Received: 21 December 2022 | Accepted: 16 January 2023

DOI: 10.1111/ene.15721

european journal of neurology
the official journal of the european academy of neurology

REVIEW ARTICLE

Functional neurological disorder in people with long COVID: A systematic review

Tiago Teodoro[1] | Jiaying Chen[1] | Jeannette Gelauff[2] | Mark J. Edwards[1]

[1]Neurosciences Research Centre, Institute of Molecular and Clinical Sciences, St George's, University of London, London, UK

[2]Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands

Correspondence
Tiago Teodoro, Department of Neurology, St George's, University of London, Blackshaw Road, London SW17 0QT, UK.
Email: tiago.teodoro@nhs.net

Abstract

Background and purpose: Acute health events, including infections, can trigger the onset of functional neurological disorder (FND). It was hypothesized that a proportion of people with long COVID might be experiencing functional symptoms.

Methods: A systematic review of studies containing original data on long COVID was performed. The frequency and characteristics of neurological symptoms were reviewed, looking for positive evidence suggesting an underlying functional disorder and the hypothesized causes of long COVID.

Results: In all, 102 studies were included in our narrative synthesis. The most consistently reported neurological symptoms were cognitive difficulties, headaches, pain, dizziness, fatigue, sleep-related symptoms and ageusia/anosmia. Overall, no evidence was found that any authors had systematically looked for positive features of FND. An exception was three studies describing temporal inconsistency. In general, the neurological symptoms were insufficiently characterized to support or refute a diagnosis of FND. Moreover, only 13 studies specifically focused on long COVID after mild infection, where the impact of confounders from the general effects of severe illness would be mitigated. Only one study hypothesized that some people with long COVID might have a functional disorder, and another eight studies a chronic-fatigue-syndrome-like response.

Discussion: Neurological symptoms are prevalent in long COVID, but poorly characterized. The similarities between some manifestations of long COVID and functional disorders triggered by acute illnesses are striking. Unfortunately, the current literature is plagued by confounders, including the mixing of patients with initial mild infection with those with severe acute medical complications. The hypothesis that long COVID might in part correspond to a functional disorder remains untested.

KEYWORDS
functional neurological disorder, long COVID, neurological symptoms

INTRODUCTION

The syndrome of long COVID is defined as the persistence of symptoms for more than 4 weeks after an acute COVID-19 infection [1]. These symptoms appear to be very diverse and include fatigue, dyspnoea, chest discomfort, cough, anosmia, joint pain, headache, sicca syndrome, rhinitis, dysgeusia, poor appetite, dizziness, vertigo, myalgias, insomnia, alopecia, sweating, diarrhoea, anxiety, impaired

See editorial by J. Hugon on page 1165.

memory, poor concentration and anxiety/depression [2]. Different terms are used to refer to this complex of diverse symptoms, and 'long COVID' is often considered to best reflect patients' experience [3]. Long COVID encompasses ongoing symptomatic COVID-19 (duration between 4 and 12 weeks) and post-COVID-19 syndrome (symptom duration greater than 12 weeks) [1].

The recognition that a large number of people have developed persistent symptoms after acute COVID-19 infection, many of whom have not been able to return to their pre-morbid state, has justifiably motivated investment of substantial time and resources into research of this condition. In parallel, this topic has been a particular focus of attention by mainstream media.

However, the pathophysiology, prognosis and best management of long COVID all remain uncertain, and it seems most likely that this diagnostic category aggregates a heterogeneous array of different pathophysiological processes. The prominence of neurological symptoms, such as memory difficulties, poor concentration and headaches, is noted but also the multisystemic character, with symptoms relatable to most organ systems.

During severe COVID-19 infection, acute neurological complications can occur. Indeed, patients often develop an acute encephalopathy. It has been proposed that the underlying mechanism is direct brain invasion [4] although evidence to support this mechanism remains limited. Indeed, an autopsy study of 41 consecutive patients with COVID-19 infection (59% admitted to intensive care) found very low levels of virus within the brain, and these levels did not correlate with neuropathological findings [5]. The pervasive microglial activation, microglial nodules and neuronophagia found were instead attributed to a combination of systemic inflammation and hypoxia/ischaemia, rather than to direct viral invasion [5]. Acute encephalopathy in COVID might therefore not be COVID-specific but instead related to systemic response to severe infection (as in sepsis) [4, 5]. Acute ischaemic stroke has been associated with acute COVID infection, but despite the well-recognized hypercoagulative state it appears to be infrequent [6].

Despite uncertainty regarding the pathophysiology of neurological complications of severe COVID infection, it seems *a priori* reasonable that different mechanisms might be relevant in at least some people who have mild COVID infection (e.g., the non-hospitalized population), who then develop persistent symptoms. However, the long COVID diagnostic category does not explicitly make a distinction between those with severe and those with mild infection.

Despite the diversity of theories put forward to account for the mechanism of long COVID and its neurological manifestations, the conspicuous absence of one common and relevant disorder is striking: functional (neurological) symptoms.

Neurologists have a special interest in functional neurological symptoms, but also recognize the common occurrence of functional symptoms in other medical specialities such as irritable bowel syndrome, functional cough, non-cardiac chest pain [7]. Functional symptoms classically lack a correlate in terms of structural damage. The diagnosis of functional neurological symptoms is positive and not merely based on ruling out other alternative conditions. A key feature is inconsistency over time, which means that symptoms often occur intermittently and/or with fluctuating severity. Symptoms are typically modulated by attention, and demonstration of distractibility is an important element of establishing a diagnosis within neurological practice.

Functional neurological disorders (FNDs) have an acute onset in about 50% cases, and this onset is commonly associated with a noxious sensory experience, such as a limb injury, a panic attack, a migraine headache or an acute viral infection (amongst many others) [7]. Based on these characteristics it would be expected to find people developing functional neurological symptoms following a COVID-19 infection, particularly considering its high incidence. FND is well recognized and can be treatable. It is therefore concerning that some patients with FND might be inappropriately labelled as long COVID, and that this might delay their correct diagnosis and management with a corresponding negative impact on prognosis.

A systematic review was therefore performed looking for evidence of patients with functional neurological symptoms amongst cohorts diagnosed with long COVID. In addition, the proposed causes of long COVID reported by these studies were reviewed to ascertain whether FND is considered by researchers as a possible contributor and to characterize the representation of FND in the long COVID literature.

METHODS

PubMed was searched on 26 October 2021 with the following search terms: 'long covid' OR 'post-acute covid' OR 'long-haul covid' OR 'long-hauler covid' OR 'chronic covid' OR 'prolonged covid'. Reference lists of selected articles were also hand searched (Figure 1). Inclusion criteria were articles published in the English language; original data; adults (≥18 years old); 'long COVID' (or equivalent term reflecting persistent symptoms following a COVID-19 infection); report of at least one neurological symptom. Exclusion criteria were case reports ($n = 1$) and review articles.

JC first identified and retrieved all original studies which could be relevant, based on title and abstract. JC and TT then independently analysed the retrieved articles and selected studies that fulfilled the inclusion/exclusion criteria. Disagreements were discussed and resolved based on consensus.

Study quality was assessed based on study design (cross-sectional, retrospective, prospective, case series), the presence and characteristics of a control group and the definition of long COVID.

The severity of acute COVID-19 infection preceding long COVID was also assessed (mild, not hospitalized; moderate, hospitalized but not requiring critical care; severe, requiring critical care). It was planned to perform a subgroup analysis for studies focusing on long COVID following a mild COVID-19 infection. This is because it was expected that these patients would be less likely to experience long-term symptoms related to structural damage of the nervous system. A qualitative analysis and narrative synthesis of evidence was performed.

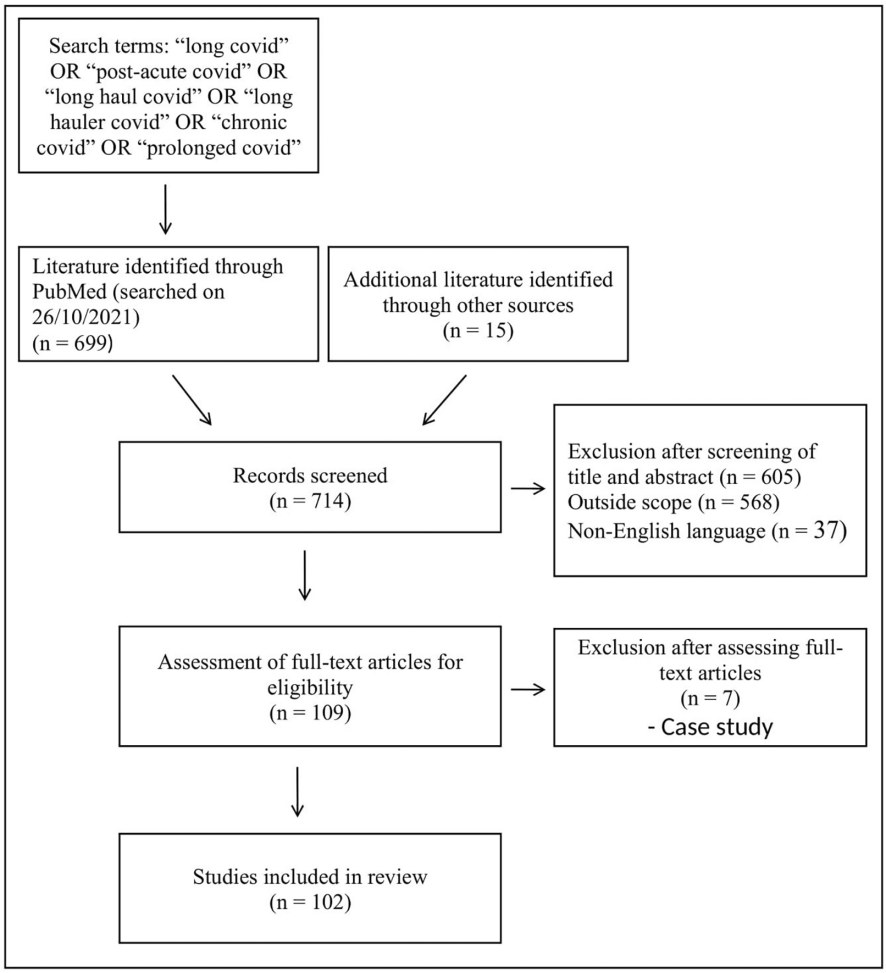

FIGURE 1 Flowchart for identification of studies.

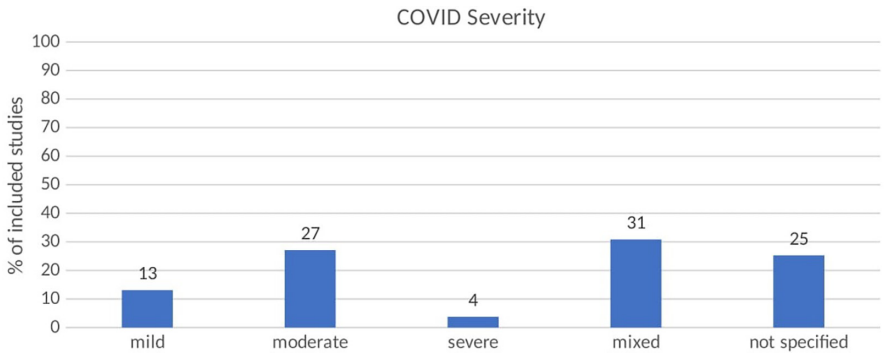

FIGURE 2 Included studies according to the severity of previous acute COVID-19 infection (for studies performing subgroup analyses for different COVID-19 severities, each subgroup analysis was counted as a different 'study').

This study protocol was registered on Prospero with the registration number CRD42022288403. Data sharing is not applicable to this article as no new data were created or analysed in this study.

RESULTS

In all, 102 studies were selected for the qualitative analysis (Figure 1). These studies included 412,726 patients who had COVID-19. Amongst selected studies, 31 studies explicitly recruited participants experiencing long COVID (including 11,860 patients). The other 71 studies recruited participants who had acute COVID-19 and who were then screened for the presence of persistent long COVID symptoms.

Study quality and characteristics

With regard to study design, 51 studies were prospective, 33 were cross-sectional, 12 studies were retrospective, two were ambidirectional/bidirectional and one was a case series. Only 18 studies included a control group. Most control groups included subjects who

also presented acutely but tested negative for COVID-19 or subjects with other acute or chronic health conditions or otherwise similar comorbidities. 95 studies only recruited patients who had an acute COVID-19 infection confirmed by reverse transcription polymerase chain reaction. 89 studies complied with the National Institute for Health and Care Excellence definition of long COVID (i.e., symptoms persisting more than 4 weeks). Only 14 studies focused on long COVID after a mild acute COVID-19 infection (not requiring hospitalization). 27 did not specify the severity of the previous acute infection and another 33 included cohorts with mixed severities (Figure 2).

Most studies reported a mean/median age between 40 and 59. Overall, the proportion of males and females (sex) participating in the study appeared to be similar. In studies recruiting subjects with confirmed COVID-19 infection, the median sample size of that group was 198 (interquartile range 116–518). In studies including a group with long COVID, the median sample size was 62 (interquartile range 23–278).

Eighty-nine provided information on pre-morbid status (either presence or absence of comorbidities) and 59 described the frequency of specific pre-existing conditions. Only six studies included patients with pre-existing dementia or cognitive dysfunction, and usually only in a very small percentage. Ten studies included participants with a psychiatric diagnosis (either depression, anxiety or not specified).

Neurological symptoms

Neurological symptoms/problems reported by patients with long COVID in the 102 studies selected for the review included fatigue, headaches, pain (including chest and rib pain, myalgia, abdominal pain and 'neuropathic' pain), dizziness (including vertigo), cognitive difficulties, memory problems, autonomic-type symptoms (palpitation, tachycardia, orthostatic hypotension), sleep-related symptoms, limb weakness, neuropathic-like sensory symptoms (e.g., tingling, burning, numbness), tremor, walking impairment, blurred vision, tinnitus, hearing loss, ageusia, anosmia and hallucinations (Figure 3). The following symptoms were reported by at least one-third of studies: fatigue; headache; pain (other than headache); dizziness (including vertigo); cognitive difficulties; sleep-related symptoms; ageusia/anosmia.

Eighty-five studies reported fatigue as a symptom of long COVID. In studies with groups exclusively including patients with long COVID (total 31 studies), the proportion of subjects reporting fatigue ranged between 35% and 98%. 62 studies reported headaches, with a frequency that ranged between 8% and 91% amongst groups of subjects with long COVID. 73 studies reported pain (other), with a frequency ranging between 11% and 87%. 34 studies reported dizziness (including vertigo), with a frequency ranging between 2% and 55%. 70 studies reported cognitive symptoms (any) (e.g., concentration difficulties, 'brain fog'), with a frequency ranging between 4% and 85%. This included 27 studies specifically reporting memory problems. 50 studies reported sleep-related symptoms, with a frequency ranging between 10% and 79%. Finally, 47 studies reported ageusia/anosmia, with a frequency ranging between 8% and 74% (Figure 4).

Persistent neurological symptoms after mild acute infection

A subgroup analysis was performed focusing on studies recruiting subjects who developed long COVID following a 'mild' COVID-19 infection. Here a pragmatic definition of 'mild' infection was used, that is, an infection not requiring admission to hospital. Fourteen studies analysing patients who had a 'mild' COVID-19 infection (i.e., not requiring hospitalization) were included. These only included three studies specifically recruiting patients experiencing long COVID after a 'mild' infection. Amongst the other 11 studies, three recruited

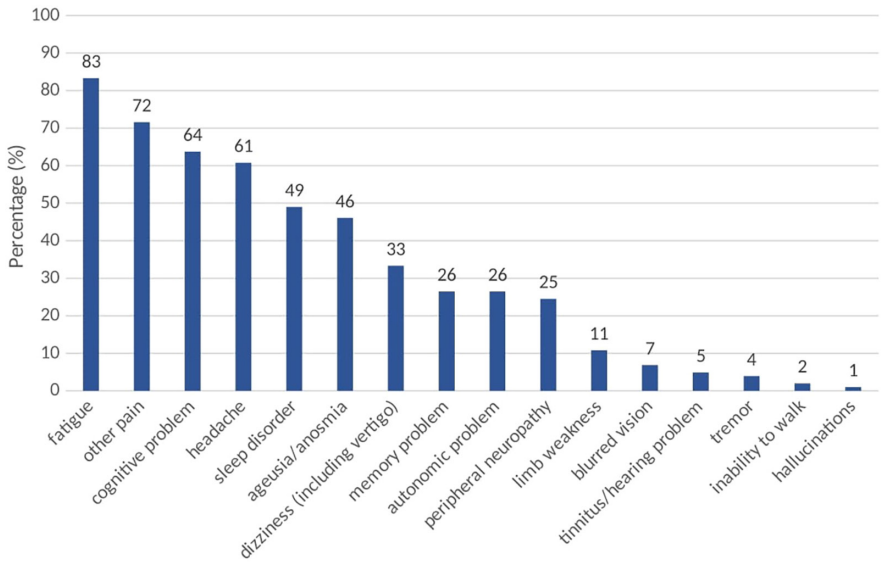

FIGURE 3 Percentage of included studies reporting each symptom.

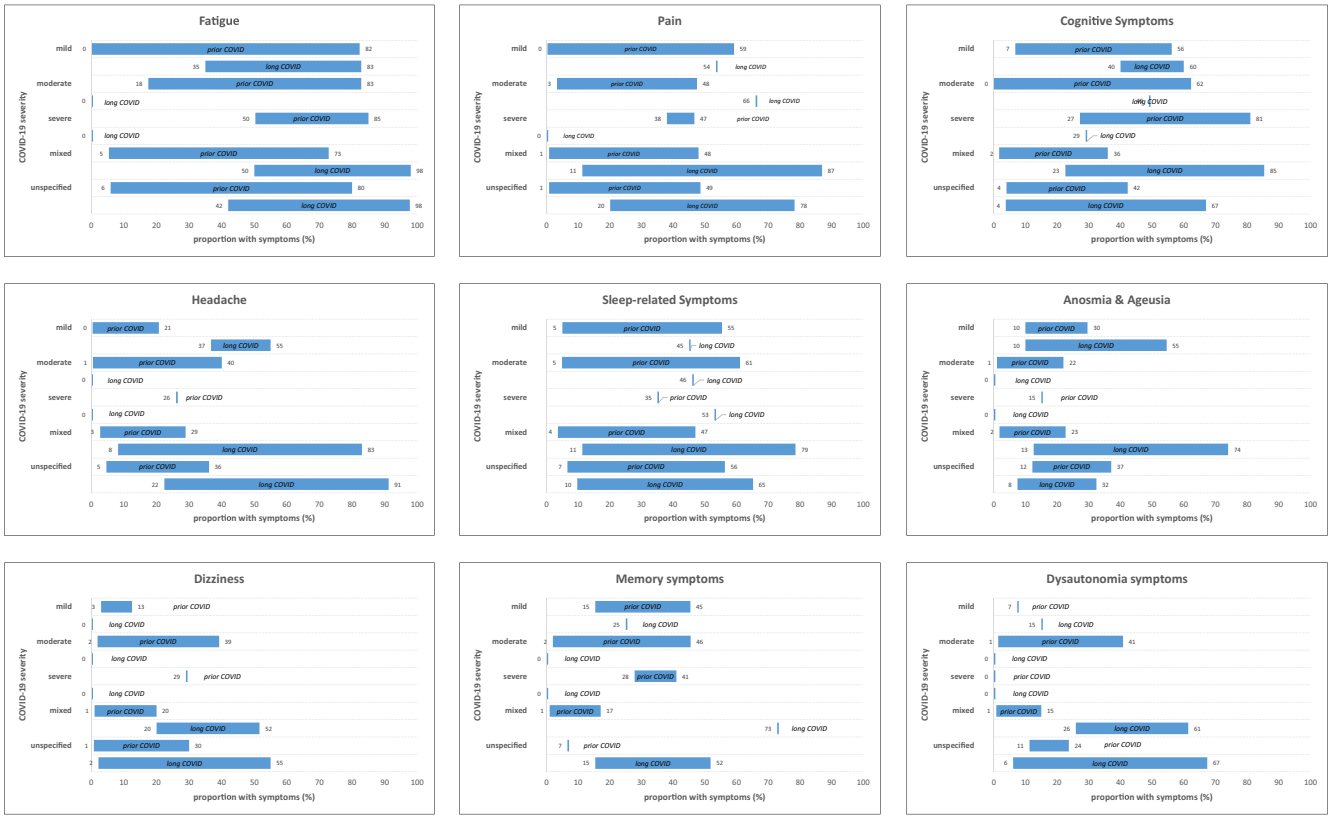

FIGURE 4 Proportion of subjects reporting each symptom (%, range) in studies recruiting participants with prior COVID-19 or participants experiencing long COVID (all included studies). The upper and lower limit of each range refers to the minimum and maximum percentage reported in the studies included in each subgroup.

patients with different severities of acute COVID-19 but performed a subgroup analysis for those who had a mild infection.

In people experiencing long COVID symptoms following a mild COVID-19 infection, the ranges for the proportions of participants experiencing each specific neurological symptom were extremely broad (Figure 4 and Appendix S1). This heterogeneity prevented further interpretation/analysis.

Study quality and characteristics of these 14 studies were overall similar to the remainder of the studies. In most studies, median/mean age was within the 40–49 years range and most participants were female. The proportion of participants with relevant pre-existing neurological or psychiatric conditions (e.g., depression, cognitive impairment) was minimal (in the few instances when these were reported). Most studies were prospective cohorts, but all the three studies specifically recruiting subjects experiencing long COVID were cross-sectional. Six out of 14 included control groups. Detailed demographics of the 14 studies are provided in Appendix S1.

Characteristics of cognitive impairment in long COVID

Only 11 studies including a formal assessment of cognition were identified [8–18]. Hampshire et al. reported significant cognitive deficits in the Great British Intelligence Test [13]. The profile was variable, with deficits across cognitive domains but larger associations for more complex tasks requiring reasoning, planning and problem solving such as verbal analogies and the Tower of London test. A subgroup analysis focusing on patients who had not been hospitalized (i.e., 'mild' COVID-19) revealed small but statistically significant deficits on a global performance score. Intriguingly, this study also reported some degree of cognitive impairment even amongst subjects who did not report cognitive symptoms.

In Johnsen et al. the frequency of significant cognitive impairments ranged from 59% to 66% for hospitalized patients and from 31% to 44% for non-hospitalized patients [14].

Borst et al. found that about one-sixth of patients reported persistent cognitive symptoms and had evidence of objective cognitive impairment [16]. The proportions were similar in hospitalized and non-hospitalized patients. None of the other studies analysing long COVID after mild COVID-19 infection included any standardized assessment of cognition.

Amongst the remaining studies including objective assessment of cognitive function but not specifically analysing people with a history of mild COVID-19, some did report an objective impairment of cognition [10–12, 17], with variable characteristics. One study reported a high frequency of coexisting mental health problems, including anxiety, depression and post-traumatic stress disorder [17], but this was not confirmed by another study [12]. In people who had

had severe COVID-19, one study described an association between cognitive impairment and the severity of lung involvement [11].

Several other studies failed to find a consistent objective impairment of cognition [8, 9, 15, 18], albeit a couple amongst these still found objective deficits at a single-patient level [18] or in a minority of patients [8]. Associations between coexisting mental health problems and subjective cognitive complaints [15] as well as neuropsychological test scores [9] were reported.

Motor symptoms in long COVID

The plan was to perform a subgroup analysis focusing on motor symptoms in the context of long COVID. Motor symptoms afford an opportunity to look for some of the most well-established positive features of FNDs, such as Hoover's sign or tremor suppression with distraction.

Overall, report frequency was low, with 10 studies describing limb weakness (782 out of 5274 subjects in seven studies where quantification was possible), four studies tremor (33 out of 1362 subjects) and another one walking impairment (80 out of 201 subjects in one study). No study reporting the presence (or absence) of features suggesting the presence of functional motor symptoms was found.

Many studies used the term 'muscle weakness' without further characterization [12, 19–22]. At times, weakness and fatigue were lumped together [23]. Four studies reported tremor, but again without further characterization [9, 17, 24, 25]. One study reported dystonia [25].

Evidence suggesting the presence of functional neurological symptoms

There was very little positive evidence to suggest that neurological symptoms of long COVID could be related to an underlying functional disorder. Symptom intermittency/fluctuations in intensity are key features of an FND. In this respect, a relapsing–remitting disease course in long COVID was reported by 80.6% patients in Tran et al. [26] and by 85.9% participants in Davis et al. [27]. Kersten et al. were able to identify relevant end-organ damage in 44.4% subjects with long COVID and considered that the remaining 65.6% subjects had functional long COVID [28]. However, this is in effect a 'negative diagnosis' (i.e., based on ruling out alternative explanations).

Taylor et al. performed a qualitative study that again found features of symptom fluctuations and variability over time [29]. Albeit nonspecific, these features are suggestive of a functional disorder. Some illustrative transcripts of patients' own words include: 'It's difficult because I keep getting new things, which is one of the frustrations of this'; 'It's weird because one minute, you can walk up the stairs and you can feel fine and the next minute, you walk up and all your muscles are killing you and your heart is batting at 120'; 'I went through this cycle of feeling a bit better'; 'And now I feel okay but I'm just waiting for the next time I feel crap again' [29].

Hypothetical causes of long COVID

In 62 studies, the authors discussed possible causes for long COVID symptoms. Proposed immune-mediated mechanisms included an inflammatory reaction (20 studies), an auto-immune process (18) and a post-viral reaction (19). Neuro-invasion by COVID-19 was proposed in seven studies. Psychosocial factors were hypothesized in 11 and Chronic fatigue syndrome (CFS)/Myalgic encephalomyelitis (ME)-like response was discussed in eight studies. Only one study [28] proposed a functional syndrome as an explanation for long COVID in a proportion of patients (those without evidence of end-organ damage, i.e., negative diagnosis). Finally, two studies explicitly argued against conflating long COVID with CSF/ME.

DISCUSSION

Little evidence was found suggesting a contribution of functional neurological symptoms to long COVID. However, FND was also only rarely considered as a possible diagnosis. FND is a common disorder and often follows an acute illness. Accordingly, there are a growing number of case reports of FND triggered by COVID-19 infection (and vaccination) [30]. This is in line with our expectations and makes even more surprising the absence of patients with FND in the long COVID cohorts reviewed here and the fact that FND was not generally considered by authors as a differential diagnosis.

The neurological symptoms most consistently associated with long COVID were cognitive difficulties, headaches, pain, dizziness, fatigue, sleep-related symptoms and ageusia/anosmia, including in the few studies that separated patients with long COVID following mild infections. However, the frequency ranges for each symptom were quite wide, possibly reflecting differences in methodology between studies. History and symptom characteristics suggest in some the presence of a functional disorder based on positive features such as intermittent course and fluctuating symptom intensity. Unfortunately, most included studies did not comment on the presence or absence of temporal 'inconsistency' or other key positive features of functional symptoms. Indeed, neurological symptoms were generally very poorly characterized. Cognitive difficulties such as memory lapses and poor concentration were amongst the most frequent neurological manifestations of long COVID. However, this prominence contrasted with a striking lack of detailed characterization of cognitive symptoms or formal neuropsychometric testing focusing on long COVID following a mild COVID-19 infection. A handful of studies did report impairment on standardized neuropsychometric assessment, but there were other methodological limitations including an insufficient characterization of the cognitive profile including tests of 'effort'. This is relevant as functional cognitive disorder can be diagnosed by the presence of cognitive impairment with

internal inconsistency [31]. It has been argued previously that functional cognitive symptoms are part of the same spectrum of cognitive difficulties reported in chronic fatigue syndrome, fibromyalgia and people with non-cognitive FNDs [32]. Unfortunately, features allowing a positive diagnosis of functional cognitive symptoms, similarly to positive features of functional motor symptoms, have not been systematically investigated in people with long COVID.

In our view, there are two major deficiencies in the current approach to long COVID syndrome. First, it is illogical to aggregate cohorts of patients with persistent symptoms following severe and very severe acute medical complications of COVID infection with those with persistent symptoms after mild to moderate acute infective symptoms as it seems likely that pathophysiological processes for persistent symptoms will be different in these two groups. Neurological symptoms such as fatigue and cognitive impairment are commonly reported multiple disorders with multiple underlying pathophysiological processes. Therefore, just because two patients with persistent symptoms after COVID infection report fatigue or cognitive impairment (particularly when these symptoms are poorly specified), it does not follow that the pathophysiological process underlying the symptoms is going to be the same. This issue, in our opinion, is made even more likely to be relevant when the initial course of the illness is so different as it is in people with severe versus mild–moderate acute illness. Patients who are hospitalized, and particularly those who required critical care, are probably at an increased risk of developing long-term symptoms [33, 34], including those due to irreversible organ damage.

The second major deficiency is the implicit assumption that persistent symptoms after COVID infection must represent a specific and unified diagnostic entity. This situation has similarities to the heavily criticized use of the term 'post-concussion syndrome' to describe people with persistent symptoms after mild traumatic brain injury. Rather than bringing clarity to diagnosis and pathophysiology (and therefore treatment development), the syndromic aggregation of symptoms in post-concussion syndrome arguably prevents the proper identification of specific treatable disorders in mild traumatic brain injury including chronic migraine, benign postural positional vertigo, FND and depression. In our opinion, research to date on long COVID risks replicating this mistake by failing to be specific about symptoms, assuming that this must be a novel and as yet unknown single entity and failing to consider if they might fit within established diagnostic categories for existing disorders.

Overall, it was disappointing to find that published evidence so far appears to ignore the possibility of a functional disorder accounting for a proportion of people with long COVID. Roughly 60% of studies proposed an underlying mechanism for long COVID, most frequently an underlying inflammatory/autoimmune/post-viral response. Only one study raised the possibility that long COVID could correspond to a functional disorder, and framed this primarily as a diagnosis of exclusion [28]. A chronic-fatigue-syndrome-type response was discussed in 7.8% of studies. Finally, 10.8% of studies related long COVID to psychosocial factors. These approaches suggest a 'mind–body' dichotomy, with functional disorders trailing behind not only inflammatory/infectious mechanisms but also 'psychosocial factors'.

The current discussion around long COVID is reminiscent of previous controversies surrounding conditions such as chronic Lyme, where symptom persistence has also been attributed to an infectious agent [35]. A prospective cohort study reported 12% of patients experiencing persistent symptoms including chronic fatigue, pain, cognitive symptoms and mood abnormalities 6 months after an acute infection [36]. Persistent symptoms occurred with a similar incidence for each infectious agent (Epstein–Barr virus, *Coxiella burnetti* and Ross River virus). This study suggests the frequent occurrence of a stereotyped post-infectious syndrome including persistent fatigue, which does not seem to relate to a specific pathogen or documented persistence of infection. One explanation for this phenomenon is that it represents triggering of functional symptoms following a health event, similar to our expectation that this would be a common route for the development of persistent physical symptoms after COVID infection.

Expectations are proposed to play a key role in the pathogenesis of functional neurological symptoms [37]. Interestingly, COVID-19 vaccine trials reported a substantial rate of nocebo responses in placebo arms [38]. This prominent nocebo effect conceivably reflects negative expectations driven by vaccine-related controversies.

Overall, most long COVID symptoms also appear to be common in the general population, with one cohort study reporting relatively high frequencies of fatigue, headaches, pain, anxiety/depression and sleep problems in people who never had COVID-19 [39].

In some patients, symptoms resulting from acute COVID-19 infection or other unrelated conditions might work as a 'primer' and, in combination with negative expectations, lead to symptom aggravation and persistence, and ultimately to the experience of long COVID. It is certainly not claimed that the underlying causes of long COVID are known, but the hypothesis that a functional disorder could play a role in some patients deserves to be considered given that this is such a common and (in some cases) treatable disorder (see the clinical vignette in Box 1).

Research agenda

One untested hypothesis is that cognitive symptoms in long COVID might be similar to archetypal functional cognitive disorder. In order to account for this possibility, future studies ought to explicitly look for positive evidence of functional cognitive symptoms, including prominent cognitive difficulties contrasting with attending alone to clinic, good conversational abilities during the consultation and relatively preserved daily function [31]. In formal neuropsychometric testing, people with functional cognitive disorder (FCD) have shown a discrepancy between impaired immediate recall and recognition but spared delayed recall and retention in Hopkins Verbal Learning Test Revised [40]. The Attention Network Test previously revealed an impairment of attention in people with functional movement disorders and chronic fatigue syndrome, and could be useful

BOX 1 A patient aged in the 20s presented to Accident and Emergency (A&E) with rapidly progressive tetraparesis over 2 days, causing inability to walk.

A year previously the patient had suffered from COVID-19, with a few days of fever and upper airway symptoms, without the need for hospitalization. However, fatigue and concentration difficulties proved to be persistent, with fluctuating severity. Physical exercise often triggered extreme fatigue, nausea and vomiting. The patient was diagnosed with long COVID. The subject stopped exercising for leisure and had trouble keeping up with studies and social life.

At presentation to A&E, neurological examination revealed positive signs of a functional neurological disorder including Hoover's sign, give-way weakness and discrepancies between the severity of weakness on limb examination and the ability to stand up without assistance.

Following diagnosis explanation, the subject was referred to an outpatient-based specialized physiotherapy programme for functional neurological disorders.

After a few months of treatment, the patient recovered significantly, not only from functional motor symptoms but also from fatigue, concentration difficulties and exercise intolerance. The subject was able to resume the premorbid daily routine.

This case highlights the existence of 'post-COVID' functional neurological symptoms and underlines the importance of making the correct diagnosis in order to guide the management strategy. Notably, patient education including diagnosis explanation and physiotherapy focusing on the functional motor symptoms were followed also by a resolution of pre-existing non-motor symptoms, which had been labelled as 'long COVID'.

to investigate an objective impairment of attention in people with long COVID [32, 41, 42]. Motor symptoms such as weakness and tremor in the context of long COVID deserve a better characterization. This would include a clear distinction between weakness and fatigue, identification of weakness secondary to critical illness polyneuromyopathy and an explicit report on the presence/absence of features suggesting functional motor symptoms such as Hoover's sign or tremor suppression with distraction.

This more specific approach to symptoms and signs in people with persistent symptoms after COVID would not only provide clearer evidence regarding the relevance of FND as a cause of symptoms but would also help to identify other underlying diagnoses and their associated pathophysiological processes. This in turn would help in the development of a stratified, evidence-based approach to diagnosis and treatment for all those with disabling persistent symptoms after COVID infection.

One in eight patients with COVID-19 are reported to develop long COVID [43], and there is an understandable drive from patients, healthcare professionals and governments to find solutions to the disabling symptoms. However, in this drive to find answers, researchers and clinicians need to appreciate the likely complexity and heterogeneity of the mechanisms for symptoms in long COVID. This includes ensuring that neuropsychiatric and functional explanations for symptoms are considered alongside other explanations without the prejudice that such explanations make symptoms less genuine or disabling or are less 'real' than more traditional biological explanations for symptoms. It is also likely that patients may have more than one diagnosis accounting for their multiple symptoms—something which runs the risk of being hidden through the use of a syndromic label such as long COVID. Without understanding these issues, it is likely that patients will not be able to access suitable treatment, and development of novel treatments and services will be delayed. This in turn will make it more likely that patients, for lack of any reasonable alternative, will end up seeking out unproven and potentially risky treatments such as plasmapheresis and anticoagulation [44]. Overall, a solid, evidence-based management approach is needed, which itself is founded on careful clinical characterization of symptoms and holistic assessment.

AUTHOR CONTRIBUTIONS

This systematic review was conceived by TT and designed by TT and MJE; JC identified original studies that could be relevant and both JC and TT independently analysed and selected studies for inclusion; JC extracted relevant information from selected studies; TT wrote the first draft; all authors contributed to data interpretation and approving the final version of the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank the reviewers for their valuable comments and suggestions.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest. There was no specific funding involved in this review.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

REFERENCES

1. Overview | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE. Accessed September 13, 2021. https://www.nice.org.uk/guidance/ng188
2. COVID-19: Evaluation and management of adults following acute viral illness—UpToDate. Accessed February 19, 2022. https://www.uptodate.com/contents/covid-19-evaluation-and-management-of-adults-following-acute-viral-illness?search=long%20cov

id&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2804110166
3. Why we need to keep using the patient made term 'Long Covid'. BMJ. Published October 1, 2020. Accessed June 6, 2022. https://blogs.bmj.com/bmj/2020/10/01/why-we-need-to-keep-using-the-patient-made-term-long-covid/
4. Pezzini A, Padovani A. Lifting the mask on neurological manifestations of COVID-19. *Nat Rev Neurol*. 2020;16(11):636-644. doi:10.1038/s41582-020-0398-3
5. Thakur KT, Miller EH, Glendinning MD, et al. COVID-19 neuropathology at Columbia University Irving Medical Center/New York Presbyterian Hospital. *Brain*. 2021;144(9):2696-2708. doi:10.1093/brain/awab148
6. Bekelis K, Missios S, Ahmad J, et al. Ischemic stroke occurs less frequently in patients with COVID-19: a multicenter cross-sectional study. *Stroke*. 2020;51(12):3570-3576. doi:10.1161/STROKEAHA.120.031217
7. Carson A, Hallett M, Stone J. Assessment of patients with functional neurologic disorders. *Handb Clin Neurol*. 2016;139:169-188. doi:10.1016/B978-0-12-801772-2.00015-1
8. Venturelli S, Benatti SV, Casati M, et al. Surviving COVID-19 in Bergamo province: a post-acute outpatient re-evaluation. *Epidemiol Infect*. 2021;149:e32. doi:10.1017/S0950268821000145
9. Mattioli F, Stampatori C, Righetti F, Sala E, Tomasi C, De Palma G. Neurological and cognitive sequelae of COVID-19: a four month follow-up. *J Neurol*. 2021;268(12):4422-4428. doi:10.1007/s00415-021-10579-6
10. Frontera JA, Yang D, Lewis A, et al. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. *J Neurol Sci*. 2021;426:117486. doi:10.1016/j.jns.2021.117486
11. Miskowiak KW, Johnsen S, Sattler SM, et al. Cognitive impairments four months after COVID-19 hospital discharge: pattern, severity and association with illness variables. *Eur Neuropsychopharmacol*. 2021;46:39-48. doi:10.1016/j.euroneuro.2021.03.019
12. Puchner B, Sahanic S, Kirchmair R, et al. Beneficial effects of multi-disciplinary rehabilitation in postacute COVID-19: an observational cohort study. *Eur J Phys Rehabil Med*. 2021;57(2):189-198. doi:10.23736/S1973-9087.21.06549-7
13. Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19. *EClinicalMedicine*. 2021;39:101044. doi:10.1016/j.eclinm.2021.101044
14. Johnsen S, Sattler SM, Miskowiak KW, et al. Descriptive analysis of long COVID sequelae identified in a multidisciplinary clinic serving hospitalised and non-hospitalised patients. *ERJ Open Res*. 2021;7(3):205-2021. doi:10.1183/23120541.00205-2021
15. Gouraud C, Bottemanne H, Lahlou-Laforêt K, et al. Association between psychological distress, cognitive complaints, and neuropsychological status after a severe COVID-19 episode: a cross-sectional study. *Front Psych*. 2021;12:725861. doi:10.3389/fpsyt.2021.725861
16. van den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment 3 months after recovery from acute coronavirus disease 2019 (COVID-19). *Clin Infect Dis*. 2021;73(5):e1089-e1098. doi:10.1093/cid/ciaa1750
17. Méndez R, Balanzá-Martínez V, Luperdi SC, et al. Long-term neuropsychiatric outcomes in COVID-19 survivors: a 1-year longitudinal study. *J Intern Med*. 2022;291(2):247-251. doi:10.1111/joim.13389
18. Dressing A, Bormann T, Blazhenets G, et al. Neuropsychological profiles and cerebral glucose metabolism in neurocognitive long COVID-syndrome. *J Nucl Med*. 2022;63(7):1058-1063. doi:10.2967/jnumed.121.262677
19. Aydin S, Unver E, Karavas E, Yalcin S, Kantarci M. Computed tomography at every step: long coronavirus disease. *Respir Investig*. 2021;59(5):622-627. doi:10.1016/j.resinv.2021.05.014
20. Gold JE, Okyay RA, Licht WE, Hurley DJ. Investigation of long COVID prevalence and its relationship to Epstein–Barr virus reactivation. *Pathogens*. 2021;10(6):763. doi:10.3390/pathogens10060763
21. Maestre-Muñiz MM, Arias Á, Mata-Vázquez E, et al. Long-term outcomes of patients with coronavirus disease 2019 at one year after hospital discharge. *J Clin Med*. 2021;10(13):2945. doi:10.3390/jcm10132945
22. Munblit D, Bobkova P, Spiridonova E, et al. Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clin Exp Allergy*. 2021;51(9):1107-1120. doi:10.1111/cea.13997
23. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-232. doi:10.1016/S0140-6736(20)32656-8
24. Osikomaiya B, Erinoso O, Wright KO, et al. 'Long COVID': persistent COVID-19 symptoms in survivors managed in Lagos state, Nigeria. *BMC Infect Dis*. 2021;21(1):304. doi:10.1186/s12879-020-05716-x
25. Romero-Duarte Á, Rivera-Izquierdo M, Guerrero-Fernández de Alba I, et al. Sequelae, persistent symptomatology and outcomes after COVID-19 hospitalization: the ANCOHVID multicentre 6-month follow-up study. *BMC Med*. 2021;19:129. doi:10.1186/s12916-021-02003-7
26. Tran VT, Riveros C, Clepier B, et al. Development and validation of the long COVID symptom and impact tools: A set of patient-reported instruments constructed from patients': Lived experience. *Clin Infect Dis*. 2022;74(2):278-287. doi:10.1093/cid/ciab352
27. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;38:101019. doi:10.1016/j.eclinm.2021.101019
28. Kersten J, Baumhardt M, Hartveg P, et al. Long COVID: distinction between organ damage and deconditioning. *J Clin Med*. 2021;10(17):3782. doi:10.3390/jcm10173782
29. Taylor AK, Kingstone T, Briggs TA, et al. 'Reluctant pioneer': a qualitative study of doctors' experiences as patients with long COVID. *Health Expect*. 2021;24(3):833-842. doi:10.1111/hex.13223
30. Fung WKW, Sa'di Q, Katzberg H, et al. Functional disorders as a common motor manifestation of COVID-19 infection or vaccination. *Eur J Neurol*. 2023;30(3):678-691. doi:10.1111/ene.15630
31. Ball HA, McWhirter L, Ballard C, et al. Functional cognitive disorder: dementia's blind spot. *Brain*. 2020;143(10):2895-2903. doi:10.1093/brain/awaa224
32. Teodoro T, Edwards MJ, Isaacs JD. A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review. *J Neurol Neurosurg Psychiatry*. 2018;89(12):1308-1319. doi:10.1136/jnnp-2017-317823
33. Martillo MA, Dangayach NS, Tabacof L, et al. Postintensive care syndrome in survivors of critical illness related to coronavirus disease 2019: cohort study from a new York City critical care recovery clinic. *Crit Care Med*. 2021;49(9):1427-1438. doi:10.1097/CCM.0000000000005014
34. Heesakkers H, van der Hoeven JG, Corsten S, et al. Clinical outcomes among patients with 1-year survival following intensive care unit treatment for COVID-19. *JAMA*. 2022;327(6):559-565. doi:10.1001/jama.2022.0040
35. Koedel U, Fingerle V, Pfister HW. Lyme neuroborreliosis—epidemiology, diagnosis and management. *Nat Rev Neurol*. 2015;11(8):446-456. doi:10.1038/nrneurol.2015.121
36. Hickie I, Davenport T, Wakefield D, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ*. 2006;333(7568):575. doi:10.1136/bmj.38933.585764.AE
37. Edwards MJ, Adams RA, Brown H, Pareés I, Friston KJ. A Bayesian account of 'hysteria'. *Brain*. 2012;135(Pt 11):3495-3512. doi:10.1093/brain/aws129

38. Haas JW, Bender FL, Ballou S, et al. Frequency of adverse events in the placebo arms of COVID-19 vaccine trials: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(1):e2143955. doi:10.1001/jamanetworkopen.2021.43955
39. Hastie CE, Lowe DJ, McAuley A, et al. Outcomes among confirmed cases and a matched comparison group in the long-COVID in Scotland study. *Nat Commun*. 2022;13(1):5663. doi:10.1038/s41467-022-33415-5
40. Ball HA, Swirski M, Newson M, Coulthard EJ, Pennington CM. Differentiating functional cognitive disorder from early neurodegeneration: a clinic-based study. *Brain Sci*. 2021;11(6):800. doi:10.3390/brainsci11060800
41. Huys ACML, Bhatia KP, Edwards MJ, Haggard P. The flip side of distractibility—executive dysfunction in functional movement disorders. *Front Neurol*. 2020;11:969. doi:10.3389/fneur.2020.00969
42. Togo F, Lange G, Natelson BH, Quigley KS. Attention network test: assessment of cognitive function in chronic fatigue syndrome. *J Neuropsychol*. 2015;9(1):1-9. doi:10.1111/jnp.12030
43. Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM. Lifelines Corona research initiative. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet*. 2022;400(10350):452-461. doi:10.1016/S0140-6736(22)01214-4
44. Davies M. Long COVID patients travel abroad for expensive and experimental 'blood washing'. *BMJ*. 2022;378:o1671. doi:10.1136/bmj.o1671

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Teodoro T, Chen J, Gelauff J, Edwards MJ. Functional neurological disorder in people with long COVID: A systematic review. *Eur J Neurol*. 2023;30:1505-1514. doi:10.1111/ene.15721