Psychiatry Research 314 (2022) 114677

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Review article

COVID-19 and first manic episodes: a systematic review

Mirella Russo [a,b], Dario Calisi [a,1], Matteo A. De Rosa [a,1], Giacomo Evangelista [a], Stefano Consoli [a], Fedele Dono [a,b], Matteo Santilli [a], Francesco Gambi [a,b], Marco Onofrj [a,b], Massimo Di Giannantonio [a], Giustino Parruti [c], Stefano L. Sensi [a,b,d,e,*]

[a] Department of Neurosciences, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy
[b] CAST - Center for Advanced Studies and Technology, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy
[c] Department of Infectious Diseases, Azienda Sanitaria Locale (AUSL) di Pescara, Pescara, Italy
[d] ITAB - Institute of Advanced Biomedical Technology, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy
[e] Institute for Mind Impairments and Neurological Disorders-iMIND, University of California, Irvine, Irvine, CA, United States

ARTICLE INFO

Keywords:
Sars-CoV-2
Mania
First manic episodes

ABSTRACT

Sars-CoV-2 is a respiratory virus that can access the central nervous system, as indicated by the presence of the virus in patients' cerebrospinal fluid and the occurrence of several neurological syndromes during and after COVID-19. Growing evidence indicates that Sars-CoV-2 can also trigger the acute onset of mood disorders or psychotic symptoms. COVID-19-related first episodes of mania, in subjects with no known history of bipolar disorder, have never been systematically analyzed. Thus, the present study assesses a potential link between the two conditions. This systematic review analyzes cases of first appearance of manic episodes associated with COVID-19. Clinical features, pharmacological therapies, and relationships with pre-existing medical conditions are also appraised.

Medical records of twenty-three patients fulfilling the current DSM-5 criteria for manic episode were included. Manic episodes started, on average, after 12.71±6.65 days from the infection onset. Psychotic symptoms were frequently reported. 82.61% of patients exhibited delusions, whereas 39.13% of patients presented hallucinations. A large discrepancy in the diagnostic workups was observed.

Mania represents an underestimated clinical presentation of COVID-19. Further studies should focus on the pathophysiological substrates of COVID-19-related mania and pursue appropriate and specific diagnostic and therapeutic workups.

1. Introduction

The 2019 coronavirus disease (COVID-19) triggered by an infection with Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is commonly associated with a variety of symptoms, including fever, cough, and fatigue (Lu et al., 2020). Many studies indicate that human coronavirus variants and SARS-CoV can infect neurons and glia, supporting the notion that the virus family affects the brain and shares similar neurovirulence (Bohmwald et al., 2018; Zubair et al., 2020). However, still unclear are the modalities and mechanisms by which the SARS-CoV-2 infection affects the Central Nervous System (CNS) functioning and produces neuropsychiatric manifestations, including manic episodes.

Manic symptoms may arise within different clinical contexts. They can be the onset presentation of Bipolar Disorder Type I (BD-I), appear in patients with a history of recurrent major depression converting to BD-I (Dols et al., 2014), or be triggered by an underlying medical condition (secondary mania) (Dubovsky, 2015). A wide variety of factors, like neurological or systemic conditions, infections, and medications, can lead to secondary mania onset (Dubovsky, 2015; Krauthammer and Klerman, 1978).

Several investigations have focused on mania's pathophysiological processes (Fišar, 2013). The high rate of family history and the proportional heritability of BD-I in genetic family studies suggest the presence of genetic background (O'Connell and Coombes, 2021). Specifically, BD-I is a polygenic/multifactorial disorder in which various single nucleotide polymorphisms (SNP), with small effect sizes, contribute to the development of the pathology (Ikeda et al., 2018). .

* Corresponding author at: Department of Neurosciences, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy
E-mail address: ssensi@uci.edu (S.L. Sensi).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.psychres.2022.114677
Received 11 March 2022; Received in revised form 6 June 2022; Accepted 8 June 2022
Available online 9 June 2022

In the presence of a "favorable" genetic background, exogenous factors may or may not reach the threshold to trigger mania in susceptible subjects, thereby calling for a critical reappraisal of the theoretical and clinical constructs underlying the concept of "primary" and "secondary" mania.

Maternal infections or smoking during pregnancy, advanced paternal age, childhood adverse events, drug/substance intake (cocaine, dopamine agonists, corticosteroids, adrenal and anabolic steroids, antidepressants) have been listed among the leading environmental risk factors (Dubovsky, 2015).

As far as the neurobiology of BD-I, the complex interplay between stress factors and disease triggers and modulators finds a central player in the impairment of the hypothalamic-pituitary axis. High levels of corticosteroids can trigger the acute onset of manic episodes upon chronic stress conditions. Over time, complex rearrangements of the neuroendocrine asset and the rewiring of brain connectivity may occur, leading to relapses that become independent from environmental triggers (Young and Juruena, 2021).

Of note, the administration of antidepressants - in cases of putative unipolar depression - can mask an undergoing patent primary BD, induce a mood switch in a primary BD, or possibly trigger secondary manic episodes (Vieta et al., 2018). It should be stressed that a very blurred line separates all these conditions to date.

Antidepressants are not the only common drugs involved in manic episodes. On rare occasions, antimicrobial drugs have been reported to induce mania (Lambrichts et al., 2017). In that respect, a systematic review has recently revealed the presence of a condition called "*antibiomania*", a secondary, strictly time-related, idiosyncratic reaction to antimicrobials that produces neuropsychiatric symptoms. This intriguing phenomenon is most frequently induced by macrolides and quinolones and possibly associated with mitochondrial dysfunction or antimicrobial interference with gamma-aminobutyric acid (GABA) signaling (Lambrichts et al., 2017). Secondary mania has also been observed in Cushing's disease, hyperparathyroidism, hypoparathyroidism, focal brain lesions associated with stroke, brain tumors (mostly right-sided, frontal- or basal ganglia-sided), multiple sclerosis, epilepsy (mostly left-sided epileptiform ictal hyperactivity, or postictal rebound hypoactivity in right-sided limbic structures), or neurodegenerative diseases like frontotemporal lobar dementia, Huntington's disease, or basal ganglia calcification (Satzer and Bond, 2016).

Infectious causes have also been indicated as mania triggers, including neurosyphilis and HIV encephalopathy (Dubovsky, 2015). Flu-induced mania has been reported, as well (Ayub et al., 2016). This is hardly surprising, given the well-known epidemic of neuropsychiatric syndromes described in subjects who survived the Spanish Flu (Czermak and Jean, 1990; Spinney, 2017). Post-encephalitic parkinsonism, the signature neurological condition associated with the viral infection, was mainly associated with movement disorders, but obsessive behavior, mood changes, personality alterations, and many other psychiatric symptoms were also reported (Khatib et al., 2021; Varatharaj et al., 2020; Zubair et al., 2020). In more recent times, COVID-19 has emerged as a critical trigger of concomitant and late-onset neuropsychiatric manifestations. Coronaviruses have been detected in the brain and cerebrospinal fluid of individuals with neurological manifestations, like seizures, encephalitis, and encephalomyelitis (Bohmwald et al., 2018). The COVID-19 infections have been linked to an increased risk of delirium onset in hospitalized patients (Helms et al., 2020; Martinotti et al., 2021; Rogers et al., 2020).

The underlying pathophysiological mechanisms are multifactorial. These include direct effects of the viral infection (including brain invasion), undergoing cerebrovascular diseases (in the context of a procoagulant state), hypoxia, altered immunological responses, pharmacological interventions, social isolation, the psychological impact of a severe and potentially fatal illness, the presence of concerns about infecting others, and/or social stigma (Diaz and Baweja, 2021; Sen et al., 2021; Troyer et al., 2020; Yesilkaya and Balcioglu, 2020). Because of the invasion of the upper respiratory tract, the virus may gain access to the brain through the olfactory nerve and retrograde axonal transport (Balcioglu et al., 2020; Brann et al., 2020). Sars-CoV-2 is also known to bind angiotensin-converting enzyme-2 (ACE-2) receptors, which are expressed in glia and neurons (Netland et al., 2008), and also immune cells (Song et al., 2020), thereby triggering the release of pro-inflammatory cytokines like TNF-a, IL-1, and IL-6 (Netland et al., 2008; Troyer et al., 2020; Yesilkaya and Balcioglu, 2020). The resulting aggressive antiviral immunoreactivity, also called "cytokine storm", is amplified by activating the complement cascade and producing cytotoxic reactive oxygen species (Dunkelberger and Song, 2010). At the same time, activated microglia can release inflammatory mediators and eventually contribute to increased glutamate availability. This promotes an overactivation of N-methyl-d-aspartate (NMDA) receptors which may ultimately lead to neural injury and cognitive and psychotic symptoms like impaired memory and hallucinations (Schou et al., 2021).

Thus, the Sars-CoV-2-related neuroinflammation and neuroinvasion may trigger, in susceptible subjects, a chain reaction culminating in neurotransmitter and neuroendocrine unbalance that ultimately affects the fine regulation of excitatory and inhibitory circuits and help generate mania or psychotic symptoms (DeLisi, 2021; Martinotti et al., 2021; Schou et al., 2021).

In the last two years, the occurrence of neuropsychiatric symptoms in COVID-19 patients has been extensively explored (Rogers et al., 2020; Varatharaj et al., 2020). However, most reports are focused on the manifestation of individual symptoms or signs (e.g., anxiety) (Rogers et al., 2020). Mood changes after Sars-Cov-2 infection seem widespread, but a systematic assessment of COVID-19 related manic/hypomanic states was missing, despite few reported isolated cases. A recent meta-analysis (Rogers et al., 2020) found a low prevalence (0.7%) of steroid-related manic episodes in COVID-19 patients, but the authors also remarked that "insomnia, emotional lability, irritability, pressured speech, and euphoria were relatively common, suggesting that although a full syndrome of mania was uncommon, subthreshold symptoms might be present". Accordingly, the assessment of COVID-related hypomanic states would be problematic, as they typically do not require medical attention and thus would inevitably be grossly underestimated. On the other hand, full-blown manic episodes are striking clinical pictures that prompt timely assessment and treatment and therefore are more likely to be observed (and documented) by physicians. Our report aimed to fill the literature gap on the potential occurrence of manic states triggered by Sars-Cov-2. A qualitative analysis of the clinical features and the possible pathophysiological links between the infection and manic episodes is also provided.

2. Methods

On October 2021, a search was performed on Google Scholar and MedLine/PubMed database employing the following keywords: 'mania AND COVID'. Fig. 1 shows the PRISMA flowchart. A total of 981 records was found on Google Scholar, and 28 were found on PubMed. After the deletion of 46 duplicates, the remaining 963 titles and abstracts were screened by six reviewers who employed the following criteria: inclusion, from 2019 onwards, of case reports and case series with a detailed history of manic disorder during a verified infection by Sars-CoV-2 (COVID-19). The exclusion criteria were: out-of-the-topic study, wrong publication type, not valid population (no COVID or mania) or study design (i.e., retrospective), other languages than English, other mood disorder before the onset of mania, and lack of abstract. Given the large number of reports on COVID-19 published in the last three years, generally not involving manic disorders, many studies (n=906) were excluded at this first step. The remaining 57 full texts were analyzed, and at least two reviewers shared the decisions on the inclusion/exclusion. After excluding 39 unfit results, either due to the lack of case description, absence of COVID-19 infection, wrong publication/study typology, or absence of available full-text, 18 papers were deemed

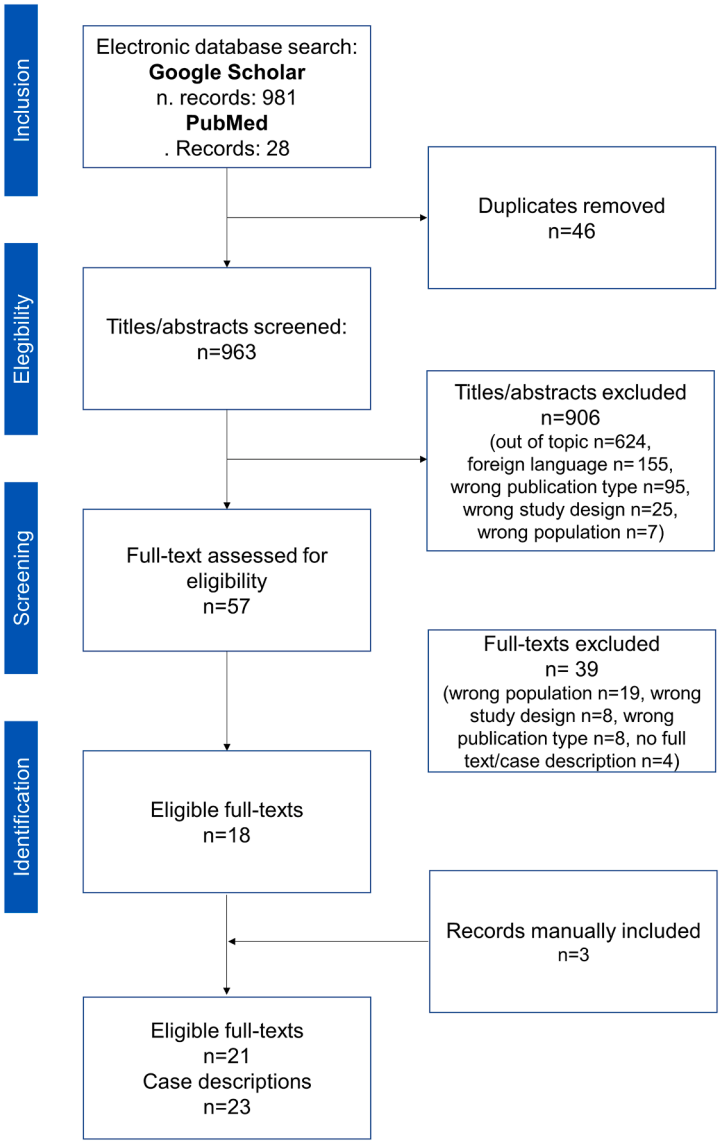

Fig. 1. PRISMA flowchart showing the systematic review process.

eligible. Three more studies, known to the authors, were manually added, and a total of 21 eligible publications was reached. Within these reports, all patients (n. 23) – fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria for manic episodes at the time of the infection and were included (American Psychiatric Association, 2013), under the supervision of the psychiatrists of our team. Reports lacking of an accurate and analyzable description of manic symptoms were excluded.

2.1. Data extraction

For each included study, we assessed: the year of publication, the number of suitable case reports, the patients' age and gender, the medical history (with greater attention paid to the psychiatric history, and the established presence of cognitive impairment), the current medical therapy. Regarding COVID-19 infection, we evaluated: the disease duration (length of the infection), the disease outcome, the latency from the start of the manic symptoms, the presence of respiratory symptoms, gastrointestinal symptoms, fever, or other related symptoms. We also checked the therapy (need for respiratory support by non-invasive ventilation or intubation, the intake of steroids), the diagnostic exams performed on the patients (computed tomography or magnetic resonance imaging of the brain, electroencephalogram, chest X-ray scan or computed tomography, laboratory exams on blood and CSF). Finally, the following features were assessed for psychiatric symptoms: (1) the presence of key symptoms of mania [i.e., elated mood, euphoria, or irritability; increased goal-directed activity or energy; grandiosity, inflated self-esteem; decreased need of sleep; increased talkativeness; racing/accelerated thoughts; distractibility; risky activities (shopping, investments, sex); psychosis (delusions; hallucinations)]: (2) therapy prescribed for the psychiatric symptoms; (3) clinical outcomes. A Composite Risk Score for Mania (MCRS) was generated for each patient. The MCRS is based on the following risk factors: previous psychiatric conditions, familial history of bipolar disorder, or pharmacological triggers.

Given the shared clinical features between first manic episodes and delirium states (i.e., psychosis and abnormal psychomotor activity), differential diagnosis was critical and made by DSM-5 criteria (American Psychiatric Association, 2013). Patients suffering from delirium were excluded based on the presence of marked fluctuations of attention and cognition along with significant alertness alterations, disorganized thinking, or consciousness impairment (American Psychiatric Association, 2013).

3. Results

Twenty-one studies were found eligible (See Supplementary Table 1). From these 21 papers, a total of 23 patients with a first manic episode that occurred during COVID-19 infection were selected. The mean age of the total sample was 44.33 ± 12.84 years (range: 16−64) and 39.13% (*n*=9) were female. Table 1 shows the demographic and medical characteristics of the sample.

Four patients (17.39 %) had a positive history of a previous psychiatric disorder. Of them, three suffered from a major depressive disorder. The last patient suffered from depression but also alcoholism and exhibited prior occurrence of a fever-related psychotic episode. As per our study criteria, none of them had been diagnosed with BD-I before the Sars-CoV-2 infection. One patient, a 16-year-old boy, has had cerebral palsy, yet no explicit mention of cognitive deficits was reported. No history of age- or neurodegenerative-related cognitive decline was reported. The most common comorbidities were systemic hypertension (*n*=5), type 2 diabetes mellitus (T2D, *n*=3), and asthma (*n*=2). All the conditions were stable. One subject suffered from dyslipidemia, one from congenital nystagmus, and another from well-controlled epilepsy. Furthermore, one patient was in post-partum. Eleven (47.83%) had not suffered from any major medical condition before the COVID-19 hospitalization. Thirteen subjects (56.52%) were not pharmacologically treated, whereas four subjects were treated with: bupropion; levetiracetam and sodium valproate; paroxetine, perindopril, fluticasone/vilanterol spray, montelukast, and triazolam; and quetiapine, respectively. Of the three diabetic patients, one was untreated for his condition, one was diagnosed with T2D at hospital admission and treated with insulin injections, and no information on the medical therapy of the third subject was available. No distinctive features in terms of mental state were observed in those patients.

COVID-19 infection courses and features of the study cohort are summarized in Table 2. The mean duration of COVID disease was eighteen days (18.73±6.59; range: 9−30 days). The mean latency between the diagnosis of infection and mania onset was twelve days (12.71 ±6.65; range: 2−21 days). The respiratory syndrome was the most common clinical feature. Three respiratory syndromes were severe (one respiratory failure and two pneumonia cases), while the remaining symptoms were generally mild (dry cough and sore throat). Fever was absent in one-fifth of the subjects (21.74%). The infection outcome was generally good. No fatal cases were described. Other symptoms were described in ten patients and included: urinary disturbances (*n*=1), headache (*n*=3), hyperhidrosis (*n*=1), asthenia (*n*=1), anosmia (*n*=1) and ageusia (*n*=1), and abdominal pain (*n*=1). Medical therapy for COVID-19 employed during the hospitalization is summarized in Table 3; however, no information was available in five cases (21.74%). Of note, two subjects (8.70%) were not treated for any COVID-19-related symptoms. Other therapies included steroids (*n*=11), antibiotics (*n*=11), hydroxychloroquine (*n*=3). Five subjects received azithromycin (in two cases, combined with cephalosporine); three patients received cephalosporins (cefuroxime or ceftriaxone); two patients were treated with piperacillin (in one case, combined with metronidazole); one patient was treated with moxifloxacin. No details are available on the "empirical antimicrobial" treatment followed by one patient. Severe respiratory symptoms made assisted ventilation necessary in two cases (one was intubated, the other only received non-invasive ventilation). One subject was sedated and intubated not for respiratory failure but to manage severe psychiatric symptoms.

Table 1
Demographics and medical history of the whole sample.

Clinical features	Positive findings	Negative findings	Not Reported
Previous psychiatric conditions	4 (17.39%)	19 (82.61%)	-
History of cognitive impairment	-	23 (100%)	-
Other comorbidities	9 (39.13%)	11 (47.83%)	3 (13.04%)
Home medical therapy	4 (17.39%)	13 (56.52%)	6 (26.09%)

Table 2
COVID-19 symptoms.

COVID-19 symptoms	Positive findings	Negativefindings	Not Reported
Respiratory symptoms	18 (78.26%)	3 (13.04%)	2 (8.70%)
Gastrointestinal symptoms	3 (13.04%)	16 (69.57%)	4 (17.39%)
Fever	13 (56.52%)	5 (21.74%)	5 (21.74%)
Other symptoms	10 (43.48%)	12 (52.17%)	1 (4.35%)
Only manic symptoms	1 (4.35%)	-	-
Outcome (Fatal)	-	23 (100%)	-

Table 3
Pharmacological and non-pharmacological treatments for COVID-19 infection.

COVID-19 therapy	Positive findings	Negative findings	Not Reported
Steroids	11 (47.83%)	8 (34.78%)	4 (17.39%)
Hydroxychloroquine	3 (13.04%)	15 (65.22%)	5 (21.74%)
Antivirals	8 (34.78%)	10 (43.48%)	5 (21.74%)
Antibiotics	11 (47.83%)	7 (30.43%)	5 (21.74%)
CPAP	2 (8.70%)	21 (91.30%)	-
Intubation	2 (8.70%)	21 (91.30%)	-

Abbreviation: CPAP= Non-invasive ventilation with Continuous Positive Airway Pressure.

The diagnostic workup, summarized in Table 4, included blood laboratory tests in nineteen subjects (82.61%). In five cases, test results were normal, while nine patients exhibited inflammatory signs, including increased ESR, PCR, IL-6, and IL-10, and altered white blood cell counts. Altered coagulation markers (D-dimer, fibrinogen) were found in four patients, whereas one patient had thrombocytosis. Two patients only showed mild anemia. Interestingly, only six patients (26.09%) underwent lumbar puncture for CSF analysis. The results were abnormal in two cases, one patient showed increased protein levels and reactivity to Sars-CoV-2 antibodies, and the other patient had mild leukocytosis and positive Sars-CoV-2 specific IgG antibodies. PCR for Sars-CoV-2 RNA was negative in both cases. Screening for autoimmune disorders was performed in five patients, with no pathological results. Thorax computed tomography (CT) scans or radiographs were performed on fourteen subjects. Of them, eleven showed pulmonary inflammatory signs, three were normal, and no information is available on the remaining ones. Brain CT scans were normal in all tested subjects (*n*=13). Of the ten (43.48%) performed magnetic resonance imaging (MRI) brain scans, five (50%) revealed abnormal findings: three were indicative of chronic small vessel disease, while two subjects presented acute abnormalities indicative of (1) hyperintensity of the splenium of the corpus callosum, with decreased diffusion coefficient, likely due to cytotoxic edema or; (2) unspecific T2 hyperintense abnormalities in the right parietal subcortical white matter. Electroencephalogram (EEG) recordings were performed only in four patients (17.39%). Two were normal. The other two showed (1) temporal epileptiform discharges and (2) focal "frontal dysfunction" right>left, with no epileptiform discharges or seizures. Neuropsychological test scores were available for eight patients (34.78%). The Young Mania Rating Scale (YMRS) (Young et al., 1978) was the most common assessment for manic symptoms (*n*=6). The mean admission score at YMRS was 36.00±6.39 (range: 27−43), indicating moderate-to-severe manic symptoms. Only two patients were screened for global cognitive functioning. One subject obtained normal scores at the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) (Folstein et al., 1975; Nasreddine et al., 2005) after an electroconvulsive therapy, and the other showed normal performances at the Addenbrooke's Cognitive Examination but impairment of inhibitory control and verbal fluency at the

Table 4
Investigations performed during hospitalization.

Assessment (Performed in *N* subjects)	Positive findings	Negative findings	Not Reported
Hematological routine (*N*=19/23)	5 (21.74%)	14 (60.87%)	4 (17.39%)
CSF (*N*=6/23)	2 (8.70%)	4 (17.39%)	17 (73.91%)
Brain CT scan (*N*=13/23)	0	13 (56.52%)	10 (43.48%)
Brain MRI scan (*N*=10/23)	2 (INF, 8.70%) 3 (ISC, 13.04%)	5 (21.74%)	13 (56.52%)
EEG (*N*=4/23)	2 (8.70%)	2 (8.70%)	19 (82.61%)
Thorax CT/X-ray (*N*=14/23)	11 (47.83%)	3 (13.04%)	9 (39.13%)
Neuropsychological tests (N=8/23)	8 (34.78%)	0	15 (65.22%)

Abbreviations= CSF: cerebrospinal fluid; CT: Computed Tomography; EEG: electroencephalogram; INF: Inflammatory signs; ISC: Ischemic lesions; MRI: Magnetic Resonance Imaging.

Table 5
Psychiatric symptoms and management.

Manic symptoms	Positive findings	Negative findings	Not Reported
Elevated mood, euphoria, or irritability	22 (95.65%)	-	1 (4.35%)
Increased goal-directed behavior or energy	17 (73.91%)	6 (26.09%)	-
Inflated self-esteem or grandiosity	17 (73.91%)	6 (26.09%)	-
Decreased need for sleep	20 (86.96%)	3 (13.04%)	-
More talkative than usual or pressure to keep talking	21 (91.30%)	2 (8.70%)	-
Flight of ideas or subjective experience that thoughts are racing	13 (56.52%)	10 (43.48%)	-
Distractibility	14 (60.87%)	9 (39.13%)	-
Excessive involvement in activities that have a high potential for painful consequences	12 (52.17%)	11 (47.83%)	-
Psychotic symptoms			
Delusions	19 (82.61%)	4 (17.39%)	-
Hallucinations	9 (39.13%)	14 (60.87%)	-
Complete resolution of manic symptoms	17 (73.91%)	6 (26.09%)	-
Pharmacological treatment			
BDZ	12 (52.17%)		
Typical Antipsychotics	7 (30.53%)		
Atypical Antipsychotics	20 (86.96%)		
Mood Stabilizers	8 (34.78%)		
ECT	1 (4.35%)		

Abbreviations: BZD: Benzodiazepines, ECT: electroconvulsive therapy.

Frontal Assessment Battery (FAB) (Dubois et al., 2000; Noone, 2015). Other neuropsychological findings are summarized in Supplementary Table 2.

Symptoms compatible with the DSM-5 clinical diagnosis of Manic Episode were observed in all patients (American Psychiatric Association, 2013). Table 5 shows the prevalence of the specific DSM-5 items. Overall, the average number of manic symptoms was 4.96±1.30. The core symptoms (persistently elevated euphoric or irritable mood and increased activity or energy) were described in all patients except for one who was, however, diagnosed with mania by the authors of the paper (perhaps they only omitted to report it). The second most common feature was the presence of increased talkative behavior or pressure to keep talking (91.30%), followed by the decreased need for sleep (86.96%). The less common symptom was the involvement in risky activities (52.17%).

As for the presence of concurrent psychotic symptoms (Table 5), delusions were the most common manifestations (*n*=19, 82.61%), followed by hallucinations (*n*=9, 39.13%). Most of the patients exhibited concurrently multiple delusional contents. Grandiosity delusions were the ones most frequently reported (*n*=13, 56.52%), followed by religious/mystic delusions (*n*=10, 43.48%). Few "*coronaphobic*" delusions (i.e., related to the fear of the virus) were also reported (*n*=2, 8.70%), while guilt or infidelity delusions were present in each patient. Hallucinations were relatively less common. Of the cases in which information was provided on the hallucinating modality, three patients (13.04%) showed only auditory hallucinations and five patients had combined auditory and visual hallucinations (21.74%). Interestingly, no cases of isolated visual simple hallucinations were reported. Two cases of catatonia were also described. All patients received pharmacological therapy for psychiatric conditions. One patient was successfully treated with electroconvulsive therapy. Monotherapy with atypical antipsychotics was employed in four patients (17.39%). The remaining nineteen patients received polytherapy that included combinations of benzodiazepines (*n*= 12, 52.17%), mood stabilizers (*n*= 8, 34.78%),

Table 6
Mania Composite Risk Score.

Score	N° of patients (%)
0	7 (30.43)
1	11 (43.83)
2	3 (13.04)
3	2 (8.70)

Number of risk factors for mania among the following: previous psychiatric conditions, familiarity for bipolar disorder, or pharmacological triggers.

atypical (*n*= 20, 86.96%) or typical antipsychotics (*n*=7, 30.43%).

Finally, we determined the MCRS (Table 6). Seven patients showed no such risk factors, eleven only had one typology of risk factors, three subjects had two of them, and two exhibited all the three typologies of risk factors. Exposure to drugs that could trigger manic episodes was the leading risk factor, observed in 60.87% of subjects. Steroid therapy was the most common (*n*=11), followed by chloroquine use (*n*=3). In four subjects, exposure to (1) bupropion, (2) paroxetine, (3) cannabis, or (4) levetiracetam, respectively, was observed and deemed a risk factor as well, as later detailed. Overall, exposure to a single trigger drug was more common (*n*=11) than simultaneous exposure to two (*n*=2), or three (*n*=1) of them. Regarding non-pharmacological risk factors, four subjects had a prior history of psychiatric disorders, whereas a family history of BD was reported in five cases. Interestingly, only two subjects had both positive family history of BD and a personal history of psychiatric disorders. As for other combinations of risk factors, a patient with a positive history of psychiatric disorders was under bupropion treatment, and three patients with a family history of BD received steroid therapy for COVID-19.

4. Discussion

The present review analyzes first episodes of mania associated with an ongoing COVID-19 infection. In one case, psychiatric symptoms were the only clinical manifestation of the infection, suggesting that the onset was not associated with relevant systemic disturbances. The absence of fever in about a fifth of subjects corroborates the notion. The average latency from the infection onset was twelve days. Therefore, an ongoing parainfective autoimmune disorder is likely the undetected missing link between the infection and the clinical features exhibited by some patients. EEG abnormalities were found in frontal brain regions, which fits with the idea that these areas are early targets for the Sars-CoV-2 retrograde neuroinvasion originating from the olfactory nerve (Cheng et al., 2020; Le Guennec et al., 2020). Furthermore, CSF positivity for Sars-CoV-2 antibodies was present in half of the tested patients, in line with direct involvement of the virus. Screening for autoimmunity was negative in all patients, indicating that no known antibodies are involved in the pathophysiological process. The presence of very mild pleocytosis in the CSF only in one patient, with normal findings in the others, does not support a significant role for cell-mediated CNS inflammatory responses. However, CSF exams were performed in too few subjects to draw safe and valid conclusions. CSF evaluations were also not repeated to assess longitudinal changes.

Overall, the present study highlights a significant **inhomogeneity of diagnostic workups** that impairs the possibility of defining the clinical features of COVID-induced mania accurately. Most patients underwent at least one neuroimaging exam (CT or MRI). However, few were evaluated with lumbar punctures and/or EEG recordings, procedures that could have helped find signs of an autoimmune process like limbic encephalitis. Thus, a complete workup could have helped detect further pathological findings in the other (untested) subjects.

The present study's design does not allow to draw statistical or epidemiological inferences; however, some clinical features of COVID-related mania should be highlighted. COVID-related manic episodes seem to present a moderately higher propensity for psychotic symptoms compared to previous observations (Canuso et al., 2008; Dunayevich and Keck, 2000) unrelated to the virus (82% vs. 68%). Conversely, catatonia was documented in relatively fewer COVID-19 patients (8.70%) compared to generic manic cohorts where catatonic signs are present in up to 47% of cases (Stuivenga and Morrens, 2014). The phenomenology of psychoses confirmed that grandiose delusions are a common finding (35-60% vs. 56%) (Dunayevich and Keck, 2000). The presence of "coronaphobia" (Arora et al., 2020; Asmundson and Taylor, 2020) in their delusional content seems a very peculiar feature of COVID-19 mania, possibly deserving further characterization (Sen et al., 2021). Moreover, an interesting finding, related to "more classic"manic symptoms, is the relatively poor engagement of patients in risky activities, which is supposedly due to both physical and legal constraints during COVID-19 infection.

To assess the **potential risk of developing mania**, we generated a composite risk score, MCRS, that evaluates the presence of previous psychiatric history, BD in family members, or any pharmacological trigger. Interestingly, seven subjects (30%) scored 0 points on MCRS, indicating a significant role of the infection in promoting the manic episode.

The iatrogenic origin of the mania cannot be ruled out in subjects under steroids, chloroquine, or (self-administered) cannabis treatment. Previous/concomitant treatment with paroxetine and bupropion was also considered a risk factor (Aggarwal and Sharma, 2011). Levetiracetam therapy was also considered a risk for mania due to the drug's capability to enhance psychiatric manifestations (Calle-López et al., 2019), although some reports indicate the drug use for BD-I (Muralidharan and Bhagwagar, 2006). Despite the well-described relationships between the occurrence of mania and the use of macrolides and quinolones, no associations were reported with the drugs used in our cohort [i.e., azithromycin, or moxifloxacin [see Medline PubMed: (azithromycin AND mania), (moxifloxacin AND mania) (Lambrichts et al., 2017)] and therefore were not considered risk factors. Nine patients did not take any medication known to trigger psychiatric symptoms. Chloroquine has been linked to several potential side effects, including mania (Bhatia et al., 2012), and is no longer recommended to treat COVID-19 infection (Gould and Norris, 2021). Of note, a word of caution on steroid administration is warranted. Steroids have been proven beneficial when administered in severe conditions (National Institutes of Health, 2021). However, inappropriate steroid prescription used as "prophylaxis" may carry side effects – as mania – without improving the patients' situation. This was the case for some of the patients in the study cohort.

As for cannabis, a three-fold increased risk for mania development has been reported by a recent meta-analysis, a risk interpreted as a "moderate association" by the authors (Gibbs et al., 2015). However, the role of cannabis in triggering first episodes of mania is still debated (Bally et al., 2014; Etyemez et al., 2020; Gibbs et al., 2015), and there are no valid indications for its use in COVID-19.

Our composite risk score also included a familial history of BD since a lifetime hazard of 5-10% – 7-fold higher than the general population – is carried by first-degree family members of bipolar subjects (Rowland and Marwaha, 2018). Genomic studies indicate a role for alterations of neurotrophic factors (like BDNF), monoamine catabolizing enzymes and transporters, altered calcium channel activity, and alterations of GABA receptor subunits. These contributing factors are critical targets of the current pharmacological treatment for BD, including lithium, valproate sodium, carbamazepine, and lamotrigine.

A **pathophysiological** pathway seems to involve polymorphisms of TLR2 (a receptor involved in innate **immunity** processes), and Toxoplasma gondii indicated as a binomial risk factor for BD (Oliveira et al., 2016). Furthermore, a genetic predisposition to BD-I has been linked to polymorphisms of glycogen synthase kinase-3 (GSK3), an enzyme that promotes pro-inflammatory responses and inhibits anti-inflammatory and cytoprotective activities (Pereira et al., 2021). Increased blood

levels of acute-phase proteins are also observed during manic episodes (Anderson and Maes, 2015; Pereira et al., 2021). In contrast, levels of cytokines and their receptors like TNF-α, IL-6, soluble IL-6R, and IL-1R, IL-2R have been indicated to vary according to the mood polarity and be enhanced in manic states (Rosenblat and McIntyre, 2016). Some anti-inflammatory drugs (like acetylsalicylic acid, celecoxib, and infliximab) have been repurposed as add-on therapies to modulate the inflammatory response of BD-I (Pereira et al., 2021), in line with the putative presence of a pro-inflammatory setting favoring BD-I onset (Dickerson et al., 2013; Hamdani et al., 2012; Leboyer et al., 2012) and corticosteroid desensitization of the hypothalamic-pituitary-adrenal axis due to chronic stress (Maletic and Raison, 2014). However, inflammatory changes may represent epiphenomena. Thus, further studies are needed to disentangle the complex interplay among genetic predisposition to BD-I, immune system alterations, microbe/viral infections, and psychiatric disorders.

Another potential link between COVID-19 and BD-I may also rely upon the dysregulation of the Renin-Angiotensin-Aldosterone system (**RAAS**). Sars-CoV-2 neurotropism has been associated with the virus's capability to bind and downregulate the Angiotensin-Converting Enzyme 2 (ACE2) (Baig et al., 2020; Cheng et al., 2020). In contrast, lower ACE levels were found in plasma samples of bipolar patients in non-euthymic states (Sanches et al., 2021) (unfortunately, the authors did not stratify the patients accordingly to the presence of ongoing manic/hypomanic or depressive episodes). Of note, experimental studies have suggested the possibility of inhibiting the Sars-CoV-2 neuroinvasion by blocking ACE2 receptors (Song et al., 2021).

From a **topographical** point of view, frontal lobe dysfunction and cortical thinning have been associated with BD-I and the frequency of manic states (Abé et al., 2021; Mikolas et al., 2021; Takeuchi et al., 2021). Changes in prefrontal cortex volumes, thickness, and the gyrification index have been consistently observed in BD-I patients and, to a lesser degree, close relatives (Librenza-Garcia et al., 2021). This is noteworthy since the frontal lobes appear to be preferentially targeted by coronaviruses (Netland et al., 2008; Toniolo et al., 2021). Their dysfunction may represent a crucial mechanism shared by BD-I and COVID-related conditions.

In conclusion, our review provides evidence for the occurrence of first episodes of mania during COVID-19 infection. Depicting the clinical features and the potential risk factors, along with the most common findings revealed by instrumental investigation, may help the clinician diagnose such a condition. Shared pathophysiological features are also reviewed, yet further research is needed to disentangle the complex processes linking the onset of acute mood and psychotic disorders and COVID-19 infections.

5. Limitations

BD-I is a multifactorial psychiatric disorder. Many additional factors have likely played a role in the cases of parainfective mania that we discussed. Unfortunately, key demographic information was not available. For instance, previous studies have indicated that high creativity, high occupational level, and urban life set are linked to an increased risk of BD-I (the latter specifically with psychotic BD-I) (Rowland and Marwaha, 2018). Thus, socioeconomic status, environmental context, or personality traits, factors that were not assessed in the reviewed cases, could be of interest and worth further investigation.

Methods caveat: In the screening phase of the systematic review, papers were deemed as of "wrong publication type" if not case reports or case series (e.g., reviews). Moreover, papers considered of the "Wrong study design" were original publications that might mention mania but did not assess clinical features relevant to the subjects. Preclinical studies also fell in this category. The exclusion of non-English papers was due to the absence in our team of speakers of languages other than English. Although very common (Jackson and Kuriyama, 2019), we recognize that the "English-language bias" must be acknowledged as a study limitation. Also, the literature search found some titles that had no abstract or main text attached and were therefore excluded.

Reports surviving the first screening phase were then screened for final inclusion/exclusion. In a few cases, the authors did not directly mention Mania and only described the simultaneous occurrence of "psychiatric symptoms". When compatible with the DSM-5 criteria for Mania, we included these studies. The inclusion/exclusion of all cases was supervised by expert psychiatrists present in the team.

Our study only includes results of published data. No attempts to contact the authors of the original papers were made to avoid including un-reviewed and misleading information, however, cases missing crucial information were excluded by the study.

Data availability statement

Data is available on request.

Funding

SLS is supported by research funding from the Italian Department of Health (RF-2013–02358785 and NET-2011-02346784-1), the AIRAlzh Onlus (ANCC-COOP), from the Alzheimer's Association - Part the Cloud: Translational Research Funding for Alzheimer's Disease (18PTC-19-602325) and the Alzheimer's Association - GAAIN Exploration to Evaluate Novel Alzheimer's Queries (GEENA-Q-19-596282).

Declaration of Competing Interest

Nothing to disclose.

Acknowledgments

MR conceptualized the manuscript. MR, DC, MADR, FG, MDG, GE, SC, FD, and MS revised the literature. MR, DC, and MADR produced the first draft. FG, MO, MDG, GP, and SLS revised the manuscript. SLS supervised, organized, and generated the final version of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114677.

References

Abé, C., Ching, C.R.K., Liberg, B., Lebedev, A.V, Agartz, I., Akudjedu, T.N., et al., 2021. Longitudinal structural brain changes in bipolar disorder: a multicenter neuroimaging study of 1232 individuals by the ENIGMA bipolar disorder working group. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2021.09.008.

Aggarwal, A., Sharma, R.C., 2011. Bupropion-induced mania and hypomania: a report of two cases. J. Neuropsychiatry Clin. Neurosci. 23, E51–E52. https://doi.org/10.1176/jnp.23.2.jnpe51.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-5TM. Arlington, Arlington, VA.

Anderson, G., Maes, M., 2015. Bipolar disorder: role of immune-inflammatory cytokines, oxidative and nitrosative stress and tryptophan catabolites. Curr. Psychiatry Rep. 17, 8. https://doi.org/10.1007/s11920-014-0541-1.

Arora, A., Jha, A.K., Alat, P., Das, S.S., 2020. Understanding coronaphobia. Asian J. Psychiatr. 54, 102384 https://doi.org/10.1016/j.ajp.2020.102384.

Asmundson, G.J.G., Taylor, S., 2020. Coronaphobia: fear and the 2019-nCoV outbreak. J. Anxiety Disord. 70, 102196 https://doi.org/10.1016/j.janxdis.2020.102196.

Ayub, S., Kanner, J., Riddle, M., Romano, G., 2016. Influenza-induced mania. J. Neuropsychiatry Clin. Neurosci. https://doi.org/10.1176/appi.neuropsych.15080208.

Baig, A.M., Khaleeq, A., Ali, U., Syeda, H., 2020. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem. Neurosci. 11, 995–998. https://doi.org/10.1021/acschemneuro.0c00122.

Balcioglu, Y.H., Yesilkaya, U.H., Gokcay, H., Kirlioglu, S.S., 2020. May the central nervous system be fogged by the cytokine storm in COVID-19?: An appraisal. J. Neuroimmune Pharmacol. https://doi.org/10.1007/s11481-020-09932-9.

Bally, N., Zullino, D., Aubry, J.-M., 2014. Cannabis use and first manic episode. J. Affect. Disord. 165, 103–108. https://doi.org/10.1016/j.jad.2014.04.038.

Bhatia, M.S., Jhanjee, A., Oberoi, A., 2012. A case of chloroquine-induced recurrent mania. Prim. Care Companion CNS Disord. 14 https://doi.org/10.4088/PCC.11l01302.
Bohmwald, K., Gálvez, N.M.S., Ríos, M., Kalergis, A.M., 2018. Neurologic alterations due to respiratory virus infections. Front. Cell. Neurosci. https://doi.org/10.3389/fncel.2018.00386.
Brann, D.H., Tsukahara, T., Weinreb, C., Lipovsek, M., Van den Berge, K., Gong, B., et al., 2020. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci. Adv. 6 https://doi.org/10.1126/sciadv.abc5801.
Calle-López, Y., Ladino, L.D., Benjumea-Cuartas, V., Castrillón-Velilla, D.M., Téllez-Zenteno, J.F., Wolf, P., 2019. Forced normalization: a systematic review. Epilepsia 60, 1610–1618. https://doi.org/10.1111/epi.16276.
Canuso, C.M., Bossie, C.A., Zhu, Y., Youssef, E., Dunner, D.L., 2008. Psychotic symptoms in patients with bipolar mania. J. Affect. Disord. 111, 164–169. https://doi.org/10.1016/j.jad.2008.02.014.
Cheng, Q., Yang, Y., Gao, J., 2020. Infectivity of human coronavirus in the brain. EBioMedicine 56, 102799. https://doi.org/10.1016/j.ebiom.2020.102799.
Czermak, M., Jean, T., 1990. [Von Economo-Cruchet lethargic encephalitis and its relation to HIV infection]. Encephale 16, 375–382.
DeLisi, L.E., 2021. A commentary revisiting the viral hypothesis of schizophrenia: onset of a schizophreniform disorder subsequent to SARS CoV-2 infection. Psychiatry Res. 295, 113573.
Diaz, A.D., Baweja, R., 2021. The role of neurotropism in psychiatric patients with COVID-19. Eur. Arch. Psychiatry Clin. Neurosci. https://doi.org/10.1007/s00406-020-01197-w.
Dickerson, F., Stallings, C., Origoni, A., Vaughan, C., Katsafanas, E., Khushalani, S., Yolken, R., 2013. A combined marker of inflammation in individuals with mania. PLoS One 8, e73520. https://doi.org/10.1371/journal.pone.0073520.
Dols, A., Kupka, R.W., Van Lammeren, A., Beekman, A.T., Sajatovic, M., Stek, M.L., 2014. The prevalence of late-life mania: a review. Bipolar Disord. https://doi.org/10.1111/bdi.12104.
Dubois, B., Slachevsky, A., Litvan, I., Pillon, B., 2000. The FAB: a frontal assessment battery at bedside. Neurology 55, 1621–1626. https://doi.org/10.1212/wnl.55.11.1621.
Dubovsky, S.L., 2015. Mania. Continuum (Minneap. Minn). 21, 737–755. https://doi.org/10.1212/01.CON.0000466663.28026.6f.
Dunayevich, E., Keck, P.E.J., 2000. Prevalence and description of psychotic features in bipolar mania. Curr. Psychiatry Rep. 2, 286–290. https://doi.org/10.1007/s11920-000-0069-4.
Dunkelberger, J.R., Song, W.C., 2010. Complement and its role in innate and adaptive immune responses. Cell Res. 20, 34–50. https://doi.org/10.1038/cr.2009.139.
Etyemez, S., Currie, T.T., Hamilton, J.E., Weaver, M.F., Findley, J.C., Soares, J., Selek, S., 2020. Cannabis use: a co-existing condition in first-episode bipolar mania patients. J. Affect. Disord. 263, 289–291. https://doi.org/10.1016/j.jad.2019.11.097.
Fišar, Z., 2013. Pathophysiology of mood disorders and mechanisms of action of antidepressants and mood stabilizers. Endocannabinoid Regulation of Monoamines in Psychiatric and Neurological Disorders. Springer, New York, pp. 103–134. https://doi.org/10.1007/978-1-4614-7940-6_6.
Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. Mini-mental state. J. Psychiatr. Res. 12, 189–198. https://doi.org/10.1016/0022-3956(75)90026-6.
Gibbs, M., Winsper, C., Marwaha, S., Gilbert, E., Broome, M., Singh, S.P., 2015. Cannabis use and mania symptoms: a systematic review and meta-analysis. J. Affect. Disord. 171, 39–47. https://doi.org/10.1016/j.jad.2014.09.016.
Gould, S., Norris, S.L., 2021. Contested effects and chaotic policies: the 2020 story of (hydroxy) chloroquine for treating COVID-19. Cochrane Database Syst. Rev. 3, ED000151 https://doi.org/10.1002/14651858.ED000151.
Hamdani, N., Tamouza, R., Leboyer, M., 2012. Immuno- inflammatory markers of bipolar disorder: a review of evidence. Front. Biosci. (Elite Ed) 4, 2170–2182. https://doi.org/10.2741/534.
Helms, J., Kremer, S., Merdji, H., Schenck, M., Severac, F., Clere-Jehl, R., et al., 2020. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. Crit. Care 24. https://doi.org/10.1186/s13054-020-03200-1.
Ikeda, M., Saito, T., Kondo, K., Iwata, N., 2018. Genome-wide association studies of bipolar disorder: a systematic review of recent findings and their clinical implications. Psychiatry Clin. Neurosci. https://doi.org/10.1111/pcn.12611.
Jackson, J.L., Kuriyama, A., 2019. How often do systematic reviews exclude articles not published in English? J. Gen. Intern. Med. 34, 1388–1389. https://doi.org/10.1007/s11606-019-04976-x.
Khatib, M.Y., Mahgoub, O.B., Elzain, M., Ahmed, A.A., Mohamed, A.S., Nashwan, A.J., 2021. Managing a patient with bipolar disorder associated with COVID-19: a case report from Qatar. Clin. Case Rep. 9, 2285–2288. https://doi.org/10.1002/ccr3.4015.
Krauthammer, C., Klerman, G.L., 1978. Secondary mania: manic syndromes associated with antecedent physical illness or drugs. Arch. Gen. Psychiatry 35, 1333–1339. https://doi.org/10.1001/archpsyc.1978.01770350059005.
Lambrichts, S., Van Oudenhove, L., Sienaert, P., 2017. Antibiotics and mania: a systematic review. J. Affect. Disord. https://doi.org/10.1016/j.jad.2017.05.029.
Le Guennec, L., Devianne, J., Jalin, L., Cao, A., Galanaud, D., Navarro, V., et al., 2020. Orbitofrontal involvement in a neuroCOVID-19 patient. Epilepsia 61, e90–e94. https://doi.org/10.1111/epi.16612.
Leboyer, M., Soreca, I., Scott, J., Frye, M., Henry, C., Tamouza, R., Kupfer, D.J., 2012. Can bipolar disorder be viewed as a multi-system inflammatory disease? J. Affect. Disord. 141, 1–10. https://doi.org/10.1016/j.jad.2011.12.049.
Librenza-Garcia, D., Suh, J.S., Watts, D.P., Ballester, P.L., Minuzzi, L., Kapczinski, F., Frey, B.N., 2021. Structural and functional brain correlates of neuroprogression in bipolar disorder. Curr. Top. Behav. Neurosci. 48, 197–213. https://doi.org/10.1007/7854_2020_177.
Lu, S., Wei, N., Jiang, J., Wu, L., Sheng, J., Zhou, J., Fang, Q., et al., 2020. First report of manic-like symptoms in a COVID-19 patient with no previous history of a psychiatric disorder. J. Affect. Disord. 277, 337–340. https://doi.org/10.1016/j.jad.2020.08.031.
Maletic, V., Raison, C., 2014. Integrated neurobiology of bipolar disorder. Front. Psychiatry 5. https://doi.org/10.3389/fpsyt.2014.00098.
Martinotti, G., Bonanni, L., Barlati, S., Miuli, A., Sepede, G., Prestia, D., et al., 2021. Delirium in COVID-19 patients: a multicentric observational study in Italy. Neurol. Sci. 42, 3981–3988. https://doi.org/10.1007/s10072-021-05461-2.
Mikolas, P., Bröckel, K., Vogelbacher, C., Müller, D.K., Marxen, M., Berndt, C., et al., 2021. Individuals at increased risk for development of bipolar disorder display structural alterations similar to people with manifest disease. Transl. Psychiatry 11, 485. https://doi.org/10.1038/s41398-021-01598-y.
Muralidharan, A., Bhagwagar, Z., 2006. Potential of levetiracetam in mood disorders: a preliminary review. CNS Drugs 20, 969–979. https://doi.org/10.2165/00023210-200620120-00002.
Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al., 2005. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53, 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x.
National Institutes of Health, 2021. COVID-19 treatment guidelines panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [WWW Document]. URL https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults-therapeutic-management/.
Netland, J., Meyerholz, D.K., Moore, S., Cassell, M., Perlman, S., 2008. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J. Virol. 82, 7264–7275. https://doi.org/10.1128/JVI.00737-08.
Noone, P., 2015. Addenbrooke's Cognitive Examination-III. Occup. Med. (Chic. Ill). 65, 418–420. https://doi.org/10.1093/occmed/kqv041.
O'Connell, K.S., Coombes, B.J., 2021. Genetic contributions to bipolar disorder: current status and future directions. Psychol. Med. https://doi.org/10.1017/S0033291721001252.
Oliveira, J., Kazma, R., Le Floch, E., Bennabi, M., Hamdani, N., Bengoufa, D., et al., 2016. Toxoplasma gondii exposure may modulate the influence of TLR2 genetic variation on bipolar disorder: a gene-environment interaction study. Int. J. bipolar Disord. 4, 11. https://doi.org/10.1186/s40345-016-0052-6.
Pereira, A.C., Oliveira, J., Silva, S., Madeira, N., Pereira, C.M.F., Cruz, M.T., 2021. Inflammation in Bipolar Disorder (BD): identification of new therapeutic targets. Pharmacol. Res. 163, 105325 https://doi.org/10.1016/j.phrs.2020.105325.
Rogers, J.P., Chesney, E., Oliver, D., Pollak, T.A., McGuire, P., Fusar-Poli, P., et al., 2020. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Lancet Psychiatry 7, 611–627. https://doi.org/10.1016/S2215-0366(20)30203-0.
Rosenblat, J.D., McIntyre, R.S., 2016. Bipolar disorder and inflammation. Psychiatr. Clin. N. Am. 39, 125–137. https://doi.org/10.1016/j.psc.2015.09.006.
Rowland, T.A., Marwaha, S., 2018. Epidemiology and risk factors for bipolar disorder. Ther. Adv. Psychopharmacol. 8, 251–269. https://doi.org/10.1177/2045125318769235.
Sanches, M., Colpo, G.D., Cuellar, V.A., Bockmann, T., Rogith, D., Soares, J.C., Teixeira, A.L., 2021. Decreased plasma levels of angiotensin-converting enzyme among patients with bipolar disorder. Front. Neurosci. 15, 617888 https://doi.org/10.3389/fnins.2021.617888.
Satzer, D., Bond, D.J., 2016. Mania secondary to focal brain lesions: Implications for understanding the functional neuroanatomy of bipolar disorder. Bipolar Disord. https://doi.org/10.1111/bdi.12387.
Schou, T.M., Joca, S., Wegener, G., Bay-Richter, C., 2021. Psychiatric and neuropsychiatric sequelae of COVID-19 – a systematic review. Brain. Behav. Immun. https://doi.org/10.1016/j.bbi.2021.07.018.
Sen, M., Yesilkaya, U.H., Balcioglu, Y.H., 2021. SARS-CoV-2-associated first episode of acute mania with psychotic features. J. Clin. Neurosci. 87, 29–31. https://doi.org/10.1016/j.jocn.2021.02.012.
Song, E., Zhang, C., Israelow, B., Lu-Culligan, A., Prado, A.V., Skriabine, S., Lu, P., Weizman, O.-E., et al., 2021. Neuroinvasion of SARS-CoV-2 in human and mouse brain. J. Exp. Med. 218 https://doi.org/10.1084/jem.20202135.
Song, X., Hu, W., Yu, H., Zhao, L., Zhao, Yeqian, Zhao, X., et al., 2020. Little to no expression of angiotensin-converting enzyme-2 on most human peripheral blood immune cells but highly expressed on tissue macrophages. Cytometry. A. https://doi.org/10.1002/cyto.a.24285.
Spinney, L., 2017. Pale Rider: the Spanish flu of 1918 and How it Changed the World. PublicAffairs.
Stuivenga, M., Morrens, M., 2014. Prevalence of the catatonic syndrome in an acute inpatient sample. Front. Psychiatry.
Takeuchi, H., Kimura, R., Tomita, H., Taki, Y., Kikuchi, Y., Ono, C., et al., 2021. Polygenic risk score for bipolar disorder associates with divergent thinking and brain structures in the prefrontal cortex. Hum. Brain Mapp. 42, 6028–6037. https://doi.org/10.1002/hbm.25667.
Toniolo, S., Di Lorenzo, F., Scarioni, M., Frederiksen, K.S., Nobili, F., 2021. Is the frontal lobe the primary target of SARS-CoV-2? J. Alzheimers. Dis. 81, 75–81. https://doi.org/10.3233/JAD-210008.
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. https://doi.org/10.1016/j.bbi.2020.04.027.
Varatharaj, A., Thomas, N., Ellul, M.A., Davies, N.W.S., Pollak, T.A., Tenorio, E.L., et al., 2020. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 7, 875–882. https://doi.org/10.1016/S2215-0366(20)30287-X.
Vieta, E., Berk, M., Schulze, T.G., Carvalho, A.F., Suppes, T., Calabrese, J.R., et al., 2018. Bipolar disorders. Nat. Rev. Dis. Prim. 4 https://doi.org/10.1038/nrdp.2018.8.
Yesilkaya, U.H., Balcioglu, Y.H., 2020. Neuroimmune correlates of the nervous system involvement of COVID-19: a commentary. J. Clin. Neurosci. https://doi.org/10.1016/j.jocn.2020.05.056.
Young, A.H., Juruena, M.F., 2021. Bipolar Disorder: From Neuroscience to Treatment. Springer Nature.
Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429.
Zubair, A.S., McAlpine, L.S., Gardin, T., Farhadian, S., Kuruvilla, D.E., Spudich, S., 2020. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2020.2065.