Does COVID-19 related symptomatology indicate a transdiagnostic neuropsychiatric disorder? - Multidisciplinary implications

Goldstein Ferber S et al. COVID-19 transdiagnostic indications
Abstract
The clinical presentation that emerges from the extensive coronavirus disease 2019 (COVID-19) mental health literature suggests high correlations among many conventional psychiatric diagnoses. Arguments against use of multiple comorbidities for a single patient have been published long before the pandemic. Concurrently, diagnostic recommendations for use of transdiagnostic considerations for improved treatment have been also published in recent years. In this review, we pose the question of whether a transdiagnostic mental health disease, including psychiatric and neuropsychiatric symptomology, has emerged since the onset of the pandemic. There are many attempts to identify a syndrome related to the pandemic, but none of the validated scales is able to capture the entire psychiatric and neuropsychiatric clinical presentation in infected and non-infected individuals. These scales also only marginally touch the issue of etiology and prevalence. We suggest a working hypothesis termed Complex Stress Reaction Syndrome (CSRS) representing a global psychiatric reaction to the pandemic situation in the general population (Type A) and a neuropsychiatric reaction in infected individuals (Type B) which relates to neurocognitive and psychiatric features which are part (excluding systemic and metabolic dysfunctions) of the syndrome termed in the literature as long-COVID. We base our propositions on multidisciplinary scientific data regarding mental health during the global pandemic situation and the effects of viral infection reviewed from Google Scholar and PubMed between February 1, 2022 and March 10, 2022. Search inclusion criteria were “mental health”, “COVID-19” and “Long COVID”, English language and human studies only. We suggest that this more comprehensive way of understanding of COVID-19 complex mental health reactions may promote better prevention and treatment and serve to guide implementation of recommended administrative regulations that were recently published by the World Psychiatric Association. This review may serve as a call for an international investigation of our working hypothesis.
**Key Words:** Mental health; Symptoms; Comorbidity; Long COVID; Fatigue; Transdiagnostic


**Core Tip:** This editorial asks a question shown in its title and hidden to date in the scientific literature on coronavirus disease 2019 (COVID-19) pandemic. It integrates the immense COVID-19 and long-COVID literature on psychiatric and neuropsychiatric reactions to the pandemic in the general population. It also derives a working hypothesis on Type A and Type B of a hypothesized syndrome to be termed Complex Stress Reaction Syndrome. This working hypothesis is elaborated in the MS and supports the need to ask the transdiagnostic question in a timely manner based on a novel interdisciplinary and genuine integration of the state-of-the-art.

**INTRODUCTION**

Since the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, there increasing evidence revealed several psychiatric diagnoses suspected as being involved in the reaction of the general population to the pandemic and its related stressors. The majority of the studies investigated the comorbidity of depression and anxiety\[^{1-4}\] and others added stress\[^{5-9}\] and posttraumatic stress disorder (PTSD)\[^{10-14}\]. However, many others found a significant incidence of other symptoms that are not clearly related to these comorbidities as outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and International Classification of Diseases (ICD-11): Latent infection phobia\[^{15}\], OCD symptoms\[^{16-19}\], somatization\[^{20}\], health anxiety\[^{19,21}\], internet gaming disorder\[^{22,23}\], reports of repeated nightmares with virus-related narratives and intrusive thoughts, change in dream recall frequency\[^{24}\], addictive social media use\[^{25,26}\], thoughts of self-injury or suicide\[^{27-31}\], emotional eating and binge eating\[^{32}\], antisocial
behavior, and substance abuse to relieve stress or boredom\textsuperscript{[33]}. Thus, as the COVID-19 pandemic evolved, the psychiatric symptomatology reported progressed from single disorders to mixtures of diagnoses. These mixtures could be found even within the same patient, while a complex of symptoms derived from several diagnostic categories was found in many individuals\textsuperscript{[34-36]}. This multiplicity of diagnoses is in accordance with the recent concern that multiple diagnoses are given to single patients and that the term “comorbidity” is excessively used, thus undermining treatment focus and prevention efforts\textsuperscript{[37]}. A more accurate diagnosis could further reduce individual and organizational challenges, including, e.g., the risk for stigmatization\textsuperscript{[38]}. It is of relevance also that the World Psychiatric Association produced an ethical protocol aimed at treatment of psychiatric patients during the COVID-19 era. This protocol is relevant for new patients and those with previous psychiatric diagnoses and for both infected and non-infected people\textsuperscript{[39]}. However, how can we apply administrative regulations, and provide and allocate appropriate treatment without an available accurate diagnosis? If changes are recommended, research efforts for a valid diagnosis are warranted. In this review, we ask whether a new mental health disease has emerged since the onset of the pandemic, if its main characteristic is its transdiagnostic feature of symptomatology, and whether this new suspected syndrome may be related to the neuropsychiatric manifestation included in the general term “Long COVID”. This term contains neurological, psychiatric, and systemic symptoms in a manner which makes it difficult to differentiate for deriving appropriate treatment by different medical specialists. An accurate diagnosis has always been the starting point for the development of appropriate psychotherapeutic and pharmacological treatments, and for clinical trials examining their effectiveness. This developmental process within the professional field of psychiatry is expected to reach the identification of precise therapeutic components for further benefit of the diagnosed individual. This potential accurate diagnosis may also emerge as the initial stage for the implementation of new institutional regulations for in- and out-patients with psychiatric reactions to the pandemic and with residual
syndromes of the infection. It must be noted that accurate diagnosis has been only recently recognized as a professional need[40].

THE PSYCHIATRIC AND NEUROPSYCHIATRIC REACTIONS TO COVID-19 IN THE GENERAL POPULATION: AN INTERDISCIPLINARY APPROACH
The psychiatric COVID syndrome in the general population. The psychiatric consequences of COVID-19 have been reported according to ICD or DSM illness code in many studies to date. These studies have reported greater depression and anxiety levels compared to pre-pandemic prevalence of depressive- and anxiety-related syndromes[3,4]. Intolerance to uncertainty has been related to COVID-19 related anxieties due to the inherent uncertainty in the pandemic situation[41]. In addition, the literature reports on specific pandemic-related psychopathology. Several reports that the severity of diverse symptoms across diagnostic categories are correlated during the pandemic suggest that a link exists among these symptoms[17,42-45]. The reports of COVID-19 related symptoms evolved from single diagnostic categories to combinations of ICD-10 and DSM-5 diagnoses, often within a single patient, and altogether many individuals present with a symptom complex across several diagnostic disorders[34-36].

The reports are worldwide and related to all ages, even including pregnant mothers[46]. Several tools have been suggested in the literature following investigation and validation for identifying a mental health disorder particular to the pandemic situation. Following research, construction, and validation of the COVID Stress Scales[47], Taylor et al[45] proposed the COVID Stress Syndrome[45]. The main aspect of this syndrome is worry about the dangers of the pandemic with four additional concerns: (1) Worry regarding the personal socioeconomic impact of the pandemic; (2) Xenophobic worries regarding spread of the virus; (3) Nightmares or intrusive thoughts related to COVID-19; and (4) Compulsive checking and reassurance seeking. These researchers have also described a second set of beliefs, termed COVID-19 Disregard Syndrome. It is centered around the conviction that the viral threat is exaggerated. This belief is associated with disregard for social distancing, poor hand hygiene, and anti-vaccination attitude, also
termed as “pandemic related adjustment”[53,48]. Persian[39], Turkish[50], and Singaporean versions[51] added to the overall validation of the study in these cultures. Another transdiagnostic scale (containing 12 sub-scales) is the self-report COVID-19 Pandemic Mental Health Questionnaire, which includes patterns of contamination anxiety, paranoid ideations, and several additional beliefs, behaviors, and sources of resilience[52]. The COVID-19 quality of life scale assesses quality of life regarding mental health[53]. The COVID-19 phobia scale measures “corona phobia”[15]. Multidimensional Assessment of COVID-19-Related Fears assess related concerns[54]. Another group has suggested two additional scales: The Coronavirus Anxiety Scale (CAS) and Fear of COVID-19 Scale[55-57]. This group demonstrated how the levels of anxiety and fear, measured by these scales, co-varied with gender, age, cohabitation status, educational levels and the presence of positive cases or pandemic-related death. The CAS has been shown to have cross-cultural validity in 12 Latin American countries[58]. A different anxiety scale, validated in England, is the COVID-19 Anxiety Syndrome Scale[59]. In China, COVID-19 Related Psychological Distress has been assessed[60]. The COVID-19 Stressor Scale assesses stressor exposure and appraisal with demonstrated convergent and discriminant validity, from an online survey of a national sample (n = 437) in the United States[61]. Combined Scales for anxiety, depression and stress also exist. However, neither of these versions distinguished patients diagnosed with depression and anxiety from each other or from other psychiatric conditions, when studied during the COVID-19 quarantine period in Saudi Arabia[62]. A Chinese distress scale (used in a nationwide survey) is the COVID-19 Peritraumatic Distress Index[63]. Another approach to studying trauma in COVID-19 is to use the Impact of Event Scale with modifications for COVID-19[64]. The COVID-19 literature indicates high correlations among several symptoms in a manner that shows that the architecture of the pandemic-related mental health reactions spans the conventional DSM-5/ICD-11 criteria[8,65]. A recent narrative review of the psychometric qualities of scales noted that the heterogeneous and insufficient description of methods used to assess the psychometric characteristics of these scales may limit their usefulness for clinical and research purposes[66].
systematic review focusing on the quality of data collection addressing 37 relevant mental health cross-sectional surveys of the general public (average sample size = 5137) noted a high risk of selection bias\cite{67}. Regarding etiology, there are limited data and research. Most of the studies assumed that the COVID situation is combined from different stressors but have not shown the personality structure covariance with a specific stressor or more than one stressor. Recently it had been mentioned that the investigation of stressors is a challenge because of the independence between different stressors when they impact the elicitation of a syndrome and because of their dependency on premorbid psychiatric conditions and earlier dispositions of personality traits\cite{61,68}. Therefore, to date, we still do not know in a causative manner if the COVID-19 situation is a global source for a new psychiatric disorder or a transient stressful condition that should be dealt with from the level of personal coping perspective and coping accepted theories. The neurological component of the COVID infection as newly suspected mental health disease another insufficiently studied issue is the mental health problems associated with the viral infection following recovery, often referred to as “long COVID”. The syndrome recognized as “long COVID” has been described with heterogeneous symptomatology, including psychiatric, neurological, and systemic symptoms\cite{69-73}. These symptoms include loss of smell and/or taste, fatigue, cough, aching pain, “brain fog”, insomnia, shortness of breath, and tachycardia\cite{74-78}. The prevalence of long COVID as found in modest and large samples is around 40% of recovering individuals with different manifestations and not necessarily with all symptoms in each one patient\cite{79}. A wide range of prevalence and of prevalence over time were reported for the different symptoms\cite{74,80}. The syndrome has been recognized 12 wk to 6 mo following recovering from the acute COVID-19 infection\cite{79,81}. The long COVID syndrome has been related to the identification of the COVID virus as a multi-organ infection with differential damages to each cell type in many organs\cite{74,82,83}. The assumed underlying mechanisms are complex. They include dysregulation of mitochondria which results in systemic decrease in metabolic activity and bioenergetics at the cellular level within the nervous system. The factors underlying brain fog may
also produce additional pathogenic insults. It has been suggested that these pathological insults can progress to repetitive viral and bacterial propagation cycles[84]. The mental health symptoms have been suggested to be connected to increased susceptibility to infection due to a compromised immune system[84]. Others suggested a list of pathologies, i.e., production of inflammatory cytokines, cellular damage, and pro-coagulant state that underlie long-lasting COVID-19 symptomatology[85]. We suggest that mental health problems following recovery from COVID-19 infection result directly from damage to redox and antioxidative defenses of the cell as well as the neural basis for the fatigue manifestation, which has been identified as the most common symptom included in the long-COVID term[79,86-90]. This fatigue may be the basis for the cognitive impairment reported too. We note that the psychiatric components of long COVID may be secondary effects of the impact of the immense fatigue and neurological symptoms on emotional regulation and may not result from direct damage to neural cells. As there are conflicting results on the association of severity in the acute phase and the manifestation of long COVID syndrome, it is unclear whether there is one or more underlying mechanisms underlying this syndrome and whether there is a cascade of deteriorating effects of one or more cellular damages caused by the infection. There are only scarce research efforts to disentangle the long COVID syndrome to its psychiatric, neurological, and systemic components[28,82]. Comparisons of mental health symptomatology between infected and non-infected individuals—is there a difference? The pattern of findings appears mixed and inconsistent. While most studies reported more severe mental health disorders in infected compared to non-infected individuals, some studies did not reveal this pattern. Some representative findings from the majority of studies are as follows: (1) Prevalence of post-traumatic stress symptoms was more severe in COVID-19 survivors compared to healthy controls[91]; (2) Anxiety and depression were more prevalent in infected compared to non-infected people in a large Chinese sample[92]; (3) “Prevalence of stress, anxiety, depression, intrusion, hypervigilance, and avoidance among infected health care workers (HCWs) were significantly higher in comparison to non-infected HCWs”[93]; and (4) Suicidal ideation

8 / 13
was more prevalent in infected vs non-infected individuals, in the United States\cite{27}. Even months after recovery from the infection, depression, anxiety, and PTSD were prevalent\cite{34}. In contrast, the prevalence of psychological distress among healthcare workers in Quebec was not associated with COVID infection status\cite{95}. Furthermore, surprisingly, in a geriatric sample, the risk for depression symptoms was lower in infected (and recovering from COVID-19) individuals compared to non-infected controls\cite{96}. A study using a different approach compared the transcriptome and data on immune factor transcription (from peripheral blood mononuclear cells) between infected patients and individuals with psychiatric disorders\cite{97}. COVID-19 infected patients had a transcriptional profile prominently presenting inflammatory cytokine and interferon response genes, a profile fitting with a pro-inflammatory state. The authors also reported 39 dysregulated genes shared by COVID-19 and bipolar disorder, 22 shared with schizophrenia, and 19 with PTSD. The profile of the common genes is dominated by pro-inflammatory and cytokine factors. Finally, infected patients showed profiles of the peripheral (blood) immune system with considerable correspondence with those among the patients with the psychiatric conditions\cite{97}. In a small sample of infected patients, a neuroradiological severity clinical index was correlated significantly with injury to the CNS (measures: Glial fibrillary acidic protein, total-tau, ubiquitin carboxyl-terminal hydrolase L1), and inflammation (C-reactive protein)\cite{98}. A recent Cochrane review reported that stroke, paralysis, and altered mental status were the most frequent neurological disorders associated with COVID-19 infection\cite{99}. The authors also suggest that COVID-19 could potentially induce new-onset seizures, Guillain-Barre Syndrome, encephalitis, and other neurological disorders. In a large sample of infected individuals, in 55% of the people at least one neurological symptom was observed; the prevalence was greater in people with high body mass index and older age\cite{100}. In this study, headaches and loss of smell and taste were prevalent while seizures and stroke were the least common neurological symptoms. We conclude the following two risks based on this mixed clinical picture as it arises from the extensive COVID literature: (1) The COVID-19 situation is a multiple stressor condition posing
risks to mental health in the general population; and (2) Being infected poses an additional neuropsychiatric risk, implying that the two risks should be investigated and dealt from a psychiatric and neuropsychiatric perspectives for better diagnosis and treatment. The Complex Stress Reaction Syndrome (Type A and Type B) Diagnostic considerations: COVID-19 has been shown to elicit transdiagnostic psychiatric symptomatology\textsuperscript{[65,101,102]}. Beyond peripheral somatic effects, COVID-19 also affects the brain, as shown in neurocognitive impaired functions of recovering individuals. Therefore, we propose two sub-categories of this new perspective/syndrome. In principle, they are not mutually exclusive. Thus, we suggest including psychiatric and neuropsychiatric components in the newly suspected syndrome while excluding systemic and metabolic manifestations. The first type is found in non-COVID-19 infected people, who present with psychopathology similar to that described above. We hypothesize that the etiology of this “Type A” follows exposure to pandemic stressors, including quarantine and social isolation, fear of infection, and both social and physical distancing. “Type B” is manifested in infected individuals. We suggest that it includes neurological and psychiatric characteristics which emerge from the resulting effects of the viral infection, e.g., coagulopathy-related strokes and cranial nerve injury\textsuperscript{[103]}, and sensory impairment\textsuperscript{[104,105]}. It may be diagnosed as a part (excluding systemic and metabolic dysfunctions) of the heterogeneous syndrome, currently termed in the literature as long-COVID. It has been reported in a large sample ($n = 84285$) of COVID-19 infection survivors that those chronic neurocognitive impairments persisted, even when gender, age, racial-ethnic group, income, education level, and previously experienced medical conditions were considered. This study supported the authors’ conclusion that COVID-19-related symptoms are induced by the virus acting at multi-system levels, affecting the brain beyond the effects on other organs\textsuperscript{[106]}. Bi-directional associations between psychiatric disorders and COVID-19 infection have been suggested, based on retrospective analysis of data from a large sample\textsuperscript{[107]}. Specifically, survivors of COVID-19 infection presented an increased risk of psychiatric outcomes, and an existing psychiatric diagnosis was a risk factor for COVID-19 infection. Thus, a
clinical neurological evaluation is needed in addition to assessing psychopathology to provide a comprehensive clinical picture of COVID-19-related symptoms. The etiology of Type A is hypothesized to be linked to the multiplicity of COVID-19 situational stressors. The etiology of Type B is suggested to be mainly the consequence of the infection itself, including the virus' neuropsychiatric effects of the virus. This approach may provide an overarching framework for future studies (see Figure 1). Differential diagnosis: In contrast to traditional diagnoses, mental disorders associated with COVID-19 are different as follows: (1) PTSD diagnosis including exposure to a frightening stressor, resulting in nightmare and over-generalization to other situations. However, the COVID-19 reactions include extended exposure to complex stressors, diffused anxiety regarding infection and disease, without repeated nightmares, flashbacks or over-generalization as recently reported\cite{47}; (2) Diagnosis of Adjustment Disorder rules out PTSD and bereavement, and it displays a short stressor onset-symptoms occurrence latency. In contrast, during COVID-19, several months may elapse before symptom onset; (3) Diagnosis of Acute Stress Disorder implies a simpler stressor and a specific symptom response. In contrast, the pandemic stressors and the pattern of response are complex, as detailed above; (4) Obsessional thoughts are ego-syntonic by definition. During the pandemic, fear of contamination and associated behaviors are justified by the objective situation (e.g., need for masks, extra hygienic guidelines, social distancing); the behaviors related to these guidelines are clearly not part defined by Obsessive Compulsive Disorder; (5) The criteria for defining Generalized Anxiety Disorder list excessive worrying (on diverse issues) and shifting back and forth among them. In contrast, COVID-19-related mental health reports include anxiety that is clearly related to the several pandemic-relevant stressors\cite{47}; and (6) The diagnosis of Major Depression Disorder includes anhedonia, low affect, psychomotor agitation, unfitting guilt feelings, diminished drive and energy, trouble concentrating, and indecisiveness. Some of these symptoms, along with others, are to be found in COVID-19-related mental health reports. Future studies should address all these issues. Life span considerations: There is no agreement in the literature on the
neuropsychiatric impacts of the pandemic on children, adolescents, and youth and especially on the prevalence of the post-infection syndrome termed long-COVID[108-110]. According to available data, both psychiatric and neuropsychiatric effects are shown in young ages[110-112]. Regarding the elderly, a population with greater risk for infection and severe conditions, we suggest that premorbid psychiatric and neurological problems related to older ages may be involved in the older population’s reactions to the pandemic. Some reports support our transdiagnostic CSRS understanding even in elderly[74,113]. Therefore, further studies are warranted to evaluate the applicability of our working hypothesis across the life spans. As an elaboration of our working hypothesis, we suggest that on the axis between Type A and Type B of the proposed diagnosis, Type A may be more prevalent in younger ages, Type B may be more prevalent in older ages, and the variability in the incidence of Type A, Type B or both together may be greater during adulthood than in younger or older ages.

CONCLUSION

The clinical presentation of mental health symptomatology during the pandemic in infected and non-infected individuals implies many “comorbidities,” i.e., a transdiagnostic manifestation as arising from the literature. In the available diagnostic manuals, there are no transdiagnostic categories as yet while the study of the mental health reactions to the pandemic shows such a pattern. Additionally, the suspected mental health disorder, as we suggest diagnosing it, implies the effect of multiplicity of co-occurring stressors which result in a mixed clinical picture. Such a stress syndrome may be valid for post-pandemic days as well. Therefore, our outline for the suggested new diagnosis may be termed as CSRS, Type A, Type B. The validation of this hypothesis may relate the psychiatric and neuropsychiatric symptomatology to be treated by professional psychiatrists while other types of systemic and metabolic symptoms remain to be treated by internal medicine professionals (see Figure 1). This hypothesis has the potential to secure appropriate treatments for the suffering patients.
This review may serve as a call for a meta-analysis and systematic review of the literature as well as for an international investigation of our working hypothesis.
### PRIMARY SOURCES

<table>
<thead>
<tr>
<th>#</th>
<th>Source</th>
<th>Words Matched</th>
<th>Similarity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><a href="http://www.ncbi.nlm.nih.gov">www.ncbi.nlm.nih.gov</a></td>
<td>36</td>
<td>1%</td>
</tr>
<tr>
<td>2</td>
<td>doaj.org</td>
<td>29</td>
<td>1%</td>
</tr>
<tr>
<td>3</td>
<td>systematicreviewsjournal.biomedcentral.com</td>
<td>18</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>4</td>
<td>pubmed.ncbi.nlm.nih.gov</td>
<td>17</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>5</td>
<td>Marco Cascella, Elvio De Blasio. &quot;Chapter 4 Neurological, Psychological, and Cognitive Manifestations of Long-COVID&quot;, Springer Science and Business Media LLC, 2022</td>
<td>12</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>6</td>
<td><a href="http://www.mdpi.com">www.mdpi.com</a></td>
<td>12</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>