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Review Article

What is the COVID-19 Scenario for Psychiatric Conditions in Older Adults? A Narrative Review

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Abstract

Objectives: Given the high prevalence of coronavirus disease 19 (COVID-19), this study assessed its negative impact on mental health in older adults.
Design: Narrative review.
Setting(s): Global.
Outcome Measures: Post COVID psychiatric conditions.
Results: Mental disorders could emerge as neuro-psychiatric consequences of COVID-19 as the result of brain damage or even as the direct symptoms of virus attack to the central nervous system (CNS) or as the consequences of immune response/drug drawbacks. It was found that older individuals may experience psychiatric disorders due to the COVID-19 pandemic. Common psychological symptoms observed in COVID-19 patients were post-traumatic stress disorder (PTSD), anxiety, delirium, sleep disturbances, and depression. On the other hand, these mental health symptoms could also signal the initial phases of COVID-19 in elderly individuals.
Conclusions: It is essential to remain vigilant in recognizing psychiatric conditions as either clinical manifestations of COVID-19 or complications resulting from the infection.
Keywords: COVID-19, Psychiatric disorders, Lockdown, Older adults

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Introduction

Shortly after the pandemic of coronavirus disease 19 (COVID-19), psychiatric disorders associated with the disease became increasingly recognized, mainly in the older population. In addition to the high prevalence of psychiatric disorders among the general population owing to pandemic[1] and among high-risk populations such as healthcare workers or older people,[2] infected patients with COVID-19 are also at high risk of mental disorders.

According to several biological and psychosocial factors such as disease side-effects, extensive anxiety, social isolation, stress, unemployment, and financial issues, both infected and non-infected people are at risk of psychiatric disorders.

Old patients with COVID-19 are probably prone to psychiatric disorders owing to experiencing severe anxiety or traumatic events. Moreover, it has been well-accepted that mental disorders could emerge as neuropsychiatric consequences of COVID-19. It may appear due to (A) brain damage, (B) the direct symptoms of virus attack to the central nervous system (CNS), (C) the consequences of immune response, and (D) drug drawbacks. In brief, following infection with severe acute respiratory syndrome *coronavirus 2* (SARS-CoV-2), factors such as brain infection, blood clotting disorders, hypoxia, immune response, medical interventions, social isolation, concerns of the disease outcome or transmission of the infection to the relatives, and the like may lead to mild to severe psychiatric conditions.

It is now well-accepted that infection-related inflammation and the consequent cytokine storm are the main players of COVID-19. On the other hand, inflammation and elevated cytokines have key roles in the onset and development of mental disorders. For instance, the correlation between inflammation and depression is well documented.[3,4] SARS-CoV-2 affects and disrupts the airways and directly attacks the CNS, providing the opportunity for impaired brain function in COVID-19 patients.[5]

Due to the widespread occurrence of COVID-19 and its impact on many individuals, its detrimental effects on mental health can be particularly pronounced among older adults. It is important to acknowledge the possibility of long-term psychiatric issues, including

depression, post-traumatic stress disorder (PTSD), and atypical neuropsychiatric syndromes. A case series study from France reported that one-third of hospitalized COVID-19 patients showed psychiatric symptoms upon their discharge.[6] National survey data from a UK study revealed that in addition to increasing the prevalence of generalized mental disorders and loneliness during the COVID-19 pandemic, people with COVID-19 symptoms or a history of infection with SARS-CoV-2 were at higher risk for many general psychiatric illnesses and loneliness.

Given the psychological and social effects caused by pandemics and the impact of COVID-19 on mental health, it is imperative to take immediate and urgent measures to mitigate these negative outcomes. While numerous studies have looked into the possible increase in psychological disorders among the general population because of the COVID-19 pandemic, limited research has been performed on the adverse effects of COVID-19 on mental health. This review will analyze three main aspects of how COVID-19 affects mental health in older adults, namely, (1) the emergence of psychiatric disorders due to the virus, (2) the impact of psychosocial factors on the psychiatric symptoms of COVID-19, and (3) the involvement of biological factors in the psychiatric consequences of COVID-19.

Methods

Search Strategy

An extensive search was performed to find relevant studies regarding the impact of psychosocial factors related to the quarantine on the psychiatric sequelae of COVID-19, with a particular focus on older individuals.

This search utilized electronic databases such as PubMed, Google Scholar, and Scopus. Keywords such as "COVID-19", "psychiatric disorders", "old population", and related terms were employed to locate pertinent articles. Only studies published in English within the last 20 years were considered in this review. Relevant information from the included studies—such as study design, participant characteristics, intervention details, and significant findings—was extracted and summarized in the review. The results from the included studies were summarized and interpreted through a narrative synthesis approach. The review highlighted and discussed key themes and patterns concerning the effects of COVID-19 on mental health.

Psychiatric Disorders as a Consequence of Infection in Older Adults

It is well-accepted that a higher risk of mood disorders is common after infections, and the risk increases in severe infections. Research has shown that the risk of mood disorders increases after infections, especially in severe cases, including depression, anxiety, and PTSD, which are the most prevalent psychiatric symptoms among elderly COVID-19 patients. Bo et al examined the occurrence of PTSD symptoms in COVID-19 patients who were clinically stable. Their findings indicated that a significant majority of these patients (95% confidence interval: 94.8%–97.6%) exhibited prominent PTSD symptoms related to their COVID-19 experience before being discharged.[7] Moreover, Zhang et al assessed the psychological distress among patients with COVID-21 and reported that severe depressive syndrome and anxiety-like behavior were observed in both groups of COVID-19 patients and the general population.[8]

During the acute phase of SARS, the Middle East respiratory syndrome, and COVID-19, signs indicating the onset of delirium have been noted in elderly patients. Different factors may play a role in the manifestation of delirium signs in older individuals with COVID-19. SARS-CoV-2 can directly invade the CNS, leading to conditions such as delirium. Additionally, delirium can be manifested as the consequence of CNS inflammatory mediators' inductions as well as a failure of other organ systems. The side effects of medications or psychosocial factors can also lead to delirium. On the other hand, the risk of intensive care unit (ICU) delirium increases owing to extended mechanical ventilation and/or drawbacks of sedatives (e.g., benzodiazepines) and is fixed for a long time. Considering that ICU delirium is directly correlated with mortality rate, its monitoring and prevention are vital. It is noteworthy that some strategies, including controlling pain, preventing urinary retention, and gastrointestinal issues such as constipation, identification and treatment of nosocomial infections, and maintenance of adequate oxygen, reduce the risk of ICU delirium.[9]

Ye et al presented a case of COVID-19 with encephalitis as a clinical manifestation of COVID-19 in Wuhan.[10] Additionally, the development of other psychiatric disorders, including insomnia,[11,12] suicidal behavior and psychosis,[13] and psychotic spectrum disorders,[14,15] has been reported in several studies.

Mawhinney et al documented a case of a 41-year-old man who contracted COVID-19 and subsequently experienced an acute manic episode. The most possible underlying mechanism for such clinical protests is the invasion of the virus to the nervous system; however, the cerebrospinal fluid (CSF)-polymerase chain reaction results were negative for SARS-CoV-2. Although this may be the first report of a psychiatric disorder as a sign of the onset of COVID-19, we should be alert to considering psychiatric conditions as the clinical presentations of COVID-19. Moreover, the necessity of developing validated tests for detecting SARS-CoV-2 in the CSF was highlighted in this report.[16] On the other hand, the drawbacks of COVID-19 on mental health should be monitored in long-term programs. Any resulting PTSD or mental health conditions can significantly impair the patient's quality of life and functional capacity. However, as most people are worried about being infected and have fears of an uncontrolled phenomenon, these conditions could mainly be related to hypochondriac concerns. Obviously, some emotions such as anxiety, depression,

guilt, stigma, and anger are inevitable during infection with SARS-CoV-2. Due to their effects on the immune system, such emotional variations should be considered cautiously and profoundly. On the other hand, SARS-CoV-2 affects the brain directly or indirectly through several mechanisms,[17] which will be discussed in the following sections.

Psychosocial Factors' Impact on Psychiatric Manifestations of Coronavirus Disease 19 in Older Adults

Research on the psychological effects of quarantine during previous epidemics such as SARS and the Middle East respiratory syndrome has indicated negative impacts on mental health, including symptoms of PTSD, depression, stress, anxiety, and fear. Newly, the results of a web survey assessing the psychological impacts and levels of stress during the start of the COVID-19 pandemic have been released.[18] The feedback from 1,210 participants indicated that 8.1% experienced moderate to severe stress, while 28.8% and 16.5% reported symptoms of anxiety and depression, respectively.[19] Additionally, individuals without formal education were much more likely to experience depression during the epidemic. Elderly individuals who experienced symptoms linked to SARS-CoV-2, such as coughing, dizziness, and muscle pain, or those with chronic health conditions, showed significantly elevated levels of anxiety, depression, and stress. Factors contributing to psychological distress included a prior history of mental health issues, extended quarantine periods, fears of infection, feelings of boredom, lack of supplies and information, and financial constraints. An unavoidable part of a pandemic is isolation/quarantine, which is also a known risk factor for psychological problems. Additionally, concerns about the potential infection of family, friends, and relatives are a newly recognized aspect. Conversely, having family members suspected of having COVID-19, experiencing reduced family support, lacking social resources during isolation, facing low family income, and being increasingly exposed to social media have all been linked to a higher risk of depression and anxiety. Further, changes in living conditions are likely to cause many of the identified risk factors to contribute to a rise in the number of affected individuals. It has been frequently argued that social isolation during COVID-19 increases loneliness. Loneliness is connected to long-term health outcomes, including all-cause mortality. Several studies demonstrated that living alone is related to increased symptoms of depression,[20-22] risk of depression,[23] and mortality.[24] Critical research has shown that individuals who are isolated exhibit various immune dysregulations, including the unregulated expression of pro-inflammatory cytokine genes.[25] Numerous studies have shown that alterations in the immune system significantly contribute to mental health disorders.[26] Changes in the immune system may be associated with the negative impact of loneliness on mental health. Furthermore, inflammatory mediators seem to influence how quarantine during COVID-19 affects psychological well-being, a subject that will be further examined in the next section. Public health strategies should take into account the mental health consequences of disease control measures. It is well understood that social support from both family and work can alleviate the psychological effects of a pandemic. Separation from friends and family, restricted freedom, and uncertainty can amplify feelings of loneliness and decrease social connections, leading to an increased risk of mental health disorders. This is particularly important for individuals who have pre-existing mental health issues and those who are overall in good health. Common symptoms that may emerge in these conditions include irritability, sleep issues, emotional distress, fear, panic, frustration, and communication difficulties. Prolonged exposure to these stressors can increase the likelihood of experiencing severe mental health conditions such as mood disorders, anxiety disorders, trauma-related disorders, and obsessive-compulsive disorder (OCD). While guidelines aimed at reducing infection rates are beneficial, they may inadvertently exacerbate OCD symptoms. Common obsessions and compulsions associated with OCD—such as fears of contamination and excessive handwashing—could worsen due to heightened anxiety about infection. Some studies have indicated that excessive handwashing has increased in the post-quarantine period. Following the onset of the pandemic, there has been a notable rise in the severity of obsessions and compulsions. Additionally, the relentless stream of negative news on social media, combined with hygiene recommendations, has created a particularly stressful environment for those vulnerable to contamination fears. Lockdown measures and limitations on accessing mental health services might dissuade elderly individuals from seeking help, resulting in delays in crucial treatments. Therefore, it is vital to implement relapse prevention strategies toward the end of cognitive-behavioral therapy to decrease the danger of deterioration. Support should not just tackle present symptoms but also concentrate on enhancing relapse prevention during prolonged periods of social isolation that might persist post-lockdowns. A major contributing factor to these outcomes is likely the decrease in treatment availability during the pandemic. Consequently, it is important to encourage older patients to connect with mental health professionals. Additionally, further investigation into alternative approaches, such as online consultations and digital psychiatry, is warranted. Digital technologies have been found to be effective in supporting both one-on-one and group therapy sessions. However, while these technologies can be beneficial during lockdowns, improper use without adequate guidelines could worsen the symptoms. Our observations indicated that this stressful period has led to a notable worsening of symptoms, especially among patients who had previously experienced contamination-related symptoms but were

in remission before the quarantine.[27] These findings highlight the critical necessity of psychological and psychiatric support for both infected and non-infected individuals experiencing social isolation during the pandemic.

Biological Factors' Impact on Psychiatric Aspects of Coronavirus Disease 19

Indirect Impact on Older Adults

Clearly, SARS-CoV-2, along with social isolation, results in changes in psycho-neuroendocrine-immune systems that impact mental health. In severe COVID-19 cases, there are augmented levels of neutrophils and pro-inflammatory cytokines [e.g., *interleukin* (IL)-1 beta, *interferon*-gamma, IL-6, i*nterferon*-γ–inducible protein 10, and monocyte chemoattractant protein-1], along with a remarkable reduction in lymphocyte counts. The elevation of cytokines and the subsequent cytokine storm can trigger psychiatric symptoms, as heightened cytokine levels are often associated with various mental health disorders. If these soluble cytokines reach the brain, they may disrupt the metabolism and activity of neurotransmitters associated with various psychiatric disorders such as depression, anxiety, PTSD, and OCD.[28,29] Among various cytokines, IL-6 levels increased significantly during the infection of COVID-19 in patients' blood, which is directly correlated with the severity of the disease. Any changes in homeostasis increase the low levels of IL-6, so that the levels of IL-6 remain high even after the elimination of stress agents and cause several diseases, such as psychiatric disorders.[30-34] For example, higher levels of IL-6 in the bloodstream have been observed in people going through early episode psychosis. Therefore, individuals who have recovered from COVID-19 could have an elevated chance of experiencing psychosis because of the raised levels of cytokines.[35]

It has since been suggested that factors such as obesity, aging, and pregnancy, which impact a patient's immune system, not only heighten the severity of COVID-19 infections but are also linked to psychiatric outcomes, increasing the likelihood of psychiatric symptoms.[36, 37]

Any infection or ailment that triggers the mother's immune system during pregnancy is regarded as a potential threat for neurodevelopmental problems such as autism spectrum disorder (ASD).[38] It is widely recognized that viral infections during the initial phases of fetal development can contribute to the onset of ASD. Neuroinflammation in the CNS of the infant can be triggered by direct infection or the inflammatory reactions of the mother and/or the fetus, resulting in changes in brain development.[39] Such concerns are also required to be addressed during the epidemic of COVID-19. Nonetheless, the current evidence linking SARS-CoV-2 infection during pregnancy to the onset of ASD is inadequate and needs further research.

Moreover, neuroimmune networks may have important roles in the manifestation of psychiatric symptoms. It is well established that increased brain levels of IL-1β and IL-6 lead to the inhibition of synaptic plasticity, learning, and memory, which can also be the cause of impaired memory and cognitive losses among COVID-19 patients.

Loneliness resulting from quarantine in both infected and non-infected elderly populations has significant biological effects on mental health. A study on rats kept apart from others reported that being socially isolated led to neuroinflammation, along with increased levels of toll-like receptors, IL-6, and tumor necrosis factor alpha (TNF-α) in the hippocampus. Furthermore, plasma levels of TNF-α, IL-4, IL-10, and adrenocorticotropic hormone demonstrated a rise.[40] Recent reports have confirmed a link between loneliness and systemic inflammation, evidenced by elevated levels of C-reactive protein and IL-6 in the general population.[41] The nervous, immune, and endocrine systems appear to be key contributors to neurobehavioral deficits caused by stress from social isolation. Consequently, changes in the neuroendocrine-immune pathways can result in mental health problems, which should be considered in future research.

Direct Impact in Older Adults

SARS-CoV-2 can cause brain dysfunction and neuropsychiatric issues by accessing the brain via the olfactory nerve or the enteric nervous system.[42] SARS-CoV-2 enters human cells through the angiotensin-converting enzyme 2 (ACE2) receptor. While ACE2 is found in various organs, it is particularly abundant in the lungs and gastrointestinal tract. Additionally, ACE2 is located in the brain's endothelial cells, raising concerns about the possibility of SARS-CoV-2 accessing the CNS. In the small intestine, endothelial cells rich in ACE2 may interact with neurons in the enteric nervous system.[43] It is believed that the vagus nerve could be a potential pathway for SARS-CoV-2 to infect the body. Moreover, virus-infected white blood cells can penetrate the blood-brain barrier, transporting the virus to the brain.[44] Nonetheless, the identification of SARS-CoV-2 RNA in a patient's CSF[45] empowers the theory of evading the virus to the CNS. Additionally, the amygdala—a group of brain cells crucial for memory processing, decision-making, and emotional reactions such as fear, anxiety, and aggression—shows the expression of ACE-2 in animal studies. Therefore, these cells could be responsible for acute mental and emotional conditions during infection with SARS-CoV-2. More focus on this field is highly recommended for implementing further preventive measures and finding an ideal treatment approach for neuropsychiatric manifestations of COVID-19.

In addition to the entry route of the virus, the mechanism of neuronal death by SARS-CoV-2 requires more focus. Autophagy as an important player in several neurodegenerative and psychiatric diseases seems a candidate for further investigations of SARS-CoV-2-related neuronal death.

Conclusion

COVID-19 has appeared as the main challenge worldwide, which continues in various forms. The current global pandemic circumstance requires a multidimensional approach to healthcare delivery. The pandemic can lead to the next pandemic of psychiatric conditions through several routes. Mental health and psychiatric screening and personal interventions, regardless of the causal pathogenesis, demand special attention during and after the COVID-19 pandemic. Additionally, psychiatric follow-ups are highly recommended for patients infected with COVID-19, even several months after infection remission.

Author contributions

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Ethical approval

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Consent for publication

Considering that this was a review study, there was no need to obtain informed consent.

References

1. Wang B, Li D, Liu T, Wang H, Luo F, Liu Y. Subcutaneous injection of IFN alpha-2b for COVID-19: an observational study. Res Sq [Preprint]. July 2020. doi: https://doi.org/10.21203/rs.3.rs-46001/v2.
2. Huang Y, Zhao N. Chinese mental health burden during the COVID-19 pandemic. Asian J Psychiatr. 2020;51:102052. doi: 10.1016/j.ajp.2020.102052.
3. Lee CH, Giuliani F. The role of inflammation in depression and fatigue. Front Immunol. 2019;10:1696. doi: 10.3389/fimmu.2019.01696.
4. Nakhlband A, Farahzadi R, Saeedi N, Barzegar H, Montazersaheb S, Razi Soofiyani S. Bidirectional relations between anxiety, depression, and cancer: a review. Curr Drug Targets. 2023;24(2):118-30. doi: 10.2174/1389450123666220922094403.
5. Rahnemayan S, Sanaie S. Central nervous system as a target for SARS-CoV-2: a review article. J Exp Clin Neurosci. 2020;7(2):1-5. doi: 10.13183/jecns.v7i2.110.
6. Nalleballe K, Reddy Onteddu S, Sharma R, Dandu V, Brown A, Jasti M, et al. Spectrum of neuropsychiatric manifestations in COVID-19. Brain Behav Immun. 2020;88:71-4. doi: 10.1016/j.bbi.2020.06.020.
7. Bo HX, Li W, Yang Y, Wang Y, Zhang Q, Cheung T, et al. Posttraumatic stress symptoms and attitude toward crisis mental health services among clinically stable patients with COVID-19 in China. Psychol Med. 2021;51(6):1052-3. doi: 10.1017/s0033291720000999.
8. Zhang J, Lu H, Zeng H, Zhang S, Du Q, Jiang T, et al. The differential psychological distress of populations affected by the COVID-19 pandemic. Brain Behav Immun. 2020;87:49-50. doi: 10.1016/j.bbi.2020.04.031.
9. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Crit Care. 2020;24(1):176. doi: 10.1186/s13054-020-02882-x.
10. Payandemehr P, Azhdarzadeh M, Bahrami-Motlagh H, Hadadi A, Najmeddin F, Shahmirzaei S, et al. Interferon beta-1a as a candidate for COVID-19 treatment; an open-label single-arm clinical trial. Adv J Emerg Med. 2020;4(2s):e51. doi: 10.22114/ajem.v4i2s.454.
11. Hao F, Tan W, Jiang L, Zhang L, Zhao X, Zou Y, et al. Do psychiatric patients experience more psychiatric symptoms during COVID-19 pandemic and lockdown? A case-control study with service and research implications for immunopsychiatry. Brain Behav Immun. 2020;87:100-6. doi: 10.1016/j.bbi.2020.04.069.
12. Morin CM, Carrier J. The acute effects of the COVID-19 pandemic on insomnia and psychological symptoms. Sleep Med. 2021;77:346-7. doi: 10.1016/j.sleep.2020.06.005.
13. Valdés-Florido MJ, López-Díaz Á, Palermo-Zeballos FJ, Martínez-Molina I, Martín-Gil VE, Crespo-Facorro B, et al. Reactive psychoses in the context of the COVID-19 pandemic: clinical perspectives from a case series. Rev Psiquiatr Salud Ment. 2020;13(2):90-4. doi: 10.1016/j.rpsm.2020.04.009.
14. Huarcaya-Victoria J, Meneses-Saco A, Luna-Cuadros MA. Psychotic symptoms in COVID-19 infection: a case series from Lima, Peru. Psychiatry Res. 2020;293:113378. doi: 10.1016/j.psychres.2020.113378.
15. Brown E, Gray R, Lo Monaco S, O'Donoghue B, Nelson B, Thompson A, et al. The potential impact of COVID-19 on psychosis: a rapid review of contemporary epidemic and pandemic research. Schizophr Res. 2020;222:79-87. doi: 10.1016/j.schres.2020.05.005.
16. Mawhinney JA, Wilcock C, Haboubi H, Roshanzamir S. Neurotropism of SARS-CoV-2: COVID-19 presenting with an acute manic episode. BMJ Case Rep. 2020;13(6):e236123. doi: 10.1136/bcr-2020-236123.
17. Troyer EA, Kohn JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun. 2020;87:34-9. doi: 10.1016/j.bbi.2020.04.027.
18. Zuo Y, Liu Y, Zhong Q, Zhang K, Xu Y, Wang Z. Lopinavir/ritonavir and interferon combination therapy may help shorten the duration of viral shedding in patients with COVID-19: a retrospective study in two designated hospitals in Anhui, China. J Med Virol. 2020;92(11):2666-74. doi: 10.1002/jmv.26127.
19. Wang C, Pan R, Wan X, Tan Y, Xu L, Ho CS, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health. 2020;17(5):1729. doi: 10.3390/ijerph17051729.
20. Russell D, Taylor J. Living alone and depressive symptoms: the influence of gender, physical disability, and social support among Hispanic and non-Hispanic older adults. J Gerontol B Psychol Sci Soc Sci. 2009;64(1):95-104. doi: 10.1093/geronb/gbn002.
21. Stahl ST, Beach SR, Musa D, Schulz R. Living alone and depression: the modifying role of the perceived neighborhood

environment. Aging Ment Health. 2017;21(10):1065-71. doi: 10.1080/13607863.2016.1191060.
22. Honjo K, Tani Y, Saito M, Sasaki Y, Kondo K, Kawachi I, et al. Living alone or with others and depressive symptoms, and effect modification by residential social cohesion among older adults in Japan: the JAGES longitudinal study. J Epidemiol. 2018;28(7):315-22. doi: 10.2188/jea.JE20170065.
23. Xiu-Ying H, Qian C, Xiao-Dong P, Xue-Mei Z, Chang-Quan H. Living arrangements and risk for late life depression: a meta-analysis of published literature. Int J Psychiatry Med. 2012;43(1):19-34. doi: 10.2190/PM.43.1.b.
24. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect Psychol Sci. 2015;10(2):227-37. doi: 10.1177/1745691614568352.
25. Cole SW, Capitanio JP, Chun K, Arevalo JM, Ma J, Cacioppo JT. Myeloid differentiation architecture of leukocyte transcriptome dynamics in perceived social isolation. Proc Natl Acad Sci U S A. 2015;112(49):15142-7. doi: 10.1073/pnas.1514249112.
26. Jones KA, Thomsen C. The role of the innate immune system in psychiatric disorders. Mol Cell Neurosci. 2013;53:52-62. doi: 10.1016/j.mcn.2012.10.002.
27. Davide P, Andrea P, Martina O, Andrea E, Davide D, Mario A. The impact of the COVID-19 pandemic on patients with OCD: effects of contamination symptoms and remission state before the quarantine in a preliminary naturalistic study. Psychiatry Res. 2020;291:113213. doi: 10.1016/j.psychres.2020.113213.
28. Grace AA. Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. Nat Rev Neurosci. 2016;17(8):524-32. doi: 10.1038/nrn.2016.57.
29. Bandelow B, Baldwin D, Abelli M, Bolea-Alamanac B, Bourin M, Chamberlain SR, et al. Biological markers for anxiety disorders, OCD and PTSD: a consensus statement. Part II: neurochemistry, neurophysiology and neurocognition. World J Biol Psychiatry. 2017;18(3):162-214. doi: 10.1080/15622975.2016.1190867.
30. Balschun D, Wetzel W, Del Rey A, Pitossi F, Schneider H, Zuschratter W, et al. Interleukin-6: a cytokine to forget. FASEB J. 2004;18(14):1788-90. doi: 10.1096/fj.04-1625fje.
31. del Rey A, Balschun D, Wetzel W, Randolf A, Besedovsky HO. A cytokine network involving brain-borne IL-1β, IL-1ra, IL-18, IL-6, and TNFα operates during long-term potentiation and learning. Brain Behav Immun. 2013;33:15-23. doi: 10.1016/j.bbi.2013.05.011.
32. Schneider H, Pitossi F, Balschun D, Wagner A, del Rey A, Besedovsky HO. A neuromodulatory role of interleukin-1beta in the hippocampus. Proc Natl Acad Sci U S A. 1998;95(13):7778-83. doi: 10.1073/pnas.95.13.7778.
33. Besedovsky HO, del Rey A. Central and peripheral cytokines mediate immune-brain connectivity. Neurochem Res. 2011;36(1):1-6. doi: 10.1007/s11064-010-0252-x.
34. Tanaka T, Narazaki M, Ogata A, Kishimoto T. A new era for the treatment of inflammatory autoimmune diseases by interleukin-6 blockade strategy. Semin Immunol. 2014;26(1):88-96. doi: 10.1016/j.smim.2014.01.009.
35. Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. Am J Psychiatry. 2011;168(12):1303-10. doi: 10.1176/appi.ajp.2011.11030516.
36. Zhavoronkov A. Geroprotective and senoremediative strategies to reduce the comorbidity, infection rates, severity, and lethality in gerophilic and gerolavic infections. Aging (Albany NY). 2020;12(8):6492-510. doi: 10.18632/aging.102988.
37. Au A, Feher A, McPhee L, Jessa A, Oh S, Einstein G. Estrogens, inflammation and cognition. Front Neuroendocrinol. 2016;40:87-100. doi: 10.1016/j.yfrne.2016.01.002.
38. Bilbo SD, Block CL, Bolton JL, Hanamsagar R, Tran PK. Beyond infection - Maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. Exp Neurol. 2018;299(Pt A):241-51. doi: 10.1016/j.expneurol.2017.07.002.
39. Libbey JE, Sweeten TL, McMahon WM, Fujinami RS. Autistic disorder and viral infections. J Neurovirol. 2005;11(1):1-10. doi: 10.1080/13550280590900553.
40. Krügel U, Fischer J, Bauer K, Sack U, Himmerich H. The impact of social isolation on immunological parameters in rats. Arch Toxicol. 2014;88(3):853-5. doi: 10.1007/s00204-014-1203-0.
41. Smith KJ, Gavey S, NE RI, Kontari P, Victor C. The association between loneliness, social isolation and inflammation: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2020;112:519-41. doi: 10.1016/j.neubiorev.2020.02.002.
42. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008;82(15):7264-75. doi: 10.1128/jvi.00737-08.
43. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7. doi: 10.1002/path.1570.
44. Holmes EA, O'Connor RC, Perry VH, Tracey I, Wessely S, Arseneault L, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry. 2020;7(6):547-60. doi: 10.1016/s2215-0366(20)30168-1.
45. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis. 2020;94:55-8. doi: 10.1016/j.ijid.2020.03.062.