Distinct neurological problems are brought on by the COVID-19 coronavirus entering the brain through different receptors

Meenakshi Malhotra*, Pooja Tandon, Kritika Wadhwa, Ajeet pal singh & Amar pal singh.

Email id: imeenakshi95@gmail.com
St. Soldier College of Pharmacy, Lithran campus Behind NIT, Jalandhar-Amritsar Byepass, Jalandhar, Punjab 14400.

Abstract:

A global pandemic was caused by the COVID-19 illnesses brought on by the SARS-COV-2 coronavirus, which causes severe acute respiratory syndrome. A global lockdown has been imposed as a result of COVID-19, which also poses a threat to the global economic system. Extreme respiratory issues are brought on by COVID-19, but it can also cause long-term COVID syndrome, which is typically accompanied by cognitive impairment, such as PTSD, stress, anxiety, depression, and brain fog. Direct or indirect brain infections are involved in the aetiology of cognitive impairment. The entire world's population is impacted by COVID-19. Maintaining a healthy diet, getting enough exercise, getting enough sleep, using sauna therapy, and taking medications help reduce these issues. As a result, this analysis has shed new light on the symptoms, pathogenesis, and therapy of the brain condition associated with COVID-19.

Keywords: SARS-Coronavirus, PTSD, Anxiety, depression, brain fog.

Cognitive impairment brought on by long-term COVID-19

One of the most dangerous pandemics in recent memory is COVID-19. More than 740,000 people have died as a result of the pandemic, and there have been more than 20 million suspected cases since the initial outbreak. The severe acute respiratory syndrome (SARS-COV-2) The coronavirus type 2 The Corona virus is a member of a sizable virus family. Because it harms humans when it crosses the species barrier, the coronavirus is a zoonotic pathogen that has undergone alterations[1]. COVID-19 had an impact on more than 200 nations. SARS-CoV-2 is a respiratory illness that causes symptoms similar to pneumonia, such as coughing, colds, fevers, fatigue, and a loss of taste and smell. In severe cases, it can cause pain and ache, a sore throat, a headache, and difficulty breathing. Direct contact with an infected individual or exposure to airborne respiratory secretions from an infected patient are the two main ways that COVID-19 is spread. Infection with the severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) can alter brain functioning, particularly in areas connected to cognition, and is expected to cause a variety of psychiatric disorders. Numerous psychiatric issues brought on by COVID-19 include posttraumatic stress disorder (PTSD), anxiety, sadness, sleeplessness, and brain fog[2]. Corona virus 2019 (COVID-19) and SARS-CoV-2 infection can both affect the central nervous system directly or indirectly. Therefore, the illness associated with COVID-19 sequelae, also known as "Long COVID," also includes extremely long-lasting mental and cognitive abnormalities, including the condition known as "brain fog" [3].

COVID-19 Impacts on the Nervous System:

Acute cerebrovascular disease, Guillain-Barre and Miller Fisher syndromes, ataxia, hyposmia, ageusia, seizures, encephalitis, and sensory impairment are only a few of the neurological and neuropsychiatric complications that COVID-19 coronavirus transmission in the brain may result in (such as cognitive decline, confusion, delirium, dementia, insomnia, anxiety, depression, and psychotic spectrum disorder) [4].

COVID-19 impacts the brain in two primary ways:

- Neuronal transmission and direct infection via the hematogenous pathway
- According to Figure 3, breathing, an immune reaction, or a secondary mechanism (indirect pathway) all contributed to hypoxia [5].

The mechanism of viral penetration and brain harm:

- The pathogenesis of COVID-19 is triggered by the virus attaching to the host cell. Through membrane fusion and endocytosis, the virus penetrates the host cells after binding. In host cells, viral mRNA replication and virus maturation occur during biosynthesis [6].
- There are two ways that the SARAS-COV-2 corona virus can enter the brain via direct and indirect pathways:

(i) Direct pathway: The direct pathway includes (a) hematogenous dissemination or (b) the neural pathway.

(a) **Hematogenous dissemination** is a concern since inflammatory cytokines increase BBB instability and COVID-19 can flow through monocytes and hence should be able to cross the BBB. It may enter the brain via circumventricular organs (CVOs) and much less frequently phagocytose neurons (neurophagia) in the cortex, limbic system, and brain stem [7]. Frontal lobe restriction, restricted diffusion, and enlargement in the higher regions of the nasal hallow gap known as the olfactory cleft are all symptoms of the more common loss of smell and flavour. indicators of COVID-19 in the PNS. Guillain-Barre syndrome (GBS), a neuropathy with symptoms similar to COVID-19 illness, is the most widely known PNS condition that has been linked to the condition. It comprises a cytokine storm brought on by the immune system's exaggeration and stimulation of this disease [8].

(b) **The neural pathway:** Neurotransmitters such as the serotoninergic pathway, amygdale, cerebral cortex, substantia nigra, hippocampus, neostriatum, entorhinal cortex, and locus coeruleus are some of the neurotransmitters that allow the Corona virus to reach the central nervous system (CNS) [9]. The increased release of various inflammatory mediators such as interleukin, TNF, and other pro-inflammatory mediators caused by virus permeation inside the brain causes inflammation and a cytokine storm. Inside the host cell, the virus activates the innate immune system. The overactivation of inflammatory mediators is responsible for the damage to brain cells. This mechanism increases the risk of cognitive dysfunction, delirium, and seizures [8].

(ii) Indirect Pathway: The mechanism of infection via an indirect pathway is explained in figure 5 with a flow chart.

There are several neurological issues linked to COVID-19:

(i) Post-traumatic stress disorder: Traumatic stress has physiopathological repercussions as well as an impact on the mental-emotional chain. A progressive mental condition called post-

traumatic stress disorder (PTSD) is brought on by witnessing or experiencing terrible or life-threatening situations. Deep psychological correlates of PTSD can harm a person's daily life and pose health risks [10]. COVID-19 patients suffer from traumatic events that may lead to the occurrence of PTSD. PTSD is defined as the development of symptoms related to entry, avoidance, negative changes in cognitive and emotional perception, as well as arousal and recurrence following exposure to a tragic event. Secondly, PTSD in COVID-19 patients with intensive care unit (ICU) treatment may cause another neurological disorder such as delirium or sleep disorders [11].

(ii) Brain fog: Brain fog may be described as an emotion of intellectual confusion or a lack of mental readability. It's commonly known as "brain fog" due to the fact that it can feel like a cloud that reduces your visibility or clarity of mind. It can cause you to be forgetful and indifferent, and often discouraged and depressed. Symptoms of brain fog include short-term memory loss, problems finding words, trouble with daily thinking, difficulty getting out of bed, problems focusing, alien hand syndrome, anxiety, impaired judgement, etc.

(iii)Causes of brain fog: Severe complications at some point in COVID-19 include the following:

- Inadequate sleep: a lack of sleep can regularly result in poor brain functioning. It might impair cognitive abilities and eliminate the capacity for concentration. However, for mental wellness, 8 to 9 hours of sleep every night are required.
- Stress and Anxiety: Prolonged stress and anxiety affect mental health and the body's immune system. This could lead to intellectual exhaustion and the development of brain fog.
- Improper diet: Lack of proper nutrients and vitamins may cause brain fog.
- Changes in hormones: Multiplied ranges of certain hormones can cause brain fog, affect memory, and cause short-term cognitive impairment. In addition, lower hormone levels in some people may cause forgetfulness.
- This may be because of clogged arteries, low blood pressure, shallow respiration, or maintaining one's breathing. Worrying can cause shallow breathing.
- Kidneys and different organs are affected.
- Inflammatory response of the immune device
- Clotting
- Persistent infection may also contribute to mental fog [12,13].

(iv) Anxiety and depression: The most common mental illness is anxiety disorder. It is characterised by the disruption of attitude, thinking, behaviour, and life functions. It includes panic disorder, agoraphobia, which is a common anxiety disorder, specific phobia, social phobia, obsessive-compulsive disorder, acute stress disorder, and post-traumatic stress disorder [14]. Depression is an emotional disorder that causes a constant feeling of sadness and a loss of interest. Depression may be classified into five major classes, including: disruptive mood dysregulation disorder, major depressive disorder, prolonged depression (dysthymia), premenstrual dysphoric disorder, and depression due to another health condition. The most common symptoms of all depressive disorders are depression, emptiness, or irritability, which are accompanied by psychological and physiological changes that greatly affect a person's ability to function[15]. COVID-19 associated Anxiety and depression not only affect COVID-19 patients but also college students and adults. Several studies reveal that COVID-19 shows a negative impact on the mental health of most individuals [16].

Diagnosis:

- Physical exam: The doctor will perform a physical exam to identify the underlying causes and will also ask you about your diet, exercise routine, stress level, sleep schedule, and general physical and mental health.
- Blood test: To rule out other diseases like diabetes, inflammatory disorders, kidney diseases, liver diseases, nutritional deficiencies, and thyroid disease.
- The RT-PCR test is used to rule out infections.
- MRI and CT scans are used to rule out problems such as brain injury or brain bleeding.

Treatment:

- Nutritional balancing: A healthy food plan such as olive oil, culmination and veggies, nuts and beans, and complete grains has been confirmed to enhance questioning, memory, and brain fitness. The influence of vitamins on the immune system has been extensively pronounced. Furthermore, recent research has highlighted the importance of both a healthy diet and the proper intake of specific nutrients in COVID-19.
- Physical exercise: SARS-CoV-2 infection leads to an increase in ACE2 levels through pathological pathways, leading to neurological and cardiovascular problems, while the body's response to ACE2 exercise improves general health [17]. Physical exercise improves brain health by stimulating ACE2 receptors, which show a protective role in depression, anxiety and brain fog.
- Sufficient sleep: Proper sleep helps to prevent anxiety and depression and also paints the body and mind toward healing.

- Medications.
- Sauna therapy: Sauna therapy helps people unwind and relax [1819].

Concluding remarks

The current review shows that COVID-19 has a significant impact on mental health and poses a significant risk to the development of trauma-related illnesses, including PTSD, anxiety, depression, brain fog, etc. in high-risk individuals, such as children, adolescents, and COVID-19 survivors. Therefore, early identification of high-risk populations, early intervention, and effective management of cognitive impairment or brain disorders are essential.

- **Box-1 Receptors through which viruses enter the brain:** SARAS-CoV-2 not only affects the respiratory system, but it may also affect other organs such as the brain and cardiovascular system. Neurological complications occur in long-term COVID-19 patients and mild COVID-19 patients [20]. Recent studies have shown that viruses may penetrate into the brain through various receptors, including ACE2 (Angiotensin-Converting Enzyme 2) by activation of the transmembrane, DPP-4 (Dipeptidyl Peptidase-4), APN (Aminopeptidase N), and other possible receptors [21]. Some antibodies, known as antibodies-dependent enhancers, are also responsible for virus penetration [22]. COVID-19 also causes seizures, cranial nerve disturbances, autoimmune disorders, and neurodegenerative disorders [23].

- **Box-2 Inflammation and blood-brain barrier instability caused by viruses** significant SARS-CoV-2 infection ACE2's widespread cerebral expression affects CNS function via humoral and neural pathways, where proteases are required for viral entry. Induced brain damage is primarily characterised by neuroinflammation and destruction of the blood-brain barrier. Downregulation of ACE2, as well as transmembrane proteases serine 2 and cathepsin L. These changes favour upregulation of inflammatory cytokines and chemokines, production of reactive oxygen species, downregulation of antioxidant defence systems, and hormonal or neurotransmitter dysregulation. Neuropathological results of SARS-CoV-2 nerve infiltration [21].

References:

1. Shi, Y., Wang, G., Cai, X. peng, Deng, J. wen, Zheng, L., Zhu, H. hong, Zheng, M., Yang, B., & Chen Z (2020). ZUP. An overview of COVID-19. *J Zhejiang Univ Sci B*. Vol. 21(Issue 5,):343–360). doi:https://doi.org/10.1631/jzus.B2000083
2. Pr ep rin t n ot pe er r ev Pr ep rin t n er ed.
3. Hugon, J., Msika, E. F., Queneau, M., Farid, K., & Paquet C (2021). Long COVID: cognitive complaints (brain fog) and dysfunction of the cingulate cortex. *J Neurol*. doi:https://doi.org/10.1007/s00415-021-10655-x
4. Giannopoulou I, Galinaki S, Kollintza E, et al. COVID - 19 and post - traumatic stress disorder : The perfect ‘ storm ’ for mental health (Review). Published online 2021:1-7. doi:10.3892/etm.2021.10596
5. Davies, D. A., Adlimoghaddam, A., Benedict, •, & Albensi C (2035). The Effect of COVID-19 on NF-κB and Neurological Manifestations of Disease.. *Mol Neurobiol*. doi:https://doi.org/10.1007/s12035-021-02438-2
6. Quevedo LB De, Cattani M, Lodetti BF, Generoso JS. Neurobiology of COVID-19 : how can the virus affect the brain ? 2021;43(6):650-664. doi:10.1590/1516-4446-2020-1488
7. Boldrini M, Canoll PD, Klein RS. How COVID-19 Affects the Brain. 2021;78(6):2021-2022. doi:10.3233/JAD-181055
8. Awan HA, Diwan MN, Aamir A, et al. SARS-CoV-2 and the Brain : What Do We Know about the Causality of ‘ Cognitive COVID ? Published online 2021:1-14.
9. Pui E, Choi H, Pui B, Hui H. Depression and Anxiety in Hong Kong during COVID-19.
10. Iribarren J, Prolo P, Neagos N, Chiappelli F. Post-traumatic stress disorder: Evidence-based research for the third millennium. *Evidence-based Complement Altern Med*. 2005;2(4):503-512. doi:10.1093/ecam/neh127
11. Kaseda ET, Levine AJ. Post-traumatic stress disorder: A differential diagnostic consideration for COVID-19 survivors. *Clin Neuropsychol*. 2020;34(7-8):1498-1514. doi:10.1080/13854046.2020.1811894
12. Wilson DL. BRAIN FOG. *L.D. Wilson Consultants, Inc.* https://www.drlwilson.com/articles/brain_fog.htm. Published 2019.
13. Xia H LEA converting enzyme 2 in the brain: properties and, 10.1111/j.1471- future directions. JN 2008;107(6):1482 94. doi:, 4159.2008.05723.x P 19014390. No Title.
14. Adwas AA, Jbireal JM, Azab AE. Anxiety: Insights into Signs, Symptoms, Etiology, Pathophysiology, and Treatment. *East African Sch J Med Sci*. 2019;2(10):580-591.

https://www.researchgate.net/publication/336738068_Anxiety_Insights_into_Signs_Symptoms_Etiology_Pathophysiology_and_Treatment

15. Arif. SPCH. *Depression*. StatPearls Publishing LLC.
16. Elharake JA, Akbar F, Malik AA, Gilliam W, Omer SB. Mental Health Impact of COVID-19 among Children and College Students: A Systematic Review. *Child Psychiatry Hum Dev*. 2022;(0123456789). doi:10.1007/s10578-021-01297-1
17. De Sousa RAL, Improta-Caria AC, Aras-Júnior R, de Oliveira EM, Soci ÚPR, Cassilhas RC. Physical exercise effects on the brain during COVID-19 pandemic: links between mental and cardiovascular health. *Neurol Sci*. 2021;42(4):1325-1334. doi:10.1007/s10072-021-05082-9
18. Fernández-Quintela, A., Milton-Laskibar, I., Trepiana, J., Gómez-Zorita S, Kajarabille, N., Léniz, A., González, M., & Portillo MP (2020)., Https://doi.org/10.3390/jcm9082589. No Clinical Medicine Key Patients., Aspects in Nutritional Management of COVID-19Title.
19. Augusto, R., de Sousa, L., Cleber Improta-Caria, A., Aras-Júnior, R. M De, Oliveira, & E., Paula, Ú., Soci, R., & Cassilhas RC. (n. d.)., Https://doi.org/10.1007/s10072-021-05082-9. Physical exercise effects on Health., the brain during COVID-19 pandemic: links between mental and cardiovascularo Title.
20. Woo MS, Malsy J, Po J, et al. B RAIN AIN COMMUNICATIONS Frequent neurocognitive deficits after recovery from mild COVID-19. *BRAIN Commun*. Published online 2020:1-9. doi:10.1093/braincomms/fcaa205
21. Welcome MO, Mastorakis NE. Neuropathophysiology of coronavirus disease 2019 : neuroinflammation and blood brain barrier disruption are critical pathophysiological processes that contribute to the clinical symptoms of SARS - CoV - 2 infection. *Inflammopharmacology*. 2021;29(4):939-963. doi:10.1007/s10787-021-00806-x
22. Cheng Q, Yang Y, Gao J. EBioMedicine Infectivity of human coronavirus in the brain. *EBioMedicine*. 2020;56:102799. doi:10.1016/j.ebiom.2020.102799
23. Garrez I, Laureys G, Raedt R, Boon P. Neurological manifestations and neuro-invasive mechanisms of the severe acute respiratory syndrome coronavirus type 2. *Eur J Neurol*. 2020;2(27):1578-1587. doi:10.1111/ene.14329

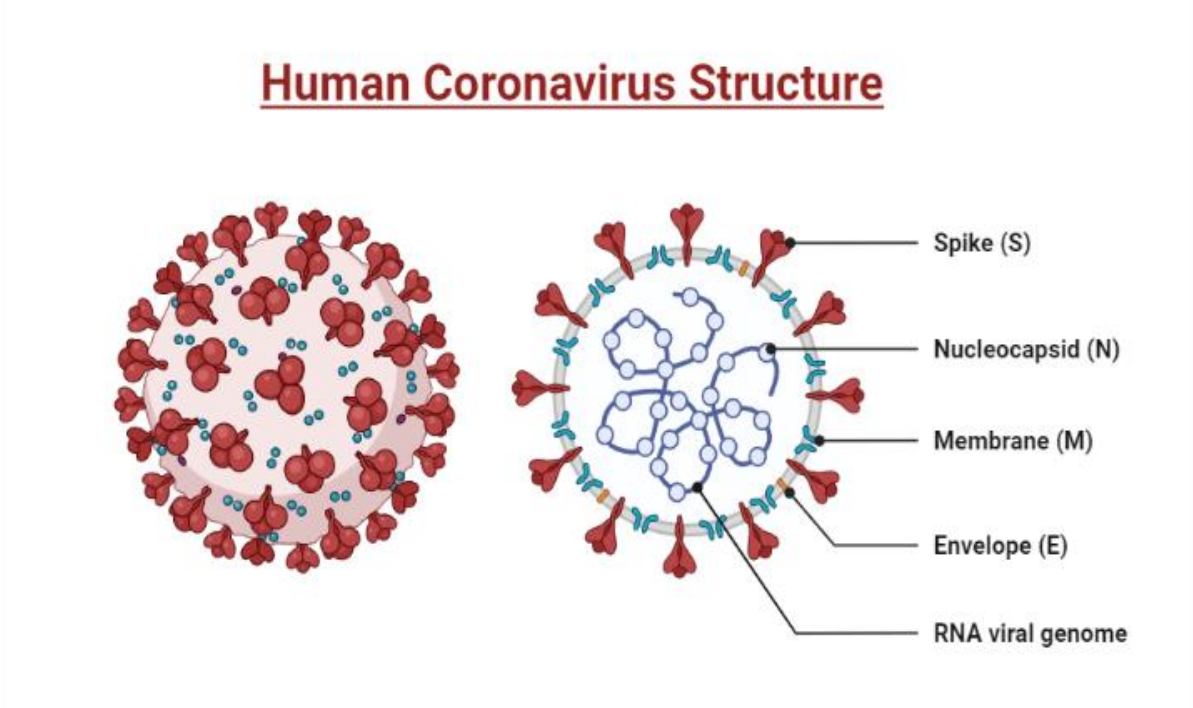

Figure 1 Representation of latest coronavirus structure.

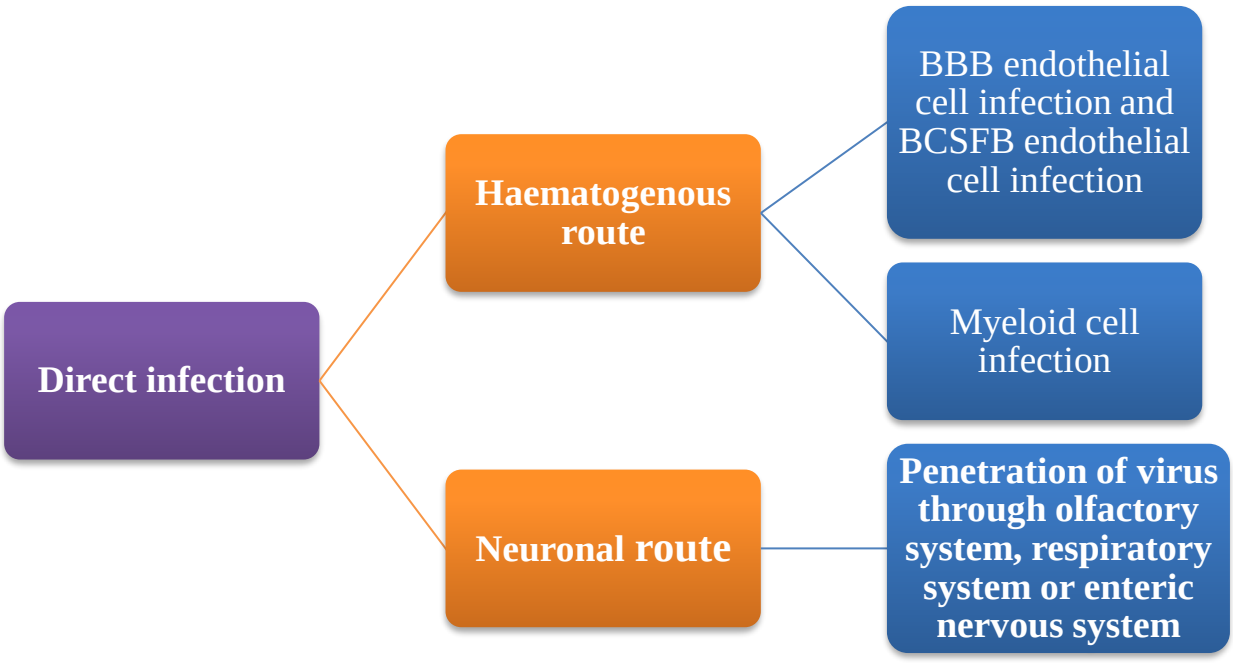

Figure 2 Diagrammatic representation of direct infection pathway of SARS-CoV-2 corona virus into brain by different routes and causes BBB (Blood Brain Barrier), BCSFB (Blood Cerebrospinal Fluid Barrier) cell infections and myeloid cell infection.

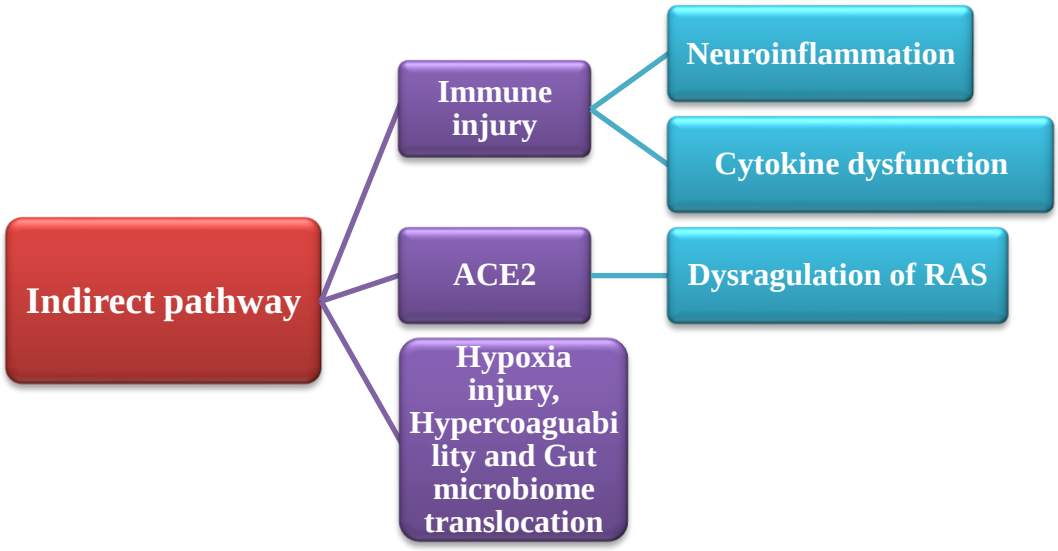

Figure 3 Diagrammatic representation of indirect infection pathway of SARS-CoV-2 corona virus into brain.

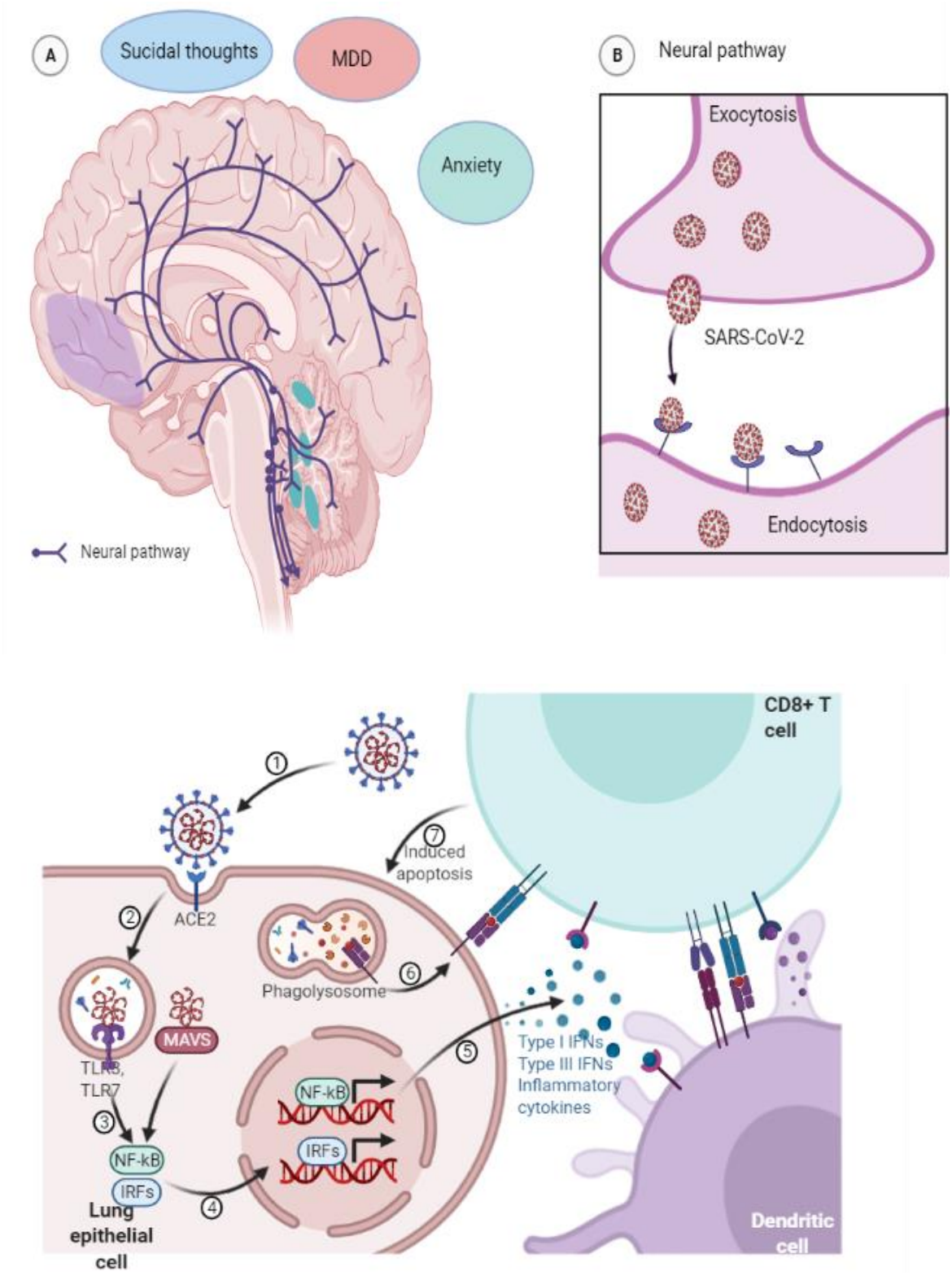

Figure 4 Mechanism of entry of virus into brain

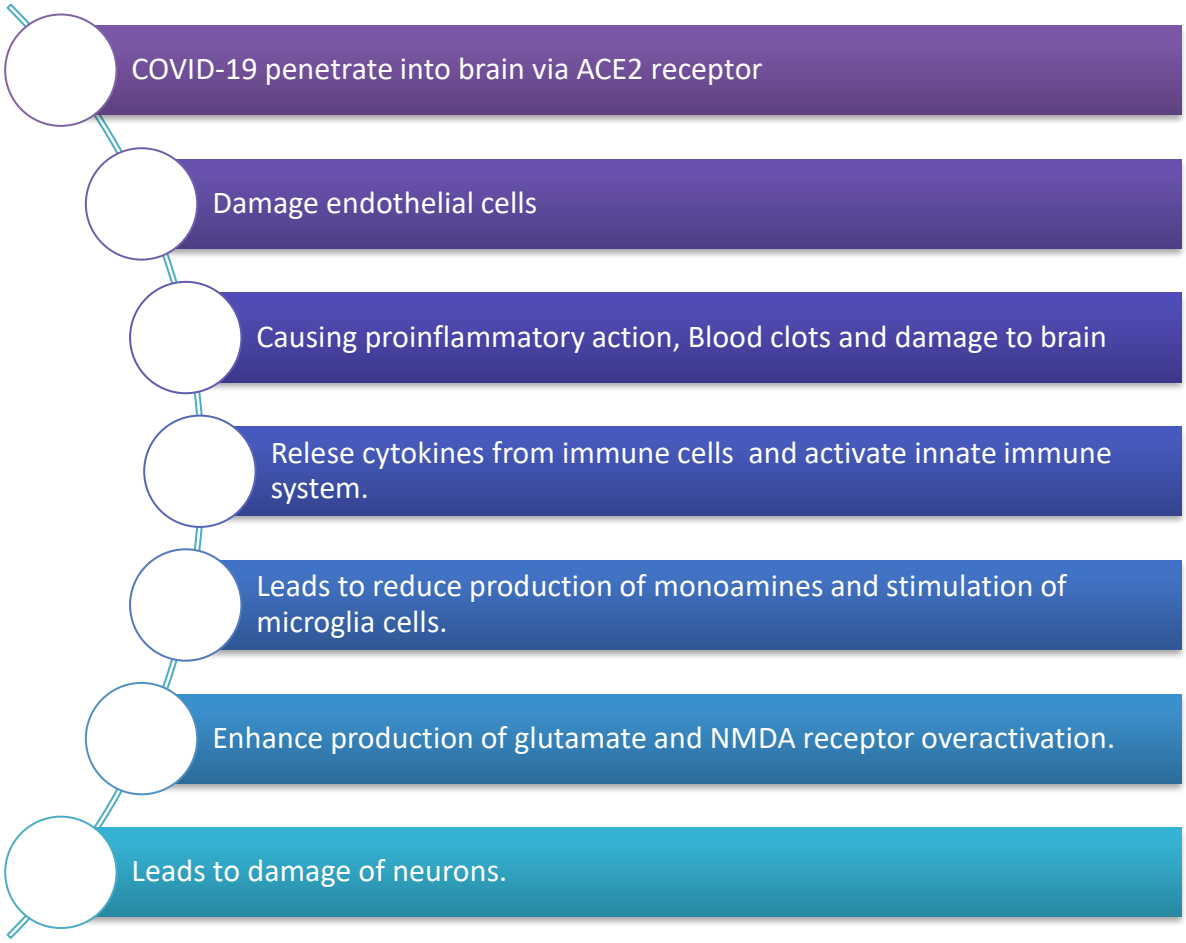

Figure 5 Flow chart represents the mechanism of COVID-19 penetration into brain via indirect infection route.

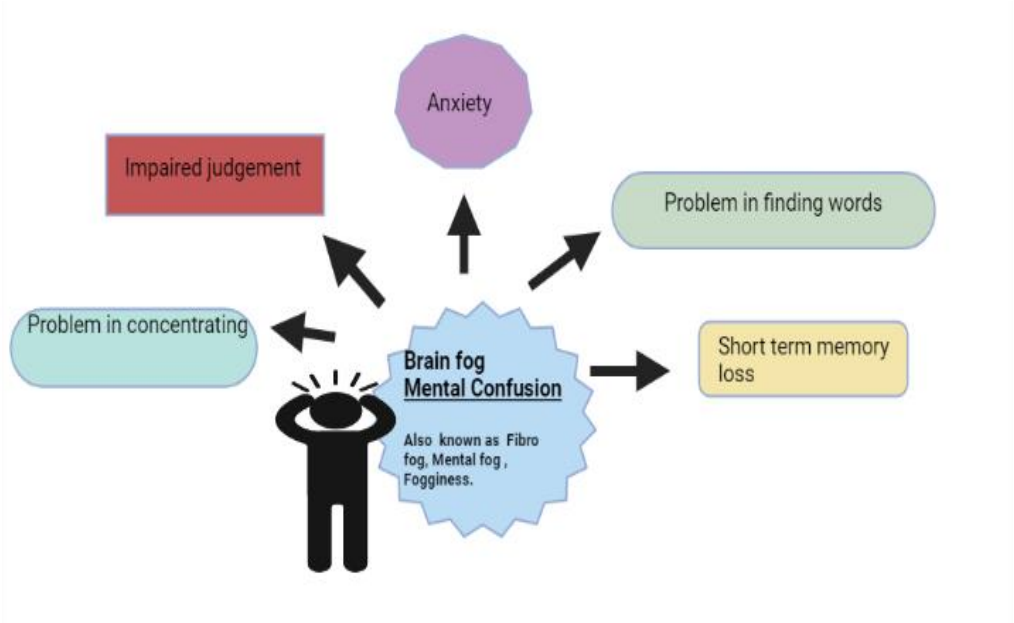

Figure 6 Symptoms of brain fog.