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## Post-traumatic stress disorder: A differential diagnostic consideration for COVID-19 survivors

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### ABSTRACT

**Objective:** SARS-CoV-2 infection and its oft-associated illness COVID-19 may lead to neuropsychological deficits, either through direct mechanisms (i.e., neurovirulence) or indirect mechanisms, most notably complications caused by the virus (e.g., stroke) or medical procedures (e.g., intubation). The history of past human coronavirus outbreaks resulting in similar health emergencies suggests there will be a substantial prevalence of post-traumatic stress disorder (PTSD) among COVID-19 survivors. To prepare neuropsychologists for the difficult task of differentiating PTSD-related from neuropathology-related deficits in the oncoming wave of COVID-19 survivors, we integrate research across a spectrum of related areas.

**Methods:** Several areas of literature were reviewed: psychiatric, neurologic, and neuropathological outcomes of SARS and MERS patients; neurological outcomes in COVID-19 survivors; PTSD associated with procedures common to COVID-19 patients; and differentiating neuropsychological deficits due to PTSD from those due to acquired brain injuries in other patient groups.

**Conclusions:** Heightened risk of PTSD occurred in MERS and SARS survivors. While data concerning COVID-19 is lacking, PTSD is known to occur in patient groups who undergo similar hospital courses, including ICU survivors, patients who are intubated and mechanically ventilated, and those that experience delirium. Research with patients who develop PTSD in the context of mild traumatic brain injury further suggests that PTSD may account for some or all of a patient's subjective cognitive complaints and neuropsychological test performance. Recommendations are provided for assessing PTSD in the context of COVID-19.

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## Introduction

Infection with severe acute respiratory syndrome due to coronavirus-2 (SARS-CoV-2) leads to coronavirus disease – 2019 (COVID-19) in an unknown percentage of individuals. Considering the ever-growing reports of neurologic complications due to

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COVID-19, neuropsychologists can expect a substantial number of survivors to present for neuropsychological evaluation in coming months and years. Such evaluations will likely involve questions of disability and be driven by patients' reports of subjective impairment. While early evidence from COVID-19 case series studies suggests that these survivors may present with a variety of neurocognitive deficits stemming from serious neurologic conditions related to the illness or its treatment, including large vessel stroke, hypoxic brain injury, encephalopathies, encephalitis, acute disseminated encephalomyelitis, and others (Ashrafi et al., 2020; Fan et al., 2020; Paterson et al., 2020), the ability to discern true (objective) from subjective deficits is likely to be complicated by psychiatric comorbidities. Indeed, research from past coronavirus outbreaks, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), indicate a high likelihood of psychiatric symptoms and disorders in COVID-19 survivors, most notably post-traumatic stress symptoms (PTSS) and post-traumatic stress disorder (PTSD) (Jeong et al., 2016; Lee et al., 2007, 2019; Mak et al., 2009, 2010; Wu et al., 2005). Evidence of the neuropsychological impact of COVID-19 is just beginning to emerge and a full understanding of the long-term side effects of the disease and its treatment may take years to catalogue. Still, as neuropsychologists prepare to evaluate COVID-19 survivors, a discussion of the neurocognitive and psychiatric sequelae of past human coronaviruses, as well as the frequent co-occurrence PTSD and acquired brain injuries, may be instructive.

### Neurocognitive sequelae of COVID-19 illness

Studies of past human coronaviruses (HCoV) and a steady stream of recent reports suggest that SARS-CoV-2 can affect the central nervous system (CNS) and subsequent neuropsychological functioning via direct and indirect routes. Concerning the former, like several other HCOVs (Glass et al., 2004; Li et al., 2016; Talbot et al., 1993), SARS-CoV-2 appears to be both neuroinvasive and neurovirulent. That is, it can breach the blood-brain barrier or gain entry to the CNS via other routes, where its presence can potentially lead to both acute and long-term neurological and neuropsychological sequelae (Arbour et al., 1999; Cristallo et al., 1997; Fazzini et al., 1992; Johnson-Lussenburg & Zheng, 1987; Morfopoulou et al., 2016; Murray et al., 1992; Stewart et al., 1992; Yeh et al., 2004). Among the indirect routes to neurologic and neuropsychological complications posed by the virus is its systemic effects. It is now established that a small minority of COVID-19 patients develop severe neurologic complications, such as infectious toxic encephalopathy, viral encephalitis, and stroke (Asadi-Pooya & Simani, 2020; Wu et al., 2020), perhaps due to the virus's potential to cause coagulopathy, thrombosis, and inflammation (Mehta et al., 2020; Zhang et al., 2020). Neurologic and neuropsychological symptoms may also arise secondary to atypical acute respiratory distress syndrome (ARDS; Dreher et al., 2020; Gattinoni et al., 2020). For example, prior research has established that ARDS survivors exhibit deficits in memory, attention, verbal fluency, processing speed, and executive function, with between 30 and 80% of patients continuing to exhibit cognitive impairment a year after ARDS (Herridge et al., 2016; Hopkins et al., 1999; Mikkelsen et al., 2012). Finally, a disproportionate number of severe COVID-19 cases have pre-existing medical

conditions that are also associated with neuropsychological deficits, including hypertension, diabetes, cardiovascular disease, cancer, and chronic respiratory illness (Ahles & Root, 2018; Bennett & Sauv , 2003; Janelins et al., 2018; Novak & Hajjar, 2010; Reijmer et al., 2011; Schou et al., 2012; van den Berg et al., 2010). Therefore, it will be a necessary and difficult task for neuropsychologists to consider complex factors and medical complications experienced by COVID-19 survivors. In short, while the exact nature and scope of the neuropsychological deficits experienced by COVID-19 survivors has yet to be established, outcomes will likely vary widely according to a number of clinical factors and individual differences.

### **PTSD among COVID-19 survivors**

A careful consideration of the neuropsychological implications associated with COVID-19 must also consider the impact of trauma experienced by survivors. However, little information has been reported regarding potential psychiatric outcomes. PTSD is defined as the development of symptoms related to intrusion, avoidance, negative alterations in cognitions and mood, and arousal and reactivity following exposure to a traumatic event (Shalev et al., 2017). Even among those who do not meet full diagnostic criteria, post-traumatic stress symptoms (PTSS) have also been associated with functional impairment (Westphal et al., 2011; Varela et al., 2011). Based on the information garnered from past human coronavirus outbreaks, specifically SARS and MERS, providers can anticipate an elevated incidence of PTSD and PTSS in COVID-19 survivors. For example, 42% of MERS survivors scored above a clinical cut-off for PTSD one year after the outbreak, with nearly 27% remaining above the cut-off after 18 months (Lee et al., 2019). Similarly, nearly 26% of SARS survivors met full diagnostic criteria for PTSD 30 months after treatment, and all identified SARS infection as their index trauma (Mak et al., 2010). These prevalence rates are far above the population average and suggest that providers should be prepared to evaluate and make recommendations regarding elevated PTSS in COVID-19 survivors. In the current pandemic, several causes of PTSD in the context of COVID-19 can be expected, as discussed next.

### ***Near death experience***

Patients with severe COVID-19 frequently present with respiratory symptoms which may progress to respiratory failure (Xie et al., 2020). Treatment for COVID-19 may involve extreme stressors for patients, including fear of death from life-threatening illness, pain from medical interventions such as endotracheal intubation, limited ability to communicate, and feelings of loss of control (Asimakopoulou & Madianos, 2014; Davydow et al., 2008; Gosselin et al., 2018). One patient described the sensation of COVID-19 respiratory infection as “it feels like you’re drowning... you think you’re going to die” (Buxbaum, 2020), and a respiratory therapist described shock at the severity of pink, frothy secretions occluding patient’s breathing tubes (Presser, 2020). Even patients with moderate illness severity who do not require hospitalization describe fear of death – one patient stated, “I did not go to sleep for three days because I was scared ... I wouldn’t wake up” (Brodsky, 2020). These anecdotes illustrate

how COVID-19 illness constitutes exposure to threatened death or serious injury, fulfilling the first diagnostic criteria for PTSD. Additionally, given that there is evidence of infection clusters within family units (Qian et al., 2020), survivors may have also experienced trauma related to witnessing severe illness or death of close family members.

### *Delirium*

Another potential cause of PTSD in COVID-19 survivors is delirium. Of particular interest to neuropsychologists, delirium has been investigated as one of the modifiable clinical risk factors for PTSD in patients who receive intensive care unit (ICU) treatment. COVID-19 patients may be at a particularly elevated risk for delirium due to a confluence of the likely neuroinvasive and neurovirulent properties of the virus itself, CNS inflammation in response to other organ system failures, the high percentage of severe COVID-19 patients who are also older adults, and ICU-specific factors such as intubation and ventilation, sedation, and prolonged isolation (Kotfis et al., 2020, O'Hanlon & Inouye, 2020). In elderly and mechanically ventilated populations, delirium may occur in up to 80% of ICU patients (Ely et al., 2004), again suggesting that survivors of severe COVID-19, who are likely to be older adults and require ventilation (Liu et al., 2020), may be at particularly high risk for delirium. Notably, prolonged delirium duration (>40 days) has been associated with higher PTSS (Bashar et al., 2018), but the presence of delirium has not been reliably associated with PTSD post-recovery (Svenningsen et al., 2015; Wolters et al., 2016). Other research has suggested that it is not delirium per se, but the recall of distressing in-ICU delusional memories that contribute to the development of PTSD in ICU survivors (Davydow et al., 2008; DiMartini et al., 2007; Jones et al., 2007).

### *ICU-related trauma*

Post-traumatic stress has been well-documented in survivors of ICU treatment (Cuthbertson et al., 2004; Griffiths et al., 2007; Patel et al., 2016; Taylor et al., 2019). Invasive ventilation and longer duration of mechanical ventilation in particular have been associated with an increased risk for PTSS (Shaw et al., 2009; Twigg et al., 2008). In Wuhan, China, the earliest epicenter of the outbreak, approximately 3.2% of COVID-19 patients required intubation and invasive ventilation (Meng et al., 2020).

Estimates of the prevalence of PTSD following ICU stays vary widely, ranging from 0-75%, with median scores falling in the high teens, well above the population prevalence of PTSD (Wade et al., 2013, Jones, 2010, Hatch et al., 2011). Risk of developing PTSD appears to depend on a number of factors including patient characteristics (e.g., age and preexisting comorbidities), and clinical treatment variables (e.g., use of sedation, restraint, and antipsychotic medications; Davydow et al., 2008; Davydow et al., 2009; Girard et al., 2007; Jones, 2010; Wade et al., 2013). Of particular note when considering COVID-19 survivors, some studies have found that patients treated in ICUs for ARDS may have even higher PTSD rates post-treatment as compared to other ICU patients, with higher prevalence of PTSD in ARDS survivors as compared to survivors of general medical ICU and cardiac surgery (Griffiths et al., 2007). PTSS appear to be present in between 30 and 40% of ARDS survivors, even months after treatment

(Mikkelsen et al., 2012; Shaw et al., 2001; Wade et al., 2013). More generally, estimates of PTSD in intubated and mechanically ventilated patients range from 14 to 51% (Gosselin et al., 2018). Among patients who require mechanical ventilation in the ICU, the most common symptoms include feelings of guilt, mood swings, sleep disturbance, and memories of panic and suffocation (Girard et al., 2007). Thus, as COVID-19 survivors who were treated in ICUs begin to present for neuropsychological evaluation, PTSS should be assessed as a part of a complete evaluation.

## The intersection between PTSD and neurocognitive functioning in COVID-19

Characterizing the cognitive profiles of COVID-19 survivors may be a complex task, as it will be difficult to disentangle the myriad potential etiologies of cognitive dysfunction in this patient population. This task will be further complicated by the possible primacy or comorbidity in a substantial proportion of survivors of PTSD/PTSS which is associated with a range of both subjective cognitive complaints (Mattson et al., 2019; Samuelson et al., 2017) and objective cognitive deficits in domains of verbal memory, sustained attention, and executive function (Aupperle et al., 2012; Brewin et al., 2007; DiGangi et al., 2017; Johnsen & Asbjørnsen, 2008; Malarbi et al., 2017; Polak et al., 2012; Vasterling et al., 2002). Considering the substantial possibility of neurologic symptomology and sequelae among COVID-19 patients, and of PTSD as a primary or secondary diagnostic consideration, understanding how PTSD manifests in other types of acquired brain injury may be instructive.

Survivors of severe COVID-19 are more likely to have a history of hypoxia and resulting acquired brain injury. These have also been associated with both cognitive and psychiatric impairments (Schultz et al., 2018) and progressive brain deterioration more than a decade after the original injury (Tobe, 2012). Both persistent neurocognitive deficits and declining mental health have been observed in ARDS survivors two years after hospital discharge (Hopkins et al., 2005), and cognitive impairment has been associated with worse health-related quality of life and greater disability status in ARDS survivors (Rothenhäusler et al., 2001). Furthermore, 79% of ARDS patients treated in an ICU recalled vivid nightmares and hallucinations (Larson et al., 2007). Other estimates suggest that between one quarter and one half of all ICU patients have limited or no memory of their treatment. In ARDS patients specifically, having no recall of ICU treatment was associated with higher rates of, and more significant, cognitive impairment up to one year after discharge (Larson et al., 2007).

Sleep dysfunction is another complicating factor considering its relationship to PTSD. Poor sleep, typically characterized by wakefulness, a high proportion of time spent in shallow sleep, and a relative low proportion of time spent in REM sleep, is a common complaint among survivors of ICU treatment (Friese et al., 2007; Weinhouse et al., 2009), and sleep problems can persist even after discharge (Dhooria et al., 2016; Lee et al., 2009). Thus, sleep dysfunction can be expected to be seen in a subset of survivors of severe COVID-19 who are treated in the ICU. Decreased sleep quality has also been documented even in non-patients during the COVID-19 lockdowns, associated with stress and anxiety (Marelli et al., 2020; Xiao et al., 2020). Sleep dysfunction

commonly occurs in both PTSD, acquired brain injury, and critical illness (Altman et al., 2017; Meeker et al., 2019; Tanev et al., 2014). Importantly, sleep quality may also contribute to cognitive deficits beyond the effects of PTSD (Gilbert et al., 2015), and has been shown to independently negatively impact cognition (Martindale et al., 2017). Poor sleep efficiency after ICU discharge may contribute to post-ICU cognitive impairment (Wilcox et al., 2013). Notably, sleep deprivation in the ICU is a potentially modifiable risk factor for delirium (Litton et al., 2016; Weinhouse et al., 2009), although findings are mixed (Kamdar et al., 2013).

Delirium, another potential cause of PTSD in COVID-19 patients, is also associated with persistent cognitive impairment and subjective memory decline several years after discharge from the hospital (Bickel et al., 2008). Diagnosis of delirium has also been linked with higher risk of later developing dementia (Jackson et al., 2004; MacLulich et al., 2009; Sprung et al., 2017). This adds an additional level of difficulty for neuropsychologists in attempting to determine the etiology of cognitive impairment in COVID-19 survivors with experienced ICU delirium.

Another consideration which includes those patients with history of mild or uncomplicated illness is the role of expectation of cognitive effects in survivors of COVID-19. Given the media coverage of neurological involvement in COVID-19 and the yet unknown disease effects on cognition, it is possible that patients may experience iatrogenic effects. The impact of negative illness perception and symptom expectation on cognition has been documented in mild traumatic brain injury (mTBI), such that negative beliefs about an injury and its effects are independently associated with persistent post-concussion symptoms (PCS) and cognitive deficits (Hou et al., 2012; Mittenberg et al., 1992; Whittaker et al., 2007). Studies of patients with comorbid PTSD and mTBI suggest that subjective cognitive complaints are greater than in patients with mTBI alone (Spencer et al., 2010). Persistent post-concussive symptoms have also been shown to be mediated by the presence of PTSD, suggesting that the experience of PCS such as subjective memory complaints arise from PTSD and not from the mTBI (Pietrzak et al., 2009; Polusny et al., 2011; Porter et al., 2018; Schneiderman et al., 2008). In the context of COVID-19, it may be several years before we are able to disentangle the contribution of PTSD versus brain injury to cognitive functioning, as there may not be clear evidence of brain damage without detailed neuropathological examination.

### **Recommendations for the neuropsychological assessment of COVID-19 survivors with psychological trauma**

In the coming months and years, COVID-19 survivors may seek neuropsychological evaluations due to subjective cognitive complaints. A subset of these patients may have been treated in ICUs, been intubated or mechanically ventilated, experienced periods of delirium, or may have experienced direct neurological impacts such as stroke. For these patients, the task for neuropsychologists will be to differentiate whether their cognitive complaints are related to psychological traumatic, premorbid deficits, non-credible effort, neurologic insult, or a combination of the above. As described above, survivors of severe COVID-19 may be more likely to have direct



neurological involvement and elevated risk for PTSD/PTSS from their illness and treatment, as compared to those with more mild illness. However, patients who recover from more mild COVID-19 may still be at risk for psychiatric symptoms or negative expectancies that impact cognition, self-report, and perception of disability.

It may be particularly difficult to differentiate the long-term effects of neurologic insult and delirium from PTSD in COVID-19 survivors given that there is currently very little known about the CNS effects of COVID-19 or SARS-Cov-2 infection or what potential neuropathology secondary to the illness exists. Considering the high likelihood of psychological trauma in COVID-19 survivors, it is important that clinicians not attribute subjective cognitive complaints or objective cognitive impairment to acquired brain injury or other medical complications without considering the contribution of PTSD or other psychiatric etiologies. In addition, considering the inevitability of disability claims and perhaps civil lawsuits related to COVID-19, feigned impairment is also likely to be a key consideration.

While diagnosis of PTSD in COVID-19 survivors may be relatively straightforward, determining the relative contribution of such disorders and COVID-19-related neuropathology to neurocognitive deficits will be challenging. There are no published data on the neuropsychological profiles of survivors of COVID-19, and considering the myriad of indirect causes, a consistent profile is unlikely. Known deficits in attention, executive function, and memory seen in PTSD patients are likely to overlap with the cognitive impairments related to COVID-19. Furthermore, subjective cognitive complaints may be driven more by psychiatric symptoms and expectations rather than actual underlying neuropathology. Additionally, at least in the intermediate-term post-acute phase, individuals who undergo ICU treatment and experience severe medical complications such as respiratory failure or neurologic insult can be fatigued, irritable, anxious, and/or depressed, which also overlap with the non-cognitive clinical symptoms of PTSD (Dolan et al., 2012; Spadaro et al., 2020). Assessment of other specific ICU-related factors which have been linked to cognitive outcomes, such as recall of ICU treatment, experience of delirium, and use of sedatives and analgesics, may be an informative addition to the clinical interview (Jackson et al., 2009). Neuropsychologists must carefully evaluate patients who are at risk of both PTSD and neurologic insult, as is the case with COVID-19 survivors.

Due to the proliferation of media coverage related to COVID-19, including reports of neurological impact, patients may have expectations of poor cognitive performance and persistent neurological symptoms after illness. Clinical experience and empirical research of TBI patients indicates that expectations related to brain injury significantly impact symptom report and neuropsychological test performance (Suhr & Gunstad, 2005; Waldron-Perrine et al., 2015). Subjective cognitive complaints arising in the context of PTSD are likely to persist far longer than cognitive impairments directly resulting from mild brain injury, although patients may attribute symptoms to the acquired brain injury alone (Verfaellie et al., 2014). Trauma-focused psychotherapies, including cognitive-behavior therapy, cognitive processing therapy, and prolonged exposure, have been shown to improve cognitive performance (Walter et al., 2010). However, patients who believe that their experienced cognitive symptoms are due to acquired brain injury may have difficulty accepting alternative explanations and the possibility



of cognitive recovery following psychotherapy. Neuropsychologists should therefore be prepared that patients with expectancies related to acquired brain injury may be resistant to treatment appropriate for neuropsychiatric conditions (Porter et al., 2018). Normalization of psychiatric symptoms in survivors of ICU treatment may be an important first step.

It may be impossible for neuropsychologists to fully disentangle the complex and likely multiple etiologies of cognitive impairment and self-reported cognitive changes in COVID-19 survivors. Given that many survivors of severe COVID-19 will be older adults, these individuals may also have already had premorbid cognitive decline or may be experiencing new cognitive impairment, further complicating the diagnostic picture of these patients. Therefore, while certain recommendations such as cognitive rehabilitation and lifestyle changes may be warranted, referrals for psychotherapy to address PTSS/PTSD may be a valuable additional treatment recommendation. Clinical experience suggests that patients may be amenable to psychotherapy recommendations framed in such a way that suggests that there are multiple routes by which their cognitive symptoms can be addressed simultaneously, increasing the likelihood of improvement of functioning and quality of life. Finally, there will undoubtedly be patients whose cognitive symptoms have no psychiatric cause, but rather result solely from direct or indirect neurological effects of the virus as described above. As research on cognition in survivors of COVID-19 continues to emerge, neuropsychologists must adapt their conceptualizations to follow the evidence.

## Conclusion

In sum, evidence from survivors of SARS and MERS, as well as groups similar to survivors of severe COVID-19 (e.g., ARDS patients and other ICU survivors), highlight the need for neuropsychologists to consider either comorbid or stand-alone PTSD in COVID-19 survivors and the consideration that post-traumatic stress may be responsible in part or in full for both subjective cognitive complaints and poor neuropsychological test performance. As evidence of the neurocognitive sequelae of COVID-19 emerges, psychological trauma should not be overlooked as an important contributor to the neuropsychological robustness and quality of life of patients seeking cognitive evaluations. Neuropsychologists working in inpatient settings may be in a position to advocate for follow-ups with patients to reduce likelihood of post-ICU PTSD.

Regardless of objective neuropsychological deficits, the subjective experience of cognitive impairment can also be very emotionally distressing to survivors and clinicians should carefully consider how both brain damage secondary to COVID-19 and secondary to PTSD may be impacting cognition. Neuropsychologists can then provide psychoeducation and treatment referrals appropriately targeted to the patient's needs to address these subjective cognitive complaints. Inpatient and rehabilitation neuropsychologists may be particularly well situated to recommend PTSS and sleep quality screenings and longitudinal psychiatric and cognitive follow-up. Psychiatric screening follow-up may be particularly important to identify those survivors whose symptoms persist beyond acute stress reactions to potentially meet full diagnostic criteria of PTSD (i.e., greater than one month after the trauma).

As a final note, the effects of psychological trauma will not be limited to the survivors themselves; frontline healthcare workers and family members may also experience PTSS and negative effects from stigmatization, as was documented in the SARS and MERS outbreaks (Lee et al., 2019; Maunder, 2004; Park et al., 2018). Neuropsychologists may also play a role in advocating for PTSS screenings and mental health outreach more broadly for frontline healthcare providers, families, and survivors of the COVID-19 pandemic.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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