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PERSPECTIVE

The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning

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Abstract

Introduction: The increasing evidence of SARS-CoV-2 impact on the central nervous system (CNS) raises key questions on its impact for risk of later life cognitive decline, Alzheimer's disease (AD), and other dementia.

Methods: The Alzheimer's Association and representatives from more than 30 countries—with technical guidance from the World Health Organization—have formed an international consortium to study the short-and long-term consequences of SARS-CoV-2 on the CNS—including the underlying biology that may contribute to AD and other dementias. This consortium will link teams from around the world covering more than 22 million COVID-19 cases to enroll two groups of individuals including people with disease, to be evaluated for follow-up evaluations at 6, 9, and 18 months, and people who are already enrolled in existing international research studies to add additional measures and markers of their underlying biology.

Conclusions: The increasing evidence and understanding of SARS-CoV-2's impact on the CNS raises key questions on the impact for risk of later life cognitive decline, AD, and other dementia. This program of studies aims to better understand the long-term consequences that may impact the brain, cognition, and functioning—including the underlying biology that may contribute to AD and other dementias.

KEYWORDS
cognitive decline, COVID-19, neuropsychiatry, SARS-CoV-2

1 | INTRODUCTION

The number is constantly changing, but it seems likely that by the time the pandemic spends its force about one in every 200 persons worldwide will have suffered an infection by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most of these individuals will survive the infection, but the public health impact of the pandemic may continue as chronic sequelae of coronavirus disease (COVID-19), resulting in disability or diminished quality of life, now attracting the term "Longcovid." Judging by what is known so far, long-term sequelae are not just likely to occur, but also likely to affect certain groups of individuals disproportionately; this only further deepens existing health disparities. Given the well-established and projected weight of neuropsychiatric disorders included in the global burden of disability, it seems particularly appropriate to take stock of what is known about the deleterious, direct effects of SARS-CoV-2 infection and COVID-19 on the central nervous system (CNS), and to project how these effects are likely to contribute to the chronic burden of disease globally in coming years. An equally important but separate issue not covered in this article is the wider societal impact of the pandemic due to its likely wider economic, social, and personal effects in the immediate and longer term.

2 | VIRAL IMPACT ON BRAIN FUNCTIONING

Neurotropic respiratory viruses have long been known to result in chronic brain pathology.[1,2] Paradigmatically, the 1918 influenza pandemic was and continues to be suspected as the underlying cause of encephalitis lethargica;[3] emerging movement disorders, profound sleep cycle abnormalities, and psychotic illness resulted in enormous burden of disease and untold suffering for affected individuals and their caregivers. Less spectacular, but perhaps more impactful at the population level, studies have suggested that common viral infections such as herpes simplex virus 1 (HSV1) may be associated with molecular processes in Alzheimer's disease (AD) dementia in human brain cells[4] and transgenic animal models.[5] Several studies have also suggested an association of HSV1 and cognitive decline.[6] Because brain inflammation accompanies the most common neurodegenerative disorders and may contribute to major psychiatric disorders, the neurological and psychiatric sequelae of COVID-19 need to be carefully tracked.[7–14]

RESEARCH IN CONTEXT

Neurotropic respiratory viruses have long been known to result in chronic brain pathology including emerging cognitive decline and dementia, movement disorders, and psychotic illness. Because brain inflammation accompanies the most common neurodegenerative disorders and may contribute to major psychiatric disorders, the neurological and psychiatric sequelae of COVID-19 need to be carefully tracked.

3 | NEUROTROPISM

Coronaviruses, especially β-coronaviruses including SARS-CoV-2, have been shown in several studies to invade the CNS.[7,12,15–17] The CoV spike glycoprotein binds angiotensin-converting enzyme 2 (ACE2) with high affinity,[18,19] and protein cleavage by specific proteases plays a key role in the brain invasion and virulence of earlier human coronavirus, and may play a role in SARS-CoV-2.[20]

SARS-CoV-2 invades respiratory and gastrointestinal epithelial cells by binding ACE2 on the cell membrane; ACE2 is also expressed in the brain, both in neurons and glia. Notably, multiple non-neuronal cell types present in the olfactory epithelium express two host receptors, ACE2 and transmembrane serine protease 2 (TMPRSS2) proteases, that facilitate SARS-CoV-2 binding, replication, and accumulation.[21] Intranasal administration of SARS-CoV-2 in mice results in rapid invasion of the brain,[22,23] and SARS-CoV-1 viral particles can be detected *post mortem* in the cerebrum, but not in the cerebellum, in humans.[24] Entry of SARS-CoV-2 into the cells through membrane fusion markedly downregulates ACE2 receptors, with loss of the catalytic effect of these receptors at the external site of the membrane.[25,26] Vascular growth factor (VEGF), which is widely distributed in the brain, may play a role in brain inflammation via the ACE2 pathway.[27] Clinical reports of patients infected with SARS-CoV-2 show that several features associated with infection and severity of the disease (ie, older age, hypertension, diabetes, cardiovascular disease) share a variable degree of ACE2 deficiency.[25,28–31] In *post mortem* brain tissue, ACE2 is expressed in the frontal cortex vasculature, and viral spike proteins cause blood-brain barrier (BBB) damage in vitro.[32]

SARS-CoV-2 neurotropism is suspected; it is based on growing evidence from clinical, pathological, and molecular studies.[7,11,12,33–47]

First, headache, hypogeusia, and anosmia appear to precede the onset of respiratory symptoms in the majority of affected patients, and ataxia and altered mental status have been documented independent of multiorgan failure.[12,21,38,48–52] There have also been documented cases of acute encephalopathy and meningoencephalitis associated with detection of SARS-CoV-2 RNA in the cerebrospinal fluid (CSF).[7,53–57] SARS-CoV-2 can also be found in the brain *post mortem*.[56] Further, pan-encephalitis and diffuse petechial hemorrhage of the entire brain have been reported,[58] particularly perivascular and interstitial encephalitis in the brain stem,[58,59] in some patients.[60]

In addition, respiratory problems due to SARS-CoV-2 are thought to be due in part to brain-stem dysregulation,[11,12,61–64] as are possibly some of the gastrointestinal symptoms.[65] Neurological symptoms may occur in their first 1 to 2 days of the clinical symptomatic phase, and cerebrovascular accidents are common within 2 weeks of the onset of the symptomatic phase.[51,65–74] While case series of para-infectious or post-infectious acute neuroinflammatory syndromes such as acute disseminated encephalomyelitis (ADEM) are reported in association with SARS-CoV-2 infection,[51,75,76] many patients with COVID-19 on intensive care units (ICUs) have corticospinal tract signs.[44] The absence of SARS-CoV-2 viral load in the CSF and the presence of oligoclonal bands in the CSF and serum of some patients suggest immune-mediated response that is not limited to intrathecal production of immunoglobulins.[8,44,56] Other common neurological manifestations include meningitis and acute demyelinating polyneuropathy.[38,49–51,68,77,78] New onset seizures, sometimes followed by anosmia, have also been reported in SARS-CoV-2–confirmed infections.[12,68,79–83] The mechanisms of causation of seizures are probably complex, and may include cortical irritation due to hemorrhages, inflammation, or metabolic changes.[12,80] Sporadic epileptiform discharges were detected in nearly half of COVID-19 patients in intensive care.[81]

Delirium can be the only presenting symptom of SARS-CoV-2 infection[84–86] even in younger patients.[56] The incidence of delirium in severely ill COVID-19 patients on ICUs is reported to be as high as 84%,[44] of which more than two thirds exhibit hyperactive delirium, despite receiving high sedation and neuroleptics.[44] The overall incidence of delirium across the clinical spectrum from mild to severely ill patients with COVID-19 is unknown. Because many patients with COVID-19 are mechanically ventilated,[87–89] a substantial proportion of patients with COVID-19 are likely to experience delirium with a currently unknown long-term outcome. In elderly patients with

dementia, delirium is a very frequent presenting symptom of SARS-CoV-2 infection[90] and carries a higher short-term mortality rate.[91]

Delirium in COVID-19 may be a feature of primary encephalopathy due to the direct intracerebral viral invasion.[92] Alternatively, secondary encephalopathy may be associated with neuroinflammatory response to SARS-Cov-2;[93,94] immune-mediated systemic response;[8,95,96] or independent complications of hypoxemia, sepsis, hypoperfusion, severe metabolic illness, and pharmacological side effects.

As evidence accumulates regarding viral neuroinvasion, there are several routes for possible transmission, including trans-synaptic transfer across infected neurons in splacnic nerves,[11,12,62,97] entry via the olfactory nerve,[21,98] infection of vascular endothelium, leukocyte migration across the BBB, and/or a conjunctival route.[11,99,100] From the olfactory bulb, SARS-CoV-2 may target the deeper parts of the brain including the thalamus and brain stem by trans-synaptic transfer described for many other viral diseases.[11,101] In some individuals, SARS-CoV-2 infection triggers a massive release of cytokines, chemokines, and other inflammation signals leading to BBB dysfunction, injury to astrocytes, activation of microglia and astrocytes promoting neuroinflammation and neuronal death.[11,62,102–104] Immune response and excessive inflammation in COVID-19 may also accelerate the progression of brain inflammatory neurodegeneration; elderly individuals are more susceptible to severe outcomes after SARS-CoV-2 infection.[105]

Because the entry points of viral invasion into the brain have direct connections to brain stem and thalamic structures, ensuing dysfunction may result in sensorimotor, mental, and behavioral disorders.[11,68,106–108] Indeed, in a case series from the UK acute alteration in personality, behavior, cognition, or consciousness was the second most common presentation of COVID-19, often occurring in younger individuals; nearly half of these individuals had new-onset psychosis, while the rest had neurocognitive (dementia-like) syndrome, or affective disorders.[51] Autoimmune encephalitides associated with antibodies against neuronal cell-surface or synaptic proteins; in those with new-onset psychosis, higher prevalence of antibodies against four other coronaviruses strains have been found,[56] and at least one confirmed case of anti-n-methyl-d-aspartate antibodies encephalitis associated with COVID-19 was reported.[109] Further, reports of individuals presenting with clinical-radiological features of limbic encephalitis and little systemic symptoms of COVID-19[56,110] suggests immune-mediated response to SARS-CoV-2.[109] Taken together, the evidence suggests a possible mechanism for SARS-CoV-2 encephalopathy and psychosis.

4 | BRAIN IMAGING

Abnormal brain imaging has emerged as a major feature of COVID-19 from all parts of the world.[111] Structural brain magnetic resonance imaging (MRI) revealed parenchymal brain abnormalities, subcortical micro- and macro-bleeds, cortico-subcortical edema, nonspecific deep white matter changes, and asymmetric olfactory bulbs *post mortem*,[112] and similar findings during hospital admission.[113–119,94,120] The abnormal imaging has been seen in an individual whose only symptom was anosmia.[121] The most common MRI findings from patients admitted to ICUs include cortical signal abnormalities on fluid-attenuated inversion recovery images, accompanied by cortical diffusion restriction or leptomeningeal enhancement, which may reflect infectious or autoimmune encephalitis, seizures, hypoglycemia, or hypoxia.[122] Acute demyelinating lesions also have been described and have been visualized on images.[76,123–125]

5 | POSSIBLE DETERMINANTS

Different host immune responses to SARS-CoV-2 infection may partially explain why males and females, young and old persons infected with this virus have markedly distinct disease severity.[126] In fact, C-reactive protein[127] and ferritin[128] levels were associated with elevated risk of COVID-19 in a dose-dependent manner, and N-terminal pro-brain natriuretic peptide (NT-proBNP) was associated with increased mortality in COVID-19 pneumonia.[129,130] Concomitant cardiac disease has an extremely poor prognosis, with higher mortality, thromboembolic events, and septic shock rates.[131]

Among hospitalized COVID-19 cases, physical inactivity, smoking, and obesity but not heavy alcohol consumption were related to increased rates of hospital admission.[127] Diabetes mellitus increases risk for dementia as well as of severe outcomes after SARS-CoV-2 infection, and is highly prevalent in certain demographics such as Black American/African Americans and Latino/Hispanic Americans,[105] and the same demographic groups appear to be at higher risk of neurological complications of COVID-19.[132] Disparities in COVID-19 hospitalizations and mortality according to ethnicity remain present, even after correcting for neighborhood, household crowding, smoking, body size, diabetes, and mental illness.[133]

6 | IMPLICATIONS FOR NEUROPSYCHIATRIC DISORDERS

Olfactory deficits have been previously reported for several viral infections,[12,134] and are characteristic of neurodegenerative disorders.[135–139] Notably, anosmia is linked to high levels of interleukin-6, an inflammatory mediator causally involved in brain disorders whose actions are blocked by tocilizumab as part of COVID-19 treatment.[140]

Systematic reviews[141,142] and meta-analysis data[143,144] have firmly established incident and prevalent stroke as independent risk factors of dementia. Likewise, typical risk factors for stroke increase the odds of dementia including coronary heart disease and carotid stenosis,[145] as well as atrial fibrillation,[146] stage 1 midlife hypertension,[147] and hyperhomocysteinemia.[148] Furthermore, MRI features of cerebral small vessel disease, ie, white matter hyperintensities, lacunes, microbleeds, perivascular spaces, and cerebral atrophy were additively associated with dementia and cognitive decline.[149–151] Therefore, it seems likely to expect that COVID-19–related cardiovascular and

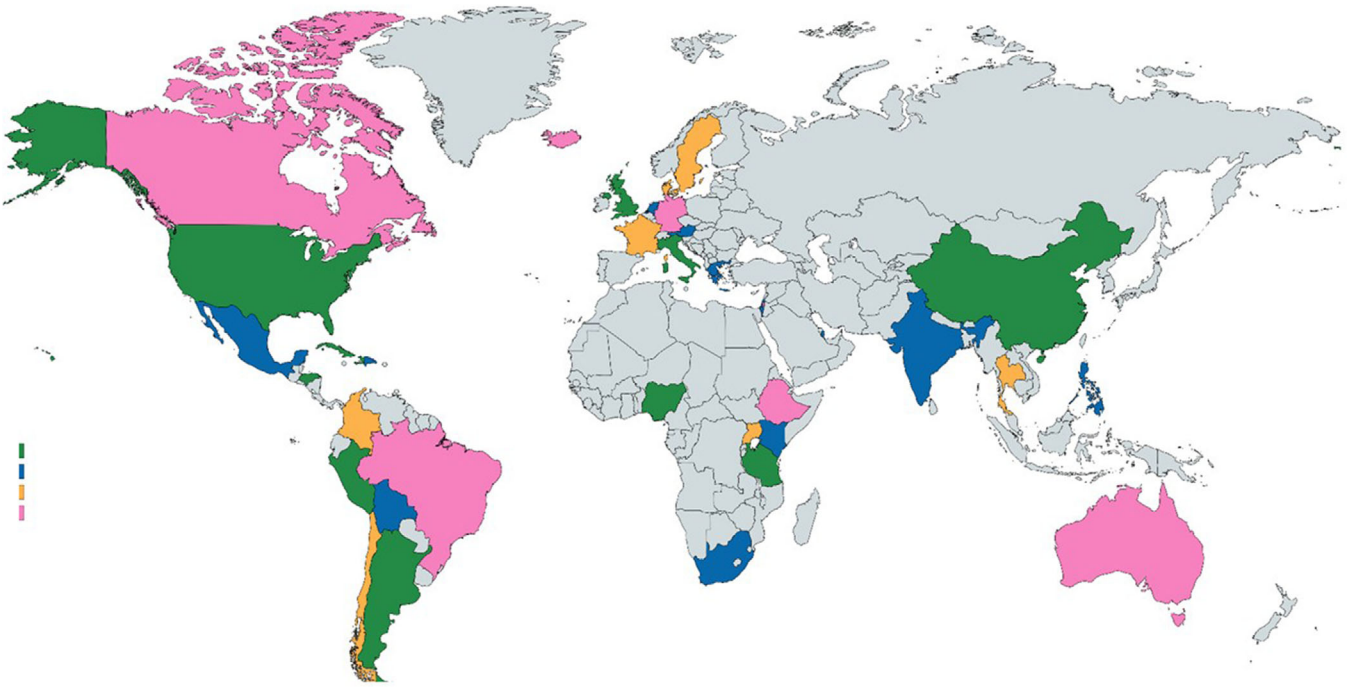

FIGURE 1 Consortium participants. Colored countries in the map represent those with at least one academic institution participating in the Consortium for Chronic Neuropsychiatric Sequelae of SARS-CoV-2

cerebrovascular disease will also contribute to a higher long-term risk of cognitive decline and dementia in recovered individuals.

Multiple lines of evidence suggest that viral infections of the brain may impact a person's risk for AD or Parkinson's disease. The present pandemic provides a unique—if unwelcome—opportunity to test the role of neurotropic viruses in a prospective fashion in individuals that have recovered from COVID-19.[152,153] The mechanisms by which neurological abnormalities result from COVID-19 remains to be fully established. Direct effects of SARS-CoV-2 itself on neuronal function and survival or glial reactivity, exaggerated cytokine responses, or anti-neuronal antibodies are all likely to contribute, as are the sequelae from cerebrovascular accidents. As pointed out above, the experience of pandemics caused by neurotropic respiratory viruses in the past—as well as the emerging data and observations of clinicians over the past several months—strongly supports an expectation of increased neuropsychiatric sequelae, including cognitive decline, motor impairment, and affective and psychotic disorders, in addition to demyelinating processes or cerebrovascular disease that occur during the acute viral infection, or may follow infection in recovered individuals.[154]

7 | PSYCHIATRIC DISORDERS

Psychiatric distress and acquired cognitive deficits after COVID-19 will likely have complex, bidirectional relationships. Impaired cognitive abilities may cause poor occupational and functional outcomes that precipitate or exacerbate mental health concerns, and poor mental health may likewise contribute to cognitive dysfunction.[155] The SARS-CoV-1 epidemic was associated with psychiatric complications. COVID-19 patients found a high level of post-traumatic stress symptoms and significantly higher level of depressive symptoms. Patients with preexisting psychiatric disorders reported worsening of psychiatric symptoms.[156] After the coronavirus pandemics in 2002 and 2012, one in five recovered individuals reported depressed mood, insomnia, anxiety, irritability, fatigue, and in one study traumatic memories and sleep disorder were frequently reported. The meta-analysis indicated that in the post-illness stage the point prevalence of post-traumatic stress disorder was 32.2%, depression was 14.9%, and anxiety disorders was 14.8%.[157]

8 | COGNITIVE DECLINE AND MOTOR IMPAIRMENT

COVID-19 results in high levels of proinflammatory cytokines, acute respiratory distress, and hypoxia, each of which may contribute to cognitive decline both in healthy and in already predisposed individuals.[14,158] After the coronavirus pandemics in 2002 and 2012, one in five recovered individuals reported memory impairment,[157] and an early report found that one in three individuals with COVID-19 had dys-executive syndrome at the time of hospital discharge.[157] Impaired cognitive abilities may cause poor occupational and functional outcomes for individuals recovered from COVID-19 that precipitate or exacerbate mental health concerns, and poor mental health may likewise contribute to cognitive dysfunction.[155]

Influenza epidemics are associated with neurological manifestations, and the H5N1 virus reportedly induces Parkinsonian pathology in mice, both findings possibly explained by the activation of

TABLE 1 COVID-19 cases per country. Numbers represent confirmed cases of COVID-19 in each country at the time of submission

Argentina	565,446
Australia	26,739
Austria	34,305
Bolivia	127,619
Brazil	4,356,690
Canada	138,555
Chile	437,983
China	85,202
Colombia	721,892
Cuba	4726
Denmark	20,571
Dominican Republic	104,110
United Kingdom	41,664
Ethiopia	64,786
Finland	8725
France	387,252
Germany	264,169
Greece	13,730
Haiti	8499
Honduras	68,620
Iceland	2174
India	5,009,290
Israel	162,273
Kenya	36,205
Mexico	671,716
Netherlands	84,778
Nigeria	56,388
Peru	733,860
Philippines	269,407
Qatar	122,214
South Africa	650,749
Spain	603,167
Sweden	87,345
Tanzania	509
Uganda	5123
United States	6,758,987
TOTAL CASES	22,735,468

inflammatory pathways.[159] However, the exact mechanisms of these effects and whether coronaviruses show a similar action remain unclear. About half of hospitalized patients are >55 years; the resulting higher age-related risk of neurodegenerative disorders is a good setting to investigate triggering and double-hit mechanisms previously hypothesized for viral infections.[160] Despite the higher mortality rate, a majority of cases are expected to recover and survive from this viral outbreak. A natural decline in ACE2 expression and the subsequent pro-inflammatory profile with aging may explain the increased severity and comorbid diabetic and hypertensive complications observed in older adults. There are potential long-term implications of SARS-CoV-2 infection in relation to accelerated brain aging, neurovascular coupling, and age-related neurodegenerative disorders.

As described above, coronaviruses can cause demyelination, neurodegeneration, and cellular senescence. SARS-CoV-2 specifically can infect endothelial cells expressing ACE2 potentially leading to further deterioration of this vascular architecture. The resulting hypoperfusion may restrict energy substrates essential for maintaining neuronal networks thereby accelerating cognitive decline in the elderly. Damage to limbic and cortical regions could cause retrograde and anterograde amnesia. As a result of ACE2 downregulation, SARS-CoV-2 infection in older adults induces aggressive secretion of pro-inflammatory cytokines.

Pro-inflammatory cytokines increase oxidative stress that damages cellular membranes and downregulates surface expression of excitatory amino acid transporters that are necessary for terminating glutamatergic signaling. The resulting elevated glutamate levels can lead to an excitotoxic environment precipitating the neuronal loss and initiating a vicious feed-forward cycle that causes further damage to the surrounding parenchyma. Viral entry into neurons may create a cytotoxic insult and initiate apoptotic pathways or create an excitatory–inhibitory imbalance. This pathway is already postulated to play a role in several neurodegenerative diseases including AD and Parkinson's disease. A slow infiltration throughout the CNS may precipitate underlying pathologies associated with age-related neurodegenerative disorders months or years after acute viral infection. The neuroinvasive potential of SARS-CoV-2 may result in senescence of several different CNS cell types including oligodendrocytes, astrocytes, and neural stem cells that can differentiate into neurons that integrate into the granule layer. Viral aggravation of underlying neuropathology has the potential to hasten the onset of or further deteriorate motor and cognitive deficits.[161]

9 | CONCLUSION AND NEXT STEPS

The increasing evidence and understanding of SARS-CoV-2's impact on the CNS raises key questions on the impact for risk of later life cognitive decline, AD, and other dementia. Scientific leaders, including the Alzheimer's Association and representatives from more than 30 countries—with technical guidance from the World Health Organization—have formed an international, multidisciplinary consortium to collect and evaluate the short- and long-term consequences of SARS-CoV-2 on the CNS. This program of studies aims to better understand the long-term consequences that may impact the brain, cognition, and functioning—including the underlying biology that may contribute to AD and other dementias.

This consortium will link study teams from around the world (Figure 1) covering more than 22 million cases at the time of submission (Table 1) to enroll two groups of individuals including people with

confirmed cases of COVID-19 sampled from hospitals that have been discharged to be evaluated for follow-up at 6, 9, and 18 months, and people who are already enrolled in existing international research studies to add additional measures and markers of their underlying biology.

CONFLICTS OF INTEREST

The authors declare no conflict of interest with the work discussed in this article.

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SUPPORTING INFORMATION

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

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