COVID-19 and neurocognitive disorders

Elizabeta B. Mukaetova-Ladinska[a,b], *Golo Kronenberg*[c,d], *and Ruma Raha-Chowdhury*[e]

Purpose of review
The COVID-19 infection results in various viral-related physical and mental health problems, joined with the long-term psychological impact of the pandemic in general. However, the accompanying neurocognitive changes remain poorly understood.

Recent findings
We synthetize the current knowledge of viral (SARS-CoV-2) induced inflammation, mechanisms to viral entry into the central nervous system and altered neurotransmitter systems to provide an informed neurobiological explanation for the rise of neurocognitive disorders (defined as per the DSM-5 criteria).

Summary
The mild and major neurocognitive disorder symptoms due to the COVID-19 pandemic provide a unique opportunity to address the early changes underlying neurocognitive impairment at both clinical and molecular level. We discuss the utilization of the available evidence for their management and future novel therapeutic opportunities.

Keywords
COVID-19 neurocognitive disorders, inflammation, neurotransmitter, stress, viral infection

INTRODUCTION

The COVID-19 pandemic has affected all segments of the world population and has proven detrimental especially to the most vulnerable groups in society. It has gravely impacted those living in poverty, that is homeless people, people unable to secure adequate shelter, refugees, migrants, displaced persons, as well as older people with disabilities or underlying health conditions. Young and indigenous people also stand to suffer disproportionately both from the pandemic as such and from its indirect effects. Importantly, many people with lower socioeconomic status already have health problems (e.g. higher rates of chronic illness, compromised immune systems and so on), which constitute important risk factors for developing a more serious manifestation of the COVID-19 infection.

The record levels of unemployment due to lockdown measures implemented to curb virus transmission, social isolation and limits on nonessential travel outside the home, closure of shops and entertainment venues, bans on mass gatherings (i.e. sports and art events) and remote working have cumulatively contributed to psychological distress, promoting a myriad of 'problem behaviours' such as increased alcohol use, excess smoking, physical inactivity, as well as associated physical problems (i.e. back pain through poor ergonomic posture, scaled-back access to health services and so on).

COVID-19 AND MENTAL HEALTH

Apart from the broad global mental health effects of the pandemic, SARS-CoV-2 has caused an additional mental health burden directly linked to the COVID-19 infection. To illustrate, nearly 20% of COVID-19 survivors develop mental health problems, that is anxiety and depression, very early in their convalescence period (14–90 days post diagnosis), with 5.8% developing the first episode of a psychiatric disorder. The incidence of a first diagnosis of dementia in the 14–90 days after COVID-19 diagnosis is 1.6%

[a]Department of Neuroscience, Psychology and Behaviour, University of Leicester, [b]The Evington Centre, Leicestershire Partnership NHS Trust, [c]College of Life Sciences, University of Leicester, [d]Leicestershire Partnership NHS Trust, Leicester and [e]Cambridge Intellectual & Developmental Disabilities Research Group, Department of Psychiatry, University of Cambridge, Cambridge, UK

Correspondence to Elizabeta B. Mukaetova-Ladinska, MD, PhD, MRCPsych, Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester LE1 7RH, UK. E-mail: eml12@le.ac.uk

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KEY POINTS

- The COVID-19 infection results in viral-related physical and mental health problems.
- The neurocognitive changes post-COVID infection and pandemic remain poorly understood.
- We provide a review of neurobiological explanation for neurocognitive disorders (defined as per the DSM-5 criteria) post COVID-19 infection/pandemic.
- The mild and major neurocognitive disorder symptoms due to the COVID-19 pandemic provide a unique opportunity to address early changes underlying neurocognitive impairment at both clinical and molecular level.

[95% confidence interval (95% CI) 1.2–2.1] in people older than 65 years [1▪]. A relevant minority of COVID-19 patients have suffered from encephalitis and stroke as a result of the viral infection and delirium has been reported frequently in those patients who required intensive care treatment (reviewed in [2▪]). In addition, the pandemic brought unexpected premature deaths. Over the last year, the SARS-CoV-2 (COVID-19) pandemic has claimed more than 1.25 million lives out of the 54 million infected (2.5%). The death rate is particularly high in the UK, reaching 4% (50 000 deaths in 1.17 million infected, as per the government statistic of 08 November 2020), in contrast to the reported 1.7–2.5% death rate in the Russian Federation and the USA, respectively.

Deaths have been recorded mostly among older people and those with chronic health conditions such as diabetes, respiratory infections, cancer and dementia, indicating that physical and mental frailty alongside old age constitute the main risk factors for SARS-CoV-2 deaths. According to the latest UK figures, COVID-19 accounted for one in 10 deaths in England [23 October 2020 (https://www.ons.gov.uk/]. Living in a care home appears to be the most relevant factor for both an increased risk of COVID-19 infection and consequent death, with Alzheimer's disease patients having a higher risk than those with other neurodegenerative dementias [3▪]. One of the reasons for this state of affairs may be insufficient testing in care homes to detect the virus and stop it from spreading. Also, elderly care home residents may not always show typical symptoms of COVID-19. Joint use of audio and video devices including mobile phones (not sanitised adequately before sharing) has also been mentioned as a source of passing on the viral infection. Additional factors, including social isolation, poor sleeping pattern, anxiety and psychological distress, may have all aggravated the problems in care homes. Although, to date, there is a paucity of research on how this situation has affected the families of the deceased and the wider population, initial reports are starting to emerge reporting that 55% of those who lost loves ones had intense grief reactions (N.M. Melhem *et al.*, unpublished data).

All of the above illustrates the multiple adverse effects of the pandemic on physical and mental health and, in particular, on the development of neurocognitive disorders (Table 1).

DSM-5 CRITERIA FOR NEUROCOGNITIVE DISORDER

As the observed mental health symptoms are a result of a prolonged and repetitive stress situation

Table 1. Causes and risk factors for neurocognitive disorders

Cause	Symptoms, mental health and physical conditions as risk factors for neurocognitive disorder
Societal experiences of living in and with COVID-19 pandemic	Social isolation Nutrition Access to healthcare Stress Intense grief reactions Anxiety OCD Alcohol and drug abuse Autoimmune diseases (RA, T1DM)
Respiratory COVID-19 (respiratory failure or laboratory biomarkers showing inflammation or organ damage)	Hypoxia PTSD Anxiety Depression Physical disability Delirium
CNS COVID-19	Encephalitis Stroke Delirium
Previous Dementia Diagnosis/Down syndrome	Increase in psychological symptoms (communication/mood: apathy, anxiety) Increase in behavioural problems (agitation, compliance with new measures) Altered routine daily activity (i.e. movement, physical inactivity) Faster cognitive decline Caregiver burden (psychological and physical, esp. in rural areas Delirium

CNS, central nervous system; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder; RA, rheumatoid arthritis; T1DM, type 1 diabetes mellitus.

(COVID-19 pandemic), affecting multiple domains of social and personal life, many of them are, thus, trauma inflicted. However, they fall short of the 'Trauma- and Stressor-Related Disorders' diagnosis as per the DSM-5 criteria that includes traumatic events as exposure to actual or threatened death/serious injury/sexual violence and experiencing repeated or extreme exposure to aversive details of the traumatic event [4]. Namely, the DSM-5 clearly states that vicarious trauma cannot be the result of repeated exposure via electronic or print media. It is understandable that the unexpected and emotionally traumatic experiences (caused by social and self-isolation, closure of schools, working from home, families kept apart and so on) and the scale we have and still continue to be witnessing could not have been predicted and considered at the time. However, the protracted repetitive psychological insults, either as result of the infection *per sé* or by proxy have already resulted in long-term mental health constructs within the long-COVID terminology or affecting the cognitive domains.

Neurocognitive disorders (NCDs) are one of these consequences. The latest DSM-5 classification introduced levels of impairment, mild and major. The latter new category encompasses the set of existing cognitive disorders contained in the DSM-IV [5], including dementia and amnestic disorder. The introduction of mild NCDs, as per the DSM-5, aimed to facilitate both clinical diagnostic and therapeutic advances [i.e. early detection and treatment of cognitive decline prior it becoming more pronounced and progress to dementia (major neurocognitive)] and researchers to advance diagnostic and therapeutic opportunities. Most importantly, the latest NCD criteria enable the stratification of NCD categories not only in terms of the known dementia subtypes, that is Alzheimer's disease, vascular dementia, Lewy Body diseases (dementia with Lewy bodies and Parkinson's disease dementia), but also NCD due to (another) medical condition and multiple causes, apart from the substance/medication-induced NCD and unspecified NCD that are also included as diagnoses. The NCD now can also be used for the more subtle cognitive problems including subclinical, and even transient disorders of cognition, or their exacerbation as a result of the psychological response to the pandemic, irrespective of the age at onset (reviewed in [6]). This is of utmost importance to prevent further cognitive deterioration.

Among the number of modifiable dementia risk factors, depression, social isolation, physical inactivity, smoking and diabetes count for 16% of the total of 40% identified modifiable dementia risk factors [7▪▪]. Posttraumatic stress disorder (PTSD) is, similarly, a strong and potentially modifiable risk factor for all-cause dementia. The latest meta-analysis based on nine electronic databases, found PTSD hazard ratio to be 1.61 ($n = 905\,896$; five studies) in veterans, and 2.11 ($n = 787\,782$; three studies) in the general population [8▪]. Obsessive compulsive disorder (OCD) has been described to segregate in families with dementia [9] and late-onset OCD has been reported as a precursor for several neurodegenerative conditions characterized by neuropathological involvement of neocortical and/or basal ganglia areas, including Alzheimer's disease [10], Lewy body dementia [11], fronto-temporal lobe dementia, amyotrophic lateral sclerosis [12] and supranuclear palsy [13]. Furthermore, disruptions in the corticostriatal activity as present in amyotrophic lateral sclerosis, fronto-temporal dementia and supranuclear palsy, also underlie the development of Parkinson's disease [14].

Although the mental health disorders *per sé* are not linked directly to Parkinsonian syndromes, the latest single case reports indicate that the COVID-19 infection alone may present with reduced nigrostriatal dopamine function, and result in acute transient Parkinson's disease in younger people (reviewed in [15▪]) and may suggest a particular susceptibility of the basal ganglia to both stress and nootropism of the SARS-CoV-2 virus. In support of this is the latest study based on a mathematical model demonstrating that the neuroanatomical distribution of small neurological symptoms due to COVID-19 infection, as seen on neuroradiological (MRI) brain scans, spreads outward from the basal ganglia to other cortical (i.e. temporo-occipital cortices) and spinal areas [16], thus placing the subcortex as one of the main brain areas that are susceptible to SARS-CoV-2 infection.

DELIRIUM IN OLDER PATIENTS WITH COVID-19

Delirium is known to be a common presenting symptom for older adults with severe disease in the emergency department but goes undetected in two-thirds of cases [17]. Delirium is an acute state of confusion characterized by altered level of consciousness, disorientation, inattention and other cognitive disturbances. It commonly affects older persons and is associated with adverse outcomes, including prolonged hospitalization and death [18]. Under-detection of delirium during COVID-19 infection may also contribute to the rise of NCD irrespective of the infectious agents, that is SARS-CoV-2 or other untreated medical conditions due to the access to medical care, or being undetected as it is the case for hypoactive delirium [19].

Most of the published evidence on delirium in COVID-19 infection relates to older people, and then predominantly for those presenting with overt, hyperactive delirium. In contrast, reports for delirium incidence and its characteristics in younger people are missing, similarly to those for hypoactive and subsyndromal delirium in both young and older people [2▪]. Bearing in mind that delirium can result in delayed neurocognitive recovery for up to 1.5 years post serious physical illness [20], it is imperative to be timely diagnosed to prevent long-term poor neurocognitive outcomes.

NEUROPATHOLOGICAL MECHANISM OF CENTRAL NERVOUS SYSTEM DAMAGE IN COVID-19 INFECTION AND THEIR RELEVANCE TO NEUROCOGNITIVE DISORDER

Many viral infections can cause serious damage to the structure and function of the central nervous system (CNS), including severe encephalitis due to coronaviruses (CoVs), toxic encephalopathy caused by severe systemic viral infection (e.g. SARS-CoV and SARS-CoV-2) and severe acute demyelinating lesions developing after viral infection [21]. Some viruses (including the SARS-CoV-2) are neurotropic and can invade nervous tissues and cause infections of immune-functioning macrophages, microglia or astrocytes in the CNS [22]. Acute viral infection is also an important cause of this disease, exemplified by a respiratory infection caused by CoVs [23]. Patients with COVID-19 often suffer from severe hypoxia and viremia, which has the potential to cause toxic encephalopathy. Its clinical symptoms are complex and diverse: patients with a mild course of the disease may develop headache, dysphoria, mental disorder and delirium, whereas those seriously affected may experience loss of consciousness, coma and paralysis [24,25].

Hypoxic brain injury

Severe pneumonia can result in systemic hypoxia leading to brain damage. The contributing factors include peripheral vasodilatation, hypercarbia, hypoxia and anaerobic metabolism with accumulation of toxic compounds. These can result in neuronal swelling and brain oedema, which ultimately result in neurological damage [26▪▪,27].

Blood circulation pathway

Proteins of various viruses can often be detected in nervous system tissue samples (such as cerebrospinal fluid or brain), suggesting that viruses can directly invade the nervous system and cause neuronal damage [28]. A typical virus enters the CNS through the blood circulation, with the virus multiplying in the vasculature and choroid plexus [29▪]. The virus is subsequently released into the blood stream to reproduce in mononuclear macrophages throughout the body. The secondary release into the blood may increase the permeability of the blood–brain barrier through the produced cytokines, thereby promoting the virus to enter the brain and cause viral encephalitis [28]. The low detectable SARS-CoV-2 viral load in the brain tissue postmortem [30▪▪] argues for blood-derived viruses presence in some of them.

Neuronal pathway

The neuronal pathway is an important vehicle for neurotropic viruses to enter the CNS. Viruses can migrate by infecting sensory or motor nerve endings, achieving retrograde or anterograde neuronal transport through the motor proteins, dynein and kinesins [31]. One of the important examples of a neuronal pathway is that of olfactory neuron transport. The unique anatomical organization of olfactory nerves and the olfactory bulb in the nasal cavity and in main olfactory bulb in forebrain effectively makes it a channel between the nasal epithelium and the CNS [28]. As a consequence, SARS-CoV-2 can enter the brain through the olfactory tract in the early stages of infection [32]. Anosmia and chemosensory dysfunction were reported as both one of the first clinical symptoms and being at least 10-fold more common in COVID-19 infection [33▪]. Although the neuroimaging reports are not conclusive, anosmia has been linked to atrophy [34] or hypometabolism of the olfactory bulb (Niesen *et al.*, unpublished data), as well as transient morphological changes in the olfactory bulb [35]. These observed clinical and neuroradiological changes may be in particularly important for the early detection of post-COVID-19 NCDs, as olfactory dysfunction has been now associated with amnestic mild cognitive impairment in HIV adults [36▪].

One of the dopaminergic pathways also originates in the olfactory bulb and it makes it, thus, another candidate for SARS-CoV-2 entry and propagation into the CNS. Dopaminergic receptors modulate the innate immune response to a viral infection (i.e. HIV [37], Ebola virus, [38]) and some viruses, such as the Japanese Encephalitis Virus (JEV), utilize the dopaminergic signal transduction pathway to increase neuronal susceptibility to infection [39]. It is, thus, not surprising that these viruses (i.e. JEV) are found in dopaminergic rich areas, such as thalamus and the midbrain (reviewed in [40]) and

therapies targeting dopamine receptors are also being investigated to mitigate viral infections [38]. SARS-CoV-2 may utilize the same pathway to gain entry in the human body [41] and also influence the autoimmune innate response.

IMMUNE-MEDIATED INJURY AND ROLE FOR CYTOKINES

Nervous system damage caused by viral infection may be mediated by the immune system [22]. The cytokine storm is due to the release of high levels of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF) and chemokines (CCL-2, CCL-3 and CCL-5) by respiratory epithelial and dendritic cells, and macrophages [42▪]. COVID-19 disease severity is characterized by increased IL-2, IL-7, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α and hyperferritinimia. The release of IL-6 causes vascular leakage, activation of complement and coagulation cascade, suggesting that mortality in COVID-19 infection might be due to virally driven hyperinflammation [43].

The persistence of COVID-19 infections and its ability to infect macrophages, microglia and astrocytes in the CNS are particularly important. A neurotropic virus can activate glial cells and induce a pro-inflammatory state [44]. IL-6, an important member of the cytokine storm, is positively correlated with the severity of COVID-19 symptoms [43]. In addition, experiments have confirmed that primary glial cells cultured *in vitro* secrete a large amount of inflammatory factors such as IL-6, IL-12, IL-15 and TNF-α after being infected with CoVs [23]. Furthermore, activation of immune cells in the brain will cause chronic inflammation and brain damage.

THE CHOLINERGIC ANTI-INFLAMMATORY PATHWAY AND THE VAGUS NERVE

The cholinergic system plays an important role in supressing excessive inflammation, as shown in experimental models of disease such as sepsis, ischaemia-reperfusion injury, haemorrhagic shock, abdominal surgery and infections (i.e. pancreatitis, colitis; [45]). The cytokine storm and the worsening of patients' health status can be dampened or even prevented by specifically targeting the vagal-driven cholinergic anti-inflammatory pathway (CAP) [46]. The CAP is a concept that involves an anti-inflammatory effect of vagal efferents by the release of acetylcholine (ACh) [47]. Nicotinic acetylcholine receptor alpha7 subunit (α7nAChRs) is required for ACh inhibition of macrophage-TNF release and cytokine modulation [48]. Apart from TNF, other pro-inflammatory cytokines such as IL-6, IL-1β were significantly decreased by vagus nerve stimulation (VNS) but not the anti-inflammatory cytokine IL-10 [46].

The vagus nerve, the longest nerve of the organism, innervates the lungs and the gastrointestinal tract, two organs which are targeted by SARS-CoV-2 (COVID-19). ACh released at the distal end of the vagus nerve acts on intrinsic neurons of the enteric nervous system, for example at the level of the gastrointestinal tract to inhibit the release of TNF by macrophages [49]. The intracellular signalling of α7nAChRs inhibits transactivational activity of the transcription factor NF-kB p65 [48] and activates Jak2 and STAT3 signalling [50]. Consequently, α7nAChRs could be a candidate, as they are expressed on immune cells regulating antigen-specific antibody and pro-inflammatory cytokines production and likely regulate the intensity of immuneresponses [51▪▪].

ROLE FOR CYTOKINES AND CHOLINERGIC SYSTEM IN NEUROCOGNITIVE DISORDER

Cognitive changes are present in both infection and neurodegenerative diseases and are associated with increased inflammatory cytokines. The cytokine and chemokine disbalance not necessarily is initiated directly from an infection, but can also arise from stressful conditions [52,53], and results in a variety of health consequences (Fig. 1), due to neurotransmitter and hormonal imbalance, neurobiological changes and even autoimmune illnesses (including rheumatoid arthritis, Type 1 diabetes mellitus).

Elevation of proinflammatory cytokines, including IL-1, IL-6 and TNF-alpha, is associated with fatigue, depression and anxiety, as well as hostility and irritability (also referred as sickness behaviours), irrespectively of the cause of the neuropsychiatric symptoms, that is whether they are triggered by an infection or prolong and repetitive stress. In support of this is the wide spectrum of cytokines and chemokines described in PTSD, that is higher levels of peripheral cytokines (IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-α) than those detected in age and sex-matched healthy controls [52], suggesting a generalized inflammatory state in these patients [54▪▪]. Similarly, altered immune response, though with somewhat conflicting results, has been described in OCD (reviewed in [55,56]). Nevertheless, the latest study demonstrated plasma levels of IL-1β, IL-6 and TNF-α were significantly higher in patients with OCD than the healthy controls [57].

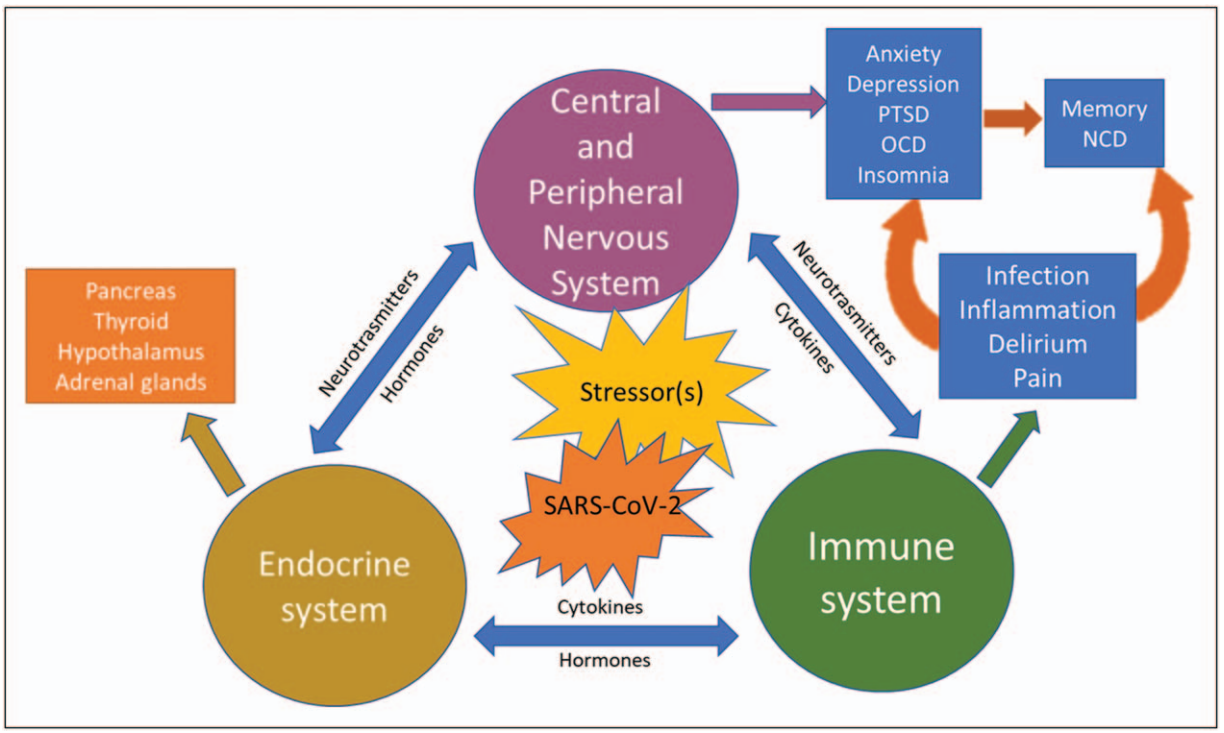

FIGURE 1. Impact of infective (i.e. SARS-CoV-2) and psychological stressors on the nervous, immune, and endocrine systems. For a more detailed explanation, see the main text. NCD, neurocognitive disorder; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.

The vagal nerve has been now considered as one of the potential viral CNS access routes in COVID-19 [30▪▪]. This is in particularly important in relation to long-term consequences of SARS-CoV-2 infection, including the development of NCD in the COVID-19 survivors. The TNF-α in physiological condition is expressed only in minor, hardly detectable levels in the brain, and is involved in higher cognitive functions, such as memory and learning. Its increase in infection and in stress conditions [58] is ameliorated by acetylcholine, or via the stimulation of the vagal nerve, that attenuates the cytokine production. It is the alpha7 nicotinic acetylcholine receptors (α7nAChRs) that are involved in mediating this anti-inflammatory response to insults due to stress, sepsis, ischemia, haemorrhage and so on.

Majority of people with dementia are now treated with antidementia drugs, predominantly cholinesterase inhibitors (i.e. donepezil, rivastigmine and galantamine). Although these drugs enhance the neurodegeneration-induced working memory decline, they appear not to be as efficient when compared to the α7nAChRs. Namely, in animal studies, the α7nAChR activation has been reported to restore both the amyloid Aβ42 induced long-term potentiation [59] and improve the Aβ25-35-induced cerebral blood flow [60]. However, the observed increase in cortical α7nAChRs may be an indirect effect of increased ACh levels *in vivo*, thus further providing support for lack of receptors activation in dementia [61]. This suggests that the antidementia drugs alone may not be sufficient to improve the anti-inflammatory and autoimmune response once the innate ACh has declined and may explain the failure of cholinesterase inhibitors clinical trials in delirium [62].

CONCLUSION

Mild NCD symptoms as a result of the COVID-19 pandemic provide a unique opportunity for researchers to address the early changes that underlie neurocognitive impairment at a clinical and molecular level and to longitudinally follow them with a view to modify their outcomes. From the studies published to date, we know that the biological markers for major NCD of Alzheimer's type develop several decades prior to overt clinical symptoms [63] and it is the convergence of multiple diseases that underpins most clinical dementia syndromes [64].

The stress related to the COVID-19 pandemic affects similarly the cytokine system and cholinergic pathways, resulting in depression and poor

cognitive performance. It is, thus, important to raise awareness for these consequences among the wider population and put into place ways of increasing people's resilience across the lifespan. Identifying biomarkers that may aid in gauging physical and mental resilience will facilitate timely interventions in preparedness for future similar health events.

The properties of SARS-CoV-2 as both a catalyzer and accelerator to brain protein aggregation [65] is another research opportunity for the dementia field in preventing the aggregate prone brain proteins, such as tau protein, β-amyloid and α-synuclein, to form the insoluble and neuronal detrimental deposits. In doing so, we can expect a new generation of therapeutics to be developed, focused on biological mechanisms to prevent and eventually reverse the neurodegenerative processes occurring with ageing and dementia.

The currently ongoing preclinical research to expand the VNS treatment in inflammatory disorders [66] is an overlooked opportunity for the management of both the SARS-CoV-2 infection and the stress-related psychological consequences living with the pandemic. Targeting the α7nAChRs through VNS could hence be another area of interest in the management of COVID-19 related physical (respiratory and gastrointestinal symptoms) and mental health symptoms, including NCD irrespective of its cause and severity.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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