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Research article

Executive function deficit in patients with long COVID syndrome: A systematic review

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ABSTRACT

Background: Post-COVID-19 condition (Long COVID) refers to a condition in which patients endure persistent symptoms for more than 12 weeks, typically occurring at least 3 months after the onset of Coronavirus disease 2019 (COVID-19) infection. It occurs when a constellation of symptoms persists following the initial illness, and this may obstruct a daily routine and impose difficulty in life. Therefore, this study aimed to systematically review published articles assessing the neurocognitive profile of long COVID patients, with a specific emphasis on executive function (EF), and to determine the correlation between EF deficits and brain alterations through the utilisation of neuroimaging modalities.

Methods: A thorough search was conducted using the PubMed/MEDLINE and Web of Science online databases following the PICOS and PRISMA 2020 guidelines. All included studies were deemed to be of high quality according to the Newcastle–Ottawa Scale (NOS).

Results: A total of 31 out of 3268 articles were included in the present study. The main outcome is the proportion of individuals with cognitive deficits, particularly in the EF domain, as detected by neuropsychological assessments. The present study also revealed that EF deficits in long COVID patients are correlated with disruptions in the frontal and cerebellar regions, affecting processes such as nonverbal reasoning, executive aspects of language, and recall. This consistent disturbance also emphasised the correlation between EF deficits and brain alterations in patients with long COVID.

Conclusion: The present study highlights the importance of evaluating EF deficits in long COVID patients. This insight has the potential to improve future treatments and interventions.

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1. Background

Long COVID is defined as "signs or symptoms that develop during or after 3 months of infection consistent with COVID-19 and continue for more than 12 weeks and are not explained by an alternative diagnosis as per the National Institute for Health and Care Excellence (NICE) guideline [1]. After the worldwide spread of the COVID-19 pandemic, long COVID syndrome has emerged as a complex medical phenomenon characterised by diverse symptoms, longevity, and severity [2,3]. The prevalence of long COVID has affected approximately 10–15 % of COVID-19 survivors [4]. It can occur at any age range and sex [4] and has been reported in acute COVID-19 patients across different severities [5]. Studies from various countries have reported that 10–50 % of COVID-19 survivors continue to experience a wide range of symptoms even several months after infection. These symptoms include headache, fatigue, respiratory difficulties, gastrointestinal symptoms, cardiovascular symptoms, insomnia, and notably, cognitive impairment (i.e., "brain fog") [6–8].

The most common domain of cognitive impairment associated with long COVID is known to be executive function (EF). EF deficit is primarily characterised by poor working memory, inhibition, and shifting skills, and is associated with prefrontal hypometabolism in patients with long COVID. It affects other domains, such as sustained attention, language, and memory [4]. Specifically, half of the long COVID patients demonstrated EF deficits after more than 12 weeks of follow-up [9,10]. Consequently, EFs may affect individuals' occupations and quality of life [1,11]. To date, little research has objectively measured cognitive impairment, especially EF deficit in patients with long COVID compared to other deficits, such as changes in respiratory function [12]. Current cognitive assessment applications are useful because they are frequently utilised to assess cognitive impairment and potential therapies in long COVID patients [13].

Consistently, SARS-CoV-2 damages cerebellar and prefrontal regions, which are associated with EF [14]. This can be further analysed with the utilisation of structural and functional neuroimaging modalities such as magnetic resonance imaging (MRI), electroencephalography (EEG), and functional magnetic resonance imaging (fMRI). The integration of advanced neuroimaging tools can further enhance our understanding of long COVID in terms of both structural and functional aspects. This approach is crucial for providing insight into the enhancement of future treatments.

In this study, we aimed to review the neurocognitive profile of long COVID patients with a specific focus on EF. Given that SARS-CoV-2 damages cerebellar and prefrontal regions, which explains EF deficits as part of long COVID [14], we are also interested in finding a correlation between EF deficits and brain alterations using the neuroimaging modalities applied in the included studies.

2. Materials and methods

2.1. PICOS, inclusion and exclusion criteria

The Population, Intervention, Comparison, Outcomes and Study (PICOS) strategy, which consists of inclusion and exclusion criteria was used as the fundamental guideline to refine the selection of articles [15–17]. Since there is no standard definition of long COVID [18], we included only the articles that aligned with the operational definition of long COVID that we established in Supplementary Table 1 [see Additional file]. In addition, the inclusion criteria were established prior to the article review and were as follows: the papers were restricted to original research in the English language, primary research that presented data on the neurocognitive profile of long COVID patients, in full-text articles and studies that focused on adults aged ≥18 years. The years of publication were automatically followed up to 4 years from the current date, as COVID-19 only emerged in early 2020. This paper is also limited to studies with any long COVID follow-up period of more than two months that adhered to the ideal parameters of the long COVID criteria from WHO, NICE, NIH and Delphi Method [1].

The exclusion criteria for articles were as follows: no full text, incomplete quantitative data, a postmortem study of COVID-19 patients, not adult reported disease, a median/mean follow-up time <4 weeks since COVID-19 infection or diagnosis, a study reporting only cognitive impairment unrelated to long COVID or an unpublished study, an abstract, systematic reviews, review papers, case reports, case studies, neurological techniques, or protocols. We also excluded articles with fewer than 10 patients with long COVID to avoid selection bias. The eligibility criteria for PICOS are summarised in Table 1.

2.2. Search strategy and study selection

A literature search was conducted using two online databases: PubMed (National Centre for Biotechnology Information) and the

Table 1
PICOS strategy for inclusion criteria in the systematic review.

PICOS	Criteria
P – Patient	Adult >18 y/o with long COVID symptoms occurs 3 months after confirmed COVID-19 infection and lasting more than 4 weeks.
I – Intervention or Exposure	Neuropsychological tests aimed at systematically characterising significant executive function changes
C – Comparison	Between studies with and without healthy controls, and between different severity of COVID-19
O – Outcome	Neurocognitive changes due to COVID-19; executive function and working memory
S – Study	All studies related to neurocognitive changes in COVID-19 except for the review, systematic review, case report, case study, and protocol

Table 2
Demographic data of participants in the studies, objective cognitive tests and findings from included studies on executive deficits in long COVID.

No	(Author, Years)	Country	Study Design	Demographic Information; n (male/female), age		Diagnosis of COVID-19	Cognitive impairment symptom	Severity of COVID-19	Follow up duration long COVID
				Long COVID patients	Healthy Controls				
1	(K W Miskowiak et al., 2021)	Denmark	Cross-sectional	29 (17/12) Mean age: 56.2 ± 10.6	100 (41/59) Mean age: 56.0 ± 6.9	PCR/IgG titer test	Attention difficulties, difficulties in daily task	NR (hospitalised patients)	3–4 months post COVID-19 infection
2	(Kamilla W. Miskowiak et al., 2023)	Denmark	Cross-sectional	14 (6/8) cognitive impacted (n = 8) cognitive intact (n = 6)	–	PCR/IgG titer test	Impaired work function, stress, depression, anxiety	NR	>12 weeks post COVID-19 infection
3	(Kamilla W. Miskowiak et al., 2023)	Denmark	Cross-sectional	194 (86/108) Mean age: 51 ± 15	150 (66/84) Mean age: 50.9 ± 9	PCR	Difficulties with memory & concentration	NR (hospitalised and non-hospitalised)[a]	7 months post COVID-19 infection
4	(Henneghan et al., 2021)	USA	Cross-sectional	52 (11/41) Age range: 22–62 y/o Mean age: 37.33 ± 12.12	–	Clinically assessed + COVID-19 experiences (COVEX) questionnaire	Depression, fatigue, anxiety, sleep disturbance	Mild/moderate	4 months post COVID-19 infection
5	(Graham et al., 2021)	USA	Prospective	50 (17/33) Mean age: 43.7 ± 11.8	50 (13/37) Mean age: 42.6 ± 10.8	RT-PCR/serology	brain fog, headache, tingling, dysgeusia, anosmia, myalgias, anosmia, fatigue	Mild (non-hospitalised)	>2 months from COVID-19 onset
6	(Mazza et al., 2021)	Italy	Prospective	226 (149/77) Age range: 26–87 y/o Mean age: 58.5 ± 12.8	–	RT-PCR	Delirium, fatigue, confusion, depression, anxiety, PTSD, obsessive-compulsive, insomnia	Mild, moderate & severe	3 months post discharge
7	(Andrei Appelt et al., 2022)	Brazil	Prospective	53 (16/37) Age range: 25–69 y/o Mean age = 42.3	30 (8/22) Age range: 21–55 y/o Mean age = 37.9	RT-PCR	long cognitive deficit in executive function, attention, language and delayed recall	Mild & moderate	12 months post COVID-19 infection
8	(Andriuta, Si-Ahmed, Roussel, J.-M. Constans et al., 2022)	France	Cross-sectional	46 (11/35) Mean age = 50.9 ± 14	1003 Mean age = 62 ± 11.3	RT-PCR/serology	Impairment of verbal memory, executive function, action speed	NR	8 months post COVID-19 infection
9	(Chang et al., 2022)	Korea	Cross-sectional	40 (7/33) Mean age = 54.74 ± 16.46	NA	RT-PCR	Brain fog, headache, hyposmia	NR	3 months post COVID-19 infection
10	(Cecchetti et al., 2022a)	Italy	Prospective	49 (36/13)	36 (20/16)	RT-PCR	Depression, PTSD	NR	8.2 ± 0.9 months post discharge
11	(Guo et al., 2022)	United Kingdom	Cross-sectional/longitudinal	181 (51/130)	185 (67/118)	–	fatigue	Mild, moderate, severe	–
12	(Bungenberg et al., 2022)	Germany	Cross-sectional	50 (22/28) Age range: 22–84 y/o Median age =	NA	RT-PCR/serology	Fatigue, reduced sleep quality, anxiety, depression	NR (hospitalised and non-hospitalised)	7.3 months post

(*continued on next page*)

Table 2 (*continued*)

No	(Author, Years)	Country	Study Design	Demographic Information; n (male/female), age		Diagnosis of COVID-19	Cognitive impairment symptom	Severity of COVID-19	Follow up duration long COVID
				Long COVID patients	Healthy Controls				
				50.5 Hospitalised = 21					COVID-19 infection
13	(Harmke B Duindam et al., 2022)	Netherland	Prospective	96 (64/35) Age range: 55–69 y/o Median age = 61	NA	RT-PCR	Anxiety, depression	Severe	6 ± 1.3 months post COVID-19 infection
14	(García-Sánchez et al., 2022)	Spain	Prospective	63 (22/41) Age range: 22–78 y/o Mean age: 51.1 ± 12.5	NA	PCR/serology	Anxiety, depression	NR (hospitalised and non-hospitalised)	3 months post COVID-19 infection
15	(L W Braga et al., 2022)	Brazil	Cross-sectional	614 (163/451) Age range: >18 y/o Mean age = 47.6 ± 11.2	NA	PCR	Memory deficits	severe	8 months post COVID-19 infection
16	(Ariza et al., 2022)	Spain	Prospective	319 Age range: 18–65 y/o	109	NR	Fatigue, memory deficits, lack of concentration, brain fog	Mild, moderate, severe	>12 weeks post COVID-19 infection
17	(Ariza et al., 2023)	Spain	Cross-sectional	319 Age range: 18–65 y/o	109	NR	Fatigue, memory deficits, lack of concentration, brain fog	Mild, moderate, severe	>12 weeks post COVID-19 infection
18	(Lauria et al., 2022)	China	Cross-sectional	100 (65/35) Mean age = 73.4 ± 6.1	NA	PCR	Memory, attention, sleep	NR	3 months after COVID-19 onset
19	(Lauria et al., 2023)	China	Cross-sectional	406 (223/183) Mean age = 54.5 ± 15.1	NA	PCR	NA	NR	3 months after COVID-19 onset
20	(Calabria et al., 2022)	Spain	Prospective	136 (49/87) Age range: 20–88 y/o Mean age = 51.7 ± 13.5	NA	PCR/serology	Fatigue	NR (hospitalised and non-hospitalised)	8 months post COVID-19 infection
21	(Damiano et al., 2022)	Brazil	Cross-sectional	425 Mean age = 55.7 ± 14.2	NA	RT-PCR/serology	Anxiety, depression, PTSD	Moderate, severe	6 months after COVID-19 infection
22	(Serrano-Castro et al., 2022)	Spain	Cross-sectional	46 (17/29) Mean age = 71 ± 10.1	40 (20/20) Mean age = 52.2 ± 2.3	NR	Anxiety, depression	Mild, moderate, severe	3–4 months post discharge
23	(Herrera et al., 2023)	Spain	Cross-sectional	214 (32/182) Normal cognition patients: 32 Cognition impairment patients: 182 Age range: 26–64 y/o Mean age = 47.48 ± 7.35	50	RT-PCR	Anxiety, depressive, sleep disturbance	NR (hospitalised and non-hospitalised)	>4 months post COVID-19 infection
24	(Voruz et al., 2023)	Switzerland	Cross-sectional	Mild = 44 Moderate =	NA	PCR/serology	Fatigue, insomnia,	Mild, moderate, severe	8 months after

(*continued on next page*)

Table 2 (*continued*)

No	(Author, Years)	Country	Study Design	Demographic Information; n (male/female), age		Diagnosis of COVID-19	Cognitive impairment symptom	Severity of COVID-19	Follow up duration long COVID
				Long COVID patients	Healthy Controls				
				42 Severe = 24			somnolence, dyspnea		COVID-19 infection
25	(Vakani et al., 2023)	United Kingdom	Cross-sectional	129 (23/106) Age range: 19–64 y/o	93 (32/61) Age range: 18–69 y/o	MyCognition database[b]	Poorer attention, executive dysfunction	NR (hospitalised and non-hospitalised)	8.8 months after COVID-19 infection
26	(He et al., 2023)	China	Cross-sectional	66 Age range: 13–66 y/o	79 Age range: 17–61 y/o	NR	Anxiety, depression, PTSD	mild	15 months post discharge
27	(Godoy-González et al., 2023)	Spain	Cross-sectional	80 (55/25) Age range: >18 y/o Mean age = 60.73	NA	NR	PTSD	NR (ICU)	12 months post-ICU discharge
28	(Gunnarsson et al., 2023)	Denmark	Cross-sectional	292 (128/164) Mean age = 51.9 ± 15.2	NA	PCR/IgG titer/initiation of clinical symptoms	Mental fatigue, exhaustation	NR (hospitalised and non-hospitalised)	>3 months post COVID-19 infection
29	(Kirchberger et al., 2023)	Germany	Prospective	372 (170/202) Age range: 18–87 y/o Mean age = 46.8 ± 15.2	NA	PCR	Problems with concentration and memory	mild	9.1 months post COVID-19 infection
30	(Costas-Carrera et al., 2022)	Spain	Prospective	58 (41/17) Age range: 37–81 y/o Mean age: 67 ± 9.31	NA	PCR	anxiety	Severe (ICU)	6 months post discharge
31	(Ollila et al., 2022)	Finland	Prospective	165 ICU:72 (44/28) Ward:49 (18/31) Home:44 (12/32)	48 (25/23) Mean age: 15.4 ± 2.9	RT-PCR/serology	Deficits in executive, visuospatial, language, concentration, short-term memory, attention tasks	Severe (ICU)	6 months post discharge

Abbreviation: PCR = polymerase chain reaction, RT-PCR = reverse transcriptase polymerase chain reaction, PTSD = post-traumatic stress disorder, ICU= Intensive Care Unit, NR = not reported, NA = not applicable.

[a] hospitalised and non-hospitalised are the hospitalisation status. Hospitalised patients are generally considered as severe COVID-19 patients, while non-hospitalised patients are those who generally experienced mild or moderate symptoms and did not require hospitalisation.

[b] MyCognition = It is a self-administered online assessment tool to assess cognitive function.

Web of Science Core Collection from Web of Science (WoS) which includes the important results only from the Science Citation Index Expanded (SCI-EXPANDED) and the Emerging Sources Citation Index (ESCI). The protocol was designed following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline as shown in the PRISMA flow diagram (Fig. 1) and according to previously published studies [17–22]. The search was oriented toward neurocognitive and EF deficits in long COVID studies, with or without healthy controls (HCs). For the searching and screening process, the Boolean operators "AND" and "OR" and inclusion keywords based on the PICOS criteria were used. The search string used was as follows: (((long COVID) OR (post-acute COVID-19 syndrome)) OR (long-haul COVID)) AND ((((cognitive) OR (cognition)) OR (neurocognitive function)) OR (executive function)), such outlined in Supplementary Table 2.

Titles, abstracts, and full-text articles were independently screened by S.M.N. The included articles were independently checked and reviewed by H.A.M. Reference lists from the included studies were also manually searched and screened for any related records using the snowballing technique. Two articles from the references were included in this paper. All the selection results were discussed a few times between S.M.N. and H.A.M. until consensus was achieved. A total of 31 articles were identified from the PubMed and WoS databases. All important data from the reports were independently collected and tabulated by S.M.N., and reviewed by H.A.M and K.H. Y. The article searches and selection began on September 1, 2023, and were completed on September 29, 2023. This paper was

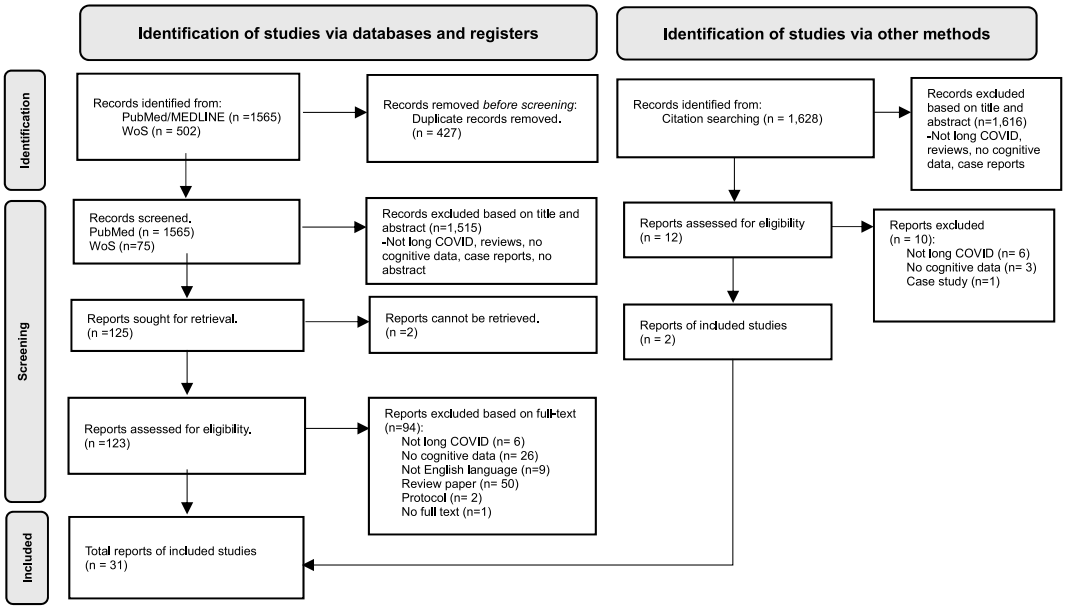

Fig. 1. Search strategy flow diagram based on PRISMA 2020 guideline for new systematic reviews which included searches of databases, registers and other sources.

thoroughly reviewed and edited by all the authors.

2.3. Quality assessment and data extraction

The quality assessment tool used was the Newcastle–Ottawa Scale (NOS), which was modified for applicable case−control studies and cohort studies, and adapted for cross-sectional studies. We performed extensive analyses to assess all included studies and rated them as high, moderate, or low NOS, and tabulated the scores as shown in the Supplementary Table 3 below. Studies in which the design was unclear were assessed according to the cross-sectional NOS. All component studies were independently rated by S.M.N. and reviewed by K.H.Y. From the eligible studies, data were extracted and recorded using the following variables: author(s) and year of publication, study country, participants' demographic information, cognitive impairment due to long COVID, and neuropsychological tests being used. Further data were systematically extracted based on the results of the cognitive tests, and the findings of the studies. Finally, we analysed the cognitive deficits that occurred in long COVID patients, which focused on the EF. This systematic review was registered under the International Prospective Register of Systematic Reviews (PROSPERO) with the registration ID: CRD4202348598.

Given the considerable heterogeneity methods and outcome measures among all included studies, a meta-analysis was not performed. Therefore, to get a more nuanced understanding of the variability findings related to long COVID's impact on brain connectivity and executive function, this paper synthesises the findings and forms a comprehensive analysis of multiple studies in terms of significant p values ($p < 0.05$), followed by the effect size (ES), which provides valuable insight into the magnitude across different studies, not only supporting the statistical significance of the experiments but also contributing to a comprehensive understanding of its practical significance. This finding can be referred in Fig. 2. The ES was compared between long COVID patients and HCs, and was measured using Cohen's *d* (d) or Bonett's delta (δ). The ES values of 0.20, 0.50, and 0.80 indicate small, moderate, and large ESs, respectively [5]. A larger ES indicated greater EF deficits on a particular neuropsychological test in long COVID patients than in HCs. For studies without HCs, ES could not be computed,; therefore, the findings of these studies were assessed qualitatively (i.e., presence or absence of impairment) [20]. Specifically, these studies reported only the number of patients showing deficits in the EF domain, when the individual score was more than 1.5 standard deviations (SDs) below the normative mean, or when more than 40 % of the patients showed impairment on the test [20].

3. Results

3.1. Search results and study quality

From the searching and screening process, 1565 and 502 records were obtained from the PubMed and WoS online databases, respectively. After removing duplicates, 1640 studies were screened by title and abstract, yielding 125 eligible studies. Ninety-four studies were further excluded following full-text screening. Based on the PICOS strategy, 29 records met the inclusion criteria of this study. In addition, 1628 records from the references of the included studies were reviewed, and 2 records met the inclusion criteria. In total, 31 studies were included in this review, as described in Table 2. 12 prospective studies and 19 cross-sectional studies.

Executive function subdomain and tests (Effect sizes)	Miskowiak, 2021 (*n*=129)	Miskowiak, 2023 (*n*=14)	Miskowiak, 2023 (*n*=194,150)	Henneghan, 2023 (*n*=52)	Graham, 2021 (*n*=100)	Mazza, 2021 (*n*=226)	Andrei, 2022 (n=53, 30)	Andriuta, 2022 (*n*=46, 1003)	Chang, 2022 (*n*=40)	Cecchetti, 2022 (*n*=46,36)	Guo, 2022 (*n*=181,185)	Bungenberg, 2022 (*n*=50)	Duindam, 2022 (*n*=96)	García-Sánchez, 2022(*n*=63)	Braga, 2022 (*n*=614)	Ariza, 2022 (*n*=319,109)	Ariza, 2023	Lauria, 2022 (*n*=100)	Lauria, 2023 (*n*=406)	Calabria, 2022 (*n*=136)	Damiano, 2022 (*n*=425)	Serrano-Castro, 2022(*n*=46,40)	Herrera, 2023 (*n*=214, 50)	Voruz, 2023 (*n*=110)	Vakani, 2023(*n*=129,93)	He, 2023 (*n*=66,79)	Godoy-González , 2023(*n*=80)	Gunnarsson, 2023(*n*=292)	Kirchberger, 2023 (*n*=372)	Costas-Carrera, 2022 (*n*=58)	Ollila, 2022 (*n*=165, 48)
No HC		Yes		Yes		Yes			Yes			Yes	Yes	Yes	Yes			Yes	Yes	Yes	Yes			Yes			Yes	Yes	Yes	Yes	
Shifting: 9																															
TMT-B	↓ 0.74	↓ 57% impaired	↓ 53% impaired	↓ 0.19			↓ 0.32	↓ 0.61	↓ 64.9% impaired	-		-	-	-		-	-	-	-	-		↓ 0.36		Z= -0.18	↓ 0.21	↓ 0.27	-	-		-	↓ 0.36
WCST											↓ 2.17																				
Inhibition: 6																															
Stroop test				↓ 0.23				↓ 0.61	↓ 64.9% impaired			-		-		-	-			-			↓ 0.76	Z= -0.12			-		-	-	↓ 0.36
VFT		↓ 57% impaired						↓ 0.61				-			-						-	↓ 0.63**					-				
ToL						↓ 50%																									
Working memory: 3																															
Digit Span Forward		-					-		35%	-		-		-		-	-	-	-	-			-	-			-		-	-	
Digit span Backward							-		↓ 42.5% impaired	↓ 0.96		-	-	-		-	-	-	-	-			↓ 0.86*	-			-		-	-	
DRT																						↓ 0.34										
Spatial Span Backward																												-				
LNS		↓ 57% impaired				-																										

Abbreviation: HC= healthy control, TMT=trail making test, WCST= Wisconsin card sorting test, VFT= verbal fluency test, ToL= Tower of London, DRT= digit retention test, LNS= letter-number-sequencing, ES= effect size

↓= impairment
- = no impairment
Effect sizes and Cohen's classification was used for size interpretation: 0.2= small, 0.5=medium, >0.8 to infinity= large (Bungenberg et al., 2022)
For studies without HC, the impairment is when the individual z-score > 1.5 SD below the normative mean., or when > 40% of the patients showed impairment on the test.
*All HC had normal scores on the test, and due to the small sample size, they estimated the ES with Hedges' correction.
**Calculated ES is from the Z-score using Cohen's d.

Fig. 2. Summary table of executive function impairment and findings using the effect sizes interpretation from included studies.

In general, all studies assessed by the quality assessment tool from the NOS were of fair quality, with only one study of moderate quality [21]. We performed a thorough analysis to evaluate the studies' quality and included only the moderate and high NOS-ranked studies in this paper. NOS scores within each category are presented for all component studies organised by design and tabulated in Supplementary Table 3 [see Additional file].

3.2. Study characteristics

Table 2 provides the detailed demographic information of the participants, their diagnosis and follow-up duration for long COVID syndrome, and their cognitive symptoms from all 31 studies. The studies included a total of 4675 patients with long COVID symptoms, which were classified as mild (n = 915), moderate (n = 274), and severe (n = 1402). Some of the studies classified the severity group as mild-moderate (n = 184), and moderate-severe (n = 425). Several studies did not report and underline the severity of COVID-19 in patients (n = 1413). This is due to the varied definitions of severity and focus across the studies, including the factors of hospitalisation, non-hospitalisation, and intensive care unit (ICU) admission of patients. Some of the studies included HCs, for which up to 1923 people participated. We included all the studies with and without HCs to allow for a more diverse representation of populations and increase the robustness of the evidence base. The patient sample size varied from 14 to 1043, and the mean age of the patients ranged from 42 to 73 years, but one study had a mean age of 37 years. This huge discrepancy in the mean age range resulted from the differences in the age ranges of the patients included in the studies, and we examined the effects of patient age on their results, as this might affect EF performance [8].

We also categorised the long COVID patients into two groups according to follow-up duration from the onset of infection: 3–6 months, and more than 6 months. As shown in the table, 14 cross-sectional and prospective studies recruited patients within a time range of 3–6 months, and 17 studies involved patients diagnosed more than 6 months postdiagnosis. This finding is significant because of the correlation between the severity of long COVID symptoms and the duration of follow-up post-infection. The patients were diagnosed with SARS-CoV-2 by the reverse transcriptase polymerase chain reaction (RT-PCR) assay and/or an antibody test (serology) or had typical clinical symptoms confirmed by an infectious disease specialist. This study covered most of the continents according to the number of studies from different countries: eight studies analysed data from Spain; four from Denmark; three from Brazil and China; two from Germany, Italy, the UK, and the USA; and one each from France, Finland, Korea, the Netherlands, and Switzerland, respectively. The quantitative synthesis mainly evaluated EF deficits due to the long duration of COVID reported in all included studies.

3.3. Data analysis

Cognitive function was evaluated using valid neuropsychological tests, as tabulated in Table 3. Among all the neuropsychological tests used, we were interested only in the outcomes of validated and well-established tests, specifically cognitive tests for EF (subdomains: inhibition, shifting, and working memory) [20]. Valid cognitive tests for assessing EF include the Trail Making Test A and B (TMT-A, TMT-B), the Stroop test, the Wisconsin Card Sorting Test (WCST), the Tower of London (TOL) test, the digit span test (DST)—both forward and backward, the verbal fluency test (VFT), the Controlled Oral Word Association Test (COWAT), the Brixton Spatial Anticipation Test (BSAT), and the Behaviour Assessment of Dysexecutive Syndrome (BADS).

Subtests derived from screening tests were not included because they frequently lack assurance and may be affected by threshold impacts, making them ineffective when used separately. These tests included not only the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Brief Assessment of Cognition in Schizophrenia (BACS), and Clock Drawing Test (CDT) and Frontal Assessment Battery (FAB), and screened for cognitive impairment in psychiatry (SCIP), but also computerised tests, such as NeuroCogFX, an online brain training test, and telephone questionnaires. All the studies reported on the cognitive profile of long COVID patients, in which EF was most significantly impaired [1]. 25 studies reported EF as their primary finding, and 6 studies reported it as secondary.

Among all the selected studies, only six used neuroimaging modalities, such as magnetic resonance imaging (MRI), electroencephalography (EEG), and positron emission tomography (PET), to link long COVID-related cognitive performance with structural and functional brain changes. These data are tabulated in Table 4. Neuroimaging findings revealed insights into the structural and functional alterations in the brain among individuals with long COVID symptoms. Notably, changes in white matter hyperintensity (WMH) volume, brain activity and FC alterations in regions linked to cognitive function have been found [7,23,24,25]. Additionally, these neuroimaging results were consistent with EF deficits in patients with long COVID. As a result, we discuss the relationship between the two elements. Apart from that, the current review does not report the assessment of certainty in the body of evidence. This is because it focuses on providing a broad overview rather than detailed evidence evaluation.

3.4. Executive function deficits

According to the unity and diversity model, findings on EF deficits in patients with long COVID syndrome can be divided into the following subdomains: task-set shifting (shifting), prepotent response inhibition (inhibition), and working memory (WM) [26]. The EF has also been found to be domain-general and associated with the frontal-parietal network [26].

3.4.1. Shifting

Shifting refers to the ability of individuals to adapt to changing circumstances and switch between tasks or mental sets. 25 of the 32 included studies assessed shifting performance in long COVID patients using the Trail Making Test Part B (TMT-B), and Wisconsin Card

Table 3
Objective cognitive tests and findings from included studies on executive deficits in long COVID.

No	Study	Neuropsychological tests used	Cognitive Function Measured	Modalities used	Cognitive Findings
1	(K W Miskowiak et al., 2021)	SCIP-D, TMT-B	Verbal learning and memory, working memory, verbal fluency, processing speed, executive function	–	- Verbal learning and executive function impairments (VLT-l: $p = 0.004$, TMT-B: $p = 0.002$). - Moderate impairments within working memory, verbal fluency and psychomotor speed (WMT: $p = 0.03$)
2	(Kamilla W. Miskowiak et al., 2023)	SCIP-D, TMT-B, RAVLT, Coding and Digit Span Forward, LNS test WAIS-III, Facial Expression Recognition Task, verbal fluency test	Verbal learning and memory, working memory, verbal fluency, processing speed	PET	- Deficits in working memory and executive function correlated with hyper cerebellar metabolism ($p = 0.03$)
3	(Kamilla W. Miskowiak et al., 2023)	SCIP-D, TMT-B	Working memory, executive function, verbal fluency, verbal learning, memory	–	- Large effect size impairment in working memory and executive function (WMT: $p < 0.001$, TMT-B: $p < 0.001$). - Moderate effect sizes within the verbal learning, verbal fluency, delayed verbal memory and psychomotor speed (VLT-L: $p < 0.001$, VFT: $p < 0.001$, VLT-D: $p < 0.001$, PMT: $p < 0.001$).
4	(Henneghan et al., 2021)	TMT-B, Stroop test, Digit symbol substitution, Immediate & delayed recall	Memory, attention, executive function	–	- 30.77 % participants performed poorly on the Stroop test and reported cognitive deficits greater than the norm.
5	(Graham et al., 2021)	NIH toolbox v2.1 instrument cognitive evaluation	Attention, working memory	–	- PROMIS fatigue quality of life T-scores moderately correlated with processing speed ($p = 0.02$), executive function ($p = 0.02$), and working memory ($p = 0.02$). - PROMIS cognition quality of life T-scores only correlated with working memory ($p = 0.02$).
6	(Mazza et al., 2021)	Brief Assessment of Cognition in Schizophrenia (BACS)	Verbal memory, verbal fluency, working memory, attention, processing speed, psychomotor, executive function	–	- Only 19 % pt showed poor scores in all domains, 16 % poor in at least one function, 17 % in two, 14 % in three, 11 % in four, 5 % in five, and 1.5 % showed no good performance at all. - Patients with psychopathology one month after discharge performed worse on verbal fluency ($p = 0.002$), information processing ($p = 0.002$), and executive functions ($p = 0.001$)
7	(Andrei Appelt et al., 2022)	MoCA, TMT-A&B, Digit span test	Sustained attention, visual processing speed, motor function, inhibition	EEG	- A decrease in brain electrical activity in Fz-F4 during rest and in F3-F7 during tasks with high cognitive demand for 6–12 months after COVID-19 infection.
8	(Andriuta, Si-Ahmed, Roussel, J.-M. Constans et al., 2022)	BNT, ROCF, French adaptation of the FCSRT, digit symbol coding test, GREFEX, TMT, stroop test	Executive function, language, action speed, visuoconstructive abilities, episodic memory,	MRI	- Predominance of slowing cognitive profile and executive dysfunction.
9	(Chang et al., 2022)	Digit span, TMT, Stroop test	Attention, processing speed, working memory, executive function	–	- 64.9 % most frequents impairments in executive function (TMT-B/Stroop word color interference test) - 52.5 % in attention/processing speed (digit span forward/TMT-A) - 42.5 % working memory (digit span backward)
10	(Cecchetti et al., 2022)	MMSE, symbol digit, digit span, TMT-A & B, phonemic fluency, RAVLT, VOSP, complex figure, SAND	Global cognition, executive function, memory, visuospatial function, language	EEG, MRI	- 16 %, 6 % and 6 % of patients showed a pure executive, memory and visual-spatial impairment, respectively. - 25 % of subjects showed a multidomain impairment (with the 23 % involving, among others, the executive domain).

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Table 3 (*continued*)

No	Study	Neuropsychological tests used	Cognitive Function Measured	Modalities used	Cognitive Findings
					- At follow-up, 36 % of patients showed an impairment in at least one cognitive domain
11	(Guo et al., 2022)	WCST, PAMT, CFT, WLRMT, MRT	Memory, language, working memory, executive function	–	- Consistent pattern of memory deficits in covid-19 patients, also with increasing self-reported ongoing symptoms. - Little to no effect of the COVID-19 infection on 2D Mental Rotation, which is thought to assess visuospatial working memory.
12	(Bungenberg et al., 2022)	MoCA, TMT-A&B, digit span backward & forward, RWT, Stroop test, VLMT, ROCFT, BNT	Attention, psychomotor speed, executive function, language, visuospatial processing, memory	MRI	- No Pt either hospitalised or non-hospitalised showed impairment in logic reasoning or SIT. - Mild deficits in attention, processing speed and memory and only a few patients showed impairment in attention and executive function tasks. - No correlation between the severity of acute COVID-19 disease, and Long COVID-19. - No clear evidence of generalized impairment on objective testing of cognitive functioning.
13	(Harmke B Duindam et al., 2022)	MoCA, TMT-A&B, letter digit substitution, digit span, NART-IQ	Executive function, processing speed	–	- 27 % were cognitively impaired based on test results. - Pt impaired for executive functioning tests (21 % TMT-B/A & 18 % Digit Span) - Information processing performances were impaired in Pt (23 % LDST & 15 % TMT-A) - Cognitively impaired Pt showed similar clinical frailty score after 6 months and reported similar anxiety and depressive symptoms.
14	(García-Sánchez et al., 2022)	RAVLT, block design test, ROCFT, digit span forward & backward, WAIS-IV, BNT, CPT-II, TMT-A&B, stroop test	Learning & long-term memory, visuospatial & visuoconstructive abilities, working memory, processing speed, language, attention, executive function	–	- multiple-domain impairment more frequent (60.3 %) than one-domain impairment. - most frequent domain impaired is attention. - 2nd is executive function (43 %) - Only executive function & attention were significantly correlated. - Hospitalisation associated with decreased performance on processing speed. - Disease duration and the cognitive domain scores were not significant.
15	(L W Braga et al., 2022)	BNIS, verbal fluency test, clock drawing test	Language, attention, orientation, visuospatial and visuoperceptive abilities, memory, executive function, working memory, visuomotor process	–	- Post-covid patients score below references on phonemic verbal fluency test, clock drawing test & BNIS suggesting persistent problems with executive function. - No correlation between patients' severity of covid symptoms and performance on neuropsychological test.
16	(Ariza et al., 2022)	MoCA, WAIS-III, RAVLT, ROCF, digit span forward&backward, TMT-A&B, COWAT, stroop test, BNT	Reasoning, verbal memory, visual memory, visuoconstructive abilities, verbal attention, working memory, motor speed, verbal fluency, language	–	- PCC group had significant poor performance in MoCA, matrix reasoning, RAVLT sum, RAVLT delayed recall, digit symbol, Stroop words, Stroop colours, Stroop interference, phonetic fluency, and semantic fluency than HC group.

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Table 3 (*continued*)

No	Study	Neuropsychological tests used	Cognitive Function Measured	Modalities used	Cognitive Findings
					- No differences in neuropsychological performance between patients with or without cognitive complaints.
17	(Ariza et al., 2023)	Updated digit test subtest using WAIS-IV	–	–	- ICU-PCC group worse in MoCA, Digit symbol, TMT B, TMT-B-A, phonetic fluency, and RMET assessments than HC group, and obtained poorer results than M-PCC group in the TMT-B and TMT-B-A. - H-PCC group showed worse performance in Digit symbol assessments than HC group.
18	(Lauria et al., 2022)	MMSE, Rey immediate recall, TMT, digit span backward & forward, frontal assessment battery, Ray delayed recall, MFTC	Memory, attention, visuospatial, psychomotor speed, working memory, verbal short-term memory	–	- 33 %, 23 %, and 20 % participants failed TMT, Digit Span Backwards, and FAB test., and showed impairment in visuoperceptual skills, selective and divided attention, working memory, verbal memory, and executive function.
19	(Lauria et al., 2023)	RAVLT, TMT-BA, digit span forward & backward, frontal assessment battery	Attention, executive function, working memory, short-term memory	–	- 26.6 %, 18.7 % and 10.9 % of subjects obtained 0 or 1 equivalent scores on TMT, Digit Span Backwards and FAB tests respectively, showing impairment in selective and divided attention, working memory, short-term memory and executive functions.
20	(Calabria et al., 2022)	MoCA, CPT-II, RAVLT, ROCFT, digit span forward & backward, BNT, block design, coding, symbol search, stroop test, TMT-A&B	Attention, short- and long-term memory, language, processing speed, visuoperceptual & visuoconstructive, executive function	–	- The most prevalent neuropsychological deficit was in long-term memory (28.7 %), executive functioning (Stroop Inhibition: 24.2 %; TMT-B: 23.5 %), and attention as measured by CTP-II.
21	(Damiano et al., 2022)	MMSE, TMT-A, verbal fluency test	Orientation, attention, verbal fluency, executive function	–	- Impairments found in sample, especially executive and attentional deficits. - High rates of attention and executive dysfunction unrelated to clinical severity.
22	(Serrano-Castro et al., 2022)	MoCA, CVLT, FCSRT, BNT, RCFT, DRT of WAIS, TMT-B&A, FAS	Episodic and working memory, executive function, attention	–	- Impairment of executive functions was substantial in Pt by the scores of the FAS animals (43.7 % abnormal), FAS vegetables (48.6 % abnormal) and FAS kitchen (33.1 % abnormal) tests. - Failure in executive function indicates that frontal lobe dysfunction is prevalent in post-Covid19 syndrome.
23	(Herrera et al., 2023)	Digit span forward & backward, TAVEC, ROCF, WAIS-IV matrix reasoning, Stroop test, fluency task	Attention, processing speed, working memory, executive function, language	–	- 85.12 % Pt had impaired score in at least one test. - Highest percentage of patients had mild impairment; Stroop W (38.90 %), action fluency (32.80 %), Stroop C (29 %), Stroop W–C (28.40 %) and TAVEC-FLR (25.10 %). - Highest number of patients showing a severe impairment; BTA (29.30 %), Stroop W (20.90 %), Stroop C (18.10 %) and Stroop W–C (12.5 %).
24	(Voruz et al., 2023)	Stroop task, TMT, digit span backward & forward, corsi test, ROCF	Executive function, memory, language, visuoperceptual & visuoconstructive function	fMRI	- Mild Pt performed TMT-B and TMT B/A significantly faster than moderate Pt.
25	(Vakani et al., 2023)	Simple reaction time task, choice reaction time task, 2-back task, TMT-B, visual recognition memory task	Processing speed, attention, working memory, executive function, memory	–	- Hospitalised Pt experience lower executive function reaction time than non-hospitalisation.

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Table 3 (*continued*)

No	Study	Neuropsychological tests used	Cognitive Function Measured	Modalities used	Cognitive Findings
					- Executive function task completion time, during processing speed and attention correlated to each other. - Higher overall long COVID symptom correlated with poorer executive function and memory in pre-pandemic cognitive data.
26	(He et al., 2023)	RTI, DSST, TMT-B, 1-back	Attention, executive function, working memory, processing speed	–	- No statistical significance between scores for depression/anxiety/PTSD and cognition. - Experience of ICU stay and self-perceived disease severity negatively associated with cognitive function.
27	(Godoy-González et al., 2023)	Digit span forward & backward WAIS-III, spatial score forward & backward WMS-III, RAVLT, SPART, SCWT, TMT-A&B, CTT, FAS WAIS-IV	Attention, learning memory, delayed recall, recognition memory, working memory, executive function, processing speed	–	- 30 % suffered objective cognitive deficits. - 27.5 % reported clinically significant subjective cognitive deficits. - Patients showed greater impairment in executive function, processing speed, and recognition memory.
28	(Gunnarsson et al., 2023)	TMT-B, SCIP	Verbal learning, memory, working memory, verbal fluency, processing speed, executive function	–	- Main findings: physical impairment in this large sample assessment is high prevalence. - Consistent correlation between all three physical function tests and two cognition tests, SCIP and TMT-B score.
29	(Kirchberger et al., 2023)	Digit span forward & backward WAIS-IV, SCWT, semantic verbal fluency test	Memory, executive function	–	- Working memory was the most strongly affected cognitive function.
30	(Costas-Carrera et al., 2022)	MoCA, digit Span Forward & Backward, Vocabulary from WAIS-III, Stroop Test, FCSRT, JLO, TMT, COWAT, ANF, BNT	Verbal memory, processing speed, language, executive function,	–	- Immediate verbal memory and learning were moderately impaired (38 %), delayed verbal memory (11.8 %), verbal fluency (34.6 %) and working memory (executive function) (6.1 %), respectively.
31	(Ollila et al., 2022)	WAIS-IV coding, continuous performance test, stroop, TMT-B, FAB with WAIS-III, delayed recall, RCF	Attention, executive function, memory	–	- ICU-treated COVID-19 Pt showed more severe long-term cognitive impairment compared to patients with less severe acute COVID-19 or HC. - Impairment mainly in domains: attention and executive functions

Abbreviation: SVFT= Semantic Verbal Fluency Test, DSST = Digit symbol substitution test, TMT = Trail Making Test, SCIP-D= Screen for Cognitive Impairment in Psychiatry Danish Version, WAIS= Wechsler Adult Intelligence Scale, LNS = Letter-Number-Sequencing, RAVLT = Rey Auditory Verbal Learning Test, VT = vigilance task, SIT = stroop interference task, BACS = brief assessment of cognition in Schizophrenia, ANT = animal naming test, COWAT = controlled oral word association test, BNT = boston naming test, ROCFT = Rey-osterrieth complex figure test, VOSP = visual object and space perception battery, MMSE-mini-mental state examination, MFCT = multiple features target cancellation test, WCST = wiconsin card sorting test, PAMT = pictorial associative memory test, CFT = category fluency test, WLRMT = word list recognition memory test, MRT = mental rotation test, RWT = Regensburger Wortflussigkeit-Test, VLMT= Auditory verbal memory test, NARTQ-IQ= National adult reading test, CPT= Conner's continuous performance test, BNIS= Barrow Neurological Institute Screen for Higher Cerebral Functions, CVLT= California verbal learning test, FCSRT= Free and cued selective reminding test, RCFT = rey complex figure test, DRT = digit retention test, FAS = phonetic verbal fluency, RTI-reaction time paradigm, WMS= Wechsler memory scale, SPART = spatial recall test, SCWT = stroop color and word test, CTT = color trails test, JLO= The Benton Judgment of Line Orientation, NA = not applicable.

Sorting Test (WCST).

Of the 23 studies that used the TMT-B, 8 reported impairment with small to moderate ESs ($\delta = 0.21–0.74$) [3,7,11,24,27–29,30]. A case series of 358 long COVID patients from 4 studies showed that 53%–64.9 % of patients were impaired in shifting [2,4,31,32]. On the other hand, one study reported impairment in patients with long COVID using the WCST with a large ES ($\delta = 2.17$) [33]. This discrepancy between findings obtained through the WCST and those obtained through the TMT-B could be because, unlike the latter, the former sets a time limit and is highly dependent on motor speed. Moreover, compensation for motor speed and limited time may obscure shifting impairments [20].

3.4.2. Inhibition

The inhibitory control helps regulate impulses and focus attention [26]. The Stroop test, VFT and ToL were used to evaluate

Table 4
Summary of neuroimaging findings from included studies that correlated with executive deficits in long COVID.

No	Study	Modalities used	Neuroimaging Findings
1	(Kamilla W. Miskowiak et al., 2023)	FDG-PET	- Deficits in working memory and executive function correlated with higher metabolism in the cerebellum ($p = 0.03$) identified in the patient group, with higher metabolism in the bilateral superior temporal pole ($p = 0.03$), amygdala ($p = 0.01$), thalamus ($p = 0.04$), and vermis ($p = 0.04$).
2	(Andrei Appelt et al., 2022)	EEG	- +ve correlation between EEG complexity during TMTA with MOCA ($p = 0.024$) in F3-F7, in 6–12 months after COVID-19 infection. - Reduction occurs in brain activity at rest in Fz-F4 areas and during high cognitive demands in the F3-F7 areas.
3	(Andriuta, Si-Ahmed, Roussel, J.-M. Constans et al., 2022)	MRI	- WMH correlated with G3 overall summary score in all localized right hemisphere of 6 regions; frontal region, postcentral region, cingulum, cortico-spinal tract, inferior longitudinal fasciculus, internal capsule and posterior arcuate fasciculus. - Global volume of WMH correlated with G3 overall summary score in the superior frontal region.
4	(Cecchetti et al., 2022)	EEG, MRI	- EEG: ↓ IAF and ↑CSD at delta frequency band in bilateral frontal and central-temporal regions, and ↑ LLC values at delta band in COVID-19 patients compared to HC. - MRI: ↑ WMH volume of total right frontal & right parieto-occipital in patients.
5	(Bungenberg et al., 2022)	MRI	- WMH presented mild in periventricular regions but no correlation with clinical outcome. - Cerebral microbleeds are more common in hospitalised patients and those who have extracorporeal membrane oxygenation support.
6	(Voruz et al., 2023)	fMRI	Severe vs mild patients = - 3 patterns ↓ FC: subregions in right DorsAttnA, SomMotA, bilateral SomMotB, leftDorsAttnB and right SalVentAttnA networks. - 1 pattern ↑ FC: between subregion in left DMN B (DefaultB) Severe vs moderate patients = - 1 pattern↓ FC: subregions in right DorsAttnA, bilateral DorsAttnB and right SalVentAttnA networks. Moderate vs mild patients = - 2 patterns↑ FC: subregions in subcortical networks, left SomMotB, cerebellum, and left TempPar networks. - Significant correlation between cognitive performance and FC by multivariate PLSC data analysis.

Abbreviation: FDG-PET = fluoro-2-deoxy-D-glucose positron emission tomography, EEG = electroencephalogram, MRI = magnetic resonance imaging, fMRI = functional magnetic resonance imaging, WMH = white matter hyperintensities, FC = functional connectivity, PLSC = partial least squares correlation, IAF = individual alpha frequency, CSD = current source density, LLC = linear lagged connectivity.

inhibition in long COVID patients. Of the 14 studies that used the Stroop test, 2 reported poor inhibition with a small ES ($\delta = 0.23$, 0.36) [3,30], while 2 others reported moderate and large ES respectively ($\delta = 0.61$, 0.76) [1,34]. Meanwhile, a single-arm study of 40 long COVID patients reported that 64.9 % of patients had impaired inhibition [31]. Sample size discrepancies may impact the variability of outcomes in the ES. For example, larger sample sizes from the Herrera et al. study ($n = 214$) led to larger ESs ($\delta = 0.76$) than did two other studies with small ESs ($n = 46$, 52) [3,30].

In terms of different age groups, patients under 50 years old exhibited a greater percentage of mild and moderate impairments (31.65 % and 22.5 %, respectively) in inhibition than did those above 50 years old (16.05 % with mild deficit) [1], suggesting that age is unlikely to be a contributing factor to impaired inhibition. This could be attributed to age-related changes in cognitive reserve and immunological response to COVID-19 [35]. Alternatively, a stronger autoimmune response in younger patients may result in cytokine storming and increased inflammation during SARS-CoV-2 infection [36], which could impact the neural circuits and developmental processes involved in EF [1]. As aging weakens the immune system, the autoimmune response in elderly people will likely be weaker than that in young patients [1]. These results also indicated that EF impairment can occur at any age range, and is associated with frontal lobe dysfunction in long COVID syndrome [27].

One individual inhibits automatic and prepotent response to produce the same words and filter irrelevant information that is unrelated to the criteria of the task [37]. Two studies using the verbal fluency test (VFT) showed impaired inhibition with moderate ES ($\delta = 0.61$, 0.63) [24,27]. With the VFT, impairments in the word storage and retrieval abilities of patients were observed [14], highlighting inhibitory control impairments in these patients. Specifically, the patients showed impairment (43.7 %, 48.6 %, and 33.1 %) in the VFT animals, VFT vegetables, and VFT kitchen tests, respectively; all of which are semantic VFT. Notably, only one study examined VFT in long COVID patients, and no study has examined phonemic VFT. We expect that phonemic VFT impairment may be more pronounced in long COVID patients compared to semantic VFT due to the absence of word retrieval strategies such as semantic categorisation [20].

Finally, one study that used the Tower of London (ToL) test showed that 50 % of long COVID patients performed significantly worse after 3 months of follow-up [9]. However, it is important to note that TOL is not a pure inhibition test, as it involves multiple executive processes (i.e., inhibition, WM, shifting). It is not entirely certain which subcomponent of the EF is impaired based on TOL alone [38].

3.4.3. Working memory (WM)

WM involves holding and manipulating information in the mind [26]. In this review, we reported studies of WM that used both forward and backward Digit Span (DS), Spatial span (SS), and digit retention test (DRT). Of these 15 studies, no study reported impaired DS Forward performance in patients, while 2 reported impaired DS Backward in long COVID patients with large ESs (δ = 0.86–0.96) [1,39]. A single-arm study with 40 long COVID patients also reported that 42.5 % of patients were impaired in WM using DS backward [31], and 57 % using the LNS test [4],; in addition to a study reported impaired verbal span WM in long COVID patients with small ES using the DRT test ($\delta = 0.34$) [27].

The DS Backward task exhibited the most significant impairment because the task places a greater EF demand on individuals, as it requires not only information recall but also the manipulation and reordering of that information in WM [40,33]. However, 12 studies showed no significant result in DS [5,7,10,41–43,44,45,46,47,48–50]. A previous systematic review indicated the role of language [20]; however, not all studies specified the language of the administered test, potentially introducing language-specific influences. Language specialisation might include specific cognitive mechanisms for manipulating linguistic elements, aiding performance in DS Backward. Those with restricted expertise in language specialisation and verbal intelligence may struggle more with the heightened demands of manipulating information, leading to a greater difference in performance between DS Forward and Backward [51].

3.5. Brain alterations associated with executive function deficits in long COVID

The use of neuropsychological assessments was significant for evaluating various cognitive functions, including EF. However, in addition to neuropsychological tests, neuroimaging techniques have been utilised to investigate structural and functional changes in the brain in detail. This could provide a correlation between cognitive impairment in long COVID and neuroimaging analysis using various neuroimaging techniques such as magnetic resonance imaging (MRI), functional MRI (fMRI), fluorodeoxyglucose positron emission tomography (FDG-PET), and electroencephalography (EEG) [2,7,32,34,52,53].

Of the 32 studies, only 6 (Table 4) reported the modalities used and correlated the neuroimaging data with cognitive performance in long COVID patients. First, FDG-PET detected hypermetabolism in the cerebellum, in additional temporal and limbic regions in patients, which correlated with more severe deficits in working memory and EF [4]. This finding was consistent with previously published FDG-PET data showing greater impairment in the amygdala, hippocampus, parahippocampal region, and frontal lobes, all of which are directly related to memory and EF [27].

Another MRI study revealed a pattern of white matter hyperintensities (WMHs) in the right-sided superior frontal region, post-central region, right cingulum, corticospinal tract, inferior longitudinal fasciculus, internal capsule, and posterior segment of the arcuate fasciculus associated with cognitive complaints in long COVID patients. The right superior frontal region and the right cingulum are known to control EF, and the global WMH volume is associated with action speed and EF [24]. These findings are consistent with those of a study by Cecchetti et al. (2022), which revealed greater volumes of right frontal and right parieto-occipital WMHs in COVID-19 patients than in controls, whereas no significant differences were detected in other regions [39]. There was no significant difference in the total brain, gray matter (GM), and white matter (WM) volume, although further analysis of long COVID patients using MRI is needed. Moreover, cerebral microbleeds were commonly detected in patients via MRI [5].

According to the EEG results, brain activity at rest in the Fz-F4 region and during periods of high cognitive demand in the F3-F7 region was reduced [7]. A lower individual alpha frequency (IAF), higher current score density (CSD), and higher linear lagged connectivity (LLC) were found in COVID-19 patients than in healthy controls [52]. On fMRI, significant FC alteration patterns were found in mild to severe patients [2]. These alterations correlate FC with cognitive performance in patients according to multivariate partial least squares correlation (PLSC) data analysis. Notably, the FC in the dorsal attention network A (DorsAttnA), bilateral dorsal attention network B (DorsAttnB), and right salience ventral attention network A (SalVentAttnA) was lower in the severe patients than in the moderate and mild patients. In addition, higher FC between subregions in the left default mode network B (DMN B) was reported in severe patients,; meanwhile, in moderate patients, FC increased in other subregions: the subcortical networks, left somatosensory motor networks b (SomMotB), cerebellum and left temPar networks [2]. Consequently, EF deficits were found in the moderate and severe groups, while mild patients displayed better EF. This is also due to the younger age of the mild patients [2].

4. Discussion

4.1. Executive function deficits, and brain alterations in long COVID patients

Consistent with the findings of previous studies [1,8,34], we found that EF is impaired in patients with long COVID. Specifically, shifting and inhibition impairments were consistently identified and may be exacerbated with time pressure. This is demonstrated by the high ES values for shifting, as measured by the Trail Making Test B (TMT-B) [54] and the Wisconsin Card Sorting Test (WCST) [33], presented in Fig. 2. Meanwhile, working memory within EF also shows impairment by high ES value using Digit span backward test [55,27], and it may be subjected to a language-specific nature. Nevertheless, these EF impairments may improve over time and are not necessarily permanent.

EF is frequently highlighted for several reasons. First, the virus may directly affect the central nervous system during acute infection, leading to neuroinflammation and damage to the brain areas associated with EF [8]. Alternatively, a study discovered that EF decline was common in the COVID-19 subacute phase and unrelated to other subjective symptoms, suggesting that it could be a symptom independent of the severity of systemic inflammation [8]. Second, EF is directly related to activities of daily living [8,34]. The virus may directly affect the central nervous system during acute infection, leading to neuroinflammation and damage to the brain

areas associated with EF. Finally, EF deficits in patients with long COVID also promote psychopathological symptoms such as anxiety, stress, depression, and PTSD [22,56,29]. These symptoms further exacerbate EF deficits [20]. The different outcomes for shifting in long COVID may be due to the improvement in the cognitive function of COVID-19 survivors over time [7]. Notably, the completion time for EF tasks, reaction times in processing speed and attention tasks were frequently correlated and showed improvement displaying small-to-medium ES [57]. These correlations were particularly evident in relation to individual long-COVID symptoms, especially arrhythmia, headache, and chest pain [28].

A substantial alteration in brain structure and function was associated with EF deficits in long COVID patients. For instance, a reduction in gray matter thickness and tissue contrast in the orbitofrontal cortex (OFC) is associated with EF deficits in long COVID patients [7]. One pathophysiological mechanism suggests that the COVID-19 virus enters the hypothalamus through the nervous terminal pathway, allowing it to spread to the medial prefrontal lobe, the region associated with EF [42]. Furthermore, by utilising FDG-PET, patients were found to have hypermetabolism in the cerebellum, and additional temporal and limbic regions. This is due to systemic immunological dysregulation and an increase in the inflammatory response following COVID-19 infection, or symptoms known as fatigue and 'brain fog'(4).

Functional alterations were observed in the salience, DAN, DMN, SMN, cerebellum, and temporal-parietal networks [2]. While a single study may not provide conclusive findings, it does offer some valuable insights into functional alterations. This included a significant correlation between cognitive performance and FC, which revealed patterns of hypoconnectivity and hyperconnectivity in severe patients but only hyperconnectivity in moderate patients [2]. Thus, from the studies included in this review, we found that long COVID-19 can be characterised as a dysexecutive syndrome, where individuals experience significant impairments involving cognitive processes related to EF, which is associated with brain imaging techniques, including fMRI. It also contributed to the identification and characterisation of brain's structural and functional alterations in long COVID.

4.2. Correlation between executive function deficit and severity of COVID-19

To our knowledge, COVID-19 virus is systemic and affects multiple organs throughout the body, including the brain, leading to neurocognitive impairments [14]. Understanding the systemic effects of COVID-19 is crucial for elucidating the complexities of long COVID and its underlying mechanisms. From the total studies, there are two points of view: one says that there is no association between the two, while the other says the opposite.

According to the first perspective, there is no relationship between the severity of acute COVID-19 infection and EF deficit in patients with long COVID, and most symptoms improve between 3 and 12 months [41,45,53]. One-third of the studies (10 studies) [5–7,12,14,56,54,58,32,59] agreed with this conjecture. For example, a study found no differences between individuals with mild or moderate COVID-19 and healthy controls (HCs) 4 months after infection [42]. In some cases, non hospitalised COVID-19 patients experienced a similar degree of neuropsychological problems as hospitalised patients do, particularly problems with EF, memory, and attention [14,21,58]. These findings were supported by the lack of correlation between neuropsychological test performances and the severity of COVID-19 symptoms.

Specifically, the probability of patients with mild COVID-19 having a long COVID cognitive disorder is as high as that of severe or hospitalised patients [14]. Remarkably, no direct association was observed between the time elapsed since hospital discharge and the severity of cognitive impairment. However, impaired EF was prevalent, irrespective of the clinical severity, with pulmonary function and respiratory symptoms post-recovery being associated with greater impairments [54,47]. This might be due to the shifting of predominantly respiratory manifestations in the acute phase of COVID-19 to the emergence of neurological symptoms during the long-term COVID [5]. On the other hand, from the second perspective (6 studies) [2,3,41,42,28,29], we found a correlation between EF deficit and the severity of COVID-19 infection. A possible explanation is that poorer EF during long COVID is associated with poorer premorbid functioning [28]. Additionally, infected individuals are likely to develop neurodegeneration and dementia in the future [41].

In summary, the relationship between the severity of acute COVID-19 and cognitive impairment in patients with long COVID has not been conclusively established, and two conflicting findings have been identified. However, further research is needed to unravel the complexities of these relationships and their implications for long-term cognitive health. Another crucial concern revolves around the longevity of cognitive impairments and the possibility of complete recovery [6,11]. Cognitive difficulties frequently persist for up to two years or more following the disease onset [60], which is also being reported in the previous systematic review [61].This finding suggested that specific cognitive domains, notably EFs, may improve over time, indicating the prospect of recovery in certain aspects [1].

For a more comprehensive analysis, we also grouped the studies in terms of different follow-up durations of long COVID syndrome patients into two groups. The first group of patients were followed up within 3–6 months of COVID-19 infection, while the second group of patients were followed up beyond 6 months. We differentiated the EF deficit findings between these groups to determine the significance of long COVID syndrome duration and severity. Based on the tests used, many studies have indicated impairment in patients despite the duration of the syndrome, and two studies have suggested that cognitive decline, especially in EF, has no significant difference between patients and HCs in terms of time [7,8]. Hence, the impairments can improve with respect to time.

4.3. Limitation

One of the intrinsic limitations of this study is the heterogeneity of the included studies, as they varied in objectives, study design, methodologies, and participant characteristics. Due to the heterogeneous outcome measures across the included studies, a meta-

analysis was not conducted as this may introduce bias and limit the generalizability of the findings. Second, half of the total studies lacked a matched healthy control group, which made it difficult to determine whether the cognitive deficits were unique to COVID-19 exposure or broader societal changes due to the pandemic [30]. Third, a small sample size and lack of assessor blinding were expected. This was due to several long COVID experiments being conducted during the pandemic. Thus, a larger sample size in future research would help to validate the findings. Fourth, we found a large discrepancy in the mean age range resulting from the differences in the age range of the patients which may introduce bias, as the more pronounced decline in EF post-COVID syndrome observed in in older patients [31,62] could be influenced by confounding factors, including the possibility that some of these cognitive impairments may be exacerbated by age. We suggest that future studies consider controlling for age to improve the accuracy of the results. Fifth, no study has specifically reported which COVID-19 variants cause severe viral infection and affect cognitive deficits. Only one study reported that patients had confirmed SARS-CoV-2 infection during the Omicron-variant era, where the severity of acute symptoms was relatively low [31]. Another systematic review also suggests that Omicron-infected individuals may have a lower risk of developing long-COVID symptoms than those infected with other variants [63].This could be an opportunity for future longitudinal research to investigate the impact of different COVID-19 variants on cognitive deficits. Sixth, the validity of findings indicating EF deficit in long COVID is also not specifically targeted in these studies, primarily because of the existence of confounding variables, including psychological symptoms. Nevertheless, it is crucial to recognise these symptoms in the clinical presentation of long COVID, as eliminating them when investigating neurocognitive function is challenging. It is also important to consider and exclude factors such as fatigue, which can impact the validity of performance assessments in patients. Seventh, lack of longitudinal data across the included studies, as most were cross-sectional. This could limit the ability to assess the long COVID impact on executive function. To address this limitation, we have included studies with varying durations of follow-up, to capture both short-term and longer-term effects of COVID-19 on executive function.

5. Conclusion

Overall, EF is predominantly impaired in patients with long COVID, which resulted in reduced performance in other neurocognitive domains. This could also be associated with the structural and functional disruptions in the brain in long COVID patients. Depressive symptoms, if present, can further impact the neurocognitive profile. It is important to understand the systemic characteristics of the COVID-19 virus and its capacity to cause persistent neurocognitive changes. Therefore, further research is needed, focusing on the local neurocognitive normative data with larger samples and performance validity testing for more precise findings.

CRediT authorship contribution statement

Siti Maisarah Nasir: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Noorazrul Yahya:** Writing – review & editing, Supervision. **Kah Hui Yap:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization. **Hanani Abdul Manan:** Writing – review & editing, Supervision, Funding acquisition.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

All the authors approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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