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# Modulating neuroinflammation in COVID-19 patients with obsessive-compulsive disorder

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## ABSTRACT

Exacerbation of symptoms of obsessive-compulsive disorder (OCD) during COVID-19 or new onset of the OCD symptoms resulting from COVID-19 infection is an understudied area of research. It is possible that increased proinflammatory immune status is associated with the onset of obsessive-compulsive symptoms in patients with COVID-19 and that targeted anti-inflammatory treatments for COVID-19 infection can mitigate the new onset of Obsessive-Compulsive (OC) spectrum symptoms. In this review, we cover OCD pathogenesis as related to COVID-19, summarize the impact of cytokines on behavior, and suggest that anti-cytokine treatments can help mitigate post-COVID-19 and new onset of the OC symptoms.

## 1. Introduction

The COVID-19 pandemic has had an unprecedented impact on the world's population. Very little is known on the effects of infection with COVID-19 on Obsessive-Compulsive (OC) spectrum patients. When preventive strategies against infection involve “repetitive behaviors” of hand-washing, there is a risk of increasing OC spectrum disorders symptoms (Banerjee, 2020). COVID-19 pandemic might trigger and reinforce obsessive thinking and compulsive behaviors, and aggravation of OCD might, in turn, correlate with worsening of anxiety and depressive symptoms (Rivera and Carballea, 2020; Nissen et al., 2020).

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), the pathogen behind COVID-19, belongs to the order of Nidovirales, member of the family Coronaviridae and subfamily Coronavirinae (Park, 2020). Scientific evidence on the effects of COVID-19 on different organs of the human body (Nalbandian et al., 2021) and especially on neurological symptoms and mental health (Ellul et al., 2020) is still evolving. Neuropsychiatric manifestations are increasingly being reported in association with COVID-19 (Muccioli et al., 2021). In a recent online cross-sectional survey, respondents who showed OCD symptoms since the start of COVID-19 were significantly more likely to have moderate to high stress levels and exhibit generalized anxiety disorder and major depressive disorder (Abba-Aji et al., 2020). Neuro-inflammatory mechanisms could be involved in the pathophysiology of the comorbid neuropsychiatric manifestations (Muccioli et al., 2021). Due to an

increase in systemic inflammation, anti-cytokine treatments emerge as a possible mechanism of treatment for COVID-19 and comorbid neuropsychiatric conditions such as depression (Kappelmann et al., 2018), anxiety (Farzanfar et al., 2018), and OCD (Kutuk et al., 2020) symptoms. More research is needed to elucidate these relationships.

Evidence from different lines of research suggests a possible role of immune abnormalities in the pathogenesis of OCD (Rao et al., 2015), especially in:

- 1) Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus infections (PANDAS), a term which was introduced by Swedo et al. (1998) in 1998 to describe a subset of childhood obsessive-compulsive disorders (OCD) and tic disorders triggered by group-A beta-hemolytic Streptococcus pyogenes infection (Moretti et al., 2008). PANDAS term has recently transformed in pediatric acute-onset neuropsychiatric syndrome (PANS) and/or Childhood Acute Neuropsychiatric Syndrome (CANS), which are both defined by the presence of typical OCD symptoms and tics (Marazziti et al., 2018).
- 2) MRI findings show that basal ganglia volume is less in children with streptococcus-associated OCD versus healthy children (Giedd et al., 2000), and basal ganglia volume might be associated with anti-basal ganglia antibody titers (Peterson et al., 2000).
- 3) Although more studies are warranted, patients with OCD might have significantly higher plasma levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  levels

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(Rao et al., 2015; Karaguzel et al., 2019). The combination of these findings opens a door for novel immunotherapeutics (Marazziti et al., 2018) options and makes studies targeting neuroinflammation timely.

This special issue of the Journal of Psychiatric Research discusses the exacerbation of OCD symptoms associated with COVID-19 due to fear of contamination and environmental stressors. However, little work has been performed in the area of exacerbation of OCD symptoms during COVID-19 infection. It is possible that increased proinflammatory status can be associated with the onset of OC symptoms in patients with COVID-19 and that treatment with anti-cytokine therapeutics can mitigate the new onset of OC Spectrum symptoms, and this is the topic of this article.

## 2. OCD and COVID-19

OCD is a highly disabling, chronic condition, causing significant impairment in social and occupational functioning (Pinto et al., 2006), and is recognized as one of the top ten causes of neuropsychiatric morbidity in terms of Disability-Adjusted Life Years (International, 2010). Based on data from a nationwide survey in US adults, the National Comorbidity Survey Replication, a lifetime prevalence of 2.3% in the general population is reported (Ruscio et al., 2010). OCD is thought to affect all ethnicities approximately equally (Pallanti, 2008).

It is possible that the COVID-19 pandemic is more poorly tolerated by individuals with contamination symptoms (in comparison to individuals with other OCD symptoms) and by individuals who did not attain a state of remission before the quarantine (Davide et al., 2020). Patients with OCD that earlier expressed concerns to be contaminated with human immunodeficiency virus (HIV) or tuberculosis may now feel more preoccupied with the COVID-19 and perform more frequent hand washing paired with increased avoidance behaviors (Fontenelle and Miguel, 2020). Davide et al. suggested that during the COVID-19 pandemic, there was a drastic rise in the severity of obsessions and compulsions in adult cases with OCD (Davide et al., 2020). There are also case reports of adult patients with worsening OCD symptoms during the COVID-19 pandemic (Kumar and Somani, 2020; French and Lyne, 2020). A recent consensus paper by the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS) advised pharmacotherapy as the first option for OCD patients with contamination fears and washing compulsions during the pandemic (Fineberg et al., 2020). It recommended substituting in vivo CBT with exposure and response prevention (ERP) with the imaginal exposure techniques due to safety concerns (Fineberg et al., 2020). There is a clear unmet need to improve strategies for relapse prevention during the time of social restrictions (Davide et al., 2020). There are not so many reports on the prevalence of OCD symptoms during the Pandemics. However, in times of easily transmissible diseases, people are urged to remain hypervigilant to prevent contamination of self and others (Abba-Aji et al., 2020).

Reports suggest residual effects of SARS-CoV-2 infection, such as fatigue, anosmia, dyspnea, chest pain, cognitive disturbances, arthralgia, and decline in quality of life (Nalbandian et al., 2021; Varatharaj et al., 2020; Paterson et al., 2020). There are also case reports of SARS-CoV-2 infection associated with encephalopathies associated with delirium and psychosis, inflammatory CNS syndromes including encephalitis, acute disseminated encephalomyelitis associated with hemorrhage, necrosis or myelitis, ischemic strokes related to a pro-thrombotic state, peripheral neurological disorders, and Guillain-Barré syndrome (Paterson et al., 2020). Although different in the mechanism of action, an interesting parallel in the neurological domain is found with other viruses known for being associated with neurological symptomatology, such as in the Spanish Influenza pandemic of 1918 and Encephalitis Lethargica (Ellul et al., 2020; Steardo et al., 2020; Pallanti et al., 2020). In 1917 the Austrian neuro-psychiatrist Constantine Von Economo described encephalitis

lethargica, characterized by sleep disturbances and parkinsonism (Lutters et al., 2018). During the acute phase of encephalitis lethargica, typical symptoms included altered personality, lability of mood, hallucinations, delirium, and catatonia-like states. In contrast, marked personality changes, obsessive-compulsive behaviors, mood disorders, and bradyphrenia were likely to emerge during the chronic phase (Lutters et al., 2018). Recent findings suggest that an autoimmune response in the basal ganglia plays a role in the etiology of this disease (Koning, 2009). It is important to highlight that viral parkinsonism was present in some patients who survived the Spanish flu pandemic in 1918 with manifested symptoms of viral encephalitis (Eldeeb et al., 2020). These findings create an overlap between these diseases immune-inflammatory etiology and highlight the involvement of the basal ganglia.

## 3. Anti-obsessional treatments with anti-inflammatory properties

Classical treatments for obsessive-compulsive disorder (OCD) include cognitive behavior therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) medication (Fineberg et al., 2018). Fluvoxamine, an SSRI with Sigma-1 receptor (S1R) agonist effects, is an efficacious treatment of the obsessive-compulsive disorder (OCD) (Pallanti and Sandner, 2007). The anti-obsessional effect of fluvoxamine is superior to non-serotonergic antidepressants (i.e., desipramine) and comparable in efficacy to clomipramine (a tricyclic antidepressant with potent serotonin reuptake inhibition) and other selective serotonin reuptake inhibitors (paroxetine and citalopram) (Dell'Osso et al., 2005). Moreover, S1R is a critical inhibitor of endoplasmic reticulum-driven inflammation (Rosen et al., 2019). Modulation of the S1R-Inositol-Requiring Enzyme 1 $\alpha$  (IRE1) pathway was shown to be beneficial in preclinical models of inflammation and sepsis (Rosen et al., 2019). Stimulation of the S1R receptor was shown to reduce debilitating effects of the inflammatory response (Anderson, 2021). It was also demonstrated in a rat model of Parkinson's disease that administering fluvoxamine may alleviate inflammation on injured striatal neurons by enhancing anti-inflammatory cytokines expression while diminishing proinflammatory cytokines (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) release in the brain (Dalle et al., 2017).

In a recent study, administration of fluvoxamine given at a dose of 100 mg three times a day for 15 days in a randomized trial setting that included 152 adult outpatients with confirmed COVID-19 (Lenze et al., 2020) correlated with a reduction of clinical deterioration (Lenze et al., 2020). More studies are needed to confirm if fluvoxamine might exhibit beneficial effects in COVID-19 patients due to its ability to significantly increase (~2–3-fold) nocturnal plasma levels of melatonin (Anderson, 2021).

Clomipramine is a tricyclic antidepressant with anti-inflammatory properties, which can easily pass the blood-brain barrier. Clomipramine is likely to decrease peripheral and central inflammation and alleviate the acute and possible long-term consequences of SARS-CoV-2 infection, but more studies are warranted (Nobile et al., 2021).

A recent meta-analysis (Kohler et al., 2018) showcased that use of antidepressants may be associated with decreased plasma levels of proinflammatory cytokines, such as IL-10, TNF $\alpha$ , and CCL-2, which are associated with COVID-19 severity (Hojo et al., 2020), as well as with reduced levels of IL-6, which is highly correlated with disease mortality (Hojo et al., 2020; Hoertel et al., 2021; Ye et al., 2020). More studies investigating the anti-inflammatory properties of classical anti-obsessional treatments and their role in mitigating COVID-19 effects are warranted.

## 4. Penetration of the SARS-CoV-2 virus in the CNS

A few hypotheses have emerged to explain how SARS-CoV-2 penetrates the CNS: hematogenous dissemination, neuronal retrograde

transport, and the passage via the nasal cavity across the cribriform plate near the olfactory bulb (Pallanti et al., 2020; Zhou et al., 2020). The virus can be spread through the body via the bloodstream and target different organs by disrupting angiotensin-converting enzyme-2 (ACE-2) bearing endothelial cells (Pallanti et al., 2020; Varga et al., 2020). Once penetrated the human body through angiotensin-converting enzyme 2 (ACE-2) receptors, SARS-CoV-2 rapidly replicates, activates the immune system and inflammatory mediators, including cytokines, and produces direct endothelial cells damage leading to thrombi and brain damage (Boldrini et al., 2021). This sequence of events likely causes acute symptoms of COVID-19 and underlies the long-term sequelae of SARS-CoV-2 infection (Wang et al., 2020). Cytokine release syndrome during COVID-19 is schematized in Fig. 1, “Cytokine release syndrome in COVID-19” below (Gubernatorova et al., 2020) (We obtained permission to use this figure from Elsevier, which was earlier published in Gubernatorova et al., “IL-6: Relevance for immunopathology of SARS-CoV-2” Cytokine Growth Factor Rev. 2020 Jun;53:13-24). During this release of pro-inflammatory cytokines, increase of alveolar vessel permeability and recruitment of cells to the site of infection form a positive loop for pathological activation of IL-6, IL-1, TNF, and other pro-inflammatory cytokines and might trigger bursts of inflammation in the human body (Gubernatorova et al., 2020), possibly including CNS (Troyer et al., 2020). It is also hypothesized that systemic inflammation induced by COVID-19 may lead to 1) decrease in monoamines and trophic factors levels, 2) activation of microglia, and 3) result in increased glutamate and N-methyl-d-aspartate (NMDA) (Boldrini et al., 2021) and excitotoxicity (Boldrini et al., 2021). Overall, these chains of events could lead to an exacerbation of pre-existing neuropsychiatric conditions (Boldrini et al., 2021). In cases of viral encephalitis, gene sequencing confirmed SARS-CoV-2’s presence in the cerebrospinal fluid, confirming its neuroinvasive potential (Pallanti et al., 2020; Zhou et al., 2020).

The following immunomodulatory therapies have been proposed in the treatment of COVID-19: intravenous immunoglobulin (IVIG), Janus kinase inhibitors (JAK) (e.g., baricitinib, ruxolitinib), anti-tumor necrosis factor- $\alpha$  (e.g., infliximab, adalimumab), granulocyte-macrophage colony-stimulating factors (e.g., nalmilumab, lenzilumab, gimsilumab),

anti-cytokines therapies such as interleukin (IL)-1 (anakinra) and IL-6 receptor antagonists (e.g., siltuximab, sarilumab, tocilizumab), and convalescent plasma, with promising to negative trials and other data (Troyer et al., 2020; Mehta et al., 2020; Rizk et al., 2020). The efficacy of corticosteroids in treating COVID-19 in a clinical setting is still equivocal, with some groups advising against their use (Russell et al., 2020). Longitudinal follow-up of psychiatric and neurological symptoms and neuroimmune status in individuals exposed to SARS-CoV-2 is needed to fully assess the long-term impact of COVID-19 and mitigate its risks (Troyer et al., 2020).

We obtained permission to use this figure from Elsevier, which was earlier published in Gubernatorova et al., “IL-6: Relevance for immunopathology of SARS-CoV-2” Cytokine Growth Factor Rev. 2020 Jun; 53:13–24.

**Post-COVID symptoms.** “Sub-acute COVID” refers to persistent symptoms four weeks after COVID-19 infection (Nalbandian et al., 2021), while “Chronic COVID” or “post-COVID-19 syndrome” describes symptoms present more than 12 weeks since the onset of acute COVID-19 and are not caused by alternative diagnoses (Nalbandian et al., 2021; Chan et al., 2020). The effects of SARS-Cov2 can manifest months or years after initial infection. Therefore it is essential to follow up with patients who have been exposed to COVID-19. Emerging reports of “long-haulers” suggest that beyond the acute and subacute setting, some patients can exhibit persistent, long-lasting clinical manifestations (Al-Aly et al., 2021). Some patients present with anosmia, while others can experience “brain fog”, newly onset anxiety, depression, psychosis, and suicidal behavior (Boldrini et al., 2021; Woo et al., 2020). Long COVID-19 also contains a sum of impairing symptoms (including breathlessness, chest pain, and palpitations) which can persist for weeks after an incidence of a mild illness (Dani et al., 2021). Thus, in a cross-sectional study of persisting symptoms in “long COVID-19” population of 384 patients (mean age 59.9 years; 62% male) with COVID-19 followed for a median of 54 days post-discharge, 53% reported persistent breathlessness, 34% cough, and 69% fatigue and 14.6% had depression (Mandal et al., 2020). In a recent study on 538 COVID-19 survivors conducted in Wuhan, China, it was found that survivors are

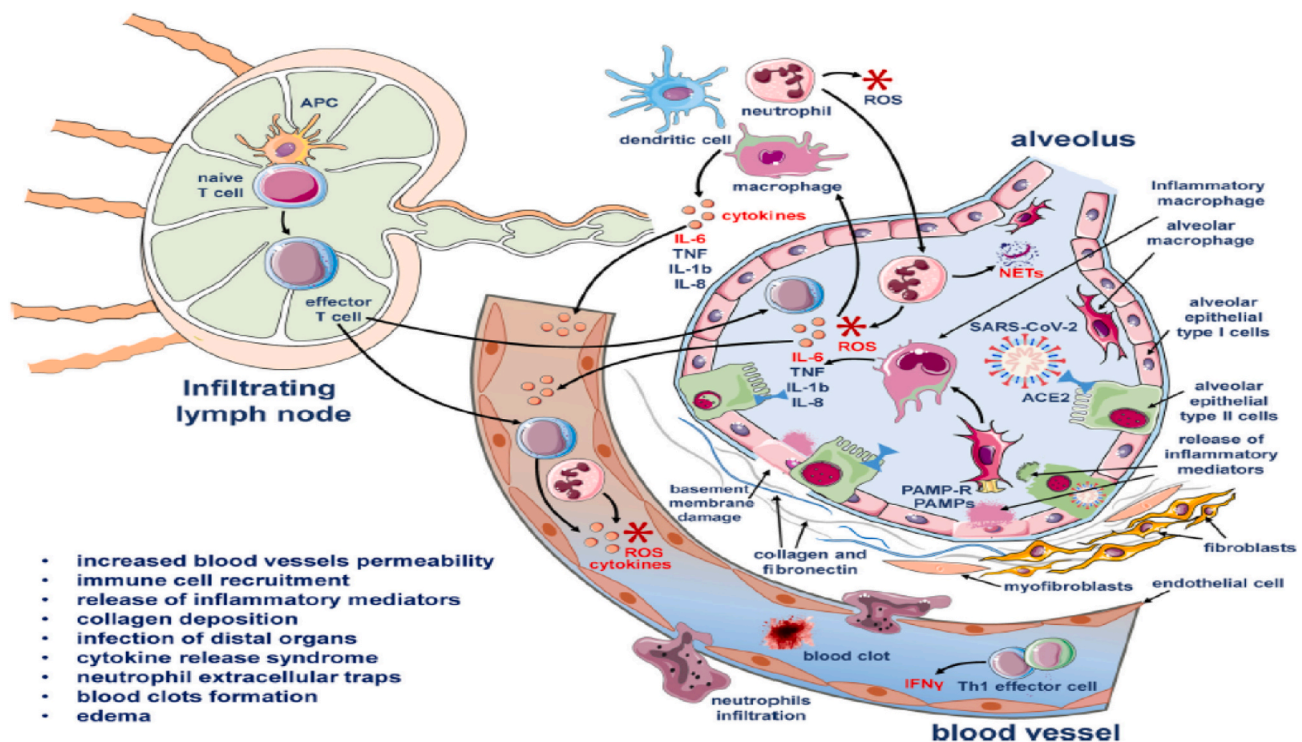


Fig. 1. Cytokine release syndrome in COVID-19.

significantly more likely to develop clinical sequelae (including psychosocial symptoms and general health symptoms) 3 months after discharge from the hospital than those without COVID-19 infection (Xiong et al., 2021). In a recent study in 236,379 patients with COVID-19 diagnosis, the estimated incidence of a neurological or psychiatric diagnosis in the following six months was 33.62% (95% CI 33.17–34.07) (Taquet et al., 2021). As to individual diagnoses, the COVID-19 cohort had estimated incidences of 17.39% (17.04–17.74) for anxiety disorder and 1.40% (1.30–1.51) for psychotic disorder (Taquet et al., 2021). In a recent study in 73,435 users of the Veteran Health Administration system users in the US with COVID-19 per 1000 patients, there was an increase in sleep-wake disorders (14.53 (11.53, 17.36)), anxiety (5.42 (3.42, 7.29)), and trauma and stress-related disorders (8.93 (6.62, 11.09)) (Al-Aly et al., 2021).

## 5. MRI findings in COVID-19 survivors

In a recent retrospective study in patients with COVID-19-associated neurologic manifestations, 36 patients presented findings of the abnormal MRI, which included ischemic strokes, leptomeningeal enhancement, and encephalitis (Kremer et al., 2020). Confusion (53%), impaired consciousness (39%), presence of clinical signs of corticospinal tract involvement (31%), agitation (31%), and headache (16%) represent the most common neurological manifestations in these individuals (Kremer et al., 2020). The long-term sequelae of COVID-19 remain unknown. Basal ganglia and other brain structures may be affected by aberrant hemorrhagic (Franceschi et al., 2020) or neuroinflammatory processes in the central nervous system (Dickman, 2001). A case report in the literature is evidencing bilateral basal ganglia hemorrhage in a confirmed COVID-19 patient (Daci et al., 2020). Therefore, basal ganglia dysfunctions might be associated with COVID-19 infection and its persistence (Pallanti et al., 2020).

In a recent study in acute COVID-19 patients, among 73 patients enrolled, 43 have presented abnormal MRI findings, which included the following findings 2–4 weeks since initial symptoms onset: acute ischemic infarct (23.3%), deep venous thrombosis (1.4%), multiple microhemorrhages (11.3%), perfusion abnormalities (47.7%), restricted diffusion foci within the corpus callosum consistent with cytotoxic lesions of the corpus callosum (CLOCC, 4.1%), multifocal white matter enhancing lesions (5%) and basal ganglia abnormalities (5%) (Chougar et al., 2020).

It is important to emphasize that individuals who experienced lockdowns and social distancing rules may also present elevated markers of inflammation (Pallanti et al., 2020; Eisenberger and Moieni, 2020). It was also described that depressed individuals might have higher levels of circulating proinflammatory markers (Eisenberger and Moieni, 2020).

Neuroinflammation is associated with a broad spectrum of neurological disorders (Brambilla, 2019) and may potentially influence GABAergic transmission (Versace et al., 2021). Peripheral cytokines could activate the microglia and the astrocytes inducing neural cytokines release and result in brain inflammation (Harry and Kraft, 2008). Maladaptation of cortical processes within the primary motor cortex (M1) related to degeneration of inhibitory GABAergic intracortical circuits has been reported in association with central fatigue syndrome (Versace et al., 2021). A pilot data suggests the use of transcranial magnetic stimulation (TMS) as a diagnostic tool based on data from 12 patients suffering from post-COVID-19 neurological complications (Versace et al., 2021). This study further finds a reduction of cortical GABAergic and possibly cholinergic activity in post-COVID-19 patients suffering from fatigue or cognitive disturbances (Versace et al., 2021). If performed in conventional frontal and temporal cortical regions, neuromodulation could be used to modulate the systemic immune response and, therefore, could contribute to prevention of COVID-19 induced neuroinflammation (Pilloni et al., 2020).

Recent meta-analysis showcased that IL-6 concentrations are 2.9-fold

higher in patients with complicated COVID-19 than in patients with the non-complicated disease (six studies;  $n = 1302$ ; 95%CI, 1.17–7.19;  $I^2 = 100\%$ ) (Coomes and Haghbayan, 2020). Macrophages produce a significant amount of IL-6. Therefore their presence may be associated with excessive inflammation during COVID-19. Macrophage activation syndrome may also be related to high serum levels of CRP during COVID-19 (Paces et al., 2020). Higher circulating levels of IL-6 and CRP are also highly predictive of the need for invasive ventilation. Therefore, they could be potentially used to guide escalation of treatment in patients with COVID-19-related hyperinflammatory syndrome (Herold et al., 2020). Some patients with COVID-19 may experience prolonged fatigue, depression, anhedonia, “brain fog”, insomnia and taste/smell alterations, and this can be accompanied by elevated levels of CRP and/or IL-6 (Versace et al., 2021). A recent meta-analysis provided evidence that cytokine modulators may serve as novel treatments for depression in chronically inflamed subjects and that their antidepressant effect might be associated with baseline symptom severity (Kappelmann et al., 2018).

## 6. Cytokines and behavior in OCD and ASD

Benros and colleagues (Benros et al., 2014) coined the term “Immune activation hypotheses” to account for the evidence that viral and bacterial-induced immune activation during the neurodevelopmental phase is a preeminent inducing factor of vulnerability to psychopathological aberrant behavioral manifestations. Early immune activation could manifest in common features of inhibitory control deficit, including OCD, chronic tics disorders, and Autism Spectrum Disorders (ASD) (Martino et al., 2020).

Obsessive-compulsive disorder (OCD) is often manifested by intrusive and unwanted thoughts, urges, or impulses that are associated with significant distress and anxiety and/or repetitive, compulsive behaviors or mental rituals (American Psychiatric, 2013). Repetitive behaviors represent acts performed by rigid rules (compulsions) that the person feels compelled to execute and which aim to decrease the resulting distress (Fontenelle and Miguel, 2020; Goodman et al., 2014). OCD is often present in individuals with Autism Spectrum Disorders (ASD), even though repetitive behaviors and intrusive, recurrent thoughts occur in both disorders and are difficult to differentiate (Postorino et al., 2017). A dysregulated immune response in the ASD population might be characterized by an elevated expression of IL-1 $\beta$ , IL-6, IL-12, TNF- $\alpha$ , and IL-23 as compared to healthy controls (Ricci et al., 2013; Masi et al., 2017). Increased IL-1 $\beta$  and IL-6 levels might also correlate with increased stereotypical behaviors in the ASD population (Ashwood et al., 2011).

Patients with OCD might have significantly higher plasma levels of IL-1 $\beta$ , IL-6, and TNF- $\alpha$  levels (Rao et al., 2015; Karaguzel et al., 2019) and considerably higher levels of TNF- $\alpha$ , IL-6, and IL-17 expression levels in peripheral blood mononuclear cells in comparison to healthy controls (Kutuk et al., 2020). Compared to healthy controls, patients with OCD have significantly increased plasma levels of CCL3, CXCL8, sTNFR1, and sTNFR2 (Fontenelle et al., 2012).

Overall, these findings suggest that a proinflammatory state can be involved both in OCD and ASD pathogenesis and open a door for novel immunotherapeutics (Marazziti et al., 2018) options and make further studies focused on neuroinflammation biomarkers timely.

## 7. Treatment targets in Covid-19, OCD, and ASD

Possible immune system-mediated treatment pathways common both for OCD and ASD and COVID-19 are summarized in Table 1 below.

**Table 1**

Possible treatment pathways are similar for immune mechanisms in OCD and COVID-19.

Immune mechanisms in OCD	Possible immune targets for the treatment of COVID-19
IL-6 (Rao et al., 2015; Karaguzel et al., 2019)	Anti-IL-6 receptor antagonists (Rizk et al., 2020) tocilizumab, sarilumab, siltuximab
TNF- $\alpha$ (Rao et al., 2015; Karaguzel et al., 2019)	Anti- TNF- $\alpha$ (Rizk et al., 2020): adalimumab, infliximab
IL-1 $\beta$ (Rao et al., 2015; Karaguzel et al., 2019)	Anti-IL-1 receptor antagonist: anakinra <sup>a</sup> , (Rizk et al., 2020)

<sup>a</sup> Anakinra is a human recombinant endogenous competitive antagonist of IL-1 $\beta$ /IL-1R1 axis (Terrone et al., 2019).

## 8. Mechanisms of tocilizumab therapeutic action in neuroinflammation

### 8.1. The role of IL-6 in neuroinflammation

Interleukin (IL)-6 is associated with the pathogenesis of autoimmune and inflammatory diseases in the human body, including several neurological disorders (neuromyelitis optica, idiopathic transverse myelitis, etc. (Hofer and Campbell, 2016)) and therefore represents one of the critical cytokines in the regulation of innate and adaptive inflammatory response (Konuk et al., 2007; Wei et al., 2013; West et al., 2019). Elevated levels of IL-6 in the brain, in turn, might contribute to the development of autism spectrum disorders via activated glia and/or maternal immune activation mechanisms (Bloch et al., 2010; Nadeem et al., 2020) and lead towards impairment of learning and memory (Wei et al., 2013). IL-6 could also be implicated in changing neural cell adhesion features, which could lead to an imbalance in inhibitory and excitatory synaptic transmissions (Wei et al., 2013).

As IL-6 activation leads to chronic inflammation, it suggests a role for anti-inflammatory treatments for COVID-19 “long-haulers patients”, especially those with elevated inflammatory markers. Blocking of IL-6 expression might represent a new pathway for therapeutics targeting dysregulated host responses in patients with COVID-19, and more research in this area is needed (Coomes and Haghbayan, 2020).

**Tocilizumab (TCZ) Reduces Inflammatory Response:** TCZ may affect CNS function through two fundamental mechanisms. First, it was shown that soluble interleukin-6 receptor (sIL-6R) levels might be associated with disease progression rate in some autoimmune conditions and psychiatric disorders (Patel et al., 2012). TCZ might bind soluble IL-6 receptors and impair them to cross the blood-brain barrier (BBB) and therefore prevent their effects on the CNS (Girgis et al., 2018). Second, IL-6 may be involved in activating a proinflammatory cascade both peripherally and centrally and thus exert its impact on the CNS (Girgis et al., 2018; Reyes and Coe, 1998). TCZ, after its binding to the IL-6 receptor, might further impair this cascade (Girgis et al., 2018). Therefore, even if TCZ cannot penetrate the BBB, TCZ might successfully neutralize the detrimental effects of IL-6 in the CNS (Girgis et al., 2018). TCZ also decreases inflammatory markers, including CRP and MIF. In a recent study in rheumatoid arthritis (n = 26), TCZ at 8 mg/kg showed a significant decrease in CRP levels from 18 mg/l to 2 mg/l and significantly improved anxiety symptoms on the HADS anxiety subscale independent of improvement in physical illness (Traki et al., 2014). In another study of adult patients with RA and primary depression, depressive symptoms correlated with IL-6 levels (p = 0.011), and TCZ significantly decreased depressive symptoms on the HADS depression subscale (p = 0.023) (Figueiredo-Braga et al., 2018). Case reports are emerging reporting the effectiveness of TCZ in treating COVID-19 induced encephalopathies (Muccioli et al., 2020; Freire-Alvarez et al., 2020), making it a plausible candidate for more extensive studies in OCD and neuro-COVID-19 indication.

**TCZ is FDA-Approved for Autoimmune Disorders:** TCZ is an FDA-approved treatment for autoimmune illness, including cytokine release

syndrome, rheumatoid arthritis, systemic juvenile idiopathic arthritis, and giant cell arteritis (Sheppard et al., 2017; Schirmer et al., 2018; Pasqualetti et al., 1990). TCZ mechanisms of action consist in binding to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and have been shown to inhibit IL-6-mediated signaling through these receptors ([https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2016/014173Orig1s010.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/014173Orig1s010.pdf)). Thus, TCZ might exert its effects in ASD via modulation of T-cell activation, induction of immunoglobulin secretion, and stimulation of hematopoietic precursor cell proliferation and differentiation. TCZ represents an entirely novel approach with a potential effect on ASD and OCD as it helps alleviate immune-inflammatory processes. Therefore, it might minimize rigidity and repetitive behaviors, symptom severity, and levels of inflammatory markers, which we expect will improve the quality of life.

### 8.2. T regulatory cells and COVID-19

In a recent study of 40 COVID-19 intensive care unit (ICU) patients, it was shown that COVID-19 patients had elevated responses of Th17 cells and diminished responses of T regulatory (T reg) cells as compared with controls, and this was associated with hyper inflammation, lung damage, and disease pathogenesis (Sadeghi et al., 2021). Uncontrolled systemic inflammation characterizing COVID-19 could, in turn, lead to adverse pregnancy outcomes in infected pregnant women (Muyayalo et al., 2020). Recently, in an animal model of Maternal Immune Activation (MIA), it was shown that adoptive transfusion of T reg cells could have therapeutic potential. That adoptive T reg cell transfer can be of use in neuropsychiatric disorders associated with immune alterations (Xu et al., 2021). More research is needed to investigate if an adoptive transfer of Treg cells could potentially alleviate post-COVID-19 symptoms and also help improve PANS/PANDAS symptomatology.

## 9. Conclusions

In this review, we described parallels of basal ganglia involvement in OCD pathogenesis, during COVID-19, in Spanish flu and encephalitis lethargica (von Economo). We outlined the anti-inflammatory properties of anti-obsessional treatments. We also reviewed mechanisms of SARS-CoV-2 virus penetration in CNS, post-COVID-19 symptoms, and MRI findings in COVID-19 survivors. We reviewed the literature as to the impact of cytokines on human behavior in OCD. We summarized how immune mechanisms involved in the pathogenesis of OCD might be targeted with the anti-cytokine therapeutics used for the treatment of COVID-19 and outlined in particular possible mechanisms of tocilizumab therapeutic action in neuroinflammation, as well as T reg cells infusions. Overall, there are inflammatory mechanisms of COVID-19 pathogenesis, which may be similar to the mechanisms of the OCD onset. Therefore, anti-cytokine treatments, such as tocilizumab, might be used to treat neuropsychiatric comorbidities in COVID-19 with the new onset OC symptoms.

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## Declaration of competing interest

Dr. Hollander has received research grants from GW Pharmaceuticals and Hoffman La-Roche. He has also received research funding from the Department of Defense and Food and Drug Administration Orphan Products Division.

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## References

- Abba-Aji, A., Li, D., Hrabok, M., et al., 2020. COVID-19 pandemic and mental health: prevalence and correlates of new-onset obsessive-compulsive symptoms in a Canadian province. *Int. J. Environ. Res. Publ. Health* 17 (19).
- Al-Aly, Z., Xie, Y., Bowe, B., 2021. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 594 (7862), 259–264.
- Anderson, G.M., 2021. Fluvoxamine, melatonin and COVID-19. *Psychopharmacology (Berlin)* 238 (2), 611.
- Ashwood, P., Krakowiak, P., Hertz-Picciotto, I., Hansen, R., Pessah, I., Van de Water, J., 2011. Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. *Brain Behav. Immun.* 25 (1), 40–45.
- Banerjee, D.D., 2020. The other side of COVID-19: impact on obsessive-compulsive disorder (OCD) and hoarding. *Psychiatr. Res.* 288, 112966.
- Benros, M.E., Eaton, W.W., Mortensen, P.B., 2014. The epidemiologic evidence linking autoimmune diseases and psychosis. *Biol. Psychiatr.* 75 (4), 300–306.
- Bloch, M.H., McGuire, J., Landeros-Weisenberger, A., Leckman, J.F., Pittenger, C., 2010. Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder. *Mol. Psychiatr.* 15 (8), 850–855.
- Boldrini, M., Canoll, P.D., Klein, R.S., 2021. How COVID-19 affects the brain. *JAMA Psychiatr.* 78 (6), 682–683.
- Brambilla, R., 2019. Neuroinflammation, the thread connecting neurological disease : cluster: "Neuroinflammatory mechanisms in neurodegenerative disorders". *Acta Neuropathol.* 137 (5), 689–691.
- Chan, A.T., Drew, D.A., Nguyen, L.H., et al., 2020. The Coronavirus pandemic epidemiology (cope) consortium: a call to action. *Cancer Epidemiol. Biomarkers Prev.* 29 (7), 1283–1289.
- Chougar, L., Shor, N., Weiss, N., et al., 2020. Retrospective observational study of brain MRI findings in patients with acute SARS-CoV-2 infection and neurologic manifestations. *Radiology* 297 (3), E313–E323.
- Coomes, E.A., Haghbayan, H., 2020. Interleukin-6 in Covid-19: a systematic review and meta-analysis. *Rev. Med. Virol.* 30 (6), 1–9.
- Daci, R., Kennelly, M., Ferris, A., et al., 2020. Bilateral basal ganglia hemorrhage in a patient with confirmed COVID-19. *AJNR Am. J. Neuroradiol.* 41 (10), 1797–1799.
- Dalle, E., Daniels, W.M., Mabandla, M.V., 2017. Fluvoxamine maleate normalizes striatal neuronal inflammatory cytokine activity in a Parkinsonian rat model associated with depression. *Behav. Brain Res.* 316, 189–196.
- Dani, M., Dirksen, A., Taraborrelli, P., et al., 2021. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin. Med.* 21 (1), e63–e67.
- Davide, P., Andrea, P., Martina, O., Andrea, E., Davide, D., Mario, A., 2020. The impact of the COVID-19 pandemic on patients with OCD: effects of contamination symptoms and remission state before the quarantine in a preliminary naturalistic study. *Psychiatr. Res.* 291, 113213.
- Dell'Osso, B., Allen, A., Hollander, E., 2005. Fluvoxamine: a selective serotonin reuptake inhibitor for the treatment of obsessive-compulsive disorder. *Expet Opin. Pharmacother.* 6 (15), 2727–2740.
- Dickman, M.S., 2001. von Economo encephalitis. *Arch. Neurol.* 58 (10), 1696–1698.
- Eisenberger, N.I., Moieni, M., 2020. Inflammation affects social experience: implications for mental health. *World Psychiatr.* 19 (1), 109–110.
- Eldeeb, M.A., Hussain, F.S., Siddiqi, Z.A., 2020. COVID-19 infection may increase the risk of parkinsonism - remember the Spanish flu? *Cytokine Growth Factor Rev.* 54, 6–7.
- Ellul, M.A., Benjamin, L., Singh, B., et al., 2020. Neurological associations of COVID-19. *Lancet Neurol.* 19 (9), 767–783.
- Farzanfar, D., Dowlati, Y., French, L.E., Lowes, M.A., Alavi, A., 2018. Inflammation: a contributor to depressive comorbidity in inflammatory skin disease. *Skin Pharmacol. Physiol.* 31 (5), 246–251.
- Figueiredo-Braga, M., Cornaby, C., Cortez, A., et al., 2018. Influence of biological therapeutics, cytokines, and disease activity on depression in rheumatoid arthritis. *J. Immunol. Res.* 2018, 5954897.
- Fineberg, N.A., Baldwin, D.S., Drummond, L.M., et al., 2018. Optimal treatment for obsessive compulsive disorder: a randomized controlled feasibility study of the clinical-effectiveness and cost-effectiveness of cognitive-behavioural therapy, selective serotonin reuptake inhibitors and their combination in the management of obsessive compulsive disorder. *Int. Clin. Psychopharmacol.* 33 (6), 334–348.
- Fineberg, N.A., Van Ameringen, M., Drummond, L., et al., 2020. How to manage obsessive-compulsive disorder (OCD) under COVID-19: a clinician's guide from the international College of obsessive compulsive spectrum disorders (ICOCs) and the obsessive-compulsive and related disorders research network (ocrn) of the European College of Neuropsychopharmacology. *Compr. Psychiatr.* 100, 152174.
- Fontenelle, L.F., Miguel, E.C., 2020. The impact of coronavirus (COVID-19) in the diagnosis and treatment of obsessive-compulsive disorder. *Depress. Anxiety* 37 (6), 510–511.
- Fontenelle, L.F., Barbosa, I.G., Luna, J.V., de Sousa, L.P., Abreu, M.N., Teixeira, A.L., 2012. A cytokine study of adult patients with obsessive-compulsive disorder. *Compr. Psychiatr.* 53 (6), 797–804.
- Franceschi, A.M., Ahmed, O., Gliberto, L., Castillo, M., 2020. Hemorrhagic posterior reversible encephalopathy syndrome as a manifestation of COVID-19 infection. *AJNR Am. J. Neuroradiol.* 41 (7), 1173–1176.
- Freire-Alvarez, E., Guillen, L., Lambert, K., et al., 2020. COVID-19-associated encephalitis successfully treated with combination therapy. *Clin. Infect Pract.* 7, 100053.
- French, I., Lyne, J., 2020. Acute exacerbation of OCD symptoms precipitated by media reports of COVID-19. *Ir. J. Psychol. Med.* 37 (4), 291–294.
- Giedd, J.N., Rapoport, J.L., Garvey, M.A., Perlmutter, S., Swedo, S.E., 2000. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. *Am. J. Psychiatr.* 157 (2), 281–283.
- Girgis, R.R., Ciarleglio, A., Choo, T., et al., 2018. A randomized, double-blind, placebo-controlled clinical trial of tocilizumab, an interleukin-6 receptor antibody, for residual symptoms in schizophrenia. *Neuropsychopharmacology* 43 (6), 1317–1323.
- Goodman, W.K., Grice, D.E., Lapidus, K.A., Coffey, B.J., 2014. Obsessive-compulsive disorder. *Psychiatr. Clin.* 37 (3), 257–267.
- Gubernatorova, E.O., Gorshkova, E.A., Polinova, A.I., Drutskaya, M.S., 2020. IL-6: Relevance for immunopathology of SARS-CoV-2. *Cytokine Growth Factor Rev.* 53, 13–24.
- Harry, G.J., Kraft, A.D., 2008. Neuroinflammation and microglia: considerations and approaches for neurotoxicity assessment. *Expet Opin. Drug Metabol. Toxicol.* 4 (10), 1265–1277.
- Herold, T., Jurinovic, V., Arnreich, C., et al., 2020. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J. Allergy Clin. Immunol.* 146 (1), 128–136 e124.
- Hoertel, N., Sanchez-Rico, M., Vernet, R., et al., 2021. Association between antidepressant use and reduced risk of intubation or death in hospitalized patients with COVID-19: results from an observational study. *Mol. Psychiatr.* 26 (9), 5199–5212.
- Hofer, M.J., Campbell, I.L., 2016. Immunoinflammatory diseases of the central nervous system - the tale of two cytokines. *Br. J. Pharmacol.* 173 (4), 716–728.
- Hojyo, S., Uchida, M., Tanaka, K., et al., 2020. How COVID-19 induces cytokine storm with high mortality. *Inflamm. Regen.* 40, 37. [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/125276s107\\_125472s0181bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125276s107_125472s0181bl.pdf).
- International, W.H.O., 2010. Classification of Diseases (ICD-10), tenth ed. World Health Organization, Geneva.
- Kappelmann, N., Lewis, G., Dantzer, R., Jones, P.B., Khandaker, G.M., 2018. Antidepressant activity of anti-cytokine treatment: a systematic review and meta-analysis of clinical trials of chronic inflammatory conditions. *Mol. Psychiatr.* 23 (2), 335–343.
- Karaguzel, E.O., Arslan, F.C., Uysal, E.K., et al., 2019. Blood levels of interleukin-1 beta, interleukin-6 and tumor necrosis factor-alpha and cognitive functions in patients with obsessive compulsive disorder. *Compr. Psychiatr.* 89, 61–66.
- Kohler, C.A., Freitas, T.H., Stubbs, B., et al., 2018. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: systematic review and meta-analysis. *Mol. Neurobiol.* 55 (5), 4195–4206.
- Koning, L., 2009. [Encephalitis lethargica in The Netherlands; renewed interest in a mysterious disease]. *Ned. Tijdschr. Geneesk.* 153, B326.
- Konuk, N., Tekin, I.O., Ozturk, U., et al., 2007. Plasma levels of tumor necrosis factor-alpha and interleukin-6 in obsessive compulsive disorder. *Mediatr. Inflamm.* 2007, 65704.
- Kremer, S., Lersy, F., Anheim, M., et al., 2020. Neurologic and neuroimaging findings in patients with COVID-19: a retrospective multicenter study. *Neurology* 95 (13), e1868–e1882.
- Kumar, A., Somani, A., 2020. Dealing with Corona virus anxiety and OCD. *Asian J Psychiatr* 51, 102053.
- Kutuk, M.O., Tufan, A.E., Kilicaslan, F., et al., 2020. Novel inflammatory targets for immunotherapies in pediatric patients with trichotillomania. *Immunobiology* 225 (3), 151913.
- Lenze, E.J., Mattar, C., Zorumski, C.F., et al., 2020. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. *J. Am. Med. Assoc.* 324 (22), 2292–2300.
- Lutters, B., Foley, P., Koehler, P.J., 2018. The centennial lesson of encephalitis lethargica. *Neurology* 90 (12), 563–567.
- Mandal, S., Barnett, J., Brill, S.E., et al., 2020. 'Long-COVID': a Cross-Sectional Study of Persisting Symptoms, Biomarker and Imaging Abnormalities Following Hospitalisation for COVID-19. *Thorax*.
- Marazziti, D., Mucci, F., Fontenelle, L.F., 2018. Immune system and obsessive-compulsive disorder. *Psychoneuroendocrinology* 93, 39–44.
- Martino, D., Johnson, I., Leckman, J.F., 2020. What does immunology have to do with normal brain development and the pathophysiology underlying tourette syndrome and related neuropsychiatric disorders? *Front. Neurol.* 11, 567407.
- Masi, A., Glozier, N., Dale, R., Guastella, A.J., 2017. The immune system, cytokines, and biomarkers in autism spectrum disorder. *Neurosci. Bull.* 33 (2), 194–204.
- Mehta, P., McAuley, D.F., Brown, M., et al., 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395 (10229), 1033–1034.
- APA. American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed.
- Moretti, G., Pasquini, M., Mandarelli, G., Tarsitani, L., Biondi, M., 2008. What every psychiatrist should know about PANDAS: a review. *Clin. Pract. Epidemiol. Ment. Health* 4, 13.
- Muccioli, L., Pensato, U., Bernabe, G., et al., 2021. Intravenous immunoglobulin therapy in COVID-19-related encephalopathy. *J. Neurol.* 268 (8), 2671–2675.
- Muccioli, L., Pensato, U., Cani, I., et al., 2020. COVID-19-related encephalopathy presenting with aphasia resolving following tocilizumab treatment. *J. Neuroimmunol.* 349, 577400.
- Muyayalo, K.P., Huang, D.H., Zhao, S.J., Xie, T., Mor, G., Liao, A.H., 2020. COVID-19 and Treg/Th17 imbalance: potential relationship to pregnancy outcomes. *Am. J. Reprod. Immunol.* 84 (5), e13304.
- Nadeem, A., Ahmad, S.F., Attia, S.M., Al-Ayadhi, L.Y., Al-Harbi, N.O., Bakheet, S.A., 2020. Dysregulation in IL-6 receptors is associated with upregulated IL-17A related signaling in CD4+ T cells of children with autism. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 97, 109783.

- Nalbandian, A., Sehgal, K., Gupta, A., et al., 2021. Post-acute COVID-19 syndrome. *Nat. Med.* 27 (4), 601–615.
- Nissen, J.B., Hojgaard, D., Thomsen, P.H., 2020. The immediate effect of COVID-19 pandemic on children and adolescents with obsessive compulsive disorder. *BMC Psychiatr.* 20 (1), 511.
- Nobile, B., Durand, M., Olie, E., et al., 2021. The anti-inflammatory effect of the tricyclic antidepressant clomipramine and its high penetration in the brain might be useful to prevent the psychiatric consequences of SARS-CoV-2 infection. *Front. Pharmacol.* 12, 615695.
- Paces, J., Strizova, Z., Smrz, D., Cerny, J., 2020. COVID-19 and the immune system. *Physiol. Res.* 69 (3), 379–388.
- Pallanti, S., 2008. Transcultural observations of obsessive-compulsive disorder. *Am. J. Psychiatr.* 165 (2), 169–170.
- Pallanti, S., Sandner, C., 2007. Treatment of depression with selective serotonin inhibitors: the role of fluvoxamine. *Int. J. Psychiatr. Clin. Pract.* 11 (3), 233–238.
- Pallanti, S., Grassi, E., Makris, N., Gasic, G.P., Hollander, E., 2020. Neurocovid-19: a clinical neuroscience-based approach to reduce SARS-CoV-2 related mental health sequelae. *J. Psychiatr. Res.* 130, 215–217.
- Park, S.E., 2020. Epidemiology, virology, and clinical features of severe acute respiratory syndrome -coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). *Clin. Exp. Pediatr.* 63 (4), 119–124.
- Pasqualetti, P., Colantonio, D., Collacciani, A., Casale, R., 1990. Socioeconomic status and survival in multiple myeloma. *Minerva Med.* 81 (10), 713–716.
- Patel, A., Zhu, Y., Kuzhikandathil, E.V., Banks, W.A., Siegel, A., Zalcan, S.S., 2012. Soluble interleukin-6 receptor induces motor stereotypies and co-localizes with gp130 in regions linked to cortico-striato-thalamo-cortical circuits. *PLoS One* 7 (7), e41623.
- Paterson, R.W., Brown, R.L., Benjamin, L., et al., 2020. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* 143 (10), 3104–3120.
- Peterson, B.S., Leckman, J.F., Tucker, D., et al., 2000. Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. *Arch. Gen. Psychiatr.* 57 (4), 364–372.
- Pilloni, G., Bikson, M., Badran, B.W., et al., 2020. Update on the use of transcranial electrical brain stimulation to manage acute and chronic COVID-19 symptoms. *Front. Hum. Neurosci.* 14, 595567.
- Pinto, A., Mancebo, M.C., Eisen, J.L., Pagano, M.E., Rasmussen, S.A., 2006. The Brown Longitudinal Obsessive Compulsive Study: clinical features and symptoms of the sample at intake. *J. Clin. Psychiatr.* 67 (5), 703–711.
- Postorino, V., Kerns, C.M., Vivanti, G., Bradshaw, J., Siracusano, M., Mazzone, L., 2017. Anxiety disorders and obsessive-compulsive disorder in individuals with autism spectrum disorder. *Curr. Psychiatr. Rep.* 19 (12), 92.
- Rao, N.P., Venkatasubramanian, G., Ravi, V., Kalmady, S., Cherian, A., Yc, J.R., 2015. Plasma cytokine abnormalities in drug-naive, comorbidity-free obsessive-compulsive disorder. *Psychiatr. Res.* 229 (3), 949–952.
- Reyes, T.M., Coe, C.L., 1998. The proinflammatory cytokine network: interactions in the CNS and blood of rhesus monkeys. *Am. J. Physiol.* 274 (1), R139–R144.
- Ricci, S., Businaro, R., Ippoliti, F., et al., 2013. Altered cytokine and BDNF levels in autism spectrum disorder. *Neurotox. Res.* 24 (4), 491–501.
- Rivera, R.M., Carballea, D., 2020. Coronavirus: a trigger for OCD and illness anxiety disorder? *Psychol. Trauma* 12 (S1), S66.
- Rizk, J.G., Kalantar-Zadeh, K., Mehra, M.R., Lavie, C.J., Rizk, Y., Forthall, D.N., 2020. Pharmac-immunomodulatory therapy in COVID-19. *Drugs* 80 (13), 1267–1292.
- Rosen, D.A., Seki, S.M., Fernandez-Castaneda, A., et al., 2019. Modulation of the sigma-1 receptor-IRE1 pathway is beneficial in preclinical models of inflammation and sepsis. *Sci. Transl. Med.* 11 (478).
- Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. *Mol. Psychiatr.* 15 (1), 53–63.
- Russell, C.D., Millar, J.E., Baillie, J.K., 2020. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 395 (10223), 473–475.
- Sadeghi, A., Tahmasebi, S., Mahmood, A., et al., 2021. Th17 and Treg cells function in SARS-CoV2 patients compared with healthy controls. *J. Cell. Physiol.* 236 (4), 2829–2839.
- Schirmer, M., Muratore, F., Salvarani, C., 2018. Tocilizumab for the treatment of giant cell arteritis. *Expert Rev. Clin. Immunol.* 14 (5), 339–349.
- Sheppard, M., Laskou, F., Stapleton, P.P., Hadavi, S., Dasgupta, B., 2017. Tocilizumab (Actemra). *Hum. Vaccines Immunother.* 13 (9), 1972–1988.
- Stearo, L., Steardo Jr., L., Zorec, R., Verkhatsky, A., 2020. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol.* 229 (3), e13473.
- Swedo, S.E., Leonard, H.L., Garvey, M., et al., 1998. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am. J. Psychiatr.* 155 (2), 264–271.
- Taquet, M., Geddes, J.R., Husain, M., Luciano, S., Harrison, P.J., 2021. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry* 8 (5), 416–427.
- Terrone, G., Frigerio, F., Balosso, S., Ravizza, T., Vezzani, A., 2019. Inflammation and reactive oxygen species in status epilepticus: biomarkers and implications for therapy. *Epilepsy Behav.* 101 (Pt B), 106275.
- Traki, L., Rostom, S., Tahiri, L., et al., 2014. Responsiveness of the EuroQol EQ-5D and hospital anxiety and depression scale (HADS) in rheumatoid arthritis patients receiving tocilizumab. *Clin. Rheumatol.* 33 (8), 1055–1060.
- Troyer, E.A., Kohn, J.N., Hong, S., 2020. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav. Immun.* 87, 34–39.
- Varatharaj, A., Thomas, N., Ellul, M.A., et al., 2020. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. *Lancet Psychiatry* 7 (10), 875–882.
- Varga, Z., Flammer, A.J., Steiger, P., et al., 2020. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 395 (10234), 1417–1418.
- Versace, V., Sebastianelli, L., Ferrazzoli, D., et al., 2021. Intracortical GABAergic dysfunction in patients with fatigue and dysexecutive syndrome after COVID-19. *Clin. Neurophysiol.* 132 (5), 1138–1143.
- Wang, F., Kream, R.M., Stefano, G.B., 2020. Long-term respiratory and neurological sequelae of COVID-19. *Med. Sci. Mon. Int. Med. J. Exp. Clin. Res.* 26, e928996.
- Wei, H., Alberts, I., Li, X., 2013. Brain IL-6 and autism. *Neuroscience* 252, 320–325.
- West, P.K., Viengkhou, B., Campbell, I.L., Hofer, M.J., 2019. Microglia responses to interleukin-6 and type I interferons in neuroinflammatory disease. *Glia* 67 (10), 1821–1841.
- Woo, M.S., Malsy, J., Pottgen, J., et al., 2020. Frequent neurocognitive deficits after recovery from mild COVID-19. *Brain Commun.* 2 (2), fcaa205.
- Xiong, Q., Xu, M., Li, J., et al., 2021. Clinical sequelae of COVID-19 survivors in Wuhan, China: a single-centre longitudinal study. *Clin. Microbiol. Infect.* 27 (1), 89–95.
- Xu, Z., Zhang, X., Chang, H., et al., 2021. Rescue of maternal immune activation-induced behavioral abnormalities in adult mouse offspring by pathogen-activated maternal Treg cells. *Nat. Neurosci.* 24 (6), 818–830.
- Ye, Q., Wang, B., Mao, J., 2020. The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. *J. Infect.* 80 (6), 607–613.
- Zhou, Z., Kang, H., Li, S., Zhao, X., 2020. Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. *J. Neurol.* 267 (8), 2179–2184.