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REVIEW ARTICLE

SARS-Cov-2 Damage on the Nervous System and Mental Health

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Abstract: The World Health Organization declared the pandemic situation caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) in March 2020, but the detailed pathophysiological mechanisms of Coronavirus disease 2019 (COVID-19) are not yet completely understood. Therefore, to date, few therapeutic options are available for patients with mild-moderate or serious disease. In addition to systemic and respiratory symptoms, several reports have documented various neurological symptoms and impairments of mental health. The current review aims to provide the available evidence about the effects of SARS-CoV-2 infection on mental health. The present data suggest that SARS-CoV-2 produces a wide range of impairments and disorders of the brain. However, a limited number of studies investigated the neuroinvasive potential of SARS-CoV-2. Although the main features and outcomes of COVID-19 are linked to severe acute respiratory illness, the possible damages on the brain should be considered, too.

Keywords: SARS-CoV-2, COVID-19, mental health, neurological diseases, brain disorders, neuroinvasive potential.

1. INTRODUCTION

January of 2020 corresponds to the emergence of the new coronavirus SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) [1]. On March 11, 2020, the World Health Organization declared Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 as a pandemic disease [2].

The clinical manifestations of the COVID-19 range from asymptomatic infection to severe disease characterized by Acute Respiratory Distress Syndrome (ARDS), septic shock, and multi-organ failure with possible fatal outcome [3].

Several reports documented that along with systemic and respiratory symptoms, a lot of patients with COVID-19 suffer from neurological symptoms [4]. On March 4, 2020, Beijing Ditan Hospital reported for the first time a case of viral encephalitis caused by the novel CoV and scientists proved the presence of SARS-CoV-2 in the cerebrospinal fluid by genome sequencing. Autopsy reports revealed brain tissue edema and partial neuronal degeneration in deceased patients [4, 5]. Moreover, Mak and co-workers established that the cumulative incidence of psychiatric disorders was up to 58.9% (53/90) after the SARS-CoV-2 outbreak [6]. Among these 53 survivors, 40 (44 % of 90) and 43 (47.8% of 90) patients suffered from depressive disorders and Post-Traumatic Stress Disorder (PTSD) at some time point after their infection, respectively [6].

This showed that COVID-19 might cause damage to the nervous system [7]. In the context of the ongoing COVID-19 pandemic, clinicians need to be informed of the effects of various CoV infections on the Central Nervous System (CNS).

The current paper aims to summarize the main SARS-CoV-2 impact on the brain functions related to COVID-19 and to yield future directions for the development of mental disorders treatments after COVID-19.

2. NEUROLOGICAL INVOLVEMENT IN COVID-19

The COVID-19 demonstrated major effects on the CNS and it is very likely to observe neurological manifestations in these patients [8-18].

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Recent publications reported the onset of various neurological symptoms in COVID-19 patients such as headache (11-13%), dizziness (8-17%), and altered state of consciousness (8-9%) [19]. At least 5% of patients showed peripheral nervous system abnormalities, including hypogeusia, hyposmia or anosmia and neuralgia, and less commonly, other symptoms acute cerebrovascular disease (3%), epilepsy (1%), and ataxia (1%) [4]. Several post-mortem studies have identified SARS-CoV expression in neurons and morphological alteration in the brain tissue, including edema, and inflammation [4,19]. Although uncommon, previous cerebrovascular disease can represent a risk factor for poor prognosis [19]. A retrospective study of Chen and co-workers conducted in Wuhan, China described the characteristics of 99 patients hospitalized with SARS-CoV-2 pneumonia [19] and reported anxiety and headache as neurological symptoms in 9% and 8%, respectively [4,19]. Mao and co-workers found that 36.4% of 214 patients had neurological symptoms directly related to the disease severity (45.5% in severe vs. 30.2% in non-severe cases) [4]. Dizziness and headache have been observed in patients with central symptoms and among the peripheral symptoms (8.9%), the most common were hypogeusia and hyposmia [4]. Significant differences were found in the number of patients with stroke (5 [5.7%] *vs*. 1 [0.8%]), alteration of the state of consciousness, severity of symptoms (13 [14.8%] *vs* 3 [2.4%]) and muscle damage (17 [19.3%] *vs* 6 [4.8%]), based on COVID-19 severity [4]. In addition, four case reports showed neurological involvement in COVID-19 patients: one 79-year-old patient was hospitalized with fever, cough, and altered consciousness due to massive intracerebral bleeding in the right hemisphere which could be explained by the presence of angiotensin-converting enzyme 2 (ACE2) receptors in the vascular endothelium [20]. The regulating function of ACE2 receptors could have been reduced by the virus, leading to an increase in arterial pressure and, consequently, vessel rupture [20].

A recent retrospective analysis performed on electronic health records found an increased incidence of neurological or psychiatric diseases among more than 236000 patients in the 6 months after the diagnosis of COVID-19, higher in those admitted to intensive care unit [21]. However, the risk was also increased in patients not requiring hospitalization.

In summary, recent evidence suggests that SARS-CoV-2 is associated with neurological dysfunction in patients with serious (but also non-serious) manifestations of COVID-19, whose mechanisms have to be clarified yet. Considering the high spread of the virus, the evidence above raises questions about possible long-term neurological consequences in COVID-19 patients.

Thus, longitudinal studies are urgently needed to determine whether the COVID-19 pandemic may lead to an increased incidence of life-long damage (including neurodegenerative disorders) in infected individuals.

3. NEUROTROPIC POTENTIAL OF SARS-COV-2

While Middle East respiratory syndrome coronaviruses (MERS-CoV) has never been isolated from neural tissues or fluids in affected human beings [22,23], the presence of virus particles and genome sequences in the brain was described for both Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and SARS-CoV-2 viruses [24-26].

Viruses may enter the CNS through three distinct routes: hematogenous dissemination, lymphatic system [27,28], or neuronal retrograde/anterograde dissemination [29,30]. Moreover, to be neuroinvasive, viruses such as SARS-CoV may use all the entry routes from the periphery [31].

In a hematogenous way, a virus can infect endothelial cells of the Blood-Brain-Barrier (BBB) or cells of the immune system for dissemination into the CNS [29, 32]. However, less than 1% of patients had a detectable level of SARS-CoV-2 in the blood, thus other routes of virus entry are of greater importance [33]. A virus can infect neurons in the periphery and retrogradely spread to CNS through the transport machinery within neurons [29,31]. *In vitro* studies showed the SARS-CoV-2 within neuronal soma and neuritis, supporting the neuronal retrograde transport and the trans-synaptic transfer [34,35].

The detailed data about the direct damage by the SARS-CoV, MERS-CoV, and SARS-CoV-2 in the CNS are presented in Table **1** [24-27, 35-51].

Moreover, SARS-CoV, MERS-CoV, and SARS-CoV-2 have shown to invade the CNS after an intranasal infection, primarily through the olfactory bulb, and then spreading to the thalamus and brainstem [36, 52, 53]. In addition, the viruses may directly enter the Cerebrospinal Fluid (CSF) crossing the non-neuronal olfactory epithelium cells [54]. The transmission from the respiratory mucosa to the nucleus of the solitary tract and the nucleus ambiguous in the brain stem by vagal dissemination has shown for some viruses (influenza A). However, the data regarding SARS-CoV-2 vagus nerve dissemination are absent, and further research is required [29].

According to Varga and co-workers (2020), SARS-CoV-2 can infect endothelial cells and cause endothelial dysfunctions and lymphocytic endotheliitis in the heart, kidney, lung, liver, and submucosal vessels of the small intestine [55]. Therefore, the virus can directly enter the brain thanks to the lymphatic vessels lining the dural sinuses, which can carry both fluid and immune cells from the CSF and are connected to the deep cervical lymph nodes [56].

Regardless of the mechanisms, patients with COVID-19 may develop some CNS and Peripheral Nerve System (PNS) symptoms, ranging from mild to fatal complications [57]. The major mechanisms of the virus damage to the CNS can be summarized as follows [57]:

- A virus-induced neuroimmunopathology, related to the Systemic Inflammatory Response Syndrome (SIRS) which frequently leads to multiple organ dysfunction (including CNS) and disseminated intravascular coagulation (a) and (b) generation of an autoimmune reaction by an adaptive immune response directed against host epitopes or proteins [57];
- A virus-induced neuropathology, characterized by a viral infection of CNS cells, leading to direct tissue damage or *via* the recruitment and activation of other

Table 1. The direct damage by the SARS-CoV, MERS-CoV, and SARS-CoV-2 in the CNS.

Type of Viruses	Virus Particles and Genome Sequences in the Brain	Demyelination of Nerve Fibers	Infiltration of Monocytes and Lymphocytes in the Brain	Degenerating and Dying Neurons	Capable of Infecting Human Neuronal Cells in *in vitro* Cell Lines	Lymphatic System	Cerebrospinal Fluid	Neurological Manifestations
SARS-CoV	Gu *et al*., 2005; Xu *et al*., 2005; Zhang *et al*., 2003	Ding *et al*., 2003	Ding *et al*., 2003	Xu *et al*., 2005	Yamashita *et al*., 2005	Nagata *et al*., 2007	Lau *et al*., 2004; Hung *et al*., 2003	Sporadic case reports
MERS-CoV	No	No	No	Li *et al*., 2016	Chan *et al*., 2013	No	No	Sporadic case reports
SARS-CoV-2	Bulfamante *et al*., 2020; Kumari *et al*., 2021; Matschke *et al*,. 2020; Paniz-Mondolfi *et al*., 2020; Song *et al*., 2021	Diez-Porras *et al*. 2020	No infiltration (Song *et al*., 2021) The presence of infiltrations (Kirschenbaum *et al*., 2020; Matschke *et al*., 2020)	Matschke *et al*., 2020; Song *et al*., 2021	Song *et al*., 2021	Bostancıklıoğlu, 2020ab	Lewis *et al*., 2021; Espíndola *et al*., 2020 (undetectable or extremely low levels); Virhammar *et al*,. 2020	Frequent

immune cells, the local production of pro-inflammatory cytokines and induction of apoptosis [31,57].

In vitro studies have shown that SARS-CoV, SARS-CoV-2, and MERS-CoV [58] can directly induce neuronal death through either an inflammatory response or autophagy. The SARS-CoV also demonstrated to infect monocytes/macrophages [24,59] and dendritic cells, by which it modulates innate immunity [60] and reach and maintain itself in the CNS [31]. Preclinical studies on transgenic mice showed that SARS-CoV-2 can infect neurons and cause their death in an ACE2-dependent manner; in particular, cells derived from pluripotent stem cells and dopaminergic neurons, but not those of the cerebral cortex, or microglia, demonstrated to be susceptible to SARS-CoV-2 infection [61]. Currently, the penetration of SARS-CoV-2 into the CNS through the damaged BBB can not be ruled out, facilitated by cytokines associated with COVID-19, including interleukin (IL)-1β, IL-6, IL-17 and tumour necrosis factor-*alpha* (TNF-α) [61]. Moreover, the size of viral particles (80-120 nm) is higher than the size of endothelial windows in the hypothalamus, but capillary cells express ACE2, and thus can potentially contribute to the penetration of the virus in the hypothalamus [62]. If this mechanism will be confirmed, the hypothalamus can serve as a gateway for the virus to the entire brain due to its broad connection.

Whether the neurological symptoms associated with COVID-19 may be consequent to the direct viral invasion of the CNS which needs to be further investigated. While some authors postulated that the brain is a site for the high replicative potential for SARS-CoV-2, other studies demonstrated that although SARS-CoV-2 has neurotropic properties and can infect neurons in patients, it did not trigger an immune response in the brain, typical of other neurotropic viruses [35]. The latter point of view is confirmed by the lack of association between the presence of SARS-CoV-2 in the CNS and the severity of neuropathological changes [63].

Thus, although the exact pathophysiological processes responsible for the neurological impact of COVID-19 are not completely understood, virus-induced neuroimmunopathology can be considered as its main mechanism.

The CS originating from the anti-virus immune response plays an important role in the development of various complications. CS has been reported in several viral infections, including influenza H5N1 and H1N1 viruses, SARS-CoV, and MERS-CoV viruses [64]. SIRS in patients with COVID-19 leads to the loss of integrity in the BBB and initiates a strong neuroinflammatory response, mainly sustained by IL-1, IL-6, and TNF-α, and characterized by reactive astrogliosis and microglial activation with subsequent demyelination and neuronal damage [65-67].

Moreover, central and peripheral pro-inflammatory and anti-inflammatory cytokines and C-reactive protein, are key elements in the physiopathology of several neuropsychiatric disorders, such as depression and bipolar disorder [68]. Thus, significant neurological and cognitive abnormalities as well as neuropsychiatric symptoms may occur or be exacerbated by the proinflammatory priming of microglia in ARDS survivors [69].

According to the study of Hopkins *et al*. (2005), the majority of ARDS survivors develop neurocognitive sequelae within 2 years from hospital discharge, including moderate to severe depression, anxiety [70], and memory impairment [71]. During the COVID-19 pandemic, ARDS was associated with cognitive impairment, such as a decline in verbal memory abilities [72]. Thus, ARDS can cause significant long-term, brain-related morbidity with neurocognitive im-

pairments, possibly related to the development of hypoxemia [73,74].

Finally, virus-neutralizing antibodies cross-reacting with brain tissue (including neuronal and glial antigens) have been detected in patients with COVID-19, suggesting a possible role of autoimmune reaction in the development of neurological complications [75,76]. In this context, it is noteworthy that immune-mediated neuropathies such as Guillain-Barré Syndrome have been reported as COVID-19 complications due to presumably a post-infectious immunological response [77-85].

Overall, the high prevalence of neurological symptoms in COVID-19 patients (about 40%) suggests the link between the SARS-CoV-2 infection and CNS pathologies [57]. However, the possible neurotropism and direct neuronal toxicity of SARS-CoV-2 requires elucidation but, as well as the effects of the systemic infection and the autoimmune response.

4. INDIRECT EFFECT OF COVID-19 ON THE CNS

It is well-known that inflammation has a major role in tissue homeostasis and protection of the injury [86]. It involves defensive cell mobilization processes, such as macrophages, which release inflammatory mediators such as cytokines, limiting the spread of pathogens and initiating tissue repair. As regards CNS inflammation, the microglial cells, along with astrocytes, are involved in mediating and modulating inflammatory processes [87]. Microglia acts as the "macrophages" in the CNS and can be activated in response to pro- or anti-inflammatory signals [88]. Following an immunological stimulation, these cells release inflammatory factors such as pro-inflammatory cytokines, eicosanoids/prostanoids, nitric oxide (NO) and neurotrophic factors that facilitates tissue restoration while acting as a defense mechanism [89]. However, if inflammation persists, it can lead to increased microglial activation, with pro-inflammatory cytokine production and oxidative stress [89] resulting in the destruction of healthy tissue and, as a result, neurological damage [90,91]. It is known that oxidative stress (*via* the production of reactive oxygen and nitrogen species) is caused by the increase in peripheral and central pro-inflammatory cytokines, such as TNF-α, IL-6, and interferon (IFN) [92,93], inducing apoptosis [92], and ultimately alterations in neurotransmitter signaling [94,95]

COVID-19 is linked to an exaggerated immune response, up to the SARS-CoV-2-induced cytokine storm, negatively associated with patient outcome. The high serum cytokine concentrations negatively regulate T cell survival and proliferation [96]. Indeed, T cell exhaustion has been proposed as a result of the SARS-CoV-2-induced cytokine storm, found to be higher in seriously infected patients [96]. As previously mentioned, the downstream effects of such a cytokine storm may include increased neuro-inflammation, decreased neuroplasticity and monoaminergic neurotransmission, and increased neuronal death [97].

These mechanisms have demonstrated to play a role in the development and progression of psychiatric diseases, too [93, 95]. Several psychiatric disorders have been linked to viral infections, though no specific virus has been identified as a causative agent [98, 99]. For example, a high pro-inflammatory cytokines level has been observed in the individuals suffering from psychotic [100,101], mood [102], and anxiety disorders [103,104] compared to healthy controls, while the therapeutic use of pro-inflammatory cytokines, such as IFN, is known to induce depressive symptoms. A similar phenomenon has been observed in the human immunodeficiency viruses (HIV)-positive patients, and it is thought to be responsible for the high prevalence of depression in these patients [97,105]. Furthermore, maternal influenza has been linked to schizophrenia and bipolar disorder with psychotic features [106]. Early life infection with influenza or other pathogens has been linked to Obsessive Compulsive Disorder (OCD) [107]. Moreover, the human endogenous retrovirus Wenv (HERV-Wenv) appears to play a role in the neurodevelopment of schizophrenia [108], by controlling immunological NO synthase expression [109], increasing NO production and microglial migration [110, 111]. Overall, these neurobiological changes are linked to increased oxidative stress, leading to monoamine changes associated with positive and negative schizophrenia-related symptoms [112, 113].

However, a recent longitudinal study found no link between common viral infections and an increased risk of mental disorders [114].

Depression symptoms increased threefold in the United States from pre-COVID-19 to post-COVID-19 era [115], with similar findings in other countries [116, 117]. The psychosocial effects of SARS-CoV-2 are causing an increase in the prevalence of anxiety disorders, which may contribute to the development of many other psychiatric diseases, such as mood disorders (depression and bipolar disorder) and schizophrenia [118,119]. Although the precise cause of this increase is unknown, these patients will usually receive standard pharmacological treatments for these mental disorders, such as antidepressants, anxiolytics and antipsychotics.

5. INDIRECT PSYCHIATRIC HARMS

The COVID-19 pandemic exerted a pervasive impact on all aspects of society, with possible consequences on mental health. We can distinguish the mental health problems that occurred during the COVID-19 pandemic according to the involved population.

5.1. General Healthy Population

The burden of mental health problems among the general population during COVID-19 has been reported by several studies [8-11]. Many of these studies have shown that the general healthy population who suffered from different levels of psychosocial stressors due to the COVID-19 pandemic had developed mental health diseases [9-11]. In particular, the fear of ongoing outbreaks, the exposure or close contact with someone with COVID-19 affected mental health and wellbeing among the general population [12,13]. The increase of the likelihood in the mental and psychological problems such as depression and anxiety, as well as a decrease in the availability of psychological intervention, can occur not only with self-quarantine measures but also without proper medical supervision [14, 15]. Some of the social stressors, such as fear of death, fear of losing loved ones,

loss of social connection, job loss and homelessness due to quarantine and self-isolation, can not only increase the burden on the mentally ill people but also cause serious mental illness (depression, anxiety) in previously healthy people [14-16]. In severe cases, all these problems can lead to post-traumatic stress disorder, but also or thoughts or attempts of suicide.

5.2. COVID-19 Patients and Other Factors

Several studies suggest that patients who tested positive for SARS-CoV-2 can have mental health problems [8, 17-18, 117,120]. Patients with a COVID-19 diagnosis had profound psychological distress, anxiety, depression, and other mental health problems compared to those who were not infected [18,117,120]. The fear of adverse health outcomes due to COVID-19 may affect mental health, highlighting the mental health aspect of a physical health problem. Anxiety can be so suppressed, that it can cause paranoia and nihilistic delusions, and relapses may occur in patients with bipolar disorder and schizophrenia [121]. Moreover, a high level of stress and an alarming level of psychological distress persisted in patients after SARS-CoV-2 even after a year [122]. Pandemic simulations emphasize the importance of reducing social contact, as this can limit the spread of the disease, so a quarantine and self-isolation strategy is right and necessary [123]. According to Chinese studies conducted to date on the mental health of different age groups of people during the COVID-19 pandemic, mixed conclusions can be drawn [124,125]. Self-isolation led to a reduction in social interactions, which did not happen during the Spanish flu pandemic in 1918-1919 years. Based on the data obtained in studies on humans [126] and non-human mammals (such as prairie voles) [127], we can say that social isolation can lead to an increase in depression.

The younger and older age people had different risks of developing mental health problems. Additionally, gender, marital status, education, and economic challenges, including unemployment, loss of income, or economic opportunity due to lockdown or other social measures, were associated with mental health problems [12, 125, 128-130]. Furthermore, living near outbreak areas impacted mental wellbeing [131]. In contrast, comorbidity like cerebrovascular diseases, heart diseases, diabetes, and other chronic conditions as a risk factor and mental diseases made individuals highly susceptible to mental health problems during this pandemic [8,120,124]. Spending more time on social media or news related to COVID-19, poor social support, stigma, insufficient personal precautions, and working in COVID designated departments were associated with a high risk of mental health problems [17,117,130]. Social exclusion prevents many people in need of psychological help from getting it, as access to psychological health resources is limited. Therefore, special psychological services for the quarantine period and self-isolation would be created to address this issue during COVID-19 pandemic.

5.3. COVID-19 and Healthcare Professionals

The psychological health condition of healthcare workers during a pandemic should not be forgotten. According to reports of the 2003 SARS-CoV outbreak and early COVID-19 data, healthcare workers experience psychological consequences, such as stress, anxiety, and fear [119,120], determined by uncertainty about the duration of the crisis, the lack of proven therapy or vaccines, and the potential shortage of health resources, including equipment for personal protection. Medical workers also worry about the consequences of social distancing, balanced by aspiration to be present in their families, and the possibility of individual and family sickness. A large amount of easily accessible information and misinformation on the Internet and social networks exacerbates all these problems. Medical workers may experience stress from providing direct care to patients with COVID-19 knowing someone who became ill or died from this disease or from having to undergo quarantine or isolation [132,133]. To ensure a healthy and strong workforce, it is important to provide psychological well-being, which can be achieved through a mitigation strategy for all scenarios. Thus, it is not surprising that those who are most at risk of psychological disorders include health workers working with patients with COVID-19. According to a survey in China, in which 1257 medical workers participated, the medical staff working with COVID-19 patients have more considerably more diagnoses of depression, anxiety, insomnia, and distress than providers who did not take care of the patients directly [132]. In another observational study of 180 health workers, anxiety and stress levels negatively affected sleep quality and self-efficacy in physicians directly working with patients with COVID-19 [134]. Importantly, the workers who have reported a strong social support had a higher level of self-efficacy and a lower degree of stress and anxiety [134]. A qualitative study by medical workers during a pandemic severe acute respiratory syndrome in 2003 in Toronto revealed that concerns about their professional responsibility to care conflicted with personal safety and the risk of infection of close persons [135]. This underlines the complexity of the problems that healthcare workers face and the dissonance that they need to coordinate. Those who do not directly care for patients with COVID-19 are not immune to psychological effects, and may be injured at a level corresponding to the general population [136]. This fact may be due to their concern for patients with the COVID-19, their colleagues at risk, and about themselves and their families [135, 136]. Reviewing the data, Brooks and co-workers (2020) recommended strategies that can minimize the psychological consequences of self-isolation through good communication, limiting their time to a minimum, providing adequate materials and practical advice on how to overcome stressful conditions and boredom [121].

6. ONGOING STUDIES

In order to fill the knowledge gap about the neurological and psychiatric involvement in COVID-19, a lot of studies are ongoing worldwide (Tables **2a** and **2b**). In particular, currently, 38 observational (with prospective, retrospective, cross-sectional design) and 28 interventional studies (randomized, non-randomized, open label, single blind, double blind, controlled trials) are recruiting adult and/or pediatric patients. The aim of these studies is commonly the detection of neurological and psychiatric manifestations, sometimes supported by specific diagnostic exam, imaging studies and/or dosage of biomarkers.

Table 2. Observational (a) and interventional (b) studies about neurological and psychiatric manifestations in patients with SARS-CoV-2 infection (www.clinicaltrials.gov)

(a)

ID	Status	Study Design	Number of Patients	Age Range (years)	Intervention	Outcome Measures	Start date/ Estimated Completion date
NCT04368390	Recruiting	Case-only	100	18 and older	-	Neuroradiological analysis of patients' brain MRI	April 2020 – April 2021
NCT04681755	Recruiting	Retrospective, case-only	55	18 and older	-	Retrospective analysis of the neurological disorder after severe SARS-CoV-2 infection	May 2020 – May 2021
NCT04448054	Recruiting	Prospective, case-only	100	18 and older	-	Percentage of patients included with at least one sign of neuromeningeal, neurosensory or neurovascular involvement on MRI imaging	May 2020 – November 2021
NCT04386083	Recruiting	Retrospective Cohort	1342	19 and older	-	Neurological Manifestations and Associated Symptoms	June 2020 - March 2021
NCT04643548	Recruiting	Prospective Cohort	20	18 and older	-	Dosage of biomarkers typically explored in intensive care unit delirium; Dosage of neuronal injury markers; Delirium assessment; Coma assessment; Pupils characteristics; Neurological abnormalities	October 2020 - August 2021
NCT04581577	Recruiting	Cross-sectional, Cohort	75	16 and older	-	Qualitative evaluation of the perceived clinical and psychosocial impact of the Covid-19 pandemic in patients with neuro-muscular and neurological disorders	September 2020 - April 2021
NCT04418609	Recruiting	Cohort	30	18 and older	-	Prevalence of neurological complications; Prevalence and outcome of severe neurological complications; Impact of neurological complications; Characteristic patterns in cerebral imaging and electroencephalography (EEG), as well as cerebrospinal fluid (CSF)	May 2020 - May 2022
NCT04745611	Recruiting	Prospective, case-only	400	18 and older	-	Life participation (social, occupational, mobility) measured by the Utrecht Scale for Evaluation of Rehabilitation-Participation - Restrictions subscale (USER-P-R). Quality of life measured by the EuroQol-5D-5L (EQ-5D-5L). Presence of MRI abnormalities; Neurological symptoms; Deficits in cognition, in memory, in visual attention and task switching, in selective attention, cognitive flexibility and processing speed, in working memory, attention and executive function; Change in depression/anxiety; Change in post-traumatic stress symptoms; Change in family burden; Change in family quality of life	December 2020 - September 2021
NCT04362930	Recruiting	Retrospective Cohort	2000	18 and older	-	Frequency of central or peripheral neurological or psychiatric symptoms; Progression of pre-existing neurological or psychiatric pathologies	April 2020 - April 2022

(Table 2a) contd….

ID	Status	Study Design	Number of Patients	Age Range (Years)	Intervention	Outcome Measures	Start Date/ Estimated Completion Date
NCT04379089	Recruiting	Prospective Cohort	1000	Up to 17	-	Prevalence of neurological manifestations and association with outcome; child and family health functions and health-related quality of life (HRQOL) outcomes	April 2020 - December 2021
NCT04883216	Recruiting	Prospective, case-only	1120	18 and older	-	Self-Leeds Assessment of Neuropathic Symptoms & Signs (S-LANSS) Pain Score; The Hospital Anxiety and Depression Scale (HADS) Score; Central Sensitization Inventory (CSI); Visual Analog Scale (VAS) for Pain	March 2021 – November 2021
NCT04354857	Recruiting	Prospective Cohort	454	18 and older	Olfactory and gustatory tests	Olfactory and gustatory loss;	March 2020 – November 2020
NCT04806880	Recruiting	Prospective Cohort	700	18 and older	Web-application support for olfactory coaching consisting of the inhalation of fragrant essential oils.	Rate of patients presenting an improvement in their anosmia; time until recovery of at least 1point in 10 (Visual Analog Scale) from anosmia; duration of anosmia	February 2021 – August 2021
NCT04406324	Recruiting	Prospective Cohort	400	18 and older	-	Diffusion Capacity for Carbon Monoxide (CO) 3 months after COVID diagnosis; Prevalence of Sleep Disordered Breathing (SDB); Prevalence of sleep disorders; Prevalence of ventilatory muscle function impairments; Prevalence of cardiac impairments	June 2020 – March 2026
NCT04497246	Recruiting	Prospective Cohort	5000	18 and older	-	Impact Event Scale-Revised (IES-R); Generalised Anxiety Disorder-7 (GAD-7); Patient Health Questionnaire-9 (PHQ-9); Insomnia severity index (ISI)	May 2020 – December 2020
NCT04510012	Recruiting	Prospective Cohort	150	18 and older	-	Cytokine response to SARS-Cov-2; Innate immune response to SARS-Cov-2; Humoral immune response; Cell mediated immune response; Neurological damage; Complement activation	March 2020 – March 2021
NCT04887220	Recruiting	Prospective Cohort	30	18 and older	-	Chronic pain in PostICU COVID19 survivors, measured by VAS scale from Brief Pain Inventory Questionnaire; Quality of life assessment; Pain characteristics; Level of anxiety and/or depression	February 2021 – May 2023
NCT04681157	Recruiting	Retrospective, case-only	300	18 and older	-	Retrospective analysis of demographic and clinical characteristics of patients with suspected or already confirmed SARS-Cov2 infection with anosmia and/or ageusia	April 2020 – April 2021
NCT04359914	Recruiting	Prospective case-control	80	Child, Adult, Older Adult	-	Assessment of neurocognitive impairment using validated tools; Measurement of biomarker levels (e.g. NSE, S100B, neurofilament proteins) derived from blood samples; neurocognitive performance; overall quality of life	April 2020 – December 2021

(Table 2a) contd….

ID	Status	Study Design	Number of Patients	Age Range (Years)	Intervention	Outcome Measures	Start Date/ Estimated Completion Date
NCT04384042	Recruiting	Retrospective case-control	60	18 and older	-	Presence or absence of olfactory and taste disturbances; Adjusted odds ratio of olfactory & taste disturbances	June 2020 – March 2021
NCT04388618	Recruiting	Prospective case-control	250	12 - 65	-	Correlation of anosmia and ageusia to covid19 positive patients; objective assessment of severity of smell and taste senses alterations in covid19 patients	June 2020 – November 2021
NCT04812041	Recruiting	Cross-sectional, Cohort	150	18 and older	-	Relationship Between Delirium Severity by CAM-ICU 7 and 4C Mortality Score of the COVID-19 Patients in ICU	January 2021 – May 2021
NCT04775017	Recruiting	Retrospective Cohort	1000	18 and older	-	Incidence of delirium	January 2021 – December 2021
NCT04885192	Recruiting	Prospective Cohort	200	18 - 80	-	Change in Pain Medication Misuse; Change in Pain Catastrophizing; Change in Depression; Change in Anxiety; Change in Suicidal Behaviour; Change in Pain Intensity	March 2021 – January 2022
NCT04401449	Recruiting	Prospective Cohort	180	18 - 80	-	Link inflammatory responses present in blood, urine and bronchoalveolar lavage with imaging of COVID-19 target organs (lungs, heart, brain and kidneys) during the earliest stages of infection and at subsequent time points as the infection and host responses evolve, through recovery.	January 2020 – May 2024
NCT04476589	Recruiting	Prospective Cohort	100	18 and older	-	Functional outcome measure. Maximum score of 29 represents high disability, minimum score of 0 represents no disability. Higher scores represent higher level of disability.	July 2020 – March 2023
NCT04466982	Recruiting	Prospective Cohort	90	18 - 85	-	Olfactory function assessed using the UPSIT and classified as Anosmia; Quality of Life	July 2020 – January 2022
NCT04524754	Recruiting	Retrospective, case-only	218	18 and older	-	Subjective on a scale from 1 to 5 (1 is the least and 5 is the best), the score will be recorded for olfaction before and after the olfactory loss; Subjective on a scale from 1 to 5 (1 is the least and 5 is the best), the score will be recorded for gustation before and after the gustatory loss	July 2020 – November 2020
NCT04799977	Recruiting	Retrospective Cohort	300	18 and older	-	Sniffin Stick Tests; Hamilton Depression Rating Scale (HDRS); Situational anxiety and anxiety trait inventory (STAI-Y); PTSD checklist for DSM-5 (PCL-5); Speech assessment test for neurological pathologies; Pyramids and Palm Trees Test; verbal memory; TAP (Test of Attentional Performance); Olfactive Identification	October 2020 – December 2022
NCT04868435	Recruiting	Prospective Cohort	400	18 and older	-	List of major trigger foods for anosmia; Typical descriptions for smell distortions; Severity of parosmia; Patterns of anosmia/parosmia symptoms in post-viral infections including Covid19	November 2020 – June 2022

(Table 2a) contd….

ID	Status	Study Design	Number of Patients	Age Range (Years)	Intervention	Outcome Measures	Start Date/ Estimated Completion Date
NCT04358042	Recruiting	Prospective Cohort	250	15 and older	-	Impact of the COVID-19 pandemic on psychiatric symptomatology (total severity score from the Impact of Event Scale-Revised)	April 2020 – January 2023
NCT04410835	Recruiting	Prospective Cohort	1000	18 and older	-	Global symptom load (Anxiety, Somatisation, Depression, Global Symptom Index); Depressive symptoms; Sleep disorders and Sleep Quality; COVID-19 associated fears and emotional responses to the pandemic	April 2020 – April 2021
NCT04760795	Recruiting	Prospective case-only	118	65 and older	-	Analysis post traumatic stress disorder measured by PTSD Check List (PCL) results; Analysis usual coping strategies measured by brief COPE (dispositional version) results; Analysis anxiety during containment measured by GAD-7 (Generalized Anxiety Disorder) results; Analysis of personalities by Big Five Inventory (BFI) scale; Analysis attachment measured by Relationship Scales Questionnaire (RSQ) scale results	November 2020 – June 2021
NCT04768153	Recruiting	Prospective Cohort	700	18 and older	-	Evaluation of presence of psychiatric disorders by questionnaire after the initiation of population-level confinement due to the COVID-19 epidemic	June 2020 – December 2021
NCT04369690	Recruiting	Prospective Cohort	1000	12 and older	-	Mental health – Stress; Mental health – Anxiety; Mental health – Depression; Moral distress in healthcare workers; Moral resilience in healthcare workers; Pittsburgh Sleep Quality Index (scores ranged from 0 to 21, higher scores indicating worse sleep disturbances)	April 2020 – April 2021
NCT04652505	Recruiting	Cross-sectional, Cohort	700	18 and older	-	Patient-reported severity of depression; Patient-reported severity of anxiety; Patient-reported severity of distress; Substance use; Patient-reported coping strategy; Patient-reported level of apathy	July 2020 – March 2021
NCT04753242	Recruiting	Cross-sectional	150	18 and older	-	Structural and process quality of COVID-19 related psychosocial consultation and liaison (CL) services	December 2020 – July 2021
NCT04902118	Recruiting	Retrospective Cohort	300	18 and older	-	Copenhagen Burnout Inventory; Epidemic attributable stress proportion	February 2020 – December 2021
NCT04496076	Active, not recruiting	Prospective Cohort	300	18 and older	-	Severe Neurologic Injury Outcomes	April 2020 – May 2021
NCT04889313	Active, not recruiting	Prospective	50	18 and older	-	Diagnosis of Somatic Symptom Disorder (SSD)	April 2021 – May 2021
NCT04496128	Active, not recruiting	Prospective Cohort	300	18 and older	-	Prevalence of neurological manifestations; Global functional outcomes using modified Rankin score (patients will be assessed on a scale score of 0 to 5 - severe disability; bedridden, incontinent and requiring constant nursing care and attention)	April 2020 – May 2021

(Table 2a) contd….

ID	Status	Study Design	Number of Patients	Age Range (Years)	Intervention	Outcome Measures	Start Date/ Estimated Completion Date
NCT04878900	Completed	Cross-sectional	100	18 - 65	-	General pain severity and global well-being assessment with the visual analog scale (VAS); Perceived Stress Scale (PSS); Pittsburgh Sleep Quality Index (PSQI); general health status scale	January 2021 – March 2021
NCT04353011	Completed	Cross-sectional	312	18 and older	-	Hospital Anxiety and Depression Scale questionnaire; Quality of life (SF36); self-reported questionnaire for painful; qualitive questionnaire	April 2020 – April 2020
NCT04427332	Completed	Prospective Cohort	376	18 and older	-	Description of the disturbances of smell and taste; Description of factors that influence smell and taste	June 2020 – October 2020
NCT04377815	Completed	Cohort	569	18 and older	-	Percentage of people reporting changes in smell/taste; Percentage of people with change in smell/taste before other symptoms; Percentage of people with persistent changes in smell and/or taste	April 2020 – June 2020
NCT04473157	Completed	Prospective, case-only	58	18 and older	-	Recovery from Anosmia	July 2020 – December 2020
NCT04916873	Completed	Observational	206	2 - 18	-	Anxiety of the caregivers of the children with cerebral palsy; Rehabilitation process of the children with cerebral palsy	May 2020 – July 2020
NCT04351399	Completed	Cross-sectional	318	18 and older	-	Frequency of patients with emotional impact (feeling of isolation); self-reported questionnaire for painful	April 2020 – May 2020
NCT04390165	Completed	Cross-sectional case-only	498	18 and older	-	Presence or absence of olfactory and taste disturbances in COVID-19 patients; Prevalence of olfactory and taste disturbances	June 2020 – November 2020
NCT04730934	Completed	Prospective Cohort	1360	18 - 65	-	Physical activity; Occupation conditions; General health condition; General pain condition; Perceived stress scale; Fibromyalgia impact questionnaire	January 2021 – February 2021
NCT04532632	Completed	Prospective	40	18 - 80	-	Incidence of taste and smell impairment in critically ill subjects	September 2020 – October 2020
NCT04459403	Completed	Cross-sectional case-only	400	18 and older	-	Psychiatric well-being, level of anxiety, symptoms of depression and coping strategies questionnaire; Prevalence and types of Psychiatric disturbances in patients with COVID-19 infection	June 2020 – Dicember 2020
NCT04357418	Completed	Retrospective	187	18 and older	-	State Anxiety assessed by the State-Trait Anxiety Inventory (STAI); Visual numeric scales assessing anger and stress; Beck Depression Inventory	April 2020 – June 2020
NCT04370210	Completed	Prospective Cohort	247	7 - 12	-	Comparison of sleep quality during COVID-19 containment between children usually followed in child psychiatry and children without follow-up; Assessment of child depression in both groups; Assessment of child anxiety in both groups; Assessment of the influence of socio-demographic factors on sleep in both groups; Measure of the correlation between child sleep quality and parents sleep quality (anxiety level) in both groups; Assessment of sleep disturbance/child anxiety/child depression based on psychiatry diagnoses in the group of children usually followed in child psychiatry	May 2020 – June 2020

(b)

ID	Status	Study Design	Number of Patients	Age Range (Years)	Intervention	Outcome Measures	Start date/ Estimated Completion date
NCT04546737	Recruiting	Non-Randomized, Single Group, Open Label	20	18 and older	Spectroscopic measurements	Variation from baseline of MRI radiological semiology in COVID-19 patients	September 2020 - May 2022
NCT04568707	Recruiting	Non-Randomized, Single Group, Open Label	200	18 and older	Blood sample for serum (serology, biomarkers) and DNA	Dosage of seric markers (anti-SARS-CoV2 IgG) or genetic markers. Neurodegenerative markers.	October 2020 - October 2022
NCT04363749	Recruiting	Non-Randomized, Parallel Assignment, Open Label	30	18 and older	15 COVID positive patients: dyspnea rating to various dyspneic stimulus; 15 healthy controls: dyspnea rating to various dyspneic stimulus	Intensity of the emotional response to hypoxic exposure; brain MRI	April 2020 - November 2021
NCT04705831	Recruiting	Phase 4, Randomized, Double Blind, Placebo Controlled, Cross-Over, Proof-of-Concept Study	40	18 - 75	Ruconest versus Placebo	Neuropsychological Measures; Patient-Rate Questionnaires	December 2020 - January 2022
NCT04495816	Recruiting	Phase 2, Randomized, Double Blind, Placebo Controlled trial	126	18 and older	Omega-3 Fatty Acid Supplement versus Placebo	Brief Smell Identification Test; Brief Questionnaire of Olfactory Dysfunction	July 2020 - August 2021
NCT04526054	Recruiting	Non-Randomized, Single Group, Open Label Diagnostic trial	30	18 and older	ENT examination of the nasal cavity; Olfactometry; (Sniffin's stick test); Brain MRI	Qualitative and quantitative morphological abnormalities of the olfactory bulb detected by MRI; olfactometry (Sniffin' test)	September 2020 - September 2021
NCT04569825	Recruiting	Early Phase 1, Randomized, Parallel Assignment, Double Blind	250	18 and older	Ophtamesone (Local Nasal Steroid) versus Normal Saline	Recovery rate of anosmia and shorten recovery time	August 2020 - October 2020
NCT04685213	Recruiting	Randomized, Parallel Assignment, Double Blind controlled trial	20	18 - 100	Electrical Stimulation versus sham	Change in gastrocnemius muscle activation, Change in ankle strength, Change in gastrocnemius muscle strength.	August 2020 - August 2021
NCT04453475	Recruiting	Randomized, Parallel Assignment, open label	1230	18 and older	Training session	Usability and effectiveness of digital interventions; Interest in digital interventions	July 2020 - December 2021
NCT04789499	Recruiting	Phase 2, Randomized, Parallel Assignment, Double Blind controlled trial	50	18 - 70	Theophylline Powder versus placebo	Clinical Global Impression Scale	March 2021 - December 2021
NCT04528329	Recruiting	Phase 4, Randomized, Parallel Assignment, open label	300	18 and older	Early-Dexamethasone versus Late-dexamethasone	Time to recovery from anosmia and/or ageusia	August 2020 - April 2021
NCT04416360	Recruiting	Non-Randomized, Single Group, Open Label	40	6 - 17	Interview by psychologists	Interview of the children/adolescents/ parents : Experience of the confinement in general related to education; related to daily family life; related to leisure, related to care	May 2020 - January 2021

(Table 2b) contd….

ID	Status	Study Design	Number of Patients	Age Range (Years)	Intervention	Outcome Measures	Start date/ Estimated Completion date
NCT03944447	Recruiting	Non-Randomized, Single Group, Open label	200000	7 and older	Cannabis	Prevention of COVID-19; Treatment of COVID-19; Treatment of Symptoms	December 2018- December 2025
NCT04726371	Recruiting	Randomized, Parallel Assignment, open label	5350	18 and older	"Tailored Best Practices" (TBP) compared to "Generic Best Practices" (GBP)	The best practice implementation fidelity and COVID-19 incidence are co-primary outcomes	January 2021 - October 2022
NCT04756856	Recruiting	Non-Randomized, Single Group, Open label	50	18 and older	Muscle-target oral nutritional supplementation	Change in Physical performance	April 2021 - December 2021
NCT04382378	Recruiting	Randomized, Parallel Assignment, single blind	120	18 and older	Neuromuscular electrical stimulation	Change of muscle wasting assessed by ultrassonogropahy; change of echointensity of rectus femoris assessed by ultrassonography; change of evoked peak torque of quadriceps femoris	February 2021 - December 2021
NCT04412330	Recruiting	Non-Randomized, Single Group, Open label	20	18 and older	ICU Recovery + Physical Therapy	Adverse events (safety); Six minute walk test; Short Performance Physical Battery; Quality of life (EQ-5DL); Cognitive function; Anxiety and Depression; PTSD and distress; Return to work; Secondary complication	May 2020 - May 2021
NCT04904497	Recruiting	Randomized, Parallel Assignment, triple blind	60	18 and older	Behavioral: Early Occupational Therapy versus standard analgesia, sedation, delirium and mobilization (ASDM) measures	Functional independence at hospital discharge; Delirium-free days; Coma-free days; Cognitive status; Motor status; Quality of life	April 2021 - December 2021
NCT04649086	Recruiting	Randomized, Parallel Assignment, open label	120	18 - 80	Rehabilitation by Eccentric exercises versus Rehabilitation by Concentric exercises	Functional walking capacity; lower extremity functioning by Short Physical Performance Battery (SPPB) score; maximum muscle strength of the quadriceps; fatigability of the quadriceps; EuroQol - 5 Dimensions (EQ-5D) questionnaire; Neuromuscular activation;	June 2020 - October 2022
NCT04636034	Recruiting	Randomized, Parallel Assignment, quadruple blinded	60	18 and older	Sphenopalatine Ganglion Block with Local Anesthetic versus Placebo	Hyperactivity in the sphenopalatine ganglion assessed by pain intensity (0-100mm on a visual analogue scale, VAS) of the postdural headache in standing position; Analgesics used daily in the week following the procedure.	January 2021 - November 2021
NCT04413006	Recruiting	Non-Randomized, Single Group, Open label	28	18 and older	Behavioral: Self-Compassion for Chronic Pain Virtual Group Treatment Program	Change over time in Scores on the Self-Compassion Scale (SCS); Change over time in Scores on the Pain Disability Index; Change over time in Depression Symptoms as measured by the Patient Health Questionnaire-9 (PHQ-9); Changes over time in Anxiety Symptoms as measured by the Generalized Anxiety Scale-7; Change over time in Quality of Life as measured by the PROMIS GLOBAL- 10; Changes over time in Mindfulness	May 2020 - March 2021

(Table 2b) contd….

ID	Status	Study Design	Number of Patients	Age Range (Years)	Intervention	Outcome Measures	Start date/ Estimated Completion date
NCT04604977	Recruiting	Non-Randomized, Single Group, Open label	25	12 - 18	Behavioral: Mindfulness	Reduction of headache days; disability score; catastrophising attitude; depression symptoms; trait-state anxiety symptoms	September 2020 - December 2021
NCT04565509	Recruiting	Randomized, Single Group, Open label	2500	5 - 90	Behavioral: General Communication Message Behavioral: Focused/Targeted Message Behavioral: Best Message Alone Behavioral: Best Message + Augmented Message or Implementation Strategy	Adoption of weekly testing by each participant; Acceptability, Feasibility, Appropriateness of Messaging/Implementation Strategy; Number of missed school days by students or work days by staff	November 2020 - September 2022
NCT04602286	Recruiting	Randomized, Parallel Assignment, quadruple blinded	292	18 and older	Meditation (1 x 20-minute guided audio training)	Pain intensity; Pain Unpleasantness; Pain Catastrophizing; State Mindfulness	October 2020 - June 2021
NCT04880135	Recruiting	Randomized, Parallel Assignment, double blinded	404	18 - 40	Supervised Versus Home-based stretching and strengthening exercise	Visual Analogue Scale; International Physical Activity Questionnaire; Neck Disability Index	March 2021 - May 2021
NCT04394169	Recruiting	Randomized, Parallel Assignment, single blinded	102	18 and older	Behavioral: Intervention program	Impact of intervention program on health-related quality of life (VAS); Impact of intervention program on chronic pain (intensity, limitation of daily activities, pain catastrophization); Impact of intervention program on anxiety or depression incidence; Impact of intervention on probable post-traumatic stress syndrome incidence	May 2020 - March 2021
NCT04455360	Recruiting	Randomized, Parallel Assignment, open label	26	18 and older	Eye Movement Desensitisation and Reprocessing Recent traumatic Event Protocol versus no intervention	Feasibility of recruitment, intervention adherence, incidence of treatment related adverse events and trial completion to final assessment timepoints; Post-Traumatic stress disorder; Anxiety and depression; Cognitive function; Health Related Quality of Life	October 2020 – Sept4ember 2021
NCT04724616	Recruiting	Randomized, Parallel Assignment, open label	60	3 - 6	Participants received our educational program for five days, with one teaching session per day versus no intervention	Change of Emotional Outcome; Change of Knowledge Outcome; Baseline Behavior of the Participants	January 2021 – June 2021
NCT04657809	Active, not recruiting	Phase 2 Randomized, Parallel Assignment, double blinded	40	18 - 70	Insulin fast dissolving film Formulated bioadhesive fast dissolving film contains 100IU of insulin Versus Placebo Comparator (Plain fast dissolving film Formulated bioadhesive fast dissolving film contains no drug)	Smell sensation improvement	October 2020 - February 2021

(Table 2b) contd….

ID	Status	Study Design	Number of Patients	Age Range (Years)	Intervention	Outcome Measures	Start Date/ Estimated Completion Date
NCT04710394	Active, not recruiting	Randomized, factorial Assignment, double blinded	240	18 - 70	Behavioral: Smell Training	University of Pennsylvania Smell Identification Test (UPSIT); Clinical Global Impression Severity (CGI-S) Scale; Olfactory Dysfunction Outcomes Rating (ODOR)	January 2021 - March 2022
NCT04361474	Active, not recruiting	Phase 3 Randomized, Parallel Assignment, single blinded	120	18 and older	Budesonide Nasal versus Physiological serum	Improvement of more than 2 points on the ODORATEST score (5) after 30 days of treatment	May 2020 - June 2021
NCT04539821	Active, not recruiting	Non-Randomized, Single Group, Open label	60	18 and older	Virtual Pain Care Management (VCPM)	The percent of patients who agree to Buprenorphine transfer	October 2020 - July 2021
NCT04470869	Active, not recruiting	Non-Randomized, sequential Assignment, Open label	129	18 and older	The interventional group (OLAF) benefit from a psychiatric follow up, from virtual visiting of the patient and video interview with ICU team. Control: relatives of patients hospitalized after the confinement measure but before the OLAF intervention.	Incidence of PTSD observed 6 months after patient's discharge from the intensive care unit; incidence of PTSD observed 6 months after patient's death in the intensive care unit	June 2020 - October 2021
NCT04456062	Active, not recruiting	Randomized, Parallel Assignment, Open label	102	18 and older	Caring Contacts versus no intervention	Hopkins Symptom Checklist-25 (HSCL-25)	August 2020 - July 2021
NCT04361344	Terminated*	Non-Randomized, Single Group, prospective, non-controlled, Open label	2	18 and older	Diagnostic (Neurodegeneration Markers and Neurological Course)	Change of neurodegeneration markers level	May 2020 - October 2020
NCT04830943	Completed	Phase 4 Non-Randomized, Single Group, Open label	100	20 - 60	Cerebrolysin	The smell and taste questionnaire component of the National Health and Nutrition Examination Survey (NHNES); The short modified version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS); The Globas Rating for smell (GRS); The Globas Rating for taste (GRT)	August 2020 - March 2021
NCT04484493	Completed	Phase 3 Randomized, Parallel Assignment, Open label	100	18 and older	Mometasone furoate nasal spray versus olfactory training	Improvement of olfaction	August 2020 - November 2020
NCT04381000	Completed	Non-Randomized, Parallel Assignment, Open label	170	18 - 80	Exercise Group versus control group	Anxiety and Depression; Quality of Life and overall health; Pain Intensity; Quality and patterns of sleep; Patients' illness perceptions; Disability	April 2020 - June 2020
NCT04466605	Completed	Randomized, Parallel Assignment, Open label	64	18 - 60	Tele-yoga therapy versus Primary care	Severity of pain; Interference of pain; Global rating of change in pain	March 2020 - July 2020
NCT04457388	Completed	Non-Randomized, Single Group, Open label	18	18 - 60	Tele-Yoga Therapy	Pain Intensity; Pain Disability; Anxiety; Depression	March 2020 – June 2020

*Objective of the study demonstrated by other research teams

Data obtained from these studies will hopefully allow to clarify the physiopathological process, in order to improve patients' outcome.

It is noteworthy that among interventional trials, only 30% (n = 12/40) includes pharmaceutical intervention; moreover, almost 60% (7/12) of these studies assess the effect of drugs or dietary supplements on smell and taste dysfunction. This is probably due to the fact that anosmia and ageusia were among the first neurological symptoms identified as COVID-19 related.

CONCLUSION

Thus, the present data suggest that SARS-CoV-2 infection can result in various CNS impairments and deteriorations. However, today, there are limited findings concerning the studying of the neuroinvasive action of SARS-CoV-2 in humans. Currently, we do not know how actually SARS-CoV-2 might negatively alter brain functions in humans and this question is still opened. Although the major clinical damage of SARS-Cov-2 in humans is linked to severe acute respiratory illness, the deleterious actions on neurological and mental health should also be considered and appropriately prevented and treated. Finally, the indirect effect of COVID-19 pandemic on mental health, related to the social distancing, isolation as well as healthcare professionals' fears and exhaustion should be addressed with specific psychological support.

LIST OF ABBREVIATIONS

ACE2	=	Angiotensin-converting Enzyme 2
ARDS	=	Acute Respiratory Distress Syndrome
BBB	=	Blood-brain-barrier
CNS	=	Central Nervous System
COVID-19	=	Coronavirus Disease 2019
CSF	=	Cerebrospinal Fluid
HIV	=	Human Immunodeficiency Viruses
IFN	=	Interferon
IL	=	Interleukin
MERS-CoV	=	Middle East Respiratory Syndrome Coronaviruses
NO	=	Nitric Oxide
OCD	=	Obsessive Compulsive Disorder
PNS	=	Peripheral Nervous System
PTSD	=	Post-traumatic Stress Disorder
SARS-CoV	=	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	=	Severe Acute Respiratory Syndrome Coronavirus-2
SIRS	=	Systemic Inflammatory Response Syndrome
TNF-α	=	Tumour Necrosis Factor-*alpha*

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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