Neuropsychological functioning in severe acute respiratory disorders caused by the coronavirus: implications for the current COVID-19 pandemic

Beth Rabinovitz, Abhishek Jaywant & Chaya B. Fridman


To link to this article: https://doi.org/10.1080/13854046.2020.1803408

Published online: 09 Sep 2020.
Neuropsychological functioning in severe acute respiratory disorders caused by the coronavirus: implications for the current COVID-19 pandemic

Beth Rabinovitza, Abhishek Jaywantb and Chaya B. Fridmana

aDepartment of Psychiatry, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY, USA; bDepartments of Rehabilitation Medicine and Psychiatry, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY, USA

ABSTRACT

Objective: The coronavirus class of respiratory viruses - including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) - has been associated with central nervous system (CNS) disease. In fact, multiple mechanisms of CNS involvement have been proposed, making it difficult to identify a unitary syndrome that can be the focus of clinical work and research. Neuropsychologists need to understand the potential cognitive and psychological sequelae of COVID-19 and the impact of the interventions (e.g., ICU, ventilation) that have been used in treating patients with severe forms of the illness.

Method: We briefly review the literature regarding the neurological and neuropsychological effects of similar coronaviruses, the limited information that has been published to date on COVID-19, and the literature regarding the long-term cognitive and psychological effects of undergoing treatment in the intensive care unit (ICU).

Results: We discuss the roles that neuropsychologists can play in assessing and treating the cognitive difficulties and psychiatric symptoms described.

Conclusions: At this time, the mechanisms, correlates, and effects of COVID-19 are poorly understood, but information gleaned from the literature on similar viruses and utilized interventions should help inform neuropsychologists as they begin to work with this population.

The novel coronavirus (SARS-CoV-2) that causes coronavirus disease (COVID-19) was first identified in China in 2019, certified as a pandemic by the World Health Organization on March 11, 2020, and has rapidly spread throughout the world resulting in devastating illness and death with wide-ranging public health implications. Common symptoms of COVID-19 include fever, chills, shortness of breath/dyspnea, and cough and can result in acute respiratory distress (Huang, Wang et al., 2020).
Increasingly noted are effects on multiple organ systems including the heart, kidneys, and possibly the central nervous system (CNS; Wang, et al., 2020). Here, we summarize the existing literature on the neurologic impact of prior coronavirus-associated diseases and utilized interventions and highlight the emergent and rapidly evolving understanding of COVID-19. We further discuss the role of neuropsychology in the context of understanding, assessing, and managing the possible CNS effects of COVID-19.

CNS impact of SARS-CoV and MERS-CoV: implications for SARS-CoV-2

Although few viruses are primarily neurotropic in nature, multiple viruses have been shown to penetrate the CNS. Viruses can be characterized as having neuroinvasive properties, or the ability to directly enter the nervous system, and neurovirulent properties, the ability to cause disease within the nervous system (Ludlow et al., 2016). Although COVID-19, the illness caused by SARS-CoV-2, is most prominently characterized by respiratory symptoms, there is mounting evidence that the SARS-CoV-2 virus, like other known human coronaviruses (SARS-CoV and MERS-CoV) presents with neurological sequelae that may be secondary to both neuroinvasive and neurovirulent mechanisms. To date, however, most of the data regarding neurological implications of infection with the SARS-CoV-2 virus come from case studies or series. Although the exact pathophysiology of neurological implications of COVID-19 remains unknown, proposed mechanisms include: direct viral invasion of the nervous system, autoimmune sequelae, hypoxia-mediated injury, sequelae of systemic proinflammatory state, possibility of brain barrier disruption secondary to SARS-CoV-2 binding to the angiotensin-converting enzyme-2 (ACE2) receptor, and coagulopathy (Manne et al., 2020; Wu et al., 2020).

Initial evidence for the possibility of neurological impact of SARS-CoV-2 stems from experience with other human coronaviruses, including those implicated in the Severe Acute Respiratory Syndrome (SARS or SARS-CoV) and Middle East Respiratory Syndrome (MERS or MERS-CoV) pandemics. SARS, which is caused by a coronavirus with high genetic similarity to SARS-CoV-2, is present in the CNS and associated with varied neurological disorders. However, it should be noted that understanding of neurological implications of the SARS virus similarly comes from case studies or studies with limited sample size. Post-mortem studies have indicated presence of SARS-CoV in the brain (Xu et al., 2005). A case series indicated that autopsy in several SARS patients revealed presence of the virus in the cortex and hypothalamus, as well as edema and neuronal degeneration (Gu et al., 2005). SARS virus was also detected in the cerebrospinal fluid of a patient who developed seizures in the context of SARS infection (Lau et al., 2004), lending further support for the theory that coronaviruses may impact the CNS. MERS is another coronavirus with demonstrated impact on CNS function and disease. A case series indicated neurological implications, characterized by altered consciousness, ataxia, and focal motor deficits in patients with MERS (Arabi et al., 2015). Furthermore, neuroimaging studies in these patients indicated bilateral hyperintensities in the white matter and subcortical structures of the brain. Animal models have demonstrated that when SARS-CoV or MERS-CoV are introduced
intranasally, the virus enters the brain and can then be found in specific areas of the brain related to respiration, including the thalamus and brainstem (Li et al., 2016).

SARS-CoV-2 is a genetically similar virus to other coronaviruses including SARS-CoV and MERS-CoV. This group of human coronaviruses falls into the class of betacoronaviruses that are associated with severe disease in humans (Huang, Wang et al., 2020). The genetic similarity between SARS-CoV-2 and SARS-CoV is reported to be 79.5% (Wu et al., 2020), while that of MERS-CoV is reported to be 50% (Lu et al., 2020). Readers are referred to Rabaan et al. (2020) for a comprehensive overview of the viral structure and mechanisms of infection of SARS-CoV, SARS-CoV-2, and MERS-CoV. SARS-CoV and SARS-CoV-2 have been shown to bind to angiotensin-converting enzyme 2 (ACE2) as a cell entry receptor, while MERS-CoV binds to dipeptidyl-peptidase 4 to enter into human cells. Emerging evidence suggests that the CoV spike glycoprotein (s protein) that binds SARS to the cell membrane is longer in the SARS-CoV-2 virus and therefore may bind the SARS-CoV-2 virus with a higher affinity to the ACE2 receptor. This has been proposed to explain the increased infectiousness of SARS-CoV-2 and is proposed to contribute to a higher neuroinvasive potential than previous CoV viruses (Natoli et al., 2020; Rabaan, et al., 2020). This is particularly concerning given widespread ACE2 expression in the brain, suggesting that SARS-CoV-2 may have the potential to infect neurons and glial cells throughout the CNS (Zubair et al., 2020). In comparison to SARS-CoV, neurological symptoms appear to occur earlier in the course of illness in SARS-CoV-2 (Mao et al., 2020), although the mechanisms behind these observed differences will continue to be the subject of further study. A review completed by Natoli et al. (2020) indicated that, as of May 2020, 34% of patients hospitalized due to COVID-19 illness were noted to experience neurological symptoms, compared with sporadic case reports for SARS-CoV. However, the extent to which neurological symptoms reflect the neuroinvasive/neurovirulent impact of the virus or are secondary to treatments associated with hospitalization remains unclear.

Table 1 provides an overview of cited studies examining the impact of the SARS-CoV-2 virus and related COVID-19 illness on CNS function. While data regarding the neurological impact of COVID-19 is still limited, patients with COVID-19 have been reported to demonstrate CNS related symptoms (Wu et al., 2020). These have included confusion, delirium, encephalitis, and seizures. Mao et al. (2020), found that about 88% (78/88) of the patients with severe illness displayed neurologic manifestations including acute cerebrovascular diseases and impaired consciousness. In attempting to characterize and to better understand the neurological syndromes that presented after patients developed COVID-19 (n = 43), the University College London Queen Square National Hospital for Neurology and Neurosurgery COVID-19 Study Group identified five categories of neurological disorders: encephalopathies (n = 10), inflammatory CNS syndromes, including encephalitis and acute disseminated encephalomyelitis (ADEM; n = 12), ischemic strokes (n = 8), peripheral neurological disorders (n = 8), and miscellaneous central disorders (n = 5) that did not fit the other categories (Paterson et al., 2020). A study of hospitalized COVID-19 patients conducted in France indicated that of 13 patients with encephalopathy of unclear etiology, eight displayed leptomeningeal enhancement and 11 patients who had perfusion studies showed bilateral frontotemporal hypoperfusion (Helms et al., 2020). In a large sample study of patients hospitalized due to COVID-19 illness, 12 of 27 patients who had an MRI
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Age</th>
<th>% Male</th>
<th>Race/Ethnicity</th>
<th>Time of Assessment</th>
<th>Measures</th>
<th>Findings/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paterson et al. (2020)</td>
<td>43 patients in London who developed neurological syndromes from 6 days before and up to 27 days following the onset of COVID-19 symptoms</td>
<td>Range = 27-73</td>
<td>56%</td>
<td>53% non-white</td>
<td>Retrospective chart review, data on the clinical, neuroradiological, neurophysiological, and laboratory features</td>
<td>Extensive medical work-up, Brain MRI, CSF PCR in subset</td>
<td>- 10 patients had parainfectious or septic encephalopathy with delirium&lt;br&gt;- 12 patients had inflammatory CNS syndromes. Nine patients within the category of ADEM&lt;br&gt;- Eight patients had ischemic stroke&lt;br&gt;- Eight patients had peripheral neurological disorders. Seven had GBS&lt;br&gt;- Five patients were difficult to categorize&lt;br&gt;- Selective and retrospective study&lt;br&gt;- Bias towards severe disease</td>
</tr>
<tr>
<td>Helms et al. (2020)</td>
<td>58 patients admitted to the ICU in France due to acute respiratory syndrome from COVID-19 Patient characteristics and comorbidities were not outlined</td>
<td>Median Age = 63</td>
<td>Not Listed</td>
<td>Not Listed</td>
<td>During ICU stay, with unexplained encephalopathic features</td>
<td>Brain MRI, Perfusion imaging</td>
<td>- Enhancement in leptomeningeal space in eight of 13 patients who underwent MRI&lt;br&gt;- Bilateral frontotemporal hypoperfusion in all 11 patients who underwent perfusion imaging&lt;br&gt;- 15 of 45 patients discharged exhibited a dysexecutive syndrome characterized by inattention, disorientation, and disorganized response to commands</td>
</tr>
<tr>
<td>Kandemerli et al. (2020)</td>
<td>50 of 235 patients in the ICU due to COVID-19 who developed neurological symptoms. Brain MRI completed in 27 of 50 patients. Comorbidities included hypertension, diabetes, cerebrovascular accident, atrial fibrillation, congestive heart failure, lung cancer, Addison’s disease</td>
<td>Mean age of patients who received MRI = 63 (range 34-87)</td>
<td>78%</td>
<td>Not Listed</td>
<td>ICU stay Median ICU stay to time of MRI = 7 days (range 0-24)</td>
<td>Brain MRI</td>
<td>- 10 of 27 patients cortical FLAIR signal abnormality and 15 of 27 patients did not exhibit any abnormalities on imaging&lt;br&gt;- Accompanying subcortical and deep white matter signal abnormality on FLAIR images were present in three patients&lt;br&gt;- Frontal lobe abnormalities in four patients</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Age</th>
<th>% Male</th>
<th>Race/ Ethnicity</th>
<th>Time of Assessment</th>
<th>Measures</th>
<th>Findings/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moriguchi et al. (2020)</td>
<td>24-year-old male</td>
<td>24 years</td>
<td>100%</td>
<td>Wuhan China</td>
<td>20 hours following admission to ICU for COVID-19 related symptoms</td>
<td>BRAIN MRI, CSF PCR</td>
<td>• Parietal lobe abnormalities in three patients&lt;br&gt;• Temporal lobe abnormalities in one patient&lt;br&gt;• Insular cortex abnormalities in three patients&lt;br&gt;• Cingulate Gyrus abnormalities in three patients&lt;br&gt;• Limitations include the multi-center and retrospective study design and lack of standardization of indications across hospitals</td>
</tr>
<tr>
<td>Duong et al. (2020)</td>
<td>41-year-old female</td>
<td>41 years</td>
<td>0%</td>
<td>Not Listed</td>
<td>ICU admission due to high fever and new onset seizures</td>
<td>Extensive medical work-up</td>
<td>• Imaging results consistent with right lateral ventriculitis and encephalitis on right mesial lobe and hippocampus&lt;br&gt;• RT-PCR detected SARS-CoV-2 mRNA in the CSF</td>
</tr>
<tr>
<td></td>
<td>Comorbidities: diabetes, obesity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang et al. (2020)</td>
<td>reported on the CSF results of the same patient in a follow-up report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poyiadji et al. (2020)</td>
<td>Female airline worker</td>
<td>Late 50's</td>
<td>0%</td>
<td>Not Listed</td>
<td>ICU hospitalization due to COVID-19 related symptoms</td>
<td>Brain MRI, Head CT, CSF and bloodwork to rule out other viruses associated with encephalitis</td>
<td>• Hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobe, and subinsular regions&lt;br&gt;• Findings consistent with acute necrotizing encephalopathy hypothesized to occur secondary to cytokine storm associated with SARS-CoV-2 illness&lt;br&gt;• Limitation: RT-PCR to assess presence of SARS-CoV-2 in the CSF was not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Age</td>
<td>% Male</td>
<td>Race/ Ethnicity</td>
<td>Time of Assessment</td>
<td>Measures</td>
<td>Findings/ Limitations</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
<td>--------</td>
<td>-----------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Oxley et al. (2020)</td>
<td>Five patients; Two with no known risk factors; One with hyperlipidemia and diabetes; One with diabetes; One with diabetes and history of stroke</td>
<td>Mean age = 40.4 (range 33-49)</td>
<td>80%</td>
<td>Not Listed</td>
<td>During hospitalization due to COVID-19 related symptoms with positive COVID-19 test</td>
<td>• Brain CT</td>
<td>• Five patients under the age of 50 admitted for symptoms of large vessel ischemic stroke compared to 73 patients younger than 50 in a typical two-week period</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• CTA</td>
<td>• Mean NIHSS greater than 17 suggesting large vessel stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Brain MRI</td>
<td>• Clinical evidence of stroke including hemiplegia, motor and sensory deficits, and altered consciousness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• NIHSS</td>
<td>• Imaging evidence of infarction</td>
</tr>
<tr>
<td>Beyrouti et al. (2020)</td>
<td>Six patients admitted to National Hospital for Neurology and Neurosurgery in London with acute ischemic stroke and COVID-19; Comorbidities include hypertension, hypercholesteremia, diabetes, atrial fibrillation, heart failure, alcohol consumption, smoking</td>
<td>Mean age = 71 (range 53-85)</td>
<td>80%</td>
<td>Not Listed</td>
<td>During ICU admission in the context of COVID-19</td>
<td>• Brain CT</td>
<td>• All six patients had large vessel occlusion with elevated D-dimer levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• CTA</td>
<td>• Three patients had multi-territory infarcts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Brain MRI</td>
<td>• Two had concurrent venous thrombosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• DWI</td>
<td>• Two patients had ischemic strokes in spite of therapeutic anticoagulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Clinical manifestation of stroke including cognitive deficits, hemianopia, confusion, motor weakness, dysarthria, sensory neglect</td>
</tr>
</tbody>
</table>

Abbreviations: ICU: intensive care unit; MRI: magnetic resonance imaging; CT: computed tomography; CSF: cerebrospinal fluid; RT-PCR: reverse transcription polymerase chain reaction; NIHSS: national institute of health stroke scale.
had acute findings, and cortical FLAIR signal abnormality was evident in 10 of 27 patients (Kandemirli et al., 2020).

Case reports provide some suggestion of direct impact of SARS-CoV-2 in the CNS. A case of viral encephalitis in the setting of COVID-19 infection with confirmed presence of SARS-CoV-2 in the cerebrospinal fluid (CSF) was reported (Moriguchi et al., 2020). An additional case study of a 41-year-old female with viral meningitis who presented with headache, fever, new onset seizures, no respiratory symptoms, but positive COVID-19 test was reported (Duong et al., 2020). The authors suggest that this may indicate CNS involvement given isolated meningoencephalitis without respiratory symptoms. Furthermore, subsequent follow-up indicated that the CSF was positive for SARS-CoV-2 using reverse transcription polymerase chain reaction (Huang, Jiang et al., 2020). Anosmia is reported as a frequent symptom of COVID-19 (Giacomelli et al., 2020; Tong et al., 2020) and occurs in the context of evidence of the ability of coronaviruses to cross into the brain through the olfactory bulb (Li et al., 2016). However, further investigation of direct cortical changes related to olfaction in patients with COVID-19 is needed.

Additional possible mechanisms of CNS dysfunction in patients with COVID-19 include cytokine storm, hypoxic injury (Wu et al., 2020), and encephalitis resulting in edema, meningitis, and inflammatory injury (Moriguchi, et al., 2020; Ye et al., 2020). A case study of a female in her late fifties with positive COVID-19 PCR nose swab reported acute hemorrhagic necrotizing encephalopathy based on lesions within the bilateral thalam, medial temporal lobes, and subinsular regions, consistent with necrotizing encephalopathy (Poyiadji et al., 2020). Necrotizing encephalopathy is thought to reflect the impact of cytokine storm on the breakdown of the blood brain barrier, without direct viral invasion of the CNS. Cerebrovascular events have also been noted in patients with COVID-19 (Wilson & Jack, 2020) and may be related to the above-mentioned factors. However, as mentioned above, SARS-CoV-2 is also noted to bind to ACE-2 receptors, which may cause increases in blood pressure and cerebrovascular events (Wrapp et al., 2020). Cardiovascular risk factors and related cerebrovascular events are particularly important to consider given evidence that patients with cardiovascular and metabolic diseases (e.g., diabetes) face greater risk of developing severe COVID-19 (Li et al., 2020). More recently, several cases of large vessel stroke have been reported, particularly in younger COVID-19 positive patients, and are proposed to be secondary to coagulopathy or vascular dysfunction associated with the virus itself (Beyrouti et al., 2020; Oxley et al., 2020). A recently published study suggests that SARS-CoV-2 directly impacts platelet function and results in platelet hyperreactivity, perhaps explaining increased risk of thrombosis observed in patients with COVID-19 (Manne et al., 2020). These proposed mechanisms are reviewed in greater detail elsewhere in this journal.

**Virus-related cognitive factors**

Current literature regarding the specific cognitive impact of virus-related CNS/neurological disease is quite limited. A study looking at 58 of 64 patients with COVID-19 admitted to a hospital in France indicated that 15 of 45 patients that were discharged exhibited a dysexecutive syndrome consisting of inattention, disorientation, and difficulties organizing response to command. It should be noted that these were patients
who received ICU treatment, and the characteristics of the patients who exhibited the
dysexecutive syndrome, including age, pre-existing medical conditions, and treatment
during the ICU stay, were not delineated (Helms et al., 2020). Follow-up to understand
persistence of dysexecutive syndrome will also be important.

There is some evidence of persistent psychiatric and cognitive concerns in recov-
ered SARS-CoV patients. Follow up of patients who recovered from SARS-CoV indicated
reports of depressed mood, as well as increased concerns regarding
concentration and memory (Chan, et al, 2003). A large meta-analysis (Rogers et al.,
2020) reviewed 72 studies that provided data on the acute and post illness neuro-
psychiatric effects of coronavirus infection, predominantly SARS and MERS. Review of
these studies suggests delirium, anxiety, depression, and insomnia characterizes the
acute phases of SARS-CoV and MERS-CoV infection. Follow-up studies ranging from
6 week to 39 months post infection with SARS-CoV or MERS-CoV indicated that more
than 15% of patients reported ongoing emotional lability, impaired concentration,
impaired memory, insomnia, and fatigue. Information regarding long-term psychiatric
effects is limited by lack of information regarding pre-existing psychiatric conditions.
Follow-up questionnaires completed by SARS survivors in Hong Kong indicated high
rates of psychiatric symptoms, including post-traumatic stress disorder (PTSD), anxiety,
and depression, as well as complaints regarding concentration and memory, even in
the convalescent phase of the illness. Cognitive symptoms appeared to be associated
with disease severity, suggesting a link between viral infection and CNS function, but
it should be noted that corticosteroid treatment was also implicated in patient report
(Sheng, et al., 2005). High levels of psychological distress in survivors continued to be
reported one year following the SARS outbreak (Lee et al., 2007), highlighting the per-
sistent burden of the illness on survivors. Etiology of neuropsychiatric consequences of
infection with coronavirus may reflect direct influence of the virus in the central nerv-
ous system, cerebrovascular disease, hypoxia, immunological response, medical
interventions, social isolation, and the impact of illness with a novel pathogen, and
fear of contaminating others (Rogers et al., 2020). In addition, it is not clear whether
reports of cognitive dysfunction are a direct consequence of virus-related variables or
subjective reports of cognitive difficulties secondary to psychiatric symptoms.
Although at this early stage it is not possible to precisely predict the specific impact
of COVID-19 on cognitive function, Abboud et al. (2020) propose that, given what we
know about other respiratory viruses including chronic neuroinflammation, COVID-19
patients - and in particular those with neurological involvement during the acute ill-
ness - may develop late neurological complications, such as demyelinating and degen-
erative disorders. As such, the authors address the need for long term follow-up.

Summary
Overall, data suggest that the coronavirus class of respiratory viruses can impact the
central nervous system through direct infiltration of neurons, as well as related CNS
disease processes. Understanding of the mechanisms through which SARS-CoV, MERS-
CoV, and more recently SARS-CoV-2 result in CNS disease is still emerging and is com-
licated by numerous confounding factors, such as comorbidities and virus-related
treatments. Continued examination of the mechanisms by which coronaviruses impact neurological functioning - both directly and indirectly - is necessary. However, given evidence that COVID-19 does in fact impact CNS function, it will be important to understand the impact of COVID-19 infection on cognitive and daily functioning immediately following recovery and over time.

**Impact of ICU interventions on cognition**

In discussing the approach that should be taken when assessing the neuropsychological sequelae of a critical illness, Hopkins (2003) emphasizes that - in addition to identifying the specific pathophysiological processes and the ensuing organ damage and system pathology associated with an illness – it is necessary to recognize the deficits that are correlated with various medical interventions used to treat that illness. The contributions of individual variables, such as age, gender, and education must also then be considered. Using such a method to understand the cognitive effects of COVID-19 requires one to study the impact of the intensive care unit (ICU) experience itself, as the early data available from multiple countries have revealed that anywhere from 15-26% of patients who tested positive for COVID-19 demonstrated severe symptoms that warranted ICU admission (Grasselli et al., 2020; Xie et al., 2020; Zhou et al., 2020). Furthermore, the contributions of invasive mechanical ventilation, sedation, and psychiatric symptoms - which are often complicating factors in the ICU setting – must be carefully considered.

**Treatment in the intensive care unit**

Hopkins and Jackson (2006) conducted a literature review of 10 cohorts and reported that the percentage of ICU survivors experiencing neurocognitive impairments ranged widely, with studies reporting anywhere from 25-78% of patients with cognitive deficits. The reader is referred to Table 2 for an overview of the prospective studies, as well as the literature reviewed below. In the general population of patients who were critically ill, 33% had neurocognitive impairment (Jackson et al., 2003). In particular, mild-to-moderate weaknesses were reported to be evident in processing speed, memory, language, and visuospatial functioning.

Within the ICU setting, the prevalence rates of cognitive difficulties amongst patients who present with Acute Respiratory Distress Syndrome (ARDS) was reported to be the most pronounced (Hopkins & Jackson, 2006). Given the propensity for COVID-19 patients to suddenly experience severe respiratory failure (Ramanathan et al., 2020), this finding is particularly relevant. Indeed, a French observational series of patients who developed ARDS due to COVID-19, discussed in a recent Letter to the Editor of *The New England Journal of Medicine* (Helms et al., 2020), revealed that encephalopathy, agitation, confusion, and corticospinal tract signs were all associated with ARDS due to SARS-CoV-2 infection. Furthermore, 33% of the discharged patients demonstrated inattention, disorientation, and/or disorganized movements upon command. Although past studies have demonstrated that cognitive functioning in ARDS patients improves during the year following patients’ discharge (Hopkins et al., 2006), ongoing weaknesses in the domains of attention, processing speed, executive function, and memory have been reported to persist in many individuals. Similar findings...
Table 2. Overview of cited studies on cognitive dysfunction in ICU survivors, including studies specifically addressing use of mechanical ventilation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Mean Age</th>
<th>% Male</th>
<th>Race/ Ethnicity</th>
<th>Level of Education</th>
<th>Time of Assessment</th>
<th>Measures</th>
<th>Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Azevedo et al. (2017)</td>
<td>413 ICU survivors (APACHE-II score (x = 21) (range = 21-48))</td>
<td>57 years (range 46-72)</td>
<td>51.7</td>
<td>Not Listed</td>
<td>11 years</td>
<td>Average = 11 months post discharge (range = 3-18 months)</td>
<td>CAM-I</td>
<td>Digit span forward and backward; RAVLT; Clock Drawing; Verbal Fluency; MMSE</td>
<td>29.1% had mild or moderate cognitive impairment (defined as two test scores 1.5 standard deviation (SD) below the mean or one test score 2 SD below the mean)</td>
</tr>
<tr>
<td>Ehlenbach et al. (2010)</td>
<td>2,929 individuals (APACHE-II score not listed)</td>
<td>74.6 ± 6.0</td>
<td>39.5%</td>
<td>88.4% White 4.9% Black 4.4% Asian 2.3% Other</td>
<td>143 years</td>
<td>Baseline and 4.1 years</td>
<td>CAM-I</td>
<td>CASI</td>
<td>CASI scores declined by 1.83 points in those with no hospitalizations, 3.81 points in individuals with a noncritical illness hospitalization, and 5.28 points in those with a critical illness hospitalization</td>
</tr>
<tr>
<td>Hopkins, Gale, and Weaver (2005)</td>
<td>66 ARDS survivors; subset of 15 brain CTs were conducted and compared to age- and sex-matched controls (APACHE-II score for individuals with CT scans (x = 17.3 ± 4.1); for individuals without scans, (x = 18.3 ± 7.0))</td>
<td>39.2 years (range 15-72)</td>
<td>60%</td>
<td>With CT scans: 12.7 years</td>
<td>With CT scans: 12.7 years</td>
<td>Hospital discharge and 1 year post-discharge</td>
<td>WAIS-R; WMS-R; RAVLT; RFT (copy, immediate and delayed recall); Trail Making Test A &amp; B; Verbal Fluency</td>
<td>At the time of discharge, all ARDS patients had cognitive impairments; At 1-year follow-up, all patients with ARDS and brain CT scans continued to have significant memory impairments, whereas their performance improved on improved on the Performance Intelligence Quotient, Visual Memory Index, Attention/ Concentration Index, and Trail Making Test Parts A &amp; B</td>
<td>Small sample size; ‘convenience cohort’, scanned for clinical purposes during their ICU stay; patients with CT scans had longer hospital stays and longer duration of mechanical ventilation</td>
</tr>
<tr>
<td>Hopkins et al. (1999)</td>
<td>55 ARDS survivors (APACHE-II score (x = 18.2 ± 5.8))</td>
<td>45.5 years (range 16-78)</td>
<td>45.4%</td>
<td>Not Listed</td>
<td>12.8 years</td>
<td>4 days before hospital discharge and 1-year follow-up</td>
<td>Activities of Daily Living scale; SF-36; SIP; WMS-R; RAVLT; RFT (copy, immediate and delayed recall); Trail Making Test A &amp; B; Verbal Fluency</td>
<td>At 1-year follow-up, ARDS survivors had no improvement on the SF-36 for role-emotional, mental health, bodily pain, and general health; At the time of hospital discharge, 100% of patients experienced cognitive impairments, whereas at 1-year follow-up, 30% demonstrated deficits on the WMS-R, and 78% had impairment in at least one cognitive domain.</td>
<td>No control group; Only patients with severe ARDS were included; it is unclear whether the results were generalized to patients with less severe forms of ARDS; Problem-solving, cognitive flexibility, and perceptual motor skills were not assessed</td>
</tr>
</tbody>
</table>
Table 2. Continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Mean Age</th>
<th>% Male</th>
<th>Race/ Ethnicity</th>
<th>Level of Education</th>
<th>Time of Assessment</th>
<th>Measures</th>
<th>Findings</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Hopkins et al. (2004)        | 74 ARDS survivors (APACHE-II score x = 18.1 ± 6.6), 66 were available for follow-up testing | 45.8 ± 16.4 years | 44.6% | 99% White, 3% Hispanic | 13.1 ± 2.3 years | Hospital discharge and 1 year post-discharge | • BDI  
• BAI  
• SCL-90-R  
• Fashingbauer Short Form MMPI | 48% experienced a decline in speed of mental processing  
BDI and BAI at 1-year follow up were within normal limits, as was self-report on the SCL-90-R and the MMPI | Small sample size  
Lack of appropriate ARDS control group, so the cognitive sequelae may be due to critical illness rather than to ARDS  
Potential contributions of practice effects  
Did not measure premorbid cognitive functioning or quality of life |
| Jackson et al. (2003)        | 34 Medical ICU survivors (APACHE score x = 24.9 ± 8.8) | 53.2 ± 15.3 years | 53% | 2% Black | Not Listed | At discharge and 6 months post discharge | • CAM-ICU  
• mBDRS  
• GCS  
• Richmond Agitation Sedation Scale  
• GDS-Short Form  
• SHN-10  
• MMSE  
• WAIS-III Digit Symbol Coding, Paired Recall  
• Thurstone Word Fluency  
• Letter-Number Sequencing  
• WMS-III, Verbal Paired Associates, Faces (Immediate and Delayed)  
• RCFT (Copy and Delayed Recall) | Cognitive sequelae were identified in 75% of patients at discharge  
At 1 year follow-up, 45% had cognitive sequelae and 29% had mild to moderate symptoms of depression and anxiety. | Small sample size  
Some individuals were excluded due to the presence of premorbid cognitive difficulties, but that was determined based on chart review and collateral report rather than baseline testing. |
| Jones et al. (2006)          | 30 mechanically ventilated ICU survivors who were not delirious (16 completed the 2-month follow up) | 54 (range = 18-78) | 56.7% | Not Listed | Not Listed | During ICU admission, on the general ward one week post ICU discharge, and in the outpatient clinic at 2-months post ICU discharge | • CAM-ICU  
• CANTAB | All patients demonstrated problems with strategic thinking and problem solving while on the ICU and 67% had some problems with memory (defined as scoring < 25%)  
Impairment of problem solving on ICU was correlated with length of ICU stay and length of hospital stay post ICU, | Small sample size  
Impairment is defined very liberally |

(continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Mean Age</th>
<th>% Male</th>
<th>Race/ Ethnicity</th>
<th>Level of Education</th>
<th>Time of Assessment</th>
<th>Measures</th>
<th>Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikkelsen et al. (2009)</td>
<td>Cross-sectional study of 79 self-reported ARDS survivors</td>
<td>43.3 ± 12.7 years</td>
<td>15%</td>
<td>Not Listed</td>
<td>14.7 years</td>
<td>1-241 months post ARDS onset (34%: 0–1 years; 34%: 1–2 years; 16%: 2–3 years; and 22%: &gt;3 years) via telephone battery</td>
<td>NCSE Orientation, Judgment</td>
<td>Cognitive function was impaired in at least one domain in 56% of the population. Memory and executive function were impacted most frequently (24% and 10%, respectively). Cognitive impairment was observed less often when &gt;3 years had elapsed since ARDS onset, but no significant differences were observed based on time from ARDS onset. Moderate to severe levels of anxiety were reported by 48% of subjects, and moderate to severe levels of depression were reported by 34% of subjects. Association between cognitive impairment and anxiety was significant even after adjusting for potential covariates. Quality of life was also reduced.</td>
<td>Participants were self-identified as having had ARDS; medical records were not reviewed. Could not account for many potential confounding variables. Highly educated sample that had access to a computer. Unknown if the findings would generalize to other populations. Inability to compare pre-morbid and post-morbid cognitive skills or emotional functioning.</td>
</tr>
<tr>
<td>Mikkelsen et al. (2012)</td>
<td>122 mechanically ventilated patients who had ALI were tested at least once; 75 patients completed all of the testing (APACHE-III score x = 85 (range = 63-102))</td>
<td>49 (range = 40-58)</td>
<td>43%</td>
<td>80% White, non-Hispanic, 11% Black, non-Hispanic, 3% Hispanic</td>
<td>Not Listed</td>
<td>2- and 12-months post hospital discharge</td>
<td>WAIS-III, Vocabulary, Similarities, WMS-III, Logical Memory I, COWAT, Hayling Sentence Completion Test, BAI, Zung Self-Rating Depression Scale</td>
<td>Long-term cognitive impairment was present in 53% of survivors who completed cognitive testing. Memory was impaired in 13%, verbal fluency was impaired in 16%, and executive function was impaired in 49% of long-term survivors.</td>
<td>Limited sample size. Unable to adjust for sedation or delirium. Did not pre-screen for pre-existing dementia or psychiatric symptoms. Did not formally assess for hearing loss prior to administering the telephone battery.</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Mean Age</th>
<th>% Male</th>
<th>Race/ Ethnicity</th>
<th>Level of Education</th>
<th>Time of Assessment</th>
<th>Measures</th>
<th>Findings</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needham et al. (2013a)</td>
<td>525 participants, from 41 US hospitals, with ALI (APACHE-III x = 92)</td>
<td>52 ± 16 years</td>
<td>53%</td>
<td>79% White Not Listed</td>
<td>Not Listed</td>
<td>6- and 12-months post ALI</td>
<td>SF-36, EQ-SD-3L, hospital anxiety and depression scale, functional assessment of chronic illness therapy fatigue interval scale, impact of events scale-revised, mini-mental state examination telephone version</td>
<td>Depression was present in 36%, PTSD in 39%, and anxiety in 62% of the participants</td>
<td>At 12-months, 42%, 37%, and 23% of survivors experienced anxiety, depression, and PTSD, respectively</td>
</tr>
<tr>
<td>Needham et al. (2013b)</td>
<td>Prospective, longitudinal, multisite study of 174 ALI patients (APACHE-III x = 83)</td>
<td>47 ± 14 years</td>
<td>50%</td>
<td>91% White</td>
<td>49% with more than high school education</td>
<td>6- and 12-months after ALI</td>
<td>COWAT, Digit Span, Hayling Sentence Completion, Logical Memory I &amp; II, Similarities</td>
<td>At 6 months, 36% of patients exhibited cognitive impairment</td>
<td>At 12 months, 25% of patients had cognitive impairment (i.e., performance &lt; 1.5 SD) in executive functioning, language, memory, verbal reasoning and concentration, and attention and working memory</td>
</tr>
<tr>
<td>Pandharipande et al. (2013)</td>
<td>821 ICU patients in in-hospital cohort (median APACHE-II score = 25 (range = 19-31))</td>
<td>Median = 61 years (range = 51-77)</td>
<td>51%</td>
<td>90% White</td>
<td>Median = 12 years</td>
<td>In hospital, 3 months post discharge and 12 months post discharge</td>
<td>CAM-ICU, RASS, RBANS, Trail Making Test A &amp; B</td>
<td>Median RBANS global cognition scores at 3 and 12 months were 79</td>
<td>At 3-month follow up, 26% scored 2 SDs below the mean</td>
</tr>
<tr>
<td></td>
<td>467 ICU survivors in follow-up cohort (median APACHE-II score = 28 (range = 19-33))</td>
<td>Median = 59 years (range = 49-69)</td>
<td>50%</td>
<td>88% White</td>
<td>Median = 12 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52%</td>
<td>Not Listed</td>
<td>Not Listed</td>
<td></td>
<td>SKT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2. Continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Description</th>
<th>Mean Age ± (SD)</th>
<th>% Male</th>
<th>Race/ Ethnicity</th>
<th>Level of Education</th>
<th>Time of Assessment</th>
<th>Measures</th>
</tr>
</thead>
</table>
| Rothenhausler et al. (2001) | 46 ARDS survivors who had been mechanically ventilated (APACHE-II score x = 22.8 ± 5.9) | 30-44 year olds, 3 45-54 year olds, 9 55-64 year olds, 4 individuals above 65 | 64 years (SD = 3.2) from ICU discharge | SF-36 (psychometrically validated German translation) | 23.9% of patients demonstrated sub-threshold or mild cognitive impairments on SKT attention skills tasks | Highly variable range in timing of follow-up assessment  
SKT did not assess all areas of cognition  
Did not measure affective symptoms |
| Sukantarat et al. (2005) | 51 ICU survivors (APACHE-II score x = 14 (range 5-34)) | 59.5 years (range 26-82) | 43.1% | Not Listed       | Not Listed         | 3- and 9-months post discharge | Hayling Sentence Completion Test  
Modified Six Element Test  
Raven’s Standard Progressive Matrices  
At 3 months, 55% performed at/below the 5th percentile on one measure and 33% performed below the 5th percentile on two measures  
At 9 months, 27% and 4% performed below the 5th percentile on one and two measures, respectively | Multifactorial pre-existing conditions  
Small sample size relative to recruited population |

Abbreviations: ALI = Acute Lung Injury, APACHE II = Acute Physiology and Chronic Health Evaluation, ARDS = Acute Respiratory Distress Syndrome, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, CAM-ICU = Confusion Assessment Measure, CANTAB = Cambridge Neuropsychological Test Automated Battery, CASI = Cognitive Abilities Screening Instrument, COWAT = Controlled Oral Word Association Test, CT = Computed Tomography, EQ-SD-3L = EuroQol, GCS = Glasgow Coma Scale, GDS = Geriatric Depression Scale, ICU = Intensive Care Unit, MMSE = Mini-Mental State Examination, MMPI = Minnesota Multiphasic Person, MBDRS = Modified Blessed Dementia Rating Scale, NCSE = Neurobehavioral Cognitive Status Examination, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, RCFT = Rey-Osterrieth Complex Figure Test, SCL-90-R = Symptom Checklist 90-R, SF-36 = Medical Outcome Study Short Form, SIP = Sickness Impact Profile, SKT = Ein Kurztest zur Erfassung von Gedächtnis- und Aufmerksamkeitsstörungen, WAIS = Wechsler Adult Intelligence Test, WMS = Wechsler Memory Scale
have been demonstrated in ICU survivors as well (Mikkelsen et al., 2012; Pandharipande et al., 2013; Sukantarat et al., 2005). As such, it should be anticipated that at least some of the aforementioned COVID-19-related cognitive deficits will persist.

It is also important to note that approximately 1/3 of patients admitted to the ICU have pre-existing cognitive impairment (Sasannejad et al., 2019). Nevertheless, hospitalization itself has been associated with a greater likelihood of developing abrupt cognitive decline (Ehlenbach et al., 2010). Furthermore, wide ranging, long-term cognitive deficits have been demonstrated in a group of ICU patients even with relatively low levels of illness severity, in whom clinicians did not suspect any cognitive impairment (de Azevedo et al., 2017).

Moreover, many patients discharged from the ICU never return to their baseline levels of cognitive functioning (Jackson et al., 2009). It has been suggested that this is due to the development of a “dysexecutive syndrome” (Baddeley & Wilson, 1988) that may vary in severity and can manifest in problems with memory, problem solving, and social decision making. Various mechanisms have been implicated in the development of such cognitive impairment in these patients, including hyperglycemia (Hopkins et al., 2006), hypoxemia (Hopkins et al., 1999), hypotension (Hopkins et al., 2004), and treatment interventions (Starr et al., 1996; Starr & Whalley, 1994).

It is important to note that there are several limitations to the above-cited studies. The race and/or ethnicity of the participants were noted in only a few of the studies. Socioeconomic status was also typically omitted in the manuscripts. Patients were admitted to the ICU for a wide variety of reasons, and their level of severity also ranged considerably across studies. Variables such as the presence of severe sepsis, psychoactive medications, and delirium were not always accounted for. Ideal control groups were inherently lacking. Furthermore, the authors were unable to test cognitive functioning before ICU admission, and premorbid cognitive function was rarely estimated. In addition, the investigators often selected to use measures that screened cognition rather than administering a more comprehensive battery of tests. As such, there are many questions that remain unanswered and many variables that have yet to be untangled. Having said that, the findings consistently highlight the need to consider that ICU survivors may experience long-term cognitive sequelae.

**Use of mechanical ventilation**

In discussing the cognitive difficulties that have been associated with treatment in the ICU, a review of the impact of mechanical ventilation is imperative given the frequency with which that tool is used in this setting. Indeed, as of April 10, 2020, 33.1% of the first 393 consecutive patients with COVID-19 who were admitted in two New York City hospitals, affiliated with our institution, experienced respiratory failure resulting in invasive mechanical ventilation (Goyal et al., 2020). As was noted in Goyal and colleagues’ correspondence to the editor of the *New England Journal of Medicine*, the percentage of patients who received invasive mechanical ventilation at these hospitals was markedly higher than the 2.3% of patients across China who underwent invasive mechanical ventilation even though the disease manifestation at the time of hospital
admission was largely comparable to that which was reported in China (Guan et al., 2020). At the time of this publication, it remained unclear whether the tenfold need for invasive mechanical ventilation was due to the degree of disease severity, treatment approaches, different virus strains, underreporting, or other factors. Regardless, it has remained evident that the secondary effects of such an intervention will need to be considered when working with patients who have later been extubated. The fact that COVID-19 patients treated at our institutions have remained on mechanical ventilation for a much longer duration than is typical for ICU patients with other respiratory problems, including ARDS (Brower et al., 2000; Gadre, 2018; Khullar, 2020), further highlights the need to consider the effects that this life-saving intervention may later have on cognition.

Prior literature examining non-COVID-19 mechanically ventilated patients who, based upon assessment immediately prior to neuropsychological testing, were non-delirious, revealed that 67% of individuals had memory impairment, and 100% of the patients had executive functioning difficulties during their ICU treatment. Difficulties remained evident over the duration of their hospital stay, and approximately half of the patients demonstrated such difficulties upon assessment two months after discharge (Jones et al., 2006). Six months after discharge, a third of mechanically ventilated patients demonstrated deficits in visual construction, visual memory, processing speed, and verbal fluency (Jackson et al., 2003). Similarly, 36% of mechanically ventilated Acute Lung Injury (ALI) patients demonstrated cognitive deficits six-months post discharge (Needham et al., 2013b). Furthermore, a prospective study of critically ill, mechanically ventilated patients revealed that 91% of individuals demonstrated cognitive impairment at discharge, and 41% of individuals continued to exhibit problems with attention, processing speed, and executive functioning six months later (Lee et al., 2005). As Hopkins and Jackson (2006) noted, the aforementioned domains of cognitive functioning have been assessed in an inconsistent manner, due largely to the need to administer very brief batteries because of the extreme fatigue that these patients experience. As such, the variability in findings across studies likely reflects, at least in part, the differences in the test batteries administered. Across studies, the most frequently reported deficit has been memory, followed by executive functioning and then attention.

While many of these patients demonstrate cognitive improvements during the first six to twelve months post discharge, a subset of mechanically ventilated individuals experienced chronic neurocognitive impairment, as well as depression and reduced quality of life (Hopkins & Jackson, 2006; Jackson et al., 2003; Mikkelsen et al., 2009, 2012; Needham et al., 2013a, 2013b). Furthermore, amongst mechanically ventilated ARDS patients who were discharged from the ICU, 25% continued to perform below the sixth percentile on measures of memory, executive functioning and mental processing six years later (Hopkins et al., 1999; Rothenhausler et al., 2001).

**Neuropsychiatric considerations**

The severe and persistent cognitive dysfunction that is experienced by ICU patients may be due to the emergence of delirium, which occurs in as many as 80% of patients
in the ICU setting (Jackson et al., 2009; Pandharipande et al., 2013; Porhomayon et al., 2016). Delirium may serve as a harbinger for subsequent cognitive decline (MacLullich et al., 2009). Bulic et al. (2017) report that, in the ICU, delirium is associated with several risk factors. Critical illness is, in and of itself, associated with delirium, particularly when there is multi-organ failure and/or when there are multiple comorbid conditions, as has been reported to be the case in many of the most severely ill COVID-19 patients (Richardson et al., 2020).

In addition, as described above, the use of mechanical ventilation places patients at increased risk of experiencing delirium. Sedation, used in the ICU while patients are on mechanical ventilation, may also trigger delirium (Bulic et al., 2017; Porhomayon et al., 2016). These risk factors can have an additive or a cumulative effect and may exacerbate pre-existing cognitive difficulties, which can then accelerate the associated decline. Francis and Kapoor (1992) were the first to propose that delirium is a marker of impaired brain reserve due to chronic disease or to subclinical dementia, and others have since noted that there appears to be a common pathogenic mechanism underlying the cognitive impairments in delirium and dementia (Eikelenboom & Hoogendijk, 1999). However, as Girard et al. (2010) point out, the fact that young patients, who are less likely to have premorbid cognitive dysfunction, experience severe cognitive impairment subsequent to delirium suggests that the deficits may be acquired by patients during this period. Porhomayon et al. (2016) list a myriad of other factors that may predispose an individual to the development of delirium including: age, anemia, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score – a point score based on 12 physiological variables, age, and underlying health that is calculated at the beginning of the ICU admission and used to determine the patient’s mortality risk for the admission (Knaus et al., 1985) - azotemia, coma, dementia, dopamine levels, elevated hepatic enzymes, fever, hyperamylasemia, hyperbilirubinemia, hypertension, hypotension, hypocalcemia, hyponatremia, infections, lorazepam use, metabolic acidosis, morphine doses, and respiratory disease. Notably, many of these factors are applicable to the discussion of such deficits in COVID-19 patients (Richardson et al., 2020). In addition, there are a multitude of events that precipitate ICU admission (e.g., significant coronary event, stroke, brain injury, etc.) and can negatively impact cognition, and as discussed above, SARS-CoV-2 itself may cause acute brain dysfunction. Furthermore, the COVID-19 pandemic has also resulted in a unique sense of isolation due to the need to remain socially distanced and to quarantine, and such extreme isolation may further contribute to disorientation, feelings of disconnectedness, and lack of awareness (Kotfis et al., 2020).

Finally, it is important to emphasize that psychological health concerns - namely depression, anxiety, and PTSD - are frequently experienced by ICU survivors (Mikkelsen et al., 2012; Proffitt & Menzies, 2019). In the months post hospital discharge, 31% of patients who were treated in the ICU, for a variety of conditions, reported experiencing depressive symptoms (Davydow et al., 2013), 38% reported symptoms of anxiety (Stevenson et al., 2013), and 13.5% reported symptoms that were consistent with PTSD (Elliott et al., 2016). Amongst survivors of critical illness, younger patients are at the highest risk developing PTSD, along with those who have pre-existing mental health conditions and those who call recall traumatic events (Jackson et al., 2020;
Wintermann et al., 2015). Depression is a pronounced problem when critical illness presents in the geriatric population (Alexopoulos et al., 2008). For some individuals, the psychological sequelae experienced may be the direct effect of CNS dysfunction and the associated biological changes (Morrison & Kastenberg, 1997), whereas for other patients, the psychiatric symptoms may be a reaction to living through a serious medical illness, difficulty adjusting to the cognitive impairment experienced in daily life, and/or an exacerbation of a pre-existing mental-health condition.

Depression, anxiety, and PTSD – alone and in tandem - can contribute to the cognitive deficits that patients experience in the months and years after they are discharged from the ICU (Bremner et al., 1993; Cohen et al., 1982; Jackson et al., 2009, 2020; Mikkelsen et al., 2012). Furthermore, the reduction in quality of life, difficulties with performance of activities of daily living, and poor decision making/problem-solving that is secondary to cognitive impairment are an outgrowth of, and can contribute to, such internalizing problems. Indeed, Mikkelsen et al. (2009) reported that, amongst ARDS survivors who experienced cognitive impairment, 61% of subjects experienced moderate or severe anxiety compared with 31% of subjects without cognitive impairment. These difficulties can also limit the effectiveness of interventions, as they may serve as a barrier to treatment adherence (Alexopoulos et al., 2008).

Summary

Taken together, it is unlikely that there is a unitary factor that can account for the cognitive impairment that COVID-19 patients who are treated in the ICU may experience during their hospital admission and in the years to come. Rather, the deficits are likely to be the outgrowth of an interaction between illness-related factors, medical comorbidities, the aforementioned ICU-related issues, and premorbid variables (Hopkins & Jackson, 2006). Regardless of the underlying causes, it will be imperative to identify and to address the unique cognitive and psychiatric sequelae experienced by COVID-19 patients who were discharged from the ICU.

Neuropsychological assessment and intervention

In light of the literature reviewed, it has become increasingly clear that neuropsychologists can play a key role in the assessment, management, and treatment of COVID-19 survivors within an interdisciplinary care setting. The unique areas of expertise and skillsets of clinical neuropsychologists have much to offer patients, yet this will likely require a flexible approach that may deviate from the normal roles and responsibilities to which neuropsychologists are accustomed.

As described above, survivors of COVID-19 who are extubated appear to be experiencing high rates of cognitive impairment, anxiety, and mood problems. Within our hospital system, many COVID-19 patients are requiring acute inpatient rehabilitation, prompting the opening of a dedicated COVID-19 recovery unit at our institution (Gupta et al., 2020). This unit is staffed by an interdisciplinary team comprised of hospitalists, physiatrists, psychiatrists, neuropsychologists, occupational therapists, physical therapists, speech-language pathologists, and nurses. Within the setting, neuropsychologists
screen for cognitive impairment, anxiety and mood symptoms, and adjustment-related difficulties. Given the acute setting and the deconditioning and debility experienced by individuals with severe COVID-19 symptoms, only limited formal assessment is possible. Nonetheless, there are several brief assessment tools that can be used at the bedside to guide treatment and discharge planning. These include the Montreal Cognitive Assessment (Nasreddine et al., 2005), Brief Memory and Executive Test (Brookes et al., 2015), Repeatable Battery for the Assessment of Neuropsychological Status (Randolph et al., 1998), Behavior Dyscontrol Scale (Grigsby et al., 1992), Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), and Geriatric Depression Scale-Short Form (Lesher & Berryhill, 1994). Brief screening tools, particularly those with alternate forms, are advantageous in serial evaluation. This is important because patients’ cognitive functioning can fluctuate and at times improve rapidly as factors such as residual delirium resolve.

Neuropsychologists are typically accustomed to more extensive testing and are adept at synthesizing and parsing through large amounts of test data to render precise characterizations of neurocognitive functioning; however, even in the absence of extensive testing, neuropsychologists are trained observers of behavior and affect. Much can be gained from sitting and observing a patient and from administering brief mental status and self-report measures at the bedside. It is possible to obtain a more complete picture of a patient’s cognitive and functional skills through collaboration with members of the OT and SLP teams, as they generally employ several standardized and validated measures of functional cognition such as the Weekly Calendar Planning Activity (Toglia, 2015), the Executive Function Performance Test (Baum et al., 2008), and the Kettle Test (Hartman-Maeir et al., 2009).

In caring for COVID-19 patients, neuropsychologists will also need to draw on their skills as clinical psychologists. Those who survive prolonged intubation are awaking to a world that is profoundly altered from when they first became ill. Due to infection control and prevention, patients are isolated in their rooms without the physical presence of family members, friends, and loved ones. Physicians and nurses often must limit the time spent in patients’ rooms to mitigate the risk of infection, which can further drive a sense of isolation. Thus, just as important as their assessment skills, if not more so, is the ability of clinical neuropsychologists and psychologists to provide brief, targeted psychotherapeutic interventions. Such interventions include psychoeducation on the nature of anxiety, sadness, anger, and grief and validation of these emotions as adaptive responses to the situation. In the inpatient setting, neuropsychologists can provide supportive psychotherapy that validates the reality of patients’ emotional experiences and draws out resilience, hope, and a sense of safety. Additional interventions may include the use of mindfulness, grounding, and distress tolerance skills adapted from mindfulness-based interventions and dialectical behavioral therapy. The “psychological first aid” model (Everly & Lating, 2017; Ruzek et al., 2007) is a useful one in considering how to provide patients with a sense of agency, safety, and relief from their distress. Further, promoting social support and connectedness will be important given patients’ isolation. Neuropsychologists may help patients use technology to connect with their loved ones and to problem-solve ways in which patients can remain connected to social support networks.
Neuropsychologists can play a similarly important role in the outpatient setting for critically ill patients discharged from the ICU setting and for those patients with mild-moderate disease who may nonetheless be experiencing high levels of anxiety and mood symptoms. As in the inpatient setting, a useful model is one in which neuropsychologists are embedded within interdisciplinary “recovery” teams (Sevin et al., 2018) to address the emotional, psychosocial, and cognitive sequelae of illness from COVID-19. Given risk of ongoing infection, such outpatient care is likely to occur via telemedicine at least in the short-term until it is safe to resume standard practice. While neuropsychologists must be mindful of concerns regarding privacy, informed consent, and test security, there is accumulating evidence for the validity of telehealth-administered neuropsychological screening using selected measures (Cullum et al., 2014). A recent meta-analysis found that performance on neuropsychological assessments—such as digit span, verbal fluency, list learning and memory, and confrontation naming—was equivalent when comparing in-person to telehealth administration (Brearly et al., 2017). Screening measures, such as the Telephone Interview for Cognitive Status (Brandt et al., 1988) and the Telephone-MoCA (Zietemann et al., 2018) have also been designed specifically for telehealth administration. In-depth clinical interviews for anxiety, depression, adjustment difficulty, and acute stress disorder/PTSD are also amenable to the telehealth format. The Inter-Organization Practice Committee (IOPC) recently released guidelines and recommendations on the use of teleneuropsychology during the COVID-19 pandemic. Providers are encouraged to consult this document for further guidance.

**Summary**

SARS-CoV-2, the virus implicated in the current COVID-19 pandemic, like other known coronaviruses, has been associated with neurological sequelae. In addition, many of the patients who present with severe COVID-19 must be monitored in the ICU, thereby further increasing the likelihood that these individuals may experience neuropsychological dysfunction during their hospitalization and in the months and years following discharge. The associated psychiatric symptoms that such patients experience exacerbates these problems. As such, neuropsychologists now have an important role to play in the assessment and treatment of COVID-19 survivors.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**References**


