post-COVID syndromes among infected adults ranges from 26% to 41%.

The incidence of post-COVID sequelae remains a significant concern, as different variants and severity levels of Coronavirus disease have been shown to cause significant sequelae. A systematic review and meta-analysis conducted by Du and his colleagues (2022) suggested no significant difference among post-COVID syndromes caused by different viral variants. Furthermore, an intriguing aspect of post-COVID sequelae is that, although they are typically observed in patients who experienced severe acute phases, they also manifest in individuals who had mild or even asymptomatic acute phases (Damiano et al., 2022; Hadad et al., 2022; Lai et al., 2023; Malkova et al., 2021).

Different studies have indicated that neurocognitive functions are among the most commonly and significantly affected by post-COVID sequelae (Birberg et al., 2022; Monje & Iwasaki, 2022). Unlike cognitive functions, which pertain solely to mental processes for

acquiring knowledge, we will focus on neurocognitive capacities. These capacities, while cognitive, are associated with the structures and functions of the brain, whose performances are observed through neuropsychological assessments. Neurocognitive assessment tools enable the estimation of behavioral performances reflecting brain function or dysfunction (Lezak et al., 2012).

A systematic review and meta-analysis by Pinzón and colleagues (2022) determined that the overall prevalence of neurocognitive disorder was 35.4% among post-COVID patients. A study of more than 1.3 million participants who had COVID-19, showed an increased incidence of cognitive impairment, seizures, dementia, and other neurocognitive conditions that persisted for at least 2 years (Taquet et al., 2022). Among the most common neurocognitive symptoms in post-COVID syndromes, fatigue (in 58% of patients with long COVID), attentional deficits (27%), and memory loss (16%) have been reported (López-León et al., 2021).

Thus, neurocognitive symptoms may appear during the acute phase, in the following period, and can persist for an extended period, exhibit fluctuations, or experience relapses over time (Bispo et al., 2022). More specifically, these symptoms can last for years, and some of them are suspected to be lifelong (Davis et al., 2023). It has been estimated that 16% of patients exhibit neurocognitive deficits two months post-infection, with the incidence rising to 26% one year later (L. A. Cysique et al., 2022). Furthermore, decreased performance on neurocognitive assessments has been observed in patients who experienced a mild acute phase of the disease (Amalakanti et al., 2021), including those who did not report any cognitive complaints (Ariza et al., 2022). Additionally, it is concerning that the efficacy of vaccines in reducing the incidence of neurocognitive sequelae appears to be minimal (Antonelli et al., 2022).

Post-COVID neurocognitive alterations are commonly associated with neurobiological disorders, particularly those affecting the brain (Monje & Iwasaki, 2022). Primary central nervous system involvement, through direct viral infiltration, and secondary manifestations impacting the nervous system via other tissues, constitute symptoms that reveal a more extensive compromise to the nervous

system than initially expected (Finsterer & Stollberger, 2020).

The neurobiological changes reported as a consequence of COVID-19 are both neuroanatomical and neurophysiological (Guo et al., 2024). Neuroanatomical abnormalities involving the nervous system have been systematically reported following COVID-19, potentially affecting patients in the medium and long term. These abnormalities are particularly noticeable in the brain and exhibit considerable variability in location and nature (Kiyak et al., 2024). Similarly, the neurophysiological consequences of Coronavirus infection, observed both in the acute phase and subsequent periods, have been consistently documented. Scientific reports confirm alterations across various physiological modalities, with significant emphasis on those measuring brain function (Haykal & Menkes, 2023). COVID-19 has the potential to impact the nervous system across all stages of the life cycle. Evidence suggests that it can alter the nervous system of fetuses *in utero* (Falahi et al., 2023), children (Singer et al., 2021), and adolescents (Guido et al., 2022). These alterations are corroborated by distinct neuropathological findings observed in *post-mortem* brain examinations (Younger, 2023). However, the risk of sequelae is estimated to be higher in adults compared to younger or child populations (Taquet et al., 2022).

Although studies, such as Zhao et al. (2023), report on the persistent effects of COVID-19 on neurocognitive performance and brain neurobiology, they notably do not address both dimensions in the same participants. The separate description precludes the possibility of describing potential associations between both dimensions. Counteracting this, some studies have called for identifying neurobiological correlates associated with neurocognitive impairments in patients who have had COVID-19 (Perrottelli et al., 2022). The analysis of studies providing comprehensive data on neurocognitive performance, alongside the report of anatomical and physiological neurobiological changes from the same participants, can enhance our understanding of the interactions among phenomena. A more in-depth examination of this topic could inform health policies related to the care of patients with neurocognitive impairments, particularly those experiencing post-

COVID-19 sequelae, by guiding efforts toward the most affected population profiles, symptomatology, and neurocognitive domains.

Therefore, the research question for this systematic review is: what are the neurobiological changes that accompany reduced neurocognitive performance in adult patients with post-COVID sequelae, as reported in scientific articles? In this way, we set ourselves the goal to investigate how post-COVID-19 sequelae impact neurocognitive performances in relation to neurobiological findings, according to the available scientific literature. To reach this goal, we propose three objectives: First, to search the specialized scientific literature for articles that report neurocognitive performances and neurobiological changes in the same participants affected by post-COVID-19 sequelae. Secondly, to synthesize the results in neurocognitive performance and neurobiological changes in those articles that have described measures in both aspects on the same participants, and lastly, to analyze the relationship between neurocognitive performances and neurobiological changes according to the accepted articles.

2. METHODS

The development of this systematic review was guided by the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses; Moher et al., 2009). To structure the research process, a protocol was developed with the study problem, its justification, objectives and methods. This is available in the Open Science Framework (OSF).

2.1 Eligibility Criteria

The main objective of this research was to review studies on possible neurocognitive sequelae in individuals after COVID-19 infection, and how this relates to neurobiological alterations. The neurocognitive evidence of interest focused on neurocognitive objective performance, without considering measures of emotional states (e.g., emotional reactivity, depression, anxiety, among others). The neurobiological evidence of

interest focused on measures of structure and function in the central nervous system, especially the brain.

2.1.1 INCLUSION CRITERIA

- Observational studies.
- Adult participant: samples from ages 18 and above.
- Samples from people who were infected with COVID-19.
- Studies that evaluated neurocognitive and neurobiological variables in the same participants.
- Research published in peer-reviewed journals.
- English language.

2.1.2 EXCLUSION CRITERIA

- Sample with neuropsychiatric/neurological diseases or brain injury previous to the infection.
- Non-human animal models.
- Books. Literature review articles. Pre-print publications.

2.2 Information Sources

The advanced search was performed in three databases: Web of Science, PubMed and Scopus. After the review process, 26 studies met the inclusion criteria. The search was carried out without year filters and was undertaken in April 2023.

2.3 Advanced Search Strategy

The advanced search syntax was: COVID AND (*Neuropsycholog** OR *Neuropsychiatr** OR *Cognitive* OR *Mental fog* OR *Brain fog* OR *Neurocognitive*) AND (*Brain* OR *Central Nervous System* OR *Neurophysiology* OR *Neurophysiological* OR *Neuroimage* OR *Neuroimaging* OR *Neurological* OR *Neuropathology* OR *Encephalopathy* OR *Pathophysiological* OR *Magnetic resonance imaging* OR *MRI* OR *Functional magnetic resonance imaging* OR *fMRI* OR *Transcranial magnetic stimulation* OR *TMS* OR

Electroencephalogram OR *EEG* OR *Non-invasive brain stimulation* OR *NIBS* OR *Positron Emission Tomography* OR *PET* OR *Computed Tomography* OR *CT* OR *CAT* OR *Electrocardiography* OR *EKG* OR *ECG*).

The search fields were “All fields” (Web of Science and PubMed) and “Title” (Scopus). Only in PubMed three filters were used to increase the precision of the search: SPECIES (Humans); LANGUAGE (English); AGE (Adult: 19+ years).

Notably, searches conducted using Spanish terms did not yield any articles meeting the selection criteria; consequently, this language was not included in the present review.

2.4 Study Selection

The study selection process was summarized in Figure 1, where the total number of articles obtained in the advanced search and those identified through other sources can be seen.

Studies selected through other sources come from the evaluation phase of the advanced search, when a relevant citation within an article was found and considered to meet the inclusion criteria for the review. The figure also summarizes the number of studies after removing duplicates and the number of studies excluded for not meeting the inclusion criteria. The advanced search was carried out by GMS (all authors' initials in the Declarations section), and the review and selection process of articles was carried out by the entire team, holding weekly meetings during the process. After a full-text review, 26 articles were selected for qualitative synthesis and analysis through vote counting based on statistical significance.

Figure 1 (Flow Diagram Based on PRISMA Guidelines) schematically represents the selection process. Table 1 presents a summary of the PRISMA checklist for this systematic review.

Figure 1.

Flow Diagram Based on PRISMA Guidelines.

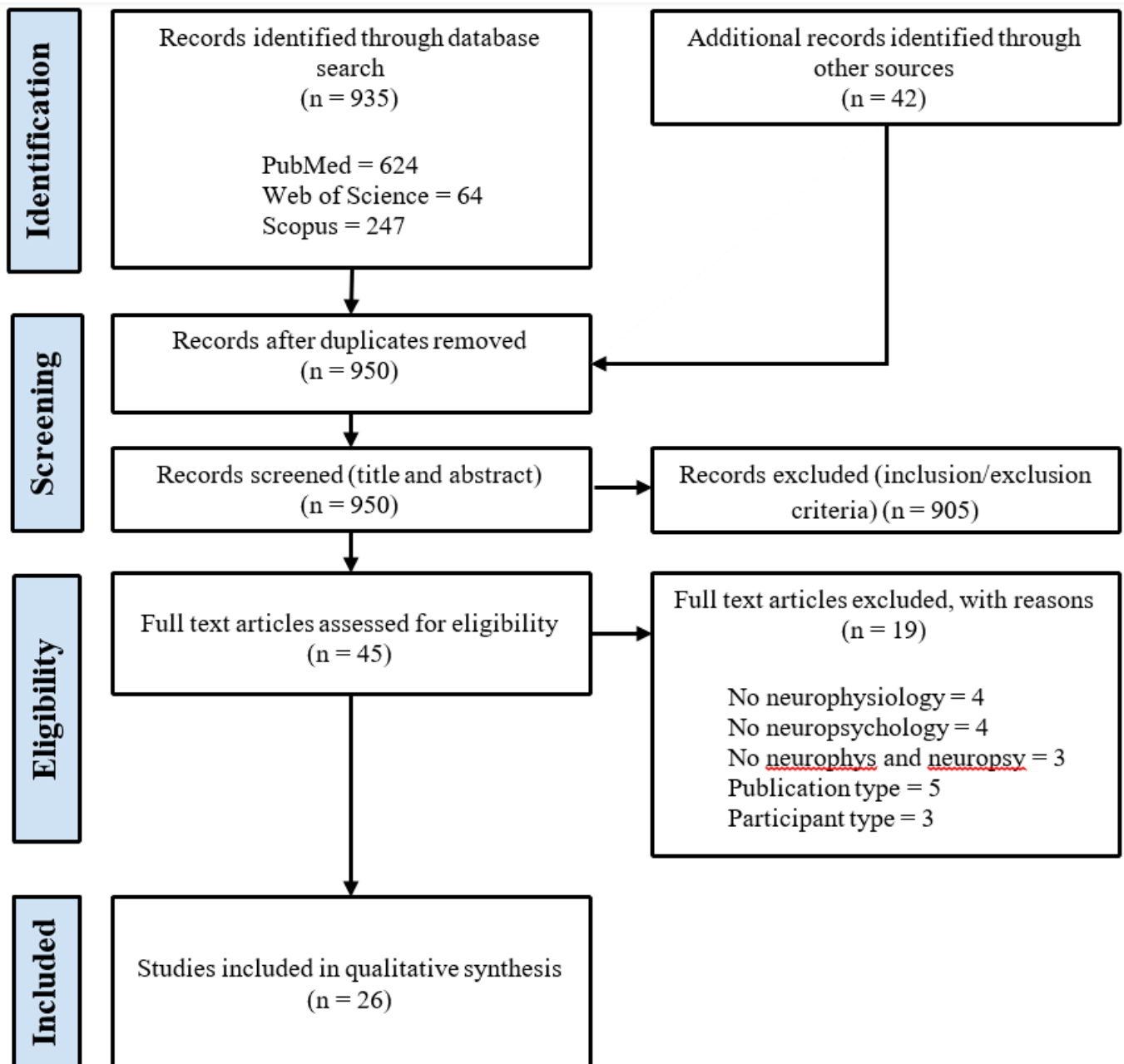


Table 1.
PRISMA Checklist.

Section and Topic	Item #	Checklist item	Reported on section
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Methods
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Methods
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Not applicable

Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Not applicable
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Methods
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Not applicable
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Results
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Results
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Results
Study characteristics	17	Cite each included study and present its characteristics.	Results
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Results
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Results

Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not applicable
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion
	23c	Discuss any limitations of the review processes used.	Discussion
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Declarations
Competing interests	26	Declare any competing interests of review authors.	Declarations
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found; template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Declarations

2.5 Data Extraction

The entire team extracted data into a database. Information was coded according to the type of study design, sample characteristics, post-COVID temporality, and neurocognitive and neurobiological evaluation techniques and outcomes.

2.6 Synthesis Method Without Meta-analysis

Vote Counting Based on Statistical Significance is suggested when data reports are inconsistent or incomplete. Using this method, findings that favor an intervention and are statistically significant can be compared with those that were not (Friedman, 2001; Higgins et al., 2019). The vote count based on statistical significance was used to analyze the rate of studies that presented statistically significant neurocognitive alterations and how many of these found a relationship between the neurocognitive alteration and the neurobiological variables. The statistical significance criterion used was $p < 0.05$.

2.7 Risk of Bias

A risk of bias analysis was carried out for each individual study as well as summary of risk of bias analysis using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies, and the Quality Assessment Tool for Case Series Studies (National Heart, Lung, and Blood Institute, 2019). This tool has been employed in prior systematic reviews (Amit et al., 2020; Costa-Cordella et al., 2021).

3. RESULTS

3.1 Description of Studies

3.1.1 STUDY SIZE

The reviewed studies encompassed a wide range of participant numbers, from 3 to 401. The least common participant count was 401 ($N = 1$), followed by counts ranging from 3 to 4 ($N = 3$), 102 to 192 ($N = 3$), 29 to 35 ($N = 4$), 8 to 20 ($N = 5$), and the most common counts fell between 46 and 74 participants ($N = 10$) (see Figure 2, Panel A). The total number of participants included in all studies was 3244.

3.1.2 PARTICIPANTS' MEAN AGE

Mean age ranged from 37.2 to 67 years ($M = 55.49$, $SD = 8.92$). One study did not provide age information (Rubega et al., 2022). The least common age range was 37 to 38 ($N = 2$), followed by 62 to 67 ($N = 6$), 42 to 50 ($N = 7$), and the most common age range was 54 to 60 ($N = 10$).

3.1.3 SEX DISTRIBUTION OF PARTICIPANTS

The distribution of participants' sex spanned from 0% to 76.09% female ($M = 45\%$, $SD = 23\%$) (see Figure 2, Panel C).

3.1.4 TIME OF EVALUATION AFTER COVID

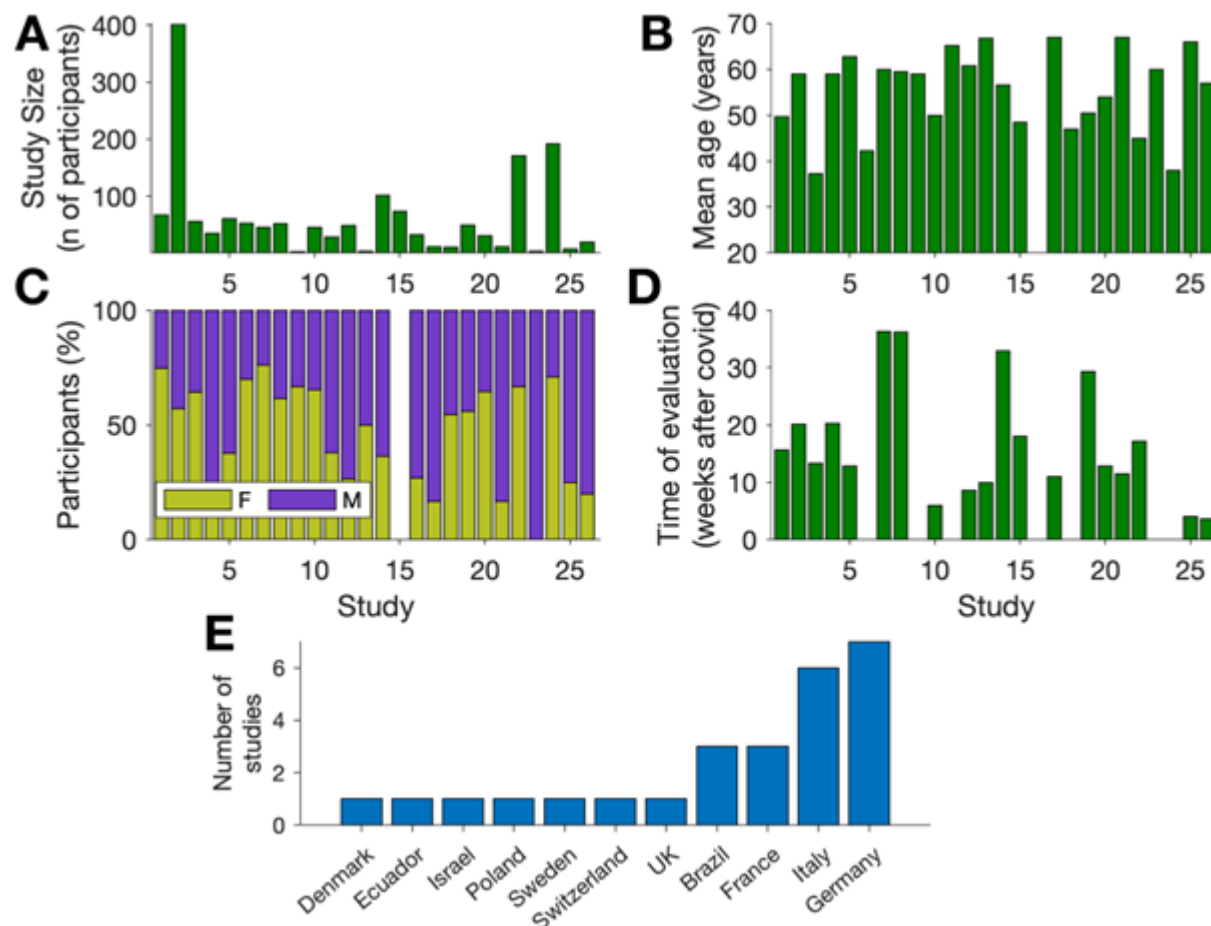
The time of neurobiological and neurocognitive evaluation of the participants ranged from 4 to 36 weeks after COVID-19 ($M = 17$, $Mdn = 13$, $SD = 10.19$ weeks). This showed an important variability across studies.

3.1.5 GEOGRAPHICAL DISTRIBUTION OF PARTICIPANTS

The majority of the reviewed studies were conducted in Germany ($N = 7$), followed by Italy ($N = 6$), Brazil and France ($N = 3$ each). The remaining articles were distributed across other European countries, Ecuador and Israel. For a detailed breakdown of the study locations, see Figure 2, Panel E.

Figure 2.

General Characteristics of the Studies Included in the Review (Source: Authors' own elaboration).



3.1.6 NEUROCOGNITIVE TESTS

Fourteen neurocognitive tests were employed across all studies, with each study utilizing one or more of these tests. The most used was MoCA (N = 15), followed by TMT (N = 11), DST (N = 8), STROOP (N = 7), ROCF (N = 6), FAB (N = 6), MMSE (N = 5), SDMT (N = 5), VFT (N = 3), BNT (N = 2), RAVLT (N = 2), SAT (N = 2), TAP (N = 2) and VOSP (N = 2). The rest of the tests were used in only one study each. For a graphical representation and abbreviations see Figure 3, top left panel.

3.1.7 NEUROCOGNITIVE DOMAINS

The neuropsychological processes examined by the authors were associated with key domains of neurocognitive function as defined by the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) (Sachdev et al., 2014), adding an additional external category termed “global cognition”. Executive function was the most studied domain (N = 35), followed by learning and memory (N = 27), global cognition (N = 24), complex attention (N = 21), language (N = 13), and perceptual-motor function (N = 11). For a visual representation, refer to Figure 3, bottom left panel. For references, see table 2.

Table 2.

General Characteristics of Selected Studies (Source: Authors' own elaboration).

Study	n COVID participants	n non-COVID participants	Sex	Study design	Neurocognitive tests	Neurocognitive domains	Neurobiological techniques	Neurobiological Processes and Structures
Ortelli et al. (2022a)	67	22	♀: 69% ♂: 31%	Cross-sectional	MoCA; FAB; STROOP; SAT; NAVON	EF; GC; CA	TMS	Motor evoked potential
Douaud et al. (2022)	401	384	♀: 57% ♂: 43%	Longitudinal	TMT; SNAP; FIS; NMT; PMT	EF; LM; CA; PM	MRI	Brain anatomy
Bispo et al. (2022)	56	37	♀: 62% ♂: 38%	Cross-sectional	MoCA; CANTAB	GC	MRI	Brain anatomy
Hellgren et al. (2022)	35	0	♀: 20% ♂: 80%	Longitudinal	RBANS	GC	MRI	Brain anatomy
Nersesjan et al. (2021)	61	0	♀: 38% ♂: 62%	Longitudinal	MoCA; CDT; 5M3WR	EF; LM; GC	CT; MRI; EEG	Brain anatomy; Brain anatomy; Electrophysiological activity
Appelt et al. (2022)	53	30	♀: 71% ♂: 29%	Longitudinal	MoCA; TMT; DST	LM; GC; CA	EEG	Electrophysiological activity
Andriuta et al. (2022)	46	0	♀: 76% ♂: 24%	Cross-sectional	MMSE; BNT; ROCF; F&C; D&P; DSCT; VFT; TMT; STROOP; BDSI	EF; LM; GC; CA; LA; PM	MRI	Brain anatomy
Del Brutto et al. (2021)	52	41	♀: 63% ♂: 37%	Longitudinal	MoCA	GC	MRI; EEG	Brain anatomy; Electrophysiological activity
Hugon et al. (2022)	3	0	♀: 67% ♂: 33%	Case report	MMSE	GC	PET	Brain metabolism
Hadad et al. (2022)	46	0	♀: 65% ♂: 35%	Cross-sectional	MoCA	GC	MRI; CT; EEG	Brain anatomy; Brain anatomy; Electrophysiological activity
Hosp et al. (2021)	29	0	♀: 38% ♂: 62%	Cross-sectional	MoCA	GC	PET; MRI	Brain metabolism; Brain anatomy
Cecchetti et al. (2022)	49	69	♀: 34% ♂: 66%	Longitudinal	MMSE; FAB; SDMT; DST; TMT; RAVLT; ROCF; VOSPB; SAND	EF; LM; GC; CA; LA; PM	MRI; EEG	Brain anatomy; Electrophysiological activity
Delorme et al. (2020)	4	0	♀: 50% ♂: 50%	Case report	MMSE; FAB	EF; GC	MRI; EEG; PET	Brain anatomy; Electrophysiological activity; Brain metabolism
Voruz et al. (2022)	102	0	♀: 36% ♂: 64%	Cross-sectional	STROOP; TMT; CLVFT; DST; CORSI; TAP; 16G&B; ROCF; BECLA; VOSPB; WAIS-IV P&M	EF; LM; CA; LA; PM	MRI; fMRI	Brain anatomy; BOLD signal
Ortelli et al. (2022b)	74	29	♀: 0% ♂: 100%	Cross-sectional	MoCA; SAT; STROOP	EF; GC; CA	TMS	Motor evoked potential

Rubega et al. (2022)	33	12	♀: 29% ♂: 71%	Cross-sectional	MoCA; FAB; STROOP; DST; RAVLT; TMT; SDMT	EF; LM; GC; CA	EEG	Electrophysiological activity
Versace et al. (2021)	12	10	♀: 23% ♂: 77%	Cross-sectional	FAB	EF	TMS	Motor evoked potential
Sklinda et al. (2021)	11	14	♀: 48% ♂: 52%	Cross-sectional	ACE-III; ROCF; CVLT; TMT; WAIS-R ST	GC; CA; LA; PM	MRI	Brain anatomy
Bungenberg et al. (2022)	50	0	♀: 56% ♂: 44%	Cross-sectional	MoCA; STROOP; TMT; DST; BNT; ROCF; TAP; RWT; VLMT	EF; LM; GC; CA; LA; PM	MRI	Brain anatomy
Dressing et al. (2022)	31	0	♀: 65% ♂: 35%	Longitudinal	HVLT; BVMT-R; DST; TMT; STROOP; SDMT; S&LFT; MoCA	EF; LM; GC; CA; LA	PET; MRI	Brain metabolism; Brain anatomy
Ortelli et al. (2021)	12	12	♀: 25% ♂: 75%	Cross-sectional	MoCA; FAB	EF; GC	TMS	Motor evoked potential
Fleischer et al. (2022)	171	0	♀: 67% ♂: 33%	Longitudinal	10WLR; d2; VFT; TMT; DST; SDMT	EF; LM; CA	MRI	Brain anatomy
Groiss et al. (2020)	4	0	♀: 0% ♂: 100%	Case report	MoCA; SDMT; MMSE	GC; CA	EEG	Electrophysiological activity
De Paula et al. (2022)	192	0	♀: 71% ♂: 29%	Cross-sectional	VFT; ROCF; LMT; TMT; VFS; SPT; DST	EF; LM; GC; CA; PM	MRI; PET	Brain anatomy; Brain metabolism
Blazhenets et al. (2021)	8	0	♀: 25% ♂: 75%	Longitudinal	MoCA	GC	PET	Brain metabolism
Rau et al. (2022)	20	35	♀: 38% ♂: 62%	Longitudinal	MoCA	GC	MRI; DMI; PET	Brain anatomy; Brain anatomy; Brain metabolism

Abbreviations (neurocognitive domains). EF: executive function. LM: learning and memory. GC: global cognition. CA: complex attention. LA: language. PM: perceptual motor functions.

3.1.8 NEUROBIOLOGICAL TECHNIQUES

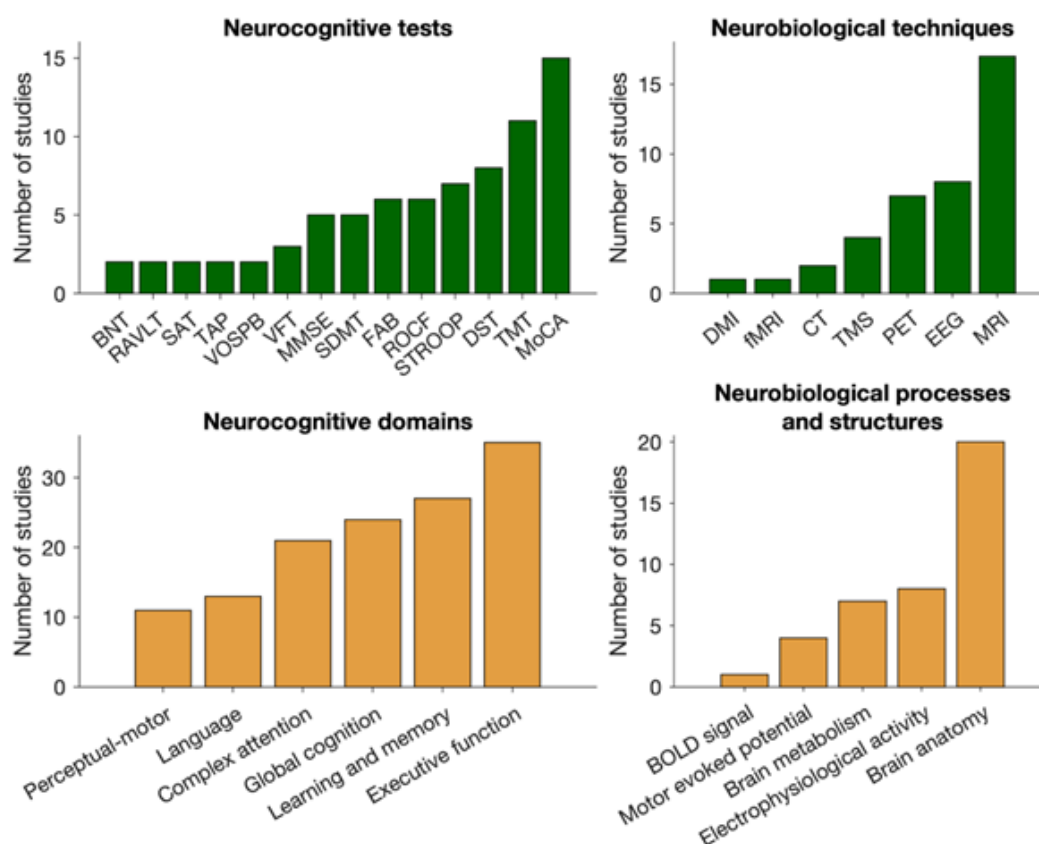
Across all studies, seven recording/imaging techniques were employed, with each study utilizing one or more techniques to investigate neurobiological processes or structures. The most frequently used technique was MRI (N = 17), followed by EEG (N = 8), PET (N = 7), TMS (N = 4), CT (N = 2), DMI (N = 1), and fMRI (N = 1). For a visual representation and abbreviations, refer to Figure 3, top right panel. For references, see table 2.

3.1.9 NEUROBIOLOGICAL PROCESSES AND STRUCTURES

Brain anatomy was the most frequently studied, assessed through MRI, CT, and DMI (N = 20), followed by electrophysiological activity (N = 8), brain metabolism (N = 7), motor evoked potentials (N = 4), and the BOLD signal (N = 1). For a visual representation, refer to Figure 3, bottom right panel. For references, see table 2.

Figure 3.

Number of Studies: Neurocognitive Tests and Domains, Neurobiological Techniques, Processes and Structures (Source: Authors' own elaboration).



Note: Number of studies that use a particular neurocognitive test (top-left), implement a given neurobiological recording technique (top-right), assess a given neurocognitive domain (bottom-left), and target a given neurobiological process or structure (bottom-right). In the case of neurocognitive tests, for visualization purposes, we included in the plot only tests that were used at least in two studies.

Abbreviations: BNT: Boston Naming Test, RAVLT: Rey Auditory Verbal Learning Test, SAT: Sustained Attention Task, TAP: Test for Attentional Performance, VOSPB: Visual Object and Space Perception battery, VFT: Verbal Fluency Test, MMSE: Mini-Mental State Evaluation, SDMT: Symbol Digit Modalities Test, FAB: Frontal Assessment Battery, ROCF: Rey-Osterrieth Complex Figure, STROOP: Stroop Task, DST: Digit Span Test, TMT: Trail Making Test, MoCA: Montreal Cognitive Assessment, DMI: Diffusion microstructure imaging, fMRI: Functional magnetic resonance imaging, CT: computed tomography, TMS: Transcranial magnetic stimulation, PET: positron emission tomography, EEG: electroencephalogram, MRI: magnetic resonance imaging. BOLD: Blood Oxygenation Level Dependent.

3.1.10 ADDITIONAL CHARACTERISTICS OF INCLUDED STUDIES

To conclude the initial description of the accepted studies, Table 2 presents the following general characteristics: study identification, number of participants who had COVID-19, number of healthy control participants, percentages of participants by sex, study design, neurocognitive tests and domains and neurobiological techniques and processes/structures, which is described in detail in the next section.

3.2 RISK OF BIAS

Studies were assessed for risk of bias using the Quality Assessment Tool for Observational Cohort and

Cross-Sectional Studies, and the Quality Assessment Tool for Case Series Studies (National Heart, Lung, and Blood Institute, 2019) as presented in Table 3. Criteria description can be found at: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>.

For each criterion, a status of compliance has been assigned: Y (yes), N (no), CD (cannot determine), NA (not applicable), and NR (not reported). Finally, each reference is assigned an overall quality rating according to the scale: Good, Fair, and Poor. GMS and CAR independently assigned a compliance level to each criterion, as well as a corresponding quality rating to each study. Any discrepancies were discussed jointly, and consensus was reached on both the criteria and ratings.

Table 3.

Summary of Risk of Bias.

References	Criteria														Quality rating
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Ortelli et al. (2022a)	Y	Y	N	Y	N	Y	Y	NA	Y	Y	Y	N	Y	Y	Fair
Douaud et al. (2022)	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	N	Y	Y	Good
Bispo et al. (2022)	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Good
Hellgren et al. (2022)	Y	Y	N	Y	N	Y	Y	NA	Y	N	Y	N	N	Y	Fair
Nersesjan et al. (2021)	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Fair
Appelt et al. (2022)	Y	Y	N	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Good
Andriuta et al. (2022)	Y	Y	N	Y	N	Y	Y	NA	Y	N	Y	Y	Y	Y	Fair
Del Brutto et al. (2021)	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Good
Hugon et al. (2022)	Y	Y	Y	N	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	Poor
Hadad et al. (2022)	Y	Y	N	Y	Y	Y	Y	NA	Y	N	Y	N	Y	Y	Good
Hosp et al. (2021)	Y	Y	N	Y	Y	Y	Y	NA	Y	Y	Y	N	Y	Y	Fair
Cecchetti et al. (2022)	Y	Y	N	Y	N	Y	Y	NA	Y	Y	Y	Y	Y	Y	Fair
Delorme et al. (2020)	Y	Y	Y	N	Y	Y	Y	NA	Y	NA	NA	NA	NA	NA	Poor
Voruz et al. (2022)	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Good

Ortelli et al. (2022b)	Y	Y	N	Y	N	Y	Y	NA	Y	Y	Y	N	Y	Y	Fair
Rubega et al. (2022)	Y	Y	N	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Fair
Versace et al. (2021)	Y	Y	N	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Fair
Sklinda et al. (2021)	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Fair
Bungenberg et al. (2022)	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	N	Y	Y	Good
Dressing et al. (2022)	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	N	N	Y	Fair
Ortelli et al. (2021)	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	N	Y	Y	Fair
Fleischer et al. (2022)	Y	Y	N	Y	N	Y	Y	NA	Y	N	Y	N	N	Y	Fair
Groiss et al. (2020)	Y	Y	N	Y	Y	N	Y	N	Y	NA	NA	NA	NA	NA	Fair
De Paula et al. (2022)	Y	Y	S	Y	Y	Y	Y	NA	Y	N	Y	N	Y	Y	Good
Blazhenets et al. (2021)	Y	Y	N	Y	N	Y	Y	NA	Y	N	Y	N	Y	Y	Fair
Rau et al. (2022)	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	Y	N	Y	Y	Fair

Among the 26 studies, 8 were rated as “Good,” 16 as “Fair,” and 2 as “Poor.” The observational studies generally adhered to key criteria such as clearly stated research questions, well-defined study populations, and consistent implementation of exposure measures. For example, Douaud et al. (2022) and Del Brutto et al. (2021) met most of the criteria, indicating robust methodologies with minimal bias. However, many observational studies, such as those by Ortelli et al. (2022 a) and Nersesjan et al. (2021), were marked as “Fair” due to shortcomings in areas like sample size justification, blinding of outcome assessors, and adjustment for confounding variables.

In contrast, the case series studies were evaluated using criteria tailored to their design. Hugon et al. (2022) and Delorme et al. (2020) exhibited significant methodological limitations, particularly in describing the intervention and statistical methods, leading to their classification as “Poor”.

To summarize, among the accepted articles, 99.57% of the COVID-19 patients were included in studies with “Fair” or “Good” quality ratings. Therefore, it is possible to assert that these limited levels of bias risk enable a reliable analysis of results within the context of this systematic review.

3.3 Neurocognitive Performance Changes

The classification of neurocognitive domains suggested by Sachdev et al. (2014), based on a DSM-5 approach, was adopted to organize the synthesis of neurocognitive test results. This classification recognizes six neurocognitive domains, namely: perceptual-motor function, language, learning and memory, complex attention, executive function and social cognition.

To the previous domains, we will add the category “global cognition” for the results reported based on the application of comprehensive batteries or tools that assess general neurocognitive performances.

Of the 26 accepted articles, 25 describe alterations in at least one neurocognitive domain, across 97 outcome reports. However, only 61 of these reports are statistically significant, of which 40 (65%) confirm a worse performance in post-COVID patients in at least one neurocognitive domain (while the remaining 35% estimate that there is no significant difference in performance between participants and healthy controls.). The descriptive count of significant results, including the mention of the publications considered, is shown in Table 4.

Table 4.

Descriptive Count of Results (Source: Authors' own elaboration).

Neurocognitive results		
Results	Studies	N Reports
Worse performance in Post-Covid patients	Ortelli et al. (2021, 2022a, 2022b); Douaud et al. (2022); Nersesjan et al. (2021); Appelt et al. (2022); Andriuta et al. (2022); Del Brutto et al. (2021); Hadad et al. (2022); Cecchetti et al. (2022); Voruz et al. (2022); Rubega et al. (2022); Bungenberg et al. (2022); De Paula et al. (2022)	40
No difference in performance in Post-Covid patients	Douaud et al. (2022); Bispo et al. (2022); Appelt et al. (2022); Hadad et al. (2022); Rubega et al. (2022); Bungenberg et al. (2022); Dressing et al. (2022); De Paula et al. (2022); Blazhenets et al. (2021)	21
	N studies with statistical report (%)	23 (88.5%)
	N statistical reports	61
Neurobiological results		
Results	Studies	N Reports
Biological findings in Post-Covid patients	Ortelli et al. (2021, 2022a, 2022b); Douaud et al. (2022); Bispo et al. (2022); Appelt et al. (2022); Hugon et al. (2022); Hosp et al. (2021); Cecchetti et al. (2022); Voruz et al. (2022); Rubega et al. (2022); Versace et al. (2021); Sklinda et al. (2021); Blazhenets et al. (2021); Rau et al. (2022)	17
No findings in Post-Covid patients	Dressing et al. (2022)	1
	N studies with statistical report (%)	16 (61.5%)
	N statistical reports	18

Among the 61 reports with statistically significant results, 40 demonstrating worse neurocognitive performance in post-COVID patients included 1,238 participants, accounting for 92.9% of the total participants considered in studies with significant outcomes. These findings include the highest percentages of confirmed poorer performance in the language (90.4% of participants in studies with significant results) and complex attention domains (79.9%).

Table 5 (Vote Count Based on Statistical Significance) outlines the frequency and proportion of reports “in favor”, meaning those supporting a significant decline in neurocognitive performance among post COVID patients, across various cognitive domains. It also details the number of post COVID participants involved in these statistically significant reports, along with the percentage they represent out of the total number of participants in all reports with significant results.

Table 5.

Vote Count Based on Statistical Significance (Source: Authors' own elaboration).

Analysis by neurocognitive domain			
	Reports in favor		
	Fr / total	n partic.	% partic.
Complex Attention	10/13	921	79.9%
Executive Function	9/12	830	75.2%
Global Cognition	8/14	411	51.4%
Language	5/6	293	90.4%
Learning and Memory	4/9	247	25.4%
Perceptual Motor Function	4/7	389	43.9%
Total	40/61	1238	92.9%

Analysis by neurobiological processes and structures			
	Reports in favor		
	Fr / total	n partic.	% partic.
Brain Anatomy	6/6	566	100%
Motor evoked potentials	4/4	165	100%
Electrophys. activity	3/3	135	100%
Brain metabolism	3/4	31	50%
BOLD signal	1/1	102	100%
Total	17/18	930	96.8%

Analysis of association: Neurocognitive domain / Neurobiological process or structure

		Reports in favor		
		Fr / total	n partic.	% partic.
Global cognition	Brain anatomy	5/5	148	100%
	Brain metabolism	2/3	37	54.4%
	Motor evoked potential	2/2	86	100%
	Electrophys. activity	1/1	49	100%
Complex attention	Electrophys. activity	2/2	102	100%
	Brain anatomy	1/1	401	100%
Perceptual motor function	Brain anatomy	1/1	50	100%
	Brain metabolism	1/1	192	100%
Learning and memory	Brain anatomy	1/1	49	100%
Total		16/17	1067	97.2%

3.4 Neurobiological Changes

The findings will be reviewed according to the neurobiological processes and structures already mentioned: brain anatomy, electrophysiological activity, brain metabolism, motor evoked potential, and BOLD signal.

Of the 26 accepted articles, 23 describe alterations in neurobiology across 39 outcome reports. However, only 18 of these reports are statistically significant, of which 17 (94%) confirm changes in neurophysiological processes or neuroanatomy in post-COVID patients compared to controls. Overall, these 17 reports co-

respond to 930 participants. The descriptive count of significant results, including the mention of the publications considered, is shown in Table 4.

The neurophysiological and neuroanatomical changes described in the accepted articles can be classified as neuropathological alterations, which are abnormalities involving nervous system disorders, either as diseases themselves or as part of them (Love et al., 2015). Table 6 provides a detailed neuropathological description of the biological changes identified by the 17 accepted studies with significant neurobiological results.

Table 6.

Neuropathological Description of Biological Changes in Post-COVID Participants (Source: Authors' own elaboration).

Neurobiology	Technique	Reference	Neuropathology	Description
Brain Anatomy	MRI	Douaud et al. (2022)	Atrophy	Reduction in global brain size in the SARS-CoV-2 cases. Reduction in grey matter thickness in the orbitofrontal cortex and parahippocampal gyrus.
		Bispo et al. (2022)	Tissue damage	Markers of tissue damage in regions connected to the primary olfactory cortex.
			Atrophy	Reduction in fiber density in the association, projection, and commissural tracts, involving arcuate fasciculus, cingulum, fornix, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, corona radiata, corticospinal tract, and corpus callosum.
		Hosp et al. (2021)	Ischemia	Micro-embolic subacute infarcts, located bilaterally in cerebellum, right corona radiata, left superior cerebellar peduncle, and right frontal cortex.
		Cecchetti et al. (2022)	White matter hyperintensities	Right frontal and right parieto-occipital WMH volumes were greater in patients when compared to controls.
		Sklinda et al. (2021)	Hypoperfusion	Cerebral hypoperfusion suggested by changes in brain metabolites in deep gray matter (both brain hemispheres) in COVID patients suffering from brain fog.
Motor evoked potentials	DMI	Rau et al. (2022)	Microstructural alterations	Widespread volume shifts from the intra- and extra-axonal space into the free water fraction (V-CSF), involving the entire supratentorial white matter, with maxima in frontal and parietal regions.
	TMS	Ortelli et al. (2022a)	Cortical hypoexcitability	Higher resting motor thresholds and reduced M1 excitability in patients.
		Ortelli et al. (2022b)		Higher resting motor threshold cortical hypoexcitability in patients.
		Ortelli et al. (2021)		Smaller motor evoked potentials in patients.
		Versace et al. (2021)	Reduced cortical inhibition	Reduced inhibition within the M1 area. Short-latency afferent inhibition mechanisms were also significantly diminished.

Electrophysiological activity	EEG	Appelt et al. (2022)	Altered electrophysiological activity	Reduction in brain activity at rest in the Fz-F4 areas and during high cognitive demands in the F3-F7 areas. A reduction in signal complexity in F3-F7 at rest was found 6-12 months after acute infection. Patients showed lower individual alpha frequency, and a greater current source densities at delta frequency band in bilateral frontal and central-temporal regions.
		Cecchetti et al. (2022)		Modification of cortical generators of sleep spindles. Slow spindles shifting towards more posterior cortical regions and fast spindle generators shifting anteriorly, in COVID-19 participants.
		Rubega et al. (2022)		
Brain metabolism	PET	Hugon et al. (2022)	Hypometabolism	Hypometabolic regions identified, affecting the pons, medial temporal lobe, left parietal and precuneus areas, cingulate cortex, orbitofrontal cortex.
		Blazhenets et al. (2021)		Initial frontoparietal and, to a lesser extent, temporal hypometabolism in chronic COVID patients.
		Rau et al. (2022)		Frontoparietal-dominant pattern of neocortical glucose hypometabolism
BOLD signal	fMRI	Voruz et al. (2022)	Hypoconnectivity	Hypoconnectivity in anosognosic patients, within and between the following networks: left default mode, bilateral somatosensory motor, right executive control, right salient ventral attention and bilateral dorsal attention networks, and right Lobules IV and V of the cerebellum.

Table 5 (Vote Count Based on Statistical Significance) outlines the frequency and proportion of reports “in favor”, meaning those supporting significant neurobiological changes among post COVID patients, across various processes and structures. It also details the number of post COVID participants involved in these statistically significant reports, along with the percentage they represent out of the total number of participants in all reports with significant results.

3.5 Association Between Neurocognitive Performances and Neurobiological Changes

Of the 26 accepted studies, 15 estimate a statistically significant association between at least one outcome in a neurocognitive domain and a neurobiological finding. Furthermore, nine studies did not estimate a significant association but provided qualitative comments or unquantifiable observations regarding potential associations between their neurobiological and neurocognitive findings. Finally, two articles (Groiss et al., 2020; Nersesjan et al., 2021) do not refer in any way to a possible association between described neurobiological and neurocognitive results.

Fifteen studies that calculated a significant association between neurobiological changes and neurocognitive domains do so through 17 reports. 16 of these (94%) confirm an association between at least one neurocognitive domain and a neurobiological process/structure. These “in favor” reports include 1,067 participants, corresponding to 97.2% of the patients considered in studies with statistically significant association results.

The results for each cognitive domain and its association with neurobiological anatomy or processes, are described as follows:

The association between global cognition and brain anatomy, evoked motor potentials, and electrophysiological activity was confirmed in all 8 reports involved, including 283 participants. The association between global cognition and brain metabolism was observed

in 2 out of 3 reports, involving 37 participants, which corresponds to 54.4% of the patients included in these studies.

The association between complex attention with electrophysiological activity and brain anatomy was confirmed in the 3 reports involved, which included 503 participants.

The association between perceptual motor function with brain anatomy and brain metabolism was documented in the two reports involved, which included 242 participants.

Finally, the association between the cognitive domain of learning and memory and brain anatomy was corroborated in the single report considered, which included 49 participants.

In summary, across all cognitive domains, 16 of the 17 reports indicated a significant association between worse neurocognitive performance and neuropathological brain changes, involving 1,067 participants, equating to 97.2% of patients in reports with statistically significant results.

Table 5 describes and shows the frequency of reports “in favor”, meaning those indicating a statistically significant association between neurocognitive domains and neurophysiological processes or neuroanatomical structures.

4. DISCUSSION

In addressing the research question regarding the neurobiological changes that accompany reduced neurocognitive performance in adult patients with post-COVID sequelae, this systematic review synthesizes findings from 26 scientific articles. These studies provided data on neurobiological and neurocognitive variables in the same participants in a stage subsequent to the acute phase of COVID-19 infection. Among these, 15 articles conducted analyses to estimate potential associations between these dimensions, resulting in 17 distinct reports. Of these reports, 16 confirmed statistically significant associations between decreased performance in at least one neurocognitive domain and corresponding neuropathological findings in the brain.

This consistent evidence underscores the relationship between neurobiological alterations and neurocognitive deficits in post-COVID patients. Despite the surge in neurobiological and neurocognitive research on COVID-19 and its sequelae, no prior systematic reviews have specifically sought to explore this association.

Our findings highlight that, although 26 studies measured neurobiological and neurocognitive variables, 11 did not estimate the association between these dimensions. This omission may be attributed to the urgency of disseminating findings in the middle of a global health crisis and the inherent limitations posed by the pandemic.

Focusing solely on neurocognitive outcomes leaves an incomplete understanding of how a tangible pathogenic agent, such as a virus, can influence mental processes. Observing concurrent neurobiological impairments alongside neurocognitive sequelae is vital to begin elucidating the mechanisms through which a virus impacts neurocognitive domains specifically and neuropsychological functioning in general. This integrated approach enables researchers to trace the pathway from viral infection to alterations in brain structure or function, thereby linking these changes to observed cognitive deficits. Such comprehensive analysis is essential for unraveling the complex interplay between biological insults and neurocognitive dysfunctions, ultimately advancing our understanding of the neuropsychological impact of viral infections.

The findings of this review align with the extensive scientific literature documenting the impact of various viruses, including poliovirus, influenza, herpes simplex, Epstein-Barr, West Nile virus, HIV and other Coronaviruses on inducing cerebral neuropathological changes (Hatanpaa & Kim, 2014; Hu et al., 2020; Love et al., 2015), as well as decrements in neurocognitive performance (Bohmwald et al., 2018; Dicke, 2015; Fruchter et al., 2015; García-Molina et al., 2015; Murray et al., 2018; Rumbaugh & Tyor, 2015; Zhang et al., 2021). Consequently, the Coronavirus is considered among the long list of pathogenic agents capable of inducing neurobiological and neuropsychological changes in a considerable proportion of infected individuals (for a detailed review, see Love et al., 2015, Chapter 19).

In our review, 10 out of 11 reports found a significant association between deficits in global cognition and neurobiological changes. Reduced global cognition has been previously reported in post-COVID patients. The meta-analysis by Crivelli et al. (2022) describes significantly lower global cognition scores compared to controls. In this meta-analysis, as well as in other studies, batteries such as Montreal Cognitive Assessment (MoCA) have played a prominent role and are considered among the most used in the neurocognitive evaluation of post-COVID sequelae (Biagianti et al., 2022; Perrottelli et al., 2022), despite not being a neuropsychological assessment specifically designed for sequelae of this viral infection. In our review, 15 of the 26 selected studies used MoCA to estimate global cognition, and in five of them, it was used as a standalone neurocognitive measure, confirming the relevance of this assessment battery in the evaluation of post-COVID neurocognitive sequelae.

Two out of three studies that estimated relationships between reduced global cognition and alterations in brain metabolism found a positive association. However, these two articles encompassed 54.4% of the total participants across these three studies. While the alteration of brain metabolism (measured by PET) in post-COVID-19 patients was confirmed by the systematic review by Okrceja et al. (2023), our review found that only a slight majority of participants showed reduced brain metabolism in certain areas linked to deficits in global cognition.

In our review, it is observed that the majority of participants in the selected articles are women. This is consistent with the scientific literature, which describes a higher prevalence of post-COVID sequelae among women in general (Fernández-de-Las-Peñas et al., 2022; Ortona et al., 2021). Regarding the time considered as post-acute for describing the post-COVID period, the majority of the accepted studies have applied the criterion of at least four weeks post-diagnosis (Nalbandian et al., 2021; NICE, 2020). However, we also observed notable variability in the post-COVID timeline, with some articles applying undefined criteria.

Among the limitations of this review, most of the studies found and accepted focus on the evaluation of

patients with cognitive complaints, omitting the inclusion of patients with anosognosia who exhibit objectively reduced performance in neurocognitive domains. Similarly, it would have been beneficial to review or accept articles that included asymptomatic COVID-19 patients who may present neurocognitive alterations, in order to cover a broader range of COVID-19 profiles that could lead to persistent neurocognitive sequelae.

The accepted studies represent diverse populations across the world, encompass various types of samples and research designs, and allow for the observation of a wide range of neurobiological and neurocognitive tests and techniques used. Within our age group of interest, described as the most affected by post-COVID neurocognitive sequelae across the life cycle (Taquet et al., 2022), our selection of accepted articles included adult participants of various ages, reviewing measurements taken at various time points following the acute phase of COVID-19, enabling a comprehensive analysis of the neurobiological and neurocognitive sequelae of Coronavirus among adult patients.

Furthermore, due to the unique characteristics of the observed problem, unlike other systematic reviews, this one has no time restrictions, collecting publications from the onset of the observed phenomenon to the time of the search.

While the heterogeneity of the included studies presents inherent challenges, it is also important to critically examine the limitations introduced by our own methodological decisions. The use of vote counting, although appropriate given the variability and incompleteness of reported effect sizes, does not consider the magnitude or directionality of findings, and may overrepresent studies based solely on statistical significance. Regarding language bias, it is important to clarify that searches were conducted in both English and Spanish; however, no Spanish-language articles met the inclusion criteria, which justifies the final restriction to English. Concerning quality appraisal, although high quality tools such as the GRADE approach (Prasad, 2024) or ROBINS-E (Higgins et al., 2024) were not applied, all accepted studies were assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart,

Lung, and Blood Institute (National Heart, Lung, and Blood Institute, 2019). This tool, composed of 14 items, evaluates key domains of internal validity in observational designs. While the lack of a more comprehensive risk of bias assessment remains a limitation, the application of this instrument provided a structured and systematic basis to judge the methodological quality of the included studies.

Finally, in terms of applications, the results of this review can inform health services about the need to obtain neurobiological and neurocognitive outcomes in patients suffering from post-COVID sequelae, regardless of whether they report cognitive complaints, to achieve more comprehensive and timely diagnoses and interventions. These findings underscore the need to improve access to neurocognitive assessment and intervention for adults affected by post-COVID sequelae. Despite robust evidence linking neurobiological alterations to neurocognitive impairments, many individuals—particularly those with mild or asymptomatic acute phases—remain undiagnosed and untreated. Without intervention, such deficits may persist or worsen over time, leading to long-term functional impairments (L. Cysique et al., 2022; Davis et al., 2023). This review is thus relevant not only for advancing scientific understanding but also for forming clinical and policy responses aimed at early detection and support for affected populations.

STATEMENTS AND DECLARATIONS

DECLARATION OF CONFLICTING INTEREST: None.

AUTHORS' INITIALS: GMS: Gabriel M. Sepúlveda. CAR: Camilo Arévalo-Romero. JMS: Josefina Mattoli-Sánchez. DRL: Daniel Rojas-Líbano”.

REFERENCES

- Amalakanti, S., Arepalli, K. V. R., & Jillella, J. P. (2021). Cognitive assessment in asymptomatic COVID-19 subjects. *Virusdisease*, 32(1), 146–149. <https://doi.org/10.1007/s13337-021-00663-w>
- Amit, N., Ismail, R., Zumrah, A. R., Mohd Nizah, M. A., Tengku Muda, T. E. A., Tat Meng, E. C., Ibrahim, N., & Che Din, N. (2020). Relationship Between Debt and Depression, Anxiety, Stress, or Suicide Ideation in Asia: A Systematic Review. *Frontiers in Psychology*, 11, 1336. <https://doi.org/10.3389/fpsyg.2020.01336>
- Antonelli, M., Penfold, R. S., Merino, J., Sudre, C. H., Molteni, E., Berry, S., Canas, L. S., Graham, M. S., Klaser, K., Modat, M., Murray, B., Kerfoot, E., Chen, L., Deng, J., Österdahl, M. F., Cheetham, N. J., Drew, D. A., Nguyen, L. H., Pujol, J. C., ... Steves, C. J. (2022). Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *The Lancet Infectious Diseases*, 22(1), 43–55. [https://doi.org/10.1016/S1473-3099\(21\)00460-6](https://doi.org/10.1016/S1473-3099(21)00460-6)
- Ariza, M., Cano, N., Segura, B., Adan, A., Bargalló, N., Caldú, X., Campabadal, A., Jurado, M. A., Mataró, M., Pueyo, R., Sala-Llonch, R., Barrué, C., Bejar, J., Cortés, C. U., NAUTILUS-Project Collaborative Group, Junqué, C., & Garolera, M. (2022). Neuropsychological impairment in post-COVID condition individuals with and without cognitive complaints. *Frontiers in Aging Neuroscience*, 14, 1029842. <https://doi.org/10.3389/fnagi.2022.1029842>
- Biagiante, B., Di Liberto, A., Nicolò Edoardo, A., Lisi, I., Nobilia, L., de Ferrabonc, G. D., Zanier, E. R., Stocchetti, N., & Brambilla, P. (2022). Cognitive Assessment in SARS-CoV-2 Patients: A Systematic Review. *Frontiers in Aging Neuroscience*, 14, 909661. <https://doi.org/10.3389/fnagi.2022.909661>
- Birberg, U., Andersson, A., Lindh, M., Hellgren, L., Divanoglou, A., & Levi, R. (2022). Neurocognitive deficits in COVID-19 patients five months after discharge from hospital. *Neuropsychological Rehabilitation*, 1–25. <https://doi.org/10.1080/09602011.2022.2125020>
- Bispo, D. D. de C., Brandão, P. R. de P., Pereira, D. A., Maluf, F. B., Dias, B. A., Paranhos, H. R., von Glehn, F., de Oliveira, A. C. P., Regattieri, N. A. T., Silva, L. S., Yasuda, C. L., Soares, A. A. de S. M., & Descoteaux, M. (2022). Brain microstructural changes and fatigue after COVID-19. *Frontiers in Neurology*, 13, 1029302. <https://doi.org/10.3389/fneur.2022.1029302>
- Bohmwald, K., Gálvez, N. M. S., Ríos, M., & Kalergis, A. M. (2018). Neurologic Alterations Due to Respiratory Virus Infections. *Frontiers in Cellular Neuroscience*, 12, 386. <https://doi.org/10.3389/fncel.2018.00386>
- Costa-Cordella, S., Arevalo-Romero, C., Parada, F. J., & Rossi, A. (2021). Social Support and Cognition: A Systematic Review. *Frontiers in Psychology*, 12, 637060. <https://doi.org/10.3389/fpsyg.2021.637060>
- Crivelli, L., Palmer, K., Calandri, I., Guekht, A., Beghi, E., Carroll, W., Frontera, J., García-Azorín, D., Westenberg, E., Winkler, A. S., Mangialasche, F., Allegri, R. F., & Kivipelto, M. (2022). Changes in cognitive functioning after COVID-19: A systematic review and meta-analysis. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 18(5), 1047–1066. <https://doi.org/10.1002/alz.12644>

Cysique, L. A., Jakabek, D., Bracken, S. G., Allen-Davidian, Y., Heng, B., Chow, S., Dehhaghi, M., Pires, A. S., Darley, D. R., Byrne, A., Phetsouphanh, C., Kelleher, A., Dore, G. J., Matthews, G. V., Guillemin, G. J., & Brew, B. J. (2022). Post-acute COVID-19 cognitive impairment and decline uniquely associate with kynurenine pathway activation: a longitudinal observational study. In *bioRxiv*. <https://doi.org/10.1101/2022.06.07.22276020>

Cysique, L., Łojek, E., Cheung, T., Cullen, B., Egbert, A., Evans, J., Garolera, M., Gawron, N., Gouse, H., Hansen, K., Holas, P., Hyniewska, S., Malinowska, E., Marcopulos, B., Merkley, T., Muñoz-Moreno, J., Ramsden, C., Salas, C., Sikkes, S., ... NeuroCOVID International Neuropsychology Taskforce. (2022). Assessment of neurocognitive functions, olfaction, taste, mental, and psychosocial health in COVID-19 in adults: Recommendations for harmonization of research and implications for clinical practice. *Journal of the International Neuropsychological Society: JINS*, 28(6), 642–660. <https://doi.org/10.1017/S1355617721000862>

Damiano, R. F., Guedes, B. F., de Rocca, C. C., de Pádua Serafim, A., Castro, L. H. M., Munhoz, C. D., Nitri, R., Filho, G. B., Miguel, E. C., Lucchetti, G., & Forlenza, O. (2022). Cognitive decline following acute viral infections: literature review and projections for post-COVID-19. *European Archives of Psychiatry and Clinical Neuroscience*, 272(1), 139–154. <https://doi.org/10.1007/s00406-021-01286-4>

Davis, H. E., McCorkell, L., Vogel, J. M., & Topol, E. J. (2023). Long COVID: major findings, mechanisms and recommendations. *Nature Reviews. Microbiology*, 21(3), 133–146. <https://doi.org/10.1038/s41579-022-00846-2>

Del Brutto, O. H., Wu, S., Mera, R. M., Costa, A. F., Recalde, B. Y., & Issa, N. P. (2021). Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: A longitudinal prospective study nested to a population cohort. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies*, 28(10), 3245–3253. <https://doi.org/10.1111/ene.14775>

Delorme, C., Paccoud, O., Kas, A., Hesters, A., Bombois, S., Shambrook, P., Boulet, A., Doukhi, D., Le Guennec, L., Godefroy, N., Maatoug, R., Fossati, P., Millet, B., Navarro, V., Bruneteau, G., Demeret, S., Pourcher, V., & CoCo-Neurosciences study group and COVID SMIT PSL study group. (2020). COVID-19-related encephalopathy: a case series with brain FDG-positron-emission tomography/computed tomography findings. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies*, 27(12), 2651–2657. <https://doi.org/10.1111/ene.14478>

Dicke, T. (2015). Waiting for the flu: cognitive inertia and the Spanish influenza pandemic of 1918-19. *Journal of the History of Medicine and Allied Sciences*, 70(2), 195–217. <https://doi.org/10.1093/jhmas/jru019>

Douaud, G., Lee, S., Alfaro-Almagro, F., Arthofer, C., Wang, C., McCarthy, P., Lange, F., Andersson, J. L. R., Griffanti, L., Duff, E., Jbabdi, S., Taschler, B., Keating, P., Winkler, A. M., Collins, R., Matthews, P. M., Allen, N., Miller, K. L., Nichols, T. E., & Smith, S. M. (2022). SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature*, 604(7907), 697–707. <https://doi.org/10.1038/s41586-022-04569-5>

Du, M., Ma, Y., Deng, J., Liu, M., & Liu, J. (2022). Comparison of Long COVID-19 Caused by Different SARS-CoV-2 Strains: A Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, 19(23). <https://doi.org/10.3390/ijerph192316010>

Falahi, S., Abdoli, A., & Kenarkoohi, A. (2023). Maternal COVID-19 infection and the fetus: Immunological and neurological perspectives. *New Microbes and New Infections*, 53, 101135. <https://doi.org/10.1016/j.nmni.2023.101135>

Fernández-de-Las-Peñas, C., Martín-Guerrero, J. D., Pellicer-Valero, Ó. J., Navarro-Pardo, E., Gómez-Mayordomo, V., Cuadrado, M. L., Arias-Navalón, J. A., Cigarán-Méndez, M., Hernández-Barrera, V., & Arendt-Nielsen, L. (2022). Female Sex Is a Risk Factor Associated with Long-Term Post-COVID Related-Symptoms but Not with COVID-19 Symptoms: The LONG-COVID-EXP-CM Multicenter Study. *Journal of Clinical Medicine Research*, 11(2). <https://doi.org/10.3390/jcm11020413>

Finsterer, J., & Stollberger, C. (2020). Update on the neurology of COVID-19. *Journal of Medical Virology*, 92(11), 2316–2318. <https://doi.org/10.1002/jmv.26000>

Friedman, L. (2001). Why vote-count reviews don't count. *Biological Psychiatry*, 49(2), 161–162. [https://doi.org/10.1016/S0006-3223\(00\)01075-1](https://doi.org/10.1016/S0006-3223(00)01075-1)

Fruchter, E., Goldberg, S., Fenchel, D., Grotto, I., Ginat, K., & Weiser, M. (2015). The impact of Herpes simplex virus type 1 on cognitive impairments in young, healthy individuals — A historical prospective study. *Schizophrenia Research*, 168(1), 292–296. <https://doi.org/10.1016/j.schres.2015.08.036>

García-Molina, A., Roig-Rovira, T., & Portell, E. (2015). Síndrome post-polio, quejas cognitivas y exploración neuropsicológica. *Rehabilitación*, 49(2), 70–74. <https://doi.org/10.1016/j.rh.2015.01.002>

Groiss, S. J., Balloff, C., Elben, S., Brandenburger, T., Müttel, T., Kindgen-Milles, D., Vollmer, C., Feldt, T., Kunstein, A., Ole Jensen, B.-E., Hartung, H.-P., Schnitzler, A., & Albrecht, P. (2020). Prolonged Neuropsychological Deficits, Central Nervous System Involvement, and Brain Stem Affection After COVID-19-A Case Series. *Frontiers in Neurology*, 11, 574004. <https://doi.org/10.3389/fneur.2020.574004>

Guido, C. A., Lucidi, F., Midulla, F., Zicari, A. M., Bove, E., Avenoso, F., Amedeo, I., Mancino, E., Nenna, R., De Castro, G., Capponi, M., Cinicola, B. L., Brindisi, G., Grisoni, F., Murciano, M., Spalice, A., & Long-Covid Group of Department of Maternal Sciences. (2022). Neurological and psychological effects of long COVID in a young population: A cross-sectional study. *Frontiers in Neurology*, 13, 925144. <https://doi.org/10.3389/fneur.2022.925144>

Guo, Z., Sun, S., Xiao, S., Chen, G., Chen, P., Yang, Z., Tang, X., Huang, L., & Wang, Y. (2024). COVID-19 is associated with changes in brain function and structure: A multimodal meta-analysis of neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, 164, 105792. <https://doi.org/10.1016/j.neubiorev.2024.105792>

Hadad, R., Khoury, J., Stanger, C., Fisher, T., Schneer, S., Ben-Hayun, R., Possin, K., Valcour, V., Aharon-Peretz, J., & Adir, Y. (2022). Cognitive dysfunction following COVID-19 infection. *Journal of Neurovirology*, 28(3), 430–437. <https://doi.org/10.1007/s13365-022-01079-y>

Hatanpaa, K. J., & Kim, J. H. (2014). Neuropathology of viral infections. *Handbook of Clinical Neurology*, 123, 193–214. <https://doi.org/10.1016/B978-0-444-53488-0.00008-0>

Haykal, M. A., & Menkes, D. L. (2023). The clinical neurophysiology of COVID-19-direct infection, long-term sequelae and para-immunization responses: A literature review. *Clinical Neurophysiology Practice*, 8, 3–11. <https://doi.org/10.1016/j.cnp.2022.09.005>

Higgins, J., Rooney, A., & et al. . (2024). *ROBINS-E tool*. <https://www.riskofbias.info/welcome/robins-e-tool>

Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., & Welch, V. (Eds.). (2019). *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons. <https://play.google.com/store/books/details?id=cTqyDwAAQBAJ>

Hugon, J., Queneau, M., Sanchez Ortiz, M., Msika, E. F., Farid, K., & Paquet, C. (2022). Cognitive decline and brainstem hypometabolism in long COVID: A case series. *Brain and Behavior*, 12(4), e2513. <https://doi.org/10.1002/brb3.2513>

Hu, J., Jolkkonen, J., & Zhao, C. (2020). Neurotropism of SARS-CoV-2 and its neuropathological alterations: Similarities with other coronaviruses. *Neuroscience and Biobehavioral Reviews*, 119, 184–193. <https://doi.org/10.1016/j.neubiorev.2020.10.012>

Kiyak, C., Ijezie, O. A., Ackah, J. A., Armstrong, M., Cowen, J., Cetinkaya, D., Burianová, H., & Akudjedu, T. N. (2024). Topographical Distribution of Neuroanatomical Abnormalities Following COVID-19 Invasion. *Clinical Neuroradiology*, 34(1), 13–31. <https://doi.org/10.1007/s00062-023-01344-5>

Lai, C.-C., Hsu, C.-K., Yen, M.-Y., Lee, P.-I., Ko, W.-C., & Hsueh, P.-R. (2023). Long COVID: An inevitable sequela of SARS-CoV-2 infection. *Journal of Microbiology, Immunology, and Infection = Wei Mian Yu Gan Ran Za Zhi*, 56(1), 1–9. <https://doi.org/10.1016/j.jmii.2022.10.003>

Lezak, M., Howieson, D., Bigler, E., & Tranel, D. (2012). *Neuropsychological assessment (5th ed.)*. Oxford University Press.

López-León, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P. A., Cuapio, A., & Villapol, S. (2021). More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. *medRxiv : The Preprint Server for Health Sciences*. <https://doi.org/10.1101/2021.01.27.21250617>

Love, S., Perry, A., Ironside, J., & Budka, H. (2015). *Greenfield's Neuropathology. Ninth Edition*. CRC Press.

Malkova, A., Kudryavtsev, I., Starshinova, A., Kudlay, D., Zinchenko, Y., Glushkova, A., Yablonskiy, P., & Shoenfeld, Y. (2021). Post COVID-19 Syndrome in Patients with Asymptomatic/Mild Form. *Pathogens*, 10(11). <https://doi.org/10.3390/pathogens10111408>

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The PRISMA Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, 6(7), e1000097. <https://doi.org/10.1371/journal.pmed.1000097>

Monje, M., & Iwasaki, A. (2022). The neurobiology of long COVID. *Neuron*, 110(21), 3484–3496. <https://doi.org/10.1016/j.neuron.2022.10.006>

Murray, K. O., Nolan, M. S., Ronca, S. E., Datta, S., Govindarajan, K., Narayana, P. A., Salazar, L., Woods, S. P., & Hasbun, R. (2018). The Neurocognitive and MRI Outcomes of West Nile Virus Infection: Preliminary Analysis Using an External Control Group. *Frontiers in Neurology*, 9, 111. <https://doi.org/10.3389/fneur.2018.00111>

Nalbandian, A., Sehgal, K., Gupta, A., Madhavan, M. V., McGroder, C., Stevens, J. S., Cook, J. R., Nordvig, A. S., Shalev, D., Sehrawat, T. S., Ahluwalia, N., Bikdeli, B., Dietz, D., Der-Nigoghossian, C., Liyanage-Don, N., Rosner, G. F., Bernstein, E. J., Mohan, S., Beckley, A. A., ... Wan, E. Y. (2021). Post-acute COVID-19 syndrome. *Nature Medicine*, 27(4), 601–615. <https://doi.org/10.1038/s41591-021-01283-z>

National Heart, Lung, and Blood Institute. (2019). *Study Quality Assessment Tools*. NHLBI, NIH. <https://www.nhlbi.nih.gov/health-topics/study-qualityassessment->

Nersesjan, V., Amiri, M., Lebech, A., Roed, C., Mens, H., Russell, L., Fonsmark, L., Berntsen, M., Sigurdsson, S. T., Carlsen, J., Langkilde, A. R., Martens, P., Lund, E. L., Hansen, K., Jespersen, B., Folke, M. N., Meden, P., Hejl, A.-M., Wamberg, C., ... Kondziella, D. (2021). Central and peripheral nervous system complications of COVID-19: a prospective tertiary center cohort with 3-month follow-up. *Journal of Neurology*, 268(9), 3086–3104. <https://doi.org/10.1007/s00415-020-10380-x>

NICE. (2020). *COVID-19 rapid guideline: managing the long-term effects of COVID-19*. National Institute for Health and Care Excellence (NICE). <https://www.ncbi.nlm.nih.gov/pubmed/33555768>

Nittas, V., Gao, M., West, E. A., Ballouz, T., Menges, D., Wulf Hanson, S., & Puhan, M. A. (2022). Long COVID Through a Public Health Lens: An Umbrella Review. *Public Health Reviews*, 43, 1604501. <https://doi.org/10.3389/phrs.2022.1604501>

Okrzeja, J., Garkowski, A., Kubas, B., & Moniuszko-Malinowska, A. (2023). Imaging and neuropathological findings in patients with Post COVID-19 Neurological Syndrome-A review. *Frontiers in Neurology*, 14, 1136348. <https://doi.org/10.3389/fneur.2023.1136348>

Ortelli, P., Ferrazzoli, D., Sebastianelli, L., Maestri, R., Dezi, S., Spampinato, D., Saltuari, L., Alibardi, A., Engl, M., Kofler, M., Quartarone, A., Koch, G., Oliviero, A., & Versace, V. (2022). Altered motor cortex physiology and dysexecutive syndrome in patients with fatigue and cognitive difficulties after mild COVID-19. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies*, 29(6), 1652–1662. <https://doi.org/10.1111/ene.15278>

Ortona, E., Buonsenso, D., Carfi, A., Malorni, W., & Long Covid Kids study group. (2021). Long COVID: an estrogen-associated autoimmune disease? *Cell Death Discovery*, 7(1), 77. <https://doi.org/10.1038/s41420-021-00464-6>

Perrottelli, A., Sansone, N., Giordano, G. M., Caporusso, E., Giuliani, L., Melillo, A., Pezzella, P., Bucci, P., Mucci, A., & Galderisi, S. (2022). Cognitive Impairment after Post-Acute COVID-19 Infection: A Systematic Review of the Literature. *Journal of Personalized Medicine*, 12(12). <https://doi.org/10.3390/jpm12122070>

Pinzon, R. T., Wijaya, V. O., Jody, A. A., Nunsio, P. N., & Buana, R. B. (2022). Persistent neurological manifestations in long COVID-19 syndrome: A systematic review and meta-analysis. *Journal of Infection and Public Health*, 15(8), 856–869. <https://doi.org/10.1016/j.jiph.2022.06.013>

Prasad, M. (2024). Introduction to the GRADE tool for rating certainty in evidence and recommendations. *Clinical Epidemiology and Global Health*, 25(101484), 101484. <https://doi.org/10.1016/j.cegh.2023.101484>

Rumbaugh, J. A., & Tyor, W. (2015). HIV-associated neurocognitive disorders: Five new things. *Neurology. Clinical Practice*, 5(3), 224–231. <https://doi.org/10.1212/CPJ.0000000000000117>

Sachdev, P. S., Blacker, D., Blazer, D. G., Ganguli, M., Jeste, D. V., Paulsen, J. S., & Petersen, R. C. (2014). Classifying neurocognitive disorders: the DSM-5 approach. *Nature Reviews. Neurology*, 10(11), 634–642. <https://doi.org/10.1038/nrneurol.2014.181>

Singer, T. G., Evankovich, K. D., Fisher, K., Demmler-Harrison, G. J., & Risen, S. R. (2021). Coronavirus Infections in the Nervous System of Children: A Scoping Review Making the Case for Long-Term Neurodevelopmental Surveillance. *Pediatric Neurology*, 117, 47–63. <https://doi.org/10.1016/j.pediatrneurol.2021.01.007>

Taquet, M., Sillett, R., Zhu, L., Mendel, J., Camplisson, I., Dercon, Q., & Harrison, P. J. (2022). Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *The Lancet Psychiatry*, 9(10), 815–827. [https://doi.org/10.1016/S2215-0366\(22\)00260-7](https://doi.org/10.1016/S2215-0366(22)00260-7)

The Lancet. (2023). Long COVID: 3 years in. *The Lancet*, 401(10379), 795. [https://doi.org/10.1016/S0140-6736\(23\)00493-2](https://doi.org/10.1016/S0140-6736(23)00493-2)
World Health Organization. (2025). WHO Coronavirus (COVID-19) Dashboard. <https://covid19.who.int/info>

Younger, D. S. (2023). Postmortem neuropathology in COVID-19: An update. *Brain Pathology*, 33(6), e13204. <https://doi.org/10.1111/bpa.13204>

Zhang, N., Zuo, Y., Jiang, L., Peng, Y., Huang, X., & Zuo, L. (2021). Epstein-Barr Virus and Neurological Diseases. *Frontiers in Molecular Biosciences*, 8, 816098. <https://doi.org/10.3389/fmolb.2021.816098>

Zhao, S., Toniolo, S., Hampshire, A., & Husain, M. (2023). Effects of COVID-19 on cognition and brain health. *Trends in Cognitive Sciences*. <https://doi.org/10.1016/j.tics.2023.08.008>