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].
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 dysfunction and lymphocytic endothelitis 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
The latter point of view is confirmed by the lack of response in the brain, typical of other neurotropic viruses that can infect neurons in patients, it did not trigger an immune that although SARS-CoV-2 has neurotropic properties and tive potential for SARS-CoV-2, other studies demonstrated authors postulated that the brain is a site for the high replica-

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. 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.

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. 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.

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. 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.

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, and memory impairment. During the COVID-19 pandemic, ARDS was associated with cognitive impairment, such as a decline in verbal memory abilities. Thus, ARDS can cause significant long-term, brain-related morbidity with neurocognitive im-

| 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 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      | Bulflamante et al., 2020; Kumar 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           | Bosantaniklioglu, 2020ab    | Frequent                  |

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 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.

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

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 neuromuscular 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 1 point 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                           |
| 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); 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; qualitative 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 – December 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              |
| 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      | Ophthamesone (Local Nasal Steroid) versus Normal Saline                     | Recovery rate of anosmia and shortened 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                                         | 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                                                                                      | February 2021 - December 2021        |
| NCT04412330  | Recruiting                  | Non-Randomized, Single Group, Open label | 20                | 18 and older      | ICU Recovery + Physical Therapy                                             | Functional independence at hospital discharge; Delirium-free days; Coma-free days; Cognitive status; Motor status; Quality of life                                                                                                                                                        | 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 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;                                                                 | April 2021 - December 2021           |
| NCT04649086  | Recruiting                  | Randomized, Parallel Assignment, open label | 120               | 18 - 80           | Rehabilitation by Eccentric exercises versus Rehabilitation by Concentric exercises | 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.                                                                                                        | June 2020 - October 2022             |
| NCT04636034  | Recruiting                  | Randomized, Parallel Assignment, quadruple blinded | 60                | 18 and older      | Sphenopalatine Ganglion Block with Local Anesthetic versus Placebo          | 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; Changes over time in Quality of Life as measured by the PROMIS GLOBAL-10; Changes over time in Mindfulness | 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 |                                                                                                                                                                                                                                                                                                                                                   | 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 - September 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 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, 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 (NHINES); 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 Coronavirus
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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