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MOOD DISORDERS (E BACA-GARCIA, SECTION EDITOR)

How Does COVID-19 Affect the Neurobiology of Suicide?

I. Conejero [1,2] · B. Nobile [1,2] · E. Olié [1,2,3] · Ph. Courtet [1,2,3]

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Abstract

Purpose of Review The aim of this review was to analyze COVID-19 effect on the biological features of suicidal vulnerability and its interaction with suicide-related biological pathways. We carried out a narrative review of international publications on the interactions of COVID-19 with the biological bases of suicide.

Recent Findings We hypothesize that SARS-CoV-2 interacts with multiple biological processes that underlie suicidal behavior, such as the renin-angiotensin system, nicotinic receptors, and central and systemic inflammation. Social distancing measures may also worsen subjective or objective social disconnection, thus increasing the risk of suicide. Interestingly, the drugs used to prevent suicide could be promising options to counteract brain damage caused by this coronavirus.

Summary SARS-CoV-2 interacts with multiple biological pathways involved in suicide and opens a new window for understanding the suicidal process. The development of suicide prevention treatments in the context of a pandemic may benefit from knowledge on these interactions.

Keywords COVID-19 · Suicidal vulnerability · Inflammation · HPA axis · Social isolation · Psychotropic treatments

Introduction

The first human cases of infection by the novel severe acute respiratory syndrome-coronavirus type 2 (SARS-CoV-2) were identified in the city of Wuhan, China, at the end of 2019. Today, with more than 100,000,000 individuals diagnosed worldwide [1], the COVID-19 outbreak has reached a large part of the world population.

Besides the respiratory symptoms, the pandemic might have an emotional impact and might favor the emergence or worsening of psychiatric symptoms in people with COVID-19 or with a specific vulnerability to mental disorders [2]. Indeed, during the previous SARS pandemic, people developed psychological symptoms due to the quarantine, or psychological stress linked to the fear of contamination. For instance, in Canada, a significant proportion of the 1057 individuals confined during the SARS epidemic reported fear symptoms (20%), sadness (18%), and even feeling of guilt (10%) [3]. Some of these symptoms persisted after 3 years of follow-up: substance use, alcohol dependence, or post-traumatic stress disorder [4]. During the current pandemic, more than 29% of patients with COVID-19 developed depressive symptoms in the province of Guangdong [5]. Moreover, around 20% of patients with a pre-existing psychiatric disorder reported worsening of their psychological state and interruption of psychiatric care during the pandemic [6]. The negative psychological impact was severe in psychiatric patients, particularly for anger, impulsivity, and suicidal ideation [7]. It was also suggested that young-old people may be at risk of increased depressive symptoms and suicidal acts [8].

The psychosocial stress imposed by the society changes in response to this pandemic may increase the vulnerability to suicidal behaviors at several levels. Social isolation, resulting from the quarantine imposed to more than a half of the world population, is a well-known risk factor for suicide [9]. Quarantine may worsen the risk of domestic violence and limit the possibilities of psychological support [10]. The announced economic crisis also is likely to influence suicide rates [11]. It has been estimated that the related rise of unemployment will lead to more suicides (up to 9570 additional

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✉ I. Conejero
ismael.conejero@gmail.com

[1] Department of Emergency Psychiatry and Acute Care, Lapeyronie Hospital, CHU Montpellier, Montpellier, France

[2] PSNREC, Univ Montpellier, INSERM, CHU de Montpellier, Montpellier, France

[3] FondaMental Foundation, Créteil, France

suicides per year) [12]. Therefore, an increase of suicide rates, as observed during the Spanish "flu" pandemic (1918), is expected [13]. Consequently, the present pandemic is a source of concern in populations facing psychosocial stressors. In many vulnerable people, the emotional, social, health, and financial consequences of this pandemic could lead to mental health problems and suicidal behaviors, in the immediate aftermath and also in the longer term. The scientific and mental health communities should proactively prepare and use this challenging period to improve suicide research and prevention.

Recent biological data suggest that SARS-CoV-2 can affect the central nervous system (CNS) [14] through biological pathways implicated in suicidal behaviors: renin-angiotensin system, inflammation system, and nicotine receptors. Social distancing measures also are leading to neurobiological changes involved in suicidal behavior, such as inflammation [15]. A better understanding of the connections between COVID-19 pathophysiology and the biology of suicide is the first step to address suicide prevention and to propose effective treatments in a pandemic context.

In this review, we propose to highlight the possible biological mechanisms through which COVID-19 may influence suicidal vulnerability and increase the risk of suicidal acts. A better understanding of this link may help to identify the populations at risk and to monitor patients with the highest suicidal risk in an adequate time window, depending on the mid- and long-term neuropsychiatric consequences. We also discuss how the COVID-19 outbreak may help to better understand the neural and biological correlates of suicidal behavior. Finally, we focus on interactions between the psychotropic medications used to treat suicidal patients and COVID-19 and discuss how these drugs might limit the inflammation induced by SARS-CoV-2.

Viral Infection: Is there a Link with Suicidal Acts?

Studies on respiratory viral infections have identified an association between infection and risk for suicide. Specifically, mood disorders have been associated with the presence of antibodies against influenza A and B viruses and a coronavirus strain (HCov-NL63) [16]. Influenza B seropositivity has been significantly associated with history of suicide attempt (OR = 2.53, CI 1.33–4.80). In general, exposure to infectious agents is an aggravating factor for the risk of self-harm [17]. This study, based on the analysis of Danish registers, showed that individuals with infections are at greater risk of deliberate self-harm compared with controls (hazard rate ratio: 1.80 (95% CI = 1.68–1.91)). Redeemed prescriptions for anti-infective medications were considered as a proxy for infection. In addition, this association depended on the infection severity, as indicated by the higher suicide risk in individuals hospitalized for infections (hazard rate ratio: 3.13 (95% CI = 1.67–5.87)) [17]. The underlying causes are multiple, including inflammatory changes [18], and microbiota modification secondary to the use of anti-infective agents and its influence on the CNS [19••]. Several mechanisms might be at work in the infection-related brain damage: retrograde axonal transport of the virus from the respiratory mucosa [14], peripheral inflammation that modulates brain function, and migration of mononuclear cells transporting the virus across the blood-brain barrier (BBB) [14]. Finally, some studies suggested that antiviral agents also could influence mood disorders, as summarized in Table 1.

Suicide attempts, completed suicides, and respiratory viruses share seasonal patterns. Human coronaviruses, respiratory syncytial virus, and influenza virus have a peak incidence during the winter months [20], immediately followed by suicide (especially violent suicide), the incidence of which is maximal in spring and early summer [21]. Only some types of respiratory enteroviruses have a peak overlapping with suicide [20]. Although a link between the annual fluctuations of suicidal acts and infections has not been demonstrated yet, they might share some determinants that follow seasonal patterns, such as the host immune characteristics. Maes et al. (1996) showed that the violent suicide peak is synchronized with variations of the CD4+/CD8+ cell ratio [22] and number of CD20+ B cells that are involved in viral immunity [23, 24]. Interestingly, CD4+ and CD8+ cell concentrations are decreased in patients with COVID-19 [25]. Finally, chronic low-grade inflammation induced by infection may increase suicide risk in the months after the viral peak incidence [26]. Therefore, in the period following the pandemic peak, the populations at risk should be closely monitored due to the effect of seasonal cyclicity, chronic immune response, and delayed neuropsychiatric sequelae [14].

COVID-19 and the Renin-Angiotensin System: A Path to Suicide

The most recent research on COVID-19 has shown that the virus enters host cells through interaction of its spike protein with the angiotensin-converting enzyme 2 (ACE-2) receptor that is expressed at the cell surface [27, 28, 29]. ACE-2 is broadly expressed in human cells, including gastrointestinal, heart, and alveolar cells [30], and CNS [31]. Consequently, concern has been raised on the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) because they might increase ACE-2 expression, particularly in the cardiovascular system and CNS [31, 32], and facilitate SARS-CoV-2 entry [30, 33].

Interestingly, previous studies established the implication of the renin-angiotensin system in suicidal vulnerability, particularly the use of ARB. In a study in which 964 people who died by suicide were matched with 3856 controls, the risk of suicide death was higher in ARB users than in ACEI users

Table 1 Main treatments tested in ongoing trials in patients with COVID-19 for which there are data on mood disorders and suicide risk [156, 157]

Treatment	Type	Mechanism of action	Effect on mood disorder and suicide risk
Chloroquine	Antimalarial	Endosomal acidification, fusion inhibitor, anti-inflammatory activity	No direct effect on suicide, but increased risk of depression [158]
Hydroxychloroquine	Antimalarial	Endosomal acidification, fusion inhibitor, anti-inflammatory activity	Increased risk of depression and suicidal ideation [159]
Lopinavir	Antiviral	Protease inhibitor	Inconclusive data, but effects on mood disorders [160–163]
Ritonavir	Antiviral	Protease inhibitor	Inconclusive data, but effects on mood disorders [160–163]
Oseltamivir	Antiviral	Potent and selective inhibitor of neuraminidase	Inconclusive data, but possible effects on mood disorders [164–166]
Interferons	Antiviral	Inhibition of viral RNA transcription, protein translation, and post-translational modification: suppress virus replication	Significant increased risk of depression, suicidal behavior [167, 168]
Tocilizumab	mAb	Humanized mAb against IL-6	Significant improvement of depressive symptomatology (from randomized controlled trials in depressed patients) [169–171]
Sarilumab	mAb	Humanized mAb against IL-6	Significant improvement of depressive symptomatology (from randomized controlled trials in depressed patients) [169–171]
Anakinra	mAb	Human IL-1 receptor antagonist	Possible positive effect on depression [172]
Adalimumab	mAb	Humanized mAb against TNFα	Significant improvement of depressive symptomatology (from randomized controlled trials in depressed patients) [169–171]
Corticosteroids	Corticosteroids	Dampen pro-inflammatory cytokines	Increased risk of mood disorders and possibly of suicidal behavior [173–175]

(OR: 1.63; 95%CI, 1.33–2.00) [34, 35]. Furthermore, the presence of the ACE insertion/deletion (I/D) polymorphism has been associated with suicidal behavior in two independent case-control studies [36, 37]. Specifically, the ACE D/D genotype was associated with higher suicide risk (OR: 2.4, 95% CI 1.2–4.8 and OR: 1.3, 95% CI 1.0–1.7, in each cohort). D allele carriers have higher ACE serum levels than I allele carriers [38]. Another study reported the association between this *ACE* polymorphism and suicidal behavior in Japanese males [36]. Similarly, Baghai et al. found an association between the single nucleotide polymorphism rs4291 in *ACE* promoter region and unipolar depression in two independent case-control samples that included, in total, 843 unrelated patients with unipolar depression and 1479 healthy controls [39]. In addition, the higher plasma concentrations of ACE linked to the presence of the D/D genotype promote the hypothalamic-pituitary-adrenal (HPA) axis activity in depressed individuals [40]. The D/D genotype has been associated also with bipolar disorders and psychotic symptoms in bipolar patients [41], all risk factors for suicide. *ACE* genetic variants have been detected in older people who meet criteria for depressive disorder and were associated with higher cortisol secretion [42].

Although SARS-CoV-2 targets the ACE-2 receptor, both homologous enzymes (ACE and ACE-2) act in brain cells through a shared enzymatic cascade (angiotensin II is produced by ACE and is an ACE-2 substrate), intracellular gene regulation, and nitric oxide release [31]. SARS-CoV-2 has neuro-invasive potential [43] and could enter the CNS by targeting the ACE-2 receptors that are widely expressed in the brain and BBB [44]. The virus decreases ACE-2 activity [45], and this might unbalance ACE/ACE-2 metabolic pathways. This could affect the vulnerability to suicide in individuals who carry the "risky" *ACE* genotypes. Moreover, ACE-2 downregulation by SARS-CoV-2 might interfere with monoamine synthesis in the brain, for instance, dopamine [46], that is implicated in mood disorders and suicidal behaviors. Hence, the hypothesis that SARS-CoV-2 infection might increase suicidal vulnerability through the renin-angiotensin system should be explored in future studies.

Interestingly, a recent review suggests that nicotine might interfere with the renin-angiotensin system [47].

SARS-CoV-2 Targets the Nicotine Receptor: What About Suicide in Smokers?

A large body of evidence supports the existence of strong relationships between tobacco consumption and suicidal behaviors. In a study on 347 psychiatric patients, smokers were more likely to attempt suicide (OR: 2.60, 95% CI 1.60–4.23)

compared with non-smokers, even after adjustment for sociodemographic and clinical data [48]. A meta-analysis reported that current smokers are at greater risk of suicidal ideation, plans, attempts, and completed suicide [49]. This association could be explained by an impairment of serotonin function by smoking [50]. The link between nicotine intake and monoamine dysfunction is suggested by the pre-synaptic localization of nicotinic cholinergic receptors on catecholamine and serotonin axons [51]. Furthermore, nicotine administration in murine models decreases serotoninergic transmission in the hippocampus and reduces firing of serotoninergic neurons in the midbrain [48, 52]. In parallel to its direct effect on suicide, the acetylcholine system is closely related to depression that in turn increases the vulnerability to suicidal acts and might be deregulated by alterations in nicotinic acetylcholine receptor signaling [53].

Recent reports showed that the nicotinic cholinergic system is dysregulated in patients with COVID-19 [54], and tobacco exposure has been associated with disease progression [55]. In addition, structural studies suggest that SARS-CoV-2 might enter the CNS by binding to nicotinic receptors [56]. According to the "nicotinic hypothesis," SARS-CoV-2 spike protein contains a motif that is homologous to the neurotoxin-like region that is found in the rabies virus that acts as nicotinic acetylcholine receptor blocker. Hence, through its interaction with the cholinergic system, SARS-CoV-2 might interfere again with suicidal vulnerability.

ACE-2 expression in bronchial epithelial cells is higher in smokers than non-smokers [57]. Moreover, nicotine upregulates ACE and its subsequent metabolic cascade in the CNS and downregulates ACE-2, further unbalancing the brain renin-angiotensin system [58, 59]. In addition, nicotinic receptors contribute to the pathophysiology of inflammation and modulate the inflammatory response, including the secretion of tumor necrosis factor α (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6) [60] that have been associated with depressive phenotypes [61] and suicidal vulnerability [62]. Altogether, the interconnexions of these different pathways show that nicotinic receptors may participate in the association between COVID-19 and suicidal behavior. However, this relationship may be modulated by a specific infection profile in smokers that has to be determined.

SARS-CoV-2, Inflammation, and HPA Axis: A Pathway Shared with Suicide

Following the viral invasion phase, SARS-CoV-2 induces a cytokine "storm" in a subgroup of patients that dramatically worsen their clinical outcome [63]. This is accompanied by the release of the pro-inflammatory cytokines IL-6, TNFα, and IL-1 [63, 64]. Cytokine release syndrome leads also to an increase of the serum levels of cytokines, C-reactive protein (CRP), and IL-2 receptor and a decrease of the CD4+/CD8+ ratio [25, 65]. COVID-19-related inflammation may also extend to the CNS through BBB breakdown, viral neuro-invasion, and cytokine secretion [66]. In the brain, SARS-CoV-2 infection can initiate chronic low-grade inflammation that alters cognitive functions and induces neurotoxicity and neurodegeneration [26], thus preparing the ground for psychiatric disorders.

Studies have reported an association between baseline blood level of cytokines and brain activation in psychiatric populations. For example, the basal level of peripheral IL-1 and IL-2 modulates the activation of cerebral networks dedicated to emotion regulation (anterior cingulate, orbitofrontal cortex, and insula) [67] in patients with history of depression. In line with the link between peripheral inflammatory markers and emotion processing, several studies have established an association between basal low-grade systemic inflammation and suicidal behaviors [68]. Indeed, CRP blood level has been associated with suicide attempts [69] and with the intensity of suicidal ideation [70]. Two meta-analyses reported increased concentration of IL-1β and IL-6 in the blood and in the brain samples from people who died by suicide [71] and reduced IL-2 plasma levels in suicidal patients [18].

Interestingly, IL-6 plays a key role in SARS-CoV-2-related inflammation [65], particularly patients with severe COVID-19 [72]. IL-6 has been linked to psychological dimensions that underlie the suicidal process (e.g., impulsivity and the choice of violent suicide attempt method) [73] and may cause depressive disorders [74]. Moreover, IL-2 receptor increase has been related to COVID-19 [25] and vulnerability to suicide [75].

Some studies have highlighted the implication of monocytes in SARS-CoV infection as host cells for viral replication [76], and through the regulation of immune-related genes, and induction of monocyte-associated immune response [77] that may be a starting point for the inflammatory storm. Monocytes are implicated also in the pathogenesis of psychiatric disorders and suicidal behaviors. Indeed, monocyte trafficking within the CNS increases in stress conditions, provides information on the peripheral immune state, and amplifies the behavioral stress response [78]. Monocyte trafficking also activates microglia, and microglial hyperactivation, especially in the anterior cingulate cortex and insula, has been detected in patients with suicidal thoughts [79••]. Microglial activation is also induced by peripheral inflammation first within the circumventricular organs, leptomeninges, and choroid plexus and then throughout the CNS [78]. Interestingly, the monocyte-to-lymphocyte ratio in peripheral blood samples has been associated with age at first suicide attempt [80], and activated monocytes are more likely to be detected in plasma from patients with depression [81]. Higher monocyte count and increased IL-6 level were observed in patients at risk for suicide [82].

Importantly, it has been proposed that the rapid action of ketamine (NMDA antagonist) significantly reduces

depression and suicidal ideation through the decrease of pro-inflammatory cytokines [83]. Its antidepressant effect partially relies on modulation of the immune response: reduction of circulating classical pro-inflammatory monocytes and increase of alternative M2 macrophages [81]. Finally, some anti-inflammatory agents (such as anti-IL6 antibodies) that are currently tested in COVID-19 have shown efficacy in individuals with mood disorders (Table 1). These findings suggest that SARS-CoV-2 infection may potentially impair the brain immune system underlying the suicidal process.

In addition, SARS-CoV-2 infection and suicidal risk are associated with modifications of the HPA axis function. Reports on previous coronavirus outbreaks have highlighted a possible interaction between coronaviruses and cortisol secretion [84]. Indeed, SARS-CoV (a coronavirus that shares high similarities with SARS-CoV-2) expresses sequences that mimic the host adrenocorticotropic hormone (ACTH). This results in the fixation of host antibodies on ACTH and blunting of cortisol secretion [85]. Moreover, SARS-CoV might also cause hypophysis dysfunction, resulting in HPA axis under-activation and hypocortisolism, which was observed in 39% of SARS-CoV survivors [86]. Although there is no direct evidence of impaired cortisol secretion in patients with COVID-19, HPA axis dysfunction is a potential consequence of this viral disease that might affect suicidal vulnerability. Indeed, blunted cortisol secretion is observed in patients with depression and lifetime history of suicide attempts [87]. Moreover, decreased cortisol secretion may precede a suicidal act [88]. The dexamethasone suppression profile may help to predict the most lethal suicidal acts during a 2-year follow-up [89]. Finally, patients at risk of suicide may show higher susceptibility to HPA dysregulation following SARS-CoV-2 infection because the virus targets the ACE-2 and the ACE/ACE-2 balance that is associated with HPA dysregulation in depressed individuals [40, 42].

Social Distancing and Vulnerability to Suicide

Human beings are social creatures: people survive and thrive by connecting with others. Currently, people around the globe have been urged to self-isolate and refrain from social interactions due to the COVID-19 pandemic. The risk of suicide may also be increased by the social consequences of the pandemic and the related lockdown: loneliness and social isolation, stigmatization and social rejection, and increase of interpersonal difficulties (e.g., domestic violence). Reynolds et al. found that loneliness was reported by 38.5% (95% CI 35.5–41.5) and social isolation by 60.6% (95% CI 57.6–63.6) of individuals ($n = 1057$) quarantined during the 2003 SARS outbreak in Canada [3]. Moreover, SARS-related studies revealed that 9.7% to 48.7% of people experienced stigmatization, abandonment, and isolation. A study on Ebola survivors showed that stigmatization concerned not only survivors or people related to a survivor [90] but also people of a specific nationality or place of residency. Recently, the WHO warned that since the COVID-19 outbreak, Chinese are victims of xenophobia and social stigmatization, with immense levels of threats online and during public interactions.

Feelings of isolation arise as a result of being quarantined [90]. Social isolation exacerbates personal and collective vulnerabilities, while limiting the accessible and familiar support options [10]. A recent review by Calati et al. (2019) suggests that social isolation (i.e., objective physical separation from other people) and loneliness (i.e., subjective distressed feeling of being alone or separated) are strongly associated with suicidal outcomes [9]. Being alone and negative family events increase suicidal ideation in recent suicide attempters. Feeling socially isolated or rejected leads to hypersensitivity to social threats [91] and increases negative relationships. At the biological level, loneliness and situations of social exclusion have been associated with increased HPA activity [91] and inflammation [92], two pathways related to suicidality [18, 71, 88]. Lonely individuals show stronger activation of the ventral striatum to pleasant pictures of objects compared with equally pleasant pictures of people, whereas the opposite is observed in non-lonely subjects. A functional circuit involving the striatal-anterior cortical midline structure plays a role in the expression of depressive symptoms and suicidal ideation [93]. In addition, loneliness has a mediating effect on the relation between the dorsolateral prefrontal cortex volume and attitudes toward suicide [94]. The regional gray matter volume of the left dorsolateral prefrontal cortex, a region involved in suicidal vulnerability, is higher in lonely individuals [95]. A review [96] on 28 fMRI studies during the Cyberball Game, a validated paradigm to study social exclusion, found several cerebral regions involved in exclusion: insula (anterior and posterior), prefrontal cortex, cingulate cortex (anterior and posterior), and temporal lobe. Dysregulation of insula and supramarginal gyrus during the exclusion versus the inclusion condition has been associated with suicidal vulnerability [97••]. These cerebral changes may affect emotional regulation, executive functions, and social cognition.

Since the COVID-19 outbreak, an increase in calls to domestic violence services has been observed in many countries [98]. It suggests an intensification of interpersonal conflicts, romantic difficulties, and child maltreatment. Indeed, the forced proximity changes the content of social interactions and may undermine the psychological resources, thus increasing the risk of aggression and domestic violence [99]. Interpersonal conflicts and affective difficulties might strongly increase the risk of suicidal acts, independently of psychiatric disorders [100]. Interestingly, affective difficulties have been associated with poor decision-making, a putative endophenotype of suicide [101]. Moreover, early exposure to maltreatment during childhood has been associated with a 3-fold higher risk of suicide attempts in adulthood [102].

Maltreatment might alter neurobiological pathways, thus decreasing the ability to cope with demands from others and increasing vulnerability to future stressors. This might enhance the risk of emergence of psychiatric disorders, including suicide [103, 104].

Preventing Suicide: At the Crossroad of Social Cohesion and Psycho-neuroimmunity

Although other recent crises have been associated with a decrease in suicidal rate due to greater social cohesion [105] related to the proximity of life-threatening events [106], it is important to anticipate the potential deleterious psychological effects of COVID-19-related social distancing and social isolation. Several types of interventions have been proposed to reduce social distress, which is associated with suicidal ideation and acts [107] and predicts suicidal behaviors at 1 year [108].

The first strategy is to target the immune response that is induced by social distress [109] and that drives the emergence of depressive symptoms and increases the risk of suicide attempts [62, 110••]. Treatments with drugs that have also anti-inflammatory properties, such as ketamine, show anti-suicidal effect immediately after their intake and for at least 1 week, independently of their anti-depressant effect [111]. Other pharmacological compounds, such as opioid molecules, modulate the activation of neural networks related to social interactions and lower the sensibility to social rejection [112] and social threats [113]. Moreover, low-dose buprenorphine efficiently reduces suicidal ideation [114••].

If future studies show that pro-inflammatory cytokines are increased in psychiatric patients during lockdown, more research will be required to evaluate pharmacological and non-pharmacological interventions (e.g., physical activity) to reduce the consequences of inflammation on health [115]. As soon as quarantine measures were put in place in many countries, the wording "social distancing" appeared. As this might aggravate feelings of loneliness and produce negative long-term health consequences, many authors requested to talk about "physical distancing," while promoting social connection [116]. Indeed, social connections help people to regulate emotions, cope with stress, and remain resilient during difficult times [117]. In these peculiar times, online interactions can help to foster a sense of connection and potentially boost psychological well-being [118]. Social connections are at the root of collective efficacy and foster hopefulness, as well as opportunities to witness and share positive emotions, compassion for others, altruism, and gratitude. Indeed, all forms of psychological support promote psychological resilience and enhance the psycho-neuroimmunity against COVID-19 [119]. As a matter of fact, self-compassion may protect against stress-induced inflammation and inflammation-related diseases [120]. Expression of gratitude, which is a very straightforward intervention for suicidal patients [121], moderates the relationships between stressful life events and IL-6 [122].

In their timely review on the psychological impact of quarantine, Brooks et al. (2020) highlighted that in order to reduce the mental health effect and to promote adherence, health authorities should emphasize the population's sense of altruism by stressing that their "staying at home" helps to keep others safe [123••]. Encouraging a shared sense of identity or purpose by acting for the common good may promote cooperative behaviors and increase shared social values (e.g., social cohesion). Social cohesion is a positive neighborhood characteristic defined by feelings of connectedness and solidarity within a community. Among many important person- and neighborhood-level characteristics, social cohesion has been inversely correlated with psychological distress and with lower IL-6 levels [124].

Psychiatrists should educate and promote methods and interventions that foster positive behavioral changes and solidarity. Encouraging people to develop empathy and cooperation while fighting the COVID-19 pandemic may contribute to building compassionate societies and empathic civilizations [125]. Social support could limit the detrimental effects of social isolation on the immune system and may help to boost the psycho-neuroimmunity against this viral infection [119]. Concomitantly, the feeling of social safety and caregiving activates reward neural networks and modulates the expression of pro-inflammatory genes [126]. Social support also helps to prevent feelings of social disconnection and suicide. Algorithms that combine brief contact interventions have been tested [127] as well as connected technologies to prevent suicide in vulnerable patients [128, 129]. A controlled study showed that acceptance and commitment therapy reduces suicidal ideation and psychological pain in high-risk patients with depression [107] and seems to have anti-inflammatory effects [130]. Engagement in art provides some forms of social support to isolated people and may increase the sense of belonging as well as protect from suicidal ideation [131]. In parallel to social connection, art also reduces cytokine levels in serum, such as IL-6 [132]. Encouraging people to share emotional experiences and to get social support should be one of the priority actions of the medical community [133]. Local organization should also help people to connect together, while adhering to physical distancing, in order to develop the sense of belongingness and of purpose [134].

COVID-19 and Psychotropic Treatments

Antidepressants (e.g., fluoxetine) reduce pro-inflammatory cytokines by attenuating the behavioral and neuroendocrine effects of immune activation [135]. Additional research is required to study the usefulness of antidepressants as part of the

anti-inflammatory strategies against COVID-19 by reducing depression and somatic symptoms.

Actually, there is no specific treatment for suicidal behavior, although antidepressants, lithium, and clozapine are commonly used [136, 137]. It would be important to assess whether these psychotropic drugs interact and worsen infection by SARS-CoV-2 and whether the virus influences their metabolism. Patients taking these drugs often have comorbidities (e.g., diabetes) that increase the infection severity. Some of these treatments have side effects (e.g., neutropenia, dyspnea) that could worsen viral infection. On the other hand, the SARS-CoV-2-related inflammation might affect the metabolism of these drugs by acting on cytochromes [138]. This might increase or decrease the plasmatic levels of psychotropic drugs, thus leading to the appearance of side effects, or to a reduction of the drug efficiency, respectively. Finally, molecules tested in clinical trials on COVID-19 (e.g., hydroxychloroquine) could also interact with psychotropic medications and mutually potentiate their side effects (e.g., cardiac side effects) [139]. Currently, there is no international consensus on the use of psychotropic drugs during this pandemic, except for clozapine [140]. However, even if an interaction between SARS-CoV-2 and psychotropic drugs may exist, it is strongly recommended to continue taking the psychotropic medications [138, 139]. Indeed, discontinuation will engender serious deleterious effects for the patients. Indeed, a brutal interruption of lithium, antidepressants, or clozapine can increase the risk of suicidal behavior [141]. Therefore, it is important and necessary to continue treatments in patients at suicide risk and to closely monitor them (e.g., regular dosage of the drug plasma levels, appearance of COVID-19 symptoms) [139, 140].

Interestingly, growing evidence suggests that some psychotropic drugs could have beneficial effects on SARS-CoV-2 infection. Indeed, some studies suggest that haloperidol and chlorpromazine should be tested for COVID-19 [142, 143]. Among treatments used in suicidal behavior, antidepressants could have potential beneficial effects in patients with COVID-19 through their impact on the cytokine "storm." Antidepressants (i.e., tricyclic antidepressants and selective serotonin reuptake inhibitors) have anti-inflammatory properties by reducing pro-inflammatory cytokines, such as IL-6, IL-1, and interferon γ. Several in vitro and in vivo (animal models) studies and trials in humans have shown the anti-inflammatory effect of these drugs at therapeutic concentrations [144–147]. Furthermore, SARS-CoV-2 could invade the CNS, because other coronaviruses (e.g., SARS-CoV and MERS-CoV) have been detected in the brain of victims and caused brain damage, notably due to inflammation [148, 149]. By passing through the BBB easily, antidepressants could reduce the inflammation induced in the brain by the virus. Moreover, some antidepressants inhibit microglial activation (a primordial vector of inflammation in the brain). For instance, it has been suggested that clomipramine is a potential treatment for multiple sclerosis due to its strong anti-inflammatory effect in the brain [150–152]. Therefore, we

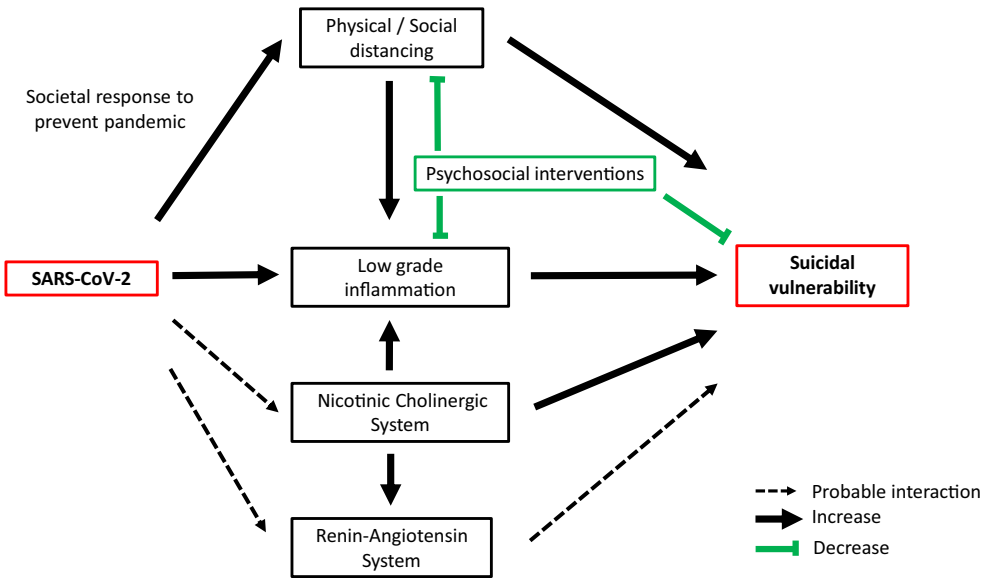

Fig. 1 Proposed model reporting the interaction between SRAS-CoV-2 and biological pathways underlying suicidal vulnerability. SARS-CoV-2 binds to ACE-2 receptors that are expressed in the central nervous system and are a key component of the renin-angiotensin system involved in suicidal vulnerability. SARS-CoV-2 targets nicotinic receptors that are involved in the pathophysiology of mood disorders and suicidal behavior. SARS-CoV-2 induces the immune response, resulting in chronic low-grade inflammation in peripheral organs and central nervous system, which is associated with suicide. The nicotinic system regulates ACE/ACE-2 expression and also the inflammatory response and may amplify COVID-19 effect on suicidal vulnerability. Social/physical distancing and feelings of social isolation may increase social pain, a key dimension leading to suicide and increasing low-grade inflammation. Psychosocial interventions may protect from suicide, attenuate social isolation, and modulate inflammatory processes. Black arrow: increase; green trait: decrease; dotted line: probable interaction

could hypothesize that antidepressants may be useful for preventing SARS-CoV-2-linked CNS inflammation and consequently for preventing or reducing the risk of emergence or worsening of suicidal behavior.

Conclusions and Research Perspectives

Altogether, our narrative review highlights several possible interactions between COVID-19 and vulnerability to suicidal behavior. We propose a biological model (Fig. 1) to explain the higher suicidal vulnerability in individuals confronted with COVID-19 directly (virus infection) or indirectly (exposed to social distancing measures). Indeed, SARS-CoV-2 affects specific biological correlates of suicide: (i) it binds to ACE-2 receptors that are widely expressed in the CNS, are a key component of the renin-angiotensin system, and have been involved in suicidal vulnerability; (ii) SARS-CoV-2 targets nicotinic receptors that are involved in the pathophysiology of mood disorders and suicidal behavior; (iii) SARS-CoV-2 induces the immune response, resulting in chronic low-grade inflammation (peripheral organs and/or brain) that has been associated with suicide; (iv) the nicotinic system regulates ACE/ACE-2 expression and also the inflammatory response and may amplify COVID-19 effect on suicidal vulnerability; and (v) social distancing and feelings of social isolation may increase social pain, a key dimension leading to suicide. Interestingly, drugs used to manage suicidal patients might also prevent inflammation and protect from some of SARS-CoV-2 deleterious effects in the CNS.

As suggested by Kim and Su (2020), it is time for immunopsychiatry services to address the biopsychosocial effects of the COVID-19 pandemic on another possible epidemic in the making: suicide [119]. Moreover, the COVID-19 outbreak and the complex biological processes underlying this infection offer new perspectives to better understand the multiple pathways leading to suicidal acts. The hypotheses described above need to be extensively tested. Longitudinal studies will help to determine the impact of chronic inflammation induced by COVID-19 on the frequency of suicidal acts in the mid- (months) and long-term (years). COVID-19 is an opportunity for investigating the naturalistic association between psychiatric symptoms and viral respiratory infections. The naturalist observation of individuals with COVID-19, use of antidepressants, and hospital admissions/visits due to suicide attempts offer a unique opportunity to go from ecological to cohort studies, which are methodologically more powerful [153].

Furthermore, genetic studies should assess the existence of common genetic variants underlying the host's viral susceptibility and suicide vulnerability to better characterize the possible interactions between pathogen and suicidal behaviors. Ecosystem features influence SARS-CoV-2 infection, whereas suicidal behaviors are driven by the psychosocial environment. Hence, possible shared environmental risk factors may underlie infection and suicide risk within a population. It is important to take them into account in future research to disentangle specific viral/neural interactions from other confounding factors. Finally, psychosocial interventions might help to modulate the host's immune response. Their efficacy for preventing morbidity related to the infection should be assessed. Interestingly, research on treatments for COVID-19 may benefit from studies on suicide because they might broaden the choice of anti-inflammatory and neuroprotective drugs. More research is required to evaluate the effectiveness of potential psycho-neuroimmunity preventive strategies to enhance resilience and prevent suicidal behavior [154]. Last, social and behavioral sciences and mental health sciences could help to align human behavior with the recommendations by epidemiologists and public health experts to fight the COVID-19 pandemic, while preventing the deleterious effects of such measures that may lead to a suicide epidemic. Would this help to build a "compassionate society and empathic civilization" [155] that might be more effective in preventing both epidemics? Probably, but much work remains to be done.

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- •• Of major importance

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