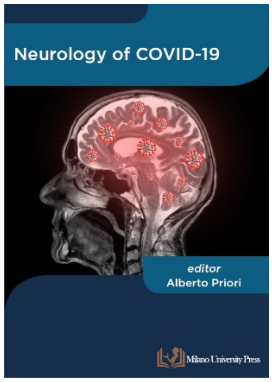

Neurology of COVID-19
Editor Alberto Priori
DOI: https://doi.org/10.54103/milanoup.57

Published by: Milano University Press
Via Festa del Perdono 7 - 20122 Milano
URL: https://milanoup.unimi.it/
E-mail: redazione.milanoup@unimi.it

Chapter 12. **Cognitive dysfunction and rehabilitation**

DOI: https://doi.org/10.54103/milanoup.57.23

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Chapter 12. Cognitive dysfunction and rehabilitation

Michelangelo Dini, Alberto Priori, Roberta Ferrucci

Introduction

COVID-19 is a respiratory disease which ranges from mild to severe and presents a wide clinical spectrum. It is primarily characterized by pneumonia and respiratory distress but can be accompanied by numerous other complications. Of these, we will focus on examining the role and relevance of cognitive dysfunction. Cognitive dysfunction is typically defined as the presence of deficits which affect one or more cognitive functions: memory, language, executive functions, attention, visuospatial abilities, etc. Cognitive dysfunction can be classified according to the severity (subjective, mild cognitive impairment, dementia), type of onset (insidious, acute), and course (progressive, chronic, transient) of illness. The causes may be many and diverse in nature, as cognitive deficits can represent the clinical manifestation of underlying neurodegenerative processes, hypoxia, hyperinflammation, cerebrovascular events, or traumatic injury being the most commonly reported.

Evidence from previous coronavirus-related respiratory diseases, such as the SARS and MERS epidemics in 2002 and 2012, respectively, has alerted scientists all over the world about the neuroinvasive potential of SARS-CoV-2. For this reason, studies aimed at assessing the incidence of neurological symptoms have been conducted since the earliest phases of the pandemic. Additionally, the fact that severe COVID-19 requires admission to the intensive care unit (ICU) and, in the most severe cases, invasive mechanical ventilation and sedation, suggests that cognitive deficits might be linked to prolonged respiratory distress, which can cause hypoxia-related brain injury. Finally, other pathological processes, such as hyperinflammation and hypercoagulability, have also been proposed as possible causes of cognitive dysfunction in COVID-19.

Rationale for cognitive dysfunction in COVID-19

As outlined above, there are many different types of pathological mechanisms that could determine cognitive dysfunction in COVID-19 patients (Figure 12.1)[1]. Therefore, it is difficult to establish exactly whether cognitive dysfunction in COVID-19 is associated with direct viral neuronal injury, or whether it results from the presence of a severe systemic disorder characterized by a combination of sepsis, hypoxia, hyperpyrexia, hypercoagulability and critical illness[2,3].

During the SARS and MERS epidemics, studies reported the presence of neurological symptoms such as altered mental status in the acute phase[4] and cognitive complaints in recovered patients[5]. A metanalysis of 72 studies on both acute and post-acute neuropsychiatric effects of coronavirus infection[6] highlighted the presence of delirium in the acute phase, and impaired concentration and memory in the long-term (range of follow-up from 6 weeks to 39 months).

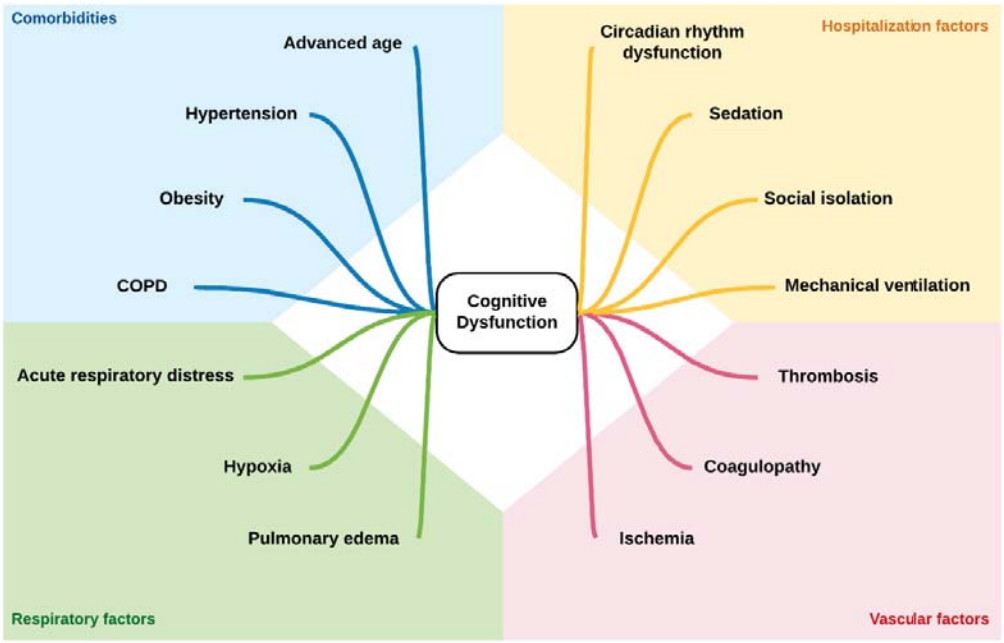
Evidence from studies on patients hospitalized for acute respiratory distress syndrome (ARDS) has highlighted a higher prevalence of delirium in intubated patients with ARDS (72%) compared to intubated patients without ARDS (53%), and non-intubated ICU patients (21%)[7]. With regards to long-term cognitive outcomes, a review of the literature has observed that there is a high prevalence of ARDS-related cognitive dysfunction and that prevalence correlates inversely with time since recovery, ranging from 70-100% in the post-acute phase and decreasing to 46-78% at 1-year follow-up, to 25-47% at two years, and to ~20% at five years[8]. The domains most affected were memory, attention, concentration, processing speed, and executive functioning[8–10]. Furthermore, studies have observed that hypoxia is associated with neuronal atrophy and subsequent ventricular enlargement, which are particularly associated with memory impairment[11,12], likely due to the demonstrated sensitivity of hippocampal neurons to hypoxic damage[13]. However, it should be noted that other authors have also found a strong association between hypoxia and executive functions deficits[10].

In addition to ARDS, it has been suggested that hyperinflammation plays a significant role in determining the severity and mortality of COVID-19[3,14]. Aberrant stress responses to acute infection have been linked to cognitive impairment through the activation of a systemic inflammation pathway associated with elevated interleukins serum levels[15], and may represent a distinct pathological pathway. This implies that the etiology of COVID-19-related acute cognitive dysfunction might be both inflammatory and non-inflammatory[16]. Indeed, evidence from *in vitro* studies shows that coronavirus-infected glial cells secrete large quantities of inflammatory factors (IL-6, IL-12, IL-15 and TNF-α)[17]. Last but not least, the cases of acute cerebrovascular disease observed in COVID-19 may themselves be linked to cytokine storm syndromes[3], but they could also result from increased D-dimer levels and severe platelet reduction[18].

Notably, risk factors associated with a higher risk of severe COVID-19 (advanced age, hypertension, obesity, diabetes)[19,20] are also associated with higher risk of cognitive impairment[21]. Finally, multiple factors related to hospital care for COVID-19 (i.e., prolonged mechanical ventilation, sedation, social isolation) are known to increase the risk of delirium[22,23], which in turn is recognized to be a potentially modifiable risk factor for long-term cognitive dysfunction[24,25].

For these reasons, clinicians should be particularly watchful for cognitive dysfunction in hospitalized COVID-19 patients, both during the acute phase and in the long term.

Figure 12.1: Factors contributing to long-term cognitive dysfunction in COVID-19 survivors



COPD: Chronic Obstructive Pulmonary Disease.

Cognitive dysfunction in COVID-19: the state of the art

Acute cognitive impairment

Evidence regarding the presence of cognitive impairment during the acute clinical phase of COVID-19 was provided as early as March 2020 by Chen et al.[26] who reported the presence of delirium in 26 of 274 (9%) patients admitted for COVID-19. Notably, they also observed that the prevalence of delirium was much higher in patients who later died (22%) compared to those who recovered (1%). Another study[27] found that, as of February 2020, 16 of 214 (7.5%) patients admitted to hospital for COVID-19 manifested impaired consciousness. This study also confirmed that the presence of impaired consciousness was associated with a greater severity of illness, as the prevalence was significantly higher in patients

with severe COVID-19 compared to other patients (14.8% vs. 24%, p <0.001)[27]. Some authors have noted that the observed percentages may underestimate the actual incidence of acute cognitive dysfunction, since the main clinical focus during this period of crisis lay in pressing organizational issues (i.e., shortages of personal protective equipment, prioritization of limited ventilation options), which may have resulted in a reduction in resources allocated to delirium prevention and management[22].

Between February and April 2020, as the epicenter of the COVID-19 pandemic began shifting towards Europe, neurologists became ever more aware of the incidence of neurological manifestations of COVID-19. In April 2020, the European Academy of Neurology (EAN) core COVID-19 Task Force[28] posted a survey asking clinicians to report the prevalence of neurological symptoms in COVID-19 patients. They collected responses from 2,343 clinicians (82% of which were neurologists) who reported the presence of impaired consciousness (29.3% of patients), psychomotor agitation (26.7%), encephalopathy (21.3%), and cerebrovascular disease (21.0%)[28]. During the same period, Helms et al.[29] reported the results of an observational study on a series of consecutive COVID-19 patients hospitalized in the ICU for ARDS. Among other neurological symptoms, the authors observed the presence of a dysexecutive syndrome, characterized by disorientation, inattention, and poorly organized behavioral response to commands, in over one-third of patients (14/39; 36%)[29].

In conclusion, according to studies published so far, the clinical profile of cognitive dysfunction in COVID-19 patients during the acute phase appears to be characterized primarily by the presence of delirium and dysexecutive syndromes. (For a more detailed discussion of delirium in COVID-19, please see the dedicated chapter.) However, to the best of our knowledge, there have been no reports of the presence of milder and more specific cognitive deficits in the acute phase of COVID-19 (i.e., during hospitalization) in the scientific literature. While there are many brief neuropsychological tools designed to rapidly assess a broad range of cognitive functions at the bedside (Mini-Mental State Examination – MMSE[30], Montreal Cognitive Assessment – MoCA[31], Frontal Assessment Battery – FAB[32], to cite some of the most widely used), several factors would have rendered their use challenging and often unfeasible. One of these is the fact that hospitals faced enormous pressure to manage a large influx of critical and infectious patients, and therefore had to prioritize pressing clinical concerns, leaving aside all those assessments that were not urgently required in order to save patients' lives. Furthermore, other environmental, structural, and organizational limitations could have made the evaluation impossible even for patients who were not being treated in the ICU (busy, noisy wards, impossibility of moving patients, mandatory use of personal protective equipment that made verbal communication difficult, etc.). For these reasons, studies that have performed formal neuropsychological assessment in COVID-19 patients have done so exclusively in the post-acute phase.

Post-acute cognitive impairment

The ongoing COVID-19 pandemic continues to affect an increasing number of people worldwide. Thanks to the advances in the clinical management of acute symptoms, there has been a parallel increase in the numbers of patients who have recovered, who nevertheless often experience persisting symptoms. This so-called "Long-COVID" syndrome is often characterized by physical symptoms (fatigue, joint and bone pain), behavioral alterations (anxiety, insomnia), and, crucially, neurological symptoms (headache, paresthesia, cognitive impairment)[33,34]. Therefore, during the course of the pandemic, researchers have begun studying the cognitive outcomes associated with COVID-19 in order to establish, not only the prevalence and quality of these deficits, but also the presence of relevant clinical, physiological, and pathological associations.

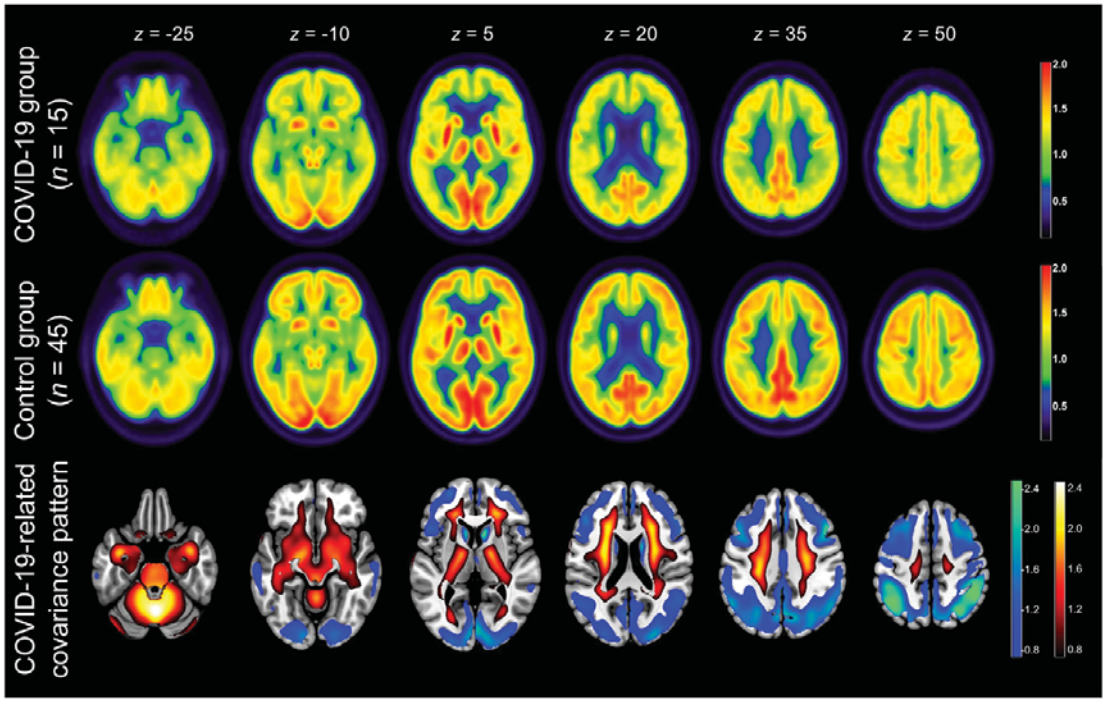
One of the first studies to report the presence of cognitive deficits following recovery from COVID-19 symptoms was conducted by Zhou et al.[35]. They observed that, between two and three weeks after clinical recovery, patients exhibited slower reaction times and performed worse in a test of continuous and selective attention compared to healthy controls. Interestingly, the authors also found a positive correlation between C-reactive protein (CRP) levels and reaction times; higher CRP levels correlated with slower reaction times[35]. Researchers in Spain[36] performed a complete neuropsychological assessment of 35 patients who recovered from COVID-19 between April and June 2020 (aged 24-60 years; mean age: 47.6±8.9 years; 19 females). Of these 35 patients, 21 (60%) had required oxygen and 7 (20%) had required admission to the ICU; the neuropsychological assessment was conducted between two and five weeks after clinical recovery. The study found deficits of memory, attention and semantic fluency in 5.7%, deficits of working memory and mental flexibility in 8.6%, and phonemic fluency deficits in 11.4%. The authors also observed that patients who had required oxygen therapy (n = 21) had lower scores in memory, attention, and executive functions, compared to other patients (n = 14)[36].

We assessed the presence of cognitive dysfunction in recovered COVID-19 patients at approximately five months from hospital discharge, by performing a complete neuropsychological assessment of 38 patients (aged 22-74 years;mean age: 53.45±12.64 years; 11 females)[37]. We found that 60.5% of our sample had deficits in at least one cognitive test, with attention and processing speed being the most affected domains (42.1% of patients). However, we also observed a significant prevalence of both verbal and visuospatial long-term memory deficits (26.3% and 18.4% of patients, respectively)[37]. Interestingly, patients who suffered from ARDS showed significantly lower scores in tests of verbal memory, and there was a positive correlation between PaO_2/FiO_2 levels and verbal memory performance. After recruiting more patients (n = 77), we observed a general stability of the cognitive profile, with an increase in the prevalence of memory deficits, likely due to the fact that we also

recruited patients who had required NIV and intubation, which confirms the link between memory deficits and ARDS (M Dini et al., 2021, unpublished data).

Other studies have assessed cognitive dysfunction in patients who have recovered from COVID-19 (see Table 12.1 for a summary). Notably, Hosp et al.[38] studied 29 patients (mean age: 65.2±14.4 years; 11 females) in the subacute phase (i.e., around one month after symptom onset) and found impaired global cognition in 18/26 patients (69%), as seen by MoCA scores <26; cognitive dysfunction was confirmed in 15 patients via detailed neuropsychological testing. The authors also performed ^{18}FDG PET scans on patients who had presented with at least 2 neurological symptoms, revealing a pattern of predominant frontoparietal hypometabolism in 10/15 (66%) patients, confirmed by comparison with a control sample via voxel-wise principal components analysis (Figure 12.2), which showed a positive correlation ($R^2 = 0.62$) with MoCA scores. Additionally, post-mortem assessment of a patient deceased for extracerebral causes revealed the presence of pronounced microgliosis with absence of neuroinflammation[38].

Figure 12.2: Result of 18FDG PET group analysis



Top and middle row: Transaxial sections of group averaged and spatially normalized ^{18}FDG PET scans in patients with COVID-19 and healthy controls. *Bottom row*: COVID-19-related spatial co-variance pattern of cerebral glucose metabolism constructed by Principal component analysis of the aforementioned groups. Reproduced from [38] with permission.

Table 12.1: Summary of data from studies on post-acute cognitive dysfunction in COVID-19 patients

Authors	Sample size	Demographic characteristics	Clinical characteristics	Illness - assessment delta	Tests used	Results
Almeria et al.[36]	35	Mean age = 47.6 ± 8.9 M/F = 16/19	60% required O_2, 20% ICU care	2-5 weeks	TAVEC, Visual Reproduction of the WMS- IV, Digit span, Letter and Numbers, TMT-A and -B, SDMT, Stroop, Phonemic and Semantic fluency, BNT	T-score < 30 in memory domains, attention and semantic fluency 5.7%, in working memory and mental flexibility (8.6%) and in phonetic fluency (11.4%)
Zhou et al.[27]	29 patients - 29 controls	Mean age = 47 ± 10.54 M/F = 18/11 - Mean age = 42.48 ± 6.94 M/F = 12/17	n/a	2-3 weeks	TMT, SCT, CPT, Digit span	Patients with COVID-19 scored lower in the correct number of the second and third parts of CPT, they also scored higher in the missing number of the third part of CPT (all $p < 0.05$).
Ferrucci et al.[37]	38	Mean age = 53.45 ± 12.64 M/F = 27/11	23.7% = no O_2 76.3% = low-flow O_2	5 months	MoCA, Rao's Brief Repeatable Battery	60.5% had at least one deficit, 42.1% had processing speed and attention deficits, 26.3% had long-term verbal memory deficits. ARDS was associated with worse verbal memory performance.
Hosp et al.[38]	29	Mean age = 65.2 ± 14.4 M/F = 18/11	10% = endotracheal intubation, 7% = NIV	1 month	MoCA, HVLT-R, TMT-A and -B, Stroop test, Digit span, SDMT, verbal fluences	MoCA performance was impaired in 18/26 patients (mean score 21.8/30)
Beaud et al.[39]	13	Mean age = 64.8 M/F = 10/3	all received mechanical ventilation	5-6 days	MoCA, FAB	MoCA= normal cognitive performances in 4 patients, mild deficits in 4 and moderate to severe deficits in 5. FAB= executive dysfunction in 8 patients.
Miskowiak et al.[40]	29 patients - 100 controls	Mean age = 56.2 ± 10.6; M/F = 17/12 - Mean age = 56 ± 6.9 M/F = 41/59	n/a	3-4 months	SCIP TMT-B	Cognitive impairment ranged from 59% to 65% depending on the applied cut-off, with verbal learning and executive functions being most affected

Méndez et al.[41]	179	Median age = 57 M/F = 105/74	49.7% = no O_2, 11.2% = nasal cannula 21.2% venturi mask 4.5% = NIV 12.8% = intubation	4 months	Immediate, and delayed memory subtests from the SCIP, animal naming test (ANT), Digit Span backward	58.7% of patients had neurocognitive impairment in at least one function. Immediate verbal memory and learning = 38%, delayed verbal memory = 11.8%, verbal fluency = 34.6%, working memory = 6.1%
Blazhenets et al.[42]	8	Mean age = 66 ± 14.23 M/F = 6/2	n/a	T1= subacute T2= 6 months	MoCA	MoCA (mean ± SD) = 19.1 ± 4.5 at the subacute stage, 23.4 ± 3.6 at 6 months. 5/8 patients remained below the normative threshold (<26/30).
Ortelli et al.[43]	12 patients 12 healthy controls (HC)	Mean age = 67 ± 9.6 M/F = 10/2 Mean age = 64.3 ± 10.5 M/F = 8/4	n/a	2-3 months	MoCA, FAB	Significantly poorer MoCA and FAB scores in patients compared to HC ($p < 0.001$).
Mattioli et al.[44]	120 COVID+ healthcare workers - 30 healthy healthcare workers	Mean age = 47.86 M/F = 30/90 - Mean age = 45.73 M/F = 8/22	118 = no O_2 1 = NIV 1 = intubation	4 months	MMSE, COWA, CVLT, TEA attention test, TOL	At least 1 impaired test: 30% (COVID-19 subjects) vs. 23.3% (non-COVID subjects). There was no statistical difference in mean scores of all the neuropsychological tests between COVID-19 and non-COVID-19 subjects
Cristillo et al.[45]	101	Age = 63.62 ± 12.9 M/F = 73/28	18 = no O_2, 68 = low-flow, 13 = NIV, 2 = intubation	6 months	MoCA	Patients with hyposmia exhibited lower MoCA score (23.2 ± 3.4 vs. 25.7 ± 2.5)

ARDS: acute respiratory distress syndrome; BNT: Boston Naming Test; COWA: Controlled Oral Word Association by categories; CPT: Continuous Performance Test; CVLT: California Verbal Learning Test; FAB: Frontal Assessment Battery; HVLT-R: Hopkins Verbal Learning Test Revised; ICU: intensive care unit; MMSE: Mini-mental State Examination; MoCA: Montreal Cognitive Assessment; NIV: Non-invasive ventilation; SCIP: Screen for Cognitive Impairment in Psychiatry; SCT: Sign Coding Test ; SDMT: Symbol Digit Modalities Test; TAVEC: Test de Aprendizaje Verbal Espana-Complutense; TMT: Trail-making Test; TOL: Tower of London test; WMS-IV: Wechsler Memory Scale –IV.

The authors conducted a follow-up study[42], repeating[18] FDG PET scans in 8 patients after six months, and observed a significant reduction in the initial pattern of frontoparietal hypometabolism, as well as an increase in temporal cortical ^{18}FDG uptake, compared to the acute phase; these results were accompanied by a significant improvement in cognition. They remarked that, although an improvement can be observed from neurophysiological data, some patients still exhibit residual impairment at six months, which is confirmed by the fact that 5/8 (62.5%) obtained MoCA scores below the normative cut-off[42]. The studies discussed so far are characterized by small samples, mainly due to the limitations imposed by the pandemic. More recent studies, however, have managed to collect data from larger samples. Méndez et al.[41], for example, studied cognitive dysfunction in a sample of 179 patients at four months after clinical recovery. Patients (median age: 57 years; 105 males) had been hospitalized for COVID-19 between March and April 2020 and had required different levels of oxygen therapy (no support: 49.7%; nasal cannula: 11.2%; venturi mask: 21.2%; NIV: 4.5%; mechanical ventilation: 12.8%). The authors found that 58.7% of patients had impairment in at least one domain, and that the most frequently impaired functions were immediate verbal memory and learning (38%), and verbal fluency (34.6%), while they found a lower prevalence of delayed verbal memory (11.8%) and working memory (6.1%) deficits. Delirium during hospitalization occurred in 8 (4.5%) patients, and was associated with an increased risk of cognitive dysfunction (OR [95%CI] = 4.05 [1.03 – 16.4])[41].

Another large sample of patients was assessed by Cristillo et al.[45] who studied a sample of 101 recovered patients at six months after discharge. Eighteen patients required no oxygen therapy, 68 required low-flow oxygen therapy, 13 required NIV oxygen therapy, while only 2 required orotracheal intubation. The authors focused on the association between hyposmia, dysgeusia and cognitive dysfunction, observing that patients who reported hyposmia at six months also obtained lower MoCA scores (23.2 ± 3.4 vs. 25.7 ± 2.4, $p < 0.001$). There was no association between hyposmia and severity of the disease, which suggests that the long-term cognitive dysfunction associated with COVID-19 might also have a non-respiratory component.

Mattioli et al.[44] conducted a study in which they assessed 120 healthcare workers who had had mild-moderate COVID-19 and 30 healthy controls, in order to assess cognitive dysfunction at four months from the diagnosis of COVID-19. The authors found that 30% of COVID-19 patients had at least one cognitive deficit at four months compared to controls (23%), although this difference was not significant. Notably, of the 120 patients, only 2 had required oxygen therapy (one NIV and one intubation); therefore, this sample is characterized by significantly milder disease severity compared to the studies discussed so far.

Methodological and practical considerations

Some key limitations need to be considered when interpreting the results of the studies which have been discussed so far. First and foremost, there is considerable variability in terms of sample size, with most studies characterized by small samples (n < 40). Additionally, most studies had an unbalanced males/female ratio, with male patients generally representing the majority of the sample, mainly because COVID-19 has been shown to affect males more severely[46] this results in higher hospitalization rates. The only exceptions were Zhou et al.[35], who studied 16 males and 19 females, and Almeria et al.[36] who studied 30 males and 90 females. There is also significant variability with regards to age as some studies assessed patients who were, on average, under 50 years of age[35,36,44], some assessed patients aged 50 – 60 years[37,40,41], and others focused on patients over 60 years of age[38,39,42,43,45]. Crucially, several studies differed in terms of the clinical characteristics of patients. Namely, some focused on patients who had recovered from severe COVID-19 (i.e., had required ICU treatment and mechanical ventilation)[39], while others focused on patients with milder illness severity[44]. The majority of studies, however, evaluated patient populations characterized by varying disease severity[36,37,41,45]. Crucially, some studies did not report the type of oxygen therapy patients received[35,40,43].

In terms of experimental design, most studies are observational in nature as they lack a control sample, and therefore they do not allow definitive conclusion regarding the role of COVID-19 on the observed cognitive dysfunction to be reached. Some conclusions may be drawn by comparing the performance of recovered patients with data from published normative studies relative to the various neuropsychological batteries and tests; this can be done either by calculating z-scores, or by categorizing patients based on published normative cutoffs. Another important methodological limitation is the fact that each study used different neuropsychological assessment batteries, which complicates the interpretation of results. Some studies administered only global assessment batteries (MoCA, FAB)[39,42,43,45] or a very limited selection of individual tests[35,40]gender- and education-matched healthy controls were also recruited. The cognitive functions of all subjects were evaluated by the iPad-based online neuropsychological tests, including the Trail Making Test (TMT, while others performed a more detailed assessment[36–38,44]. This, in addition to the fact that normative data differ across nationalities, language, and ethnicities, is likely to have contributed to the heterogeneity of the results. In conclusion, while rapid global neuropsychological tests (MoCA, MMSE, and FAB) should be considered for use during the acute phase, post-acute cognitive evaluation should be conducted using specific tests for the different cognitive domains in order to achieve greater sensitivity and to better characterize the qualitative profile of cognitive dysfunction.

Preliminary results of our study indicate that a MoCA score ≤ 25.50 at five months from clinical recovery predicted the presence of persistent cognitive

impairment (defined by the presence of deficits in at least two neuropsychological tests) at one year (sensitivity: 70.6%; scpecificity: 62.9%). Clinicians should be alerted to the risk of cognitive impairment not only when faced with patients falling below the established cut-offs, but also when observing patients who obtain borderline normal scores, since more detailed neuropsychological assessments might uncover impairment of specific cognitive domains.

Cognitive dysfunction at 1-year

As more than a year has now passed since the first peak of the pandemic, we should aim to assess the long-term course of cognitive dysfunction in recovered COVID-19 patients to establish first and foremost whether the observed deficits do persist in the long term, and secondly, whether specific patterns emerge (i.e., whether certain domains improve faster than others).

Following up on our first study[37], we recruited more patients and repeated the neuropsychological assessment at one year from hospital discharge in order to try and provide an answer to the questions outlined above. Preliminary data obtained from follow-up assessments (n: 52, T1: 5 months, T2: 12 months) highlight that the majority of patients show an improvement in all tests as time progresses, but it should be noted that a percentage of patients still exhibit cognitive deficits at one year from hospital discharge (Dini et al., unpublished data).

Cognitive rehabilitation

Considering what has been discussed so far, it is evident that cognitive rehabilitation must be included in multidisciplinary rehabilitation programs designed to improve the functional outcome of recovered COVID-19 patients[47,48]. As of today, however, few studies have assessed the effects of different cognitive rehabilitation programs in COVID-19.

An observational study[49] found that post-acute 3-week multidisciplinary rehabilitation improved respiratory, motor, and functional outcomes. Even though 29% of patients had cognitive deficits before enrolment, the authors did not report the results on cognitive functioning. Another study[50] on the effects of 6-week physical and educational rehabilitation interventions found that MoCA score significantly improved post treatment. However, since the study did not include formal cognitive rehabilitation, and did not include a control sample, it is difficult to say whether this improvement resulted from the rehabilitation intervention or from a spontaneous recovery of function. A recent study[51] assessing the effects of inpatient multidisciplinary rehabilitation interventions in patients who had recovered from COVID-19 who had required ICU treatment found improvements in cognition and speech, but also noted that a significant percentage of patients still exhibited deficits of attention, memory, and problem solving.

Given the ever-increasing number of recovered patients worldwide, rehabilitative interventions will play a significant role in determining the functional impact of the ongoing pandemic. As cognitive dysfunction represents a common symptom of the so-called "Long-COVID" syndrome, cognitive rehabilitation should be included in multidisciplinaruy rehabilitation programs. Finally, as subjective cognitive deficits can also significantly affect quality of life[52] and tend to be associated to psychological distress, anxiety and depression[53], rehabilitation programs may also benefit from the inclusion of techniques aimed at reducing psychological distress (e.g., mindfulness-based stress reduction [MBSR]).

Conclusions

Cognitive dysfunction can be observed not only during the acute phase of COVID-19, in the form of delirium and dysexecutive syndrome, but also in the post-acute phase of the disease, which is characterized by mild-moderate deficits. The qualitative profile of cognitive dysfunction is heterogeneous, probably as a result of differences between the various studies (socio-demographic variables, clinical variables, methodological differences) which are outlined above. Nevertheless, interesting results have been published linking the severity of cognitive dysfunction in the months following hospital discharge to clinical factors such as presence of ARDS[37], hyposmia[45], and inflammation[35]. It is likely that the cognitive functioning of these patients might improve as time progresses, and preliminary data seem to indicate that this is, indeed, the case. However, it is paramount that both clinicians and researchers be on the alert for the presence of cognitive dysfunction in people who had COVID-19, as it could represent a key factor in determining the functional outcome of a large number of patients worldwide.

Take-home message

- Cognitive dysfunction is common in patients with COVID-19.
- Cognitive deficits can be observed not only in the acute phase, but also in the months following recovery.
- ARDS, hyposmia/dysgeusia and hyperinflammation have all been linked with an increased risk of cognitive dysfunction.
- Cognitive deficits tend to be most severe in the first months from clinical recovery, and improve gradually in the long-term.
- Brief screening neuropsychological tests (MoCA, MMSE, FAB) may be unable to detect mild cognitive dysfunction in COVID-19 patients.

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