IMPACT OF COVID-19 ON THE INNER GPS OF THE BRAIN

Manorama Patri

Abstract

Background

The brain performs all the navigation work in the hippocampus, the region responsible for spatial orientation and memory formation like an internal global positioning system (GPS). COVID-19 has affected daily life in unprecedented ways decreasing hippocampal activity. The viral entry can alter neurotransmitter systems causing cognitive dysfunction such as learning and memory impairment. However, the accompanying alteration of neurotransmitters like dopamine (DA) and serotonin (5-HT) resulting neurocognitive changes remain poorly understood.

Objectives

To know whether DA and 5-HT, a precursor to melatonin in the pineal gland are also involved in COVID-19 pathophysiology. To find out the role of serotonergic and dopaminergic receptors in the entry of Covid-19 and explore how the additive effect of both the neurotransmitters alters the function of GPS.

Observations

In this article, we aim to present an understanding of the possible effects of COVID-19 infection on the brain and its long-term neuropsychiatric and cognitive consequences, and the role of neurotransmitters like DA and 5-HT with their neurological

* Neurological Laboratory, Department of Zoology, School of Life Sciences, Ravenshaw University, Cuttack, Odisha.

manifestations. It could be hypothesised that viral infection may be responsible for the alteration of most complex cognitive functions such as the inner Geographic Positioning System (GPS) in the brain. This article documents the dramatic changes in mental health conditions showing alteration of neurotransmitters like DA and 5-HT causing anxiety and depression.

Conclusion and Inference

The changes in day-to-day activities and sleep hours are likely to be responsible for the mood, fatigue, and cognitive changes that are commonly experienced by COVID-19 patients. This in turn may underline the reported symptoms of stress, anxiety, and depression due to the altered levels of neurotransmitters. These findings highlight the impact of COVID-19 on anxiety as well as learning, and memory, offering directions for interventions aimed at restoration of mental health through GPS.

Keywords: COVID-19; Geographic Positioning System; Serotonin; Dopamine; Learning and Memory

Over the past few decades, neuroscientists have tried to uncover the structure of the brain's neuronal circuits to better understand how the brain works. In the 20th century, researchers have gained a deep understanding of just how the brain forms and then revises the inner maps as an animal moves and revealed that the navigation systems consist of several specialized cell types known as nerve cells (i.e., neurons). Neurons are the cells within the brain that are responsible for the rapid communication of information. When neurons fire, it triggers an action potential which is a short-lasting change in the voltage across the neuronal cell membrane and releases the neurotransmitter into the small synaptic gap between cells. The neurotransmitters convey signals from one neuron to another and collectively these different neuronal cells form a dynamic map of the environment that not only operates in the present but also can be stored as a memory for later use. In response to COVID-19 worldwide, there is a grave concern about the pathophysiology of mental health disorders in the general public and health care workers that affects the Global Positioning System, (GPS) of the brain.

Neuroscientists have shown that there is a GPS in the brain. In 1971, John O'Keefe at the University College London, UK, discovered the first component of this positioning system in the brain using an animal model. He found out that the nerve cells in

the brain were activated whenever the rat was changing its position in the room. These cells are present in the area of the brain called the hippocampus. O'Keefe concluded that these 'place cells' formed a map of the room. In 2005, May-Britt Moser and her husband Edvard Moser, both from Trondheim Norway, discovered another key component of the brain's positioning system. They identified another type of nerve cell, which they called 'grid cells. These cells generate a coordinate system and allow for precise positioning and pathfinding of the nerve cells. John O'Keefe, May-Britt Moser, and Edvard Moser, the trio were awarded the 2014 Nobel Prize in Physiology or Medicine for their discoveries of cells that constitute a positioning system in the brain, i.e. an "inner GPS" in the brain. They discovered an astonishing pattern of activity in a nearby part of the brain called the entorhinal cortex, where, certain cells were activated when the rat passed multiple locations arranged in a hexagonal grid. Together with other cells the entorhinal cortex that recognise the direction of the head and the border of the room, form circuits with the place cells in the hippocampus. Recent investigations with the brain, as well as studies of patients undergoing neurosurgery, have provided evidence that place cell and grid cells also exist in humans. The discovery of GPS in humans has opened a new avenue for understanding the cognitive processes, such as memory, thinking, and planning [1].

COVID-19 affects people's mental health and quality of life, and also resulted in more than 120 million cases and 2.6 million deaths worldwide. This rapid and unprecedented pandemic has caused serious psychological problems, such as anxiety (panic attacks and post-traumatic stress) and depression [2]. Emerging and re-emerging pathogens are great challenges to public health [3]. The isolation and worry caused by the pandemic can similarly alter our brain chemistry and cause mood disorders. The virus itself can cause several neurological problems, along with anxiety and depression. In addition to mood disorders, common symptoms include fatigue, headaches, memory loss, and problems with GPS. There may be several reasons for these brain changes, including inflammation and cerebrovascular events (a syndrome caused by disruption of blood supply to the brain).

A cluster of pneumonia cases with an unknown cause occurred in Wuhan starting on December 21, 2019. Early on January 20, 2020, the novel coronavirus (2019-nCoV)–infected pneumonia (NCIP) occurred in Wuhan, China causing a disease called COVID-19 [4]. The origin of the 2019-CVs is still being investigated. SARS-CoV-2 is a

positive-sense single-stranded RNA virus, whose virion is 60–140 nm in diameter [5]. SARS-CoV-2 has four structural proteins: proteins E (envelope), M (membrane), and S (spike) which create the viral envelope and, through protein S, that is attached and fused with the membrane of a host cell. Protein N (nucleocapsid) holds the RNA genome [5, 6]. The S protein consists of subunits S1 and S2, responsible for the attachment and membrane fusion, respectively. The virus penetrates the host cell via the binding of its S-protein with the angiotensin-converting enzyme II (ACE-2) receptor, which is found in virtually all human organs in varying degrees [7]. The spike binds to human ACE2 (hACE2) in the cell membrane through the S1 subunit of the receptor-binding domain (RBD) [5]. According to a recent study [8], SARS-CoV-2 exhibits neuro-invasive potential in COVID-19 patients, especially those in severe conditions. A handful of case reports have described neurological complications in patients with COVID-19 [9, 10, and 11].

However, it remains unknown to what extent SARS-CoV-2 damages the central nervous system (CNS) in humans [12]. Viral neuron invasion/ neuro-invasion could plausibly be achieved by several routes, including transsynaptic transfer across infected neurons, entry via the olfactory nerve, infection of vascular endothelium, or leukocyte migration across the blood-brain barrier (BBB). The principal route of SARS-CoV-2 transmission is the droplet contagion; the virus enters the intranasal and oral routes, infects the olfactory sensory neurons, in whichthe olfactory nerve is the principal route for virus entry to the brain and the CNS [13, 14]. The brain pathologies associated with COVID-19 infection is likely to have a long-term impact on GPS in terms of automatic cognitive processes (Figure - Graphical abstract).

During the COVID-19 outbreak, isolated loss of sense of smell (anosmia) and loss of sense of taste (ageusia) with or without respiratory symptoms has been reported [15]. In the early stage of infection the virus infects nasal cells, accesses the brain and cerebrospinal fluid (CSF) through the olfactory nerve and olfactory bulb, and induces neural damage [16]. Moreover, COVID-19 patients might develop situations of impaired learning and memory, resulting in brain dysfunction [17, 18]. Thus, psychiatric and psychological issues (e.g., cognitive rehabilitation) should be considered in both patients and medical staff [19], to mitigate the COVID- 19associated depression and stress [20, 21]. Therefore, more research is required to understand the neuro-invasion capacity of the virus and to prevent the neuro-behavioural impact of COVID-19 in recovered

patients [19]. It has also been reported that viral infections can produce cytokines that impair neuronal firing in the hippocampus, leading to depressive-like symptoms [22]. Research suggests that the virus may gain access to the brain via the forebrain's olfactory bulb, which is important for the processing of smell. The olfactory bulb sends information about the smell to be further processed in other brain regions, including the amygdala, orbitofrontal cortex and the hippocampus – which play a major role in emotion, learning and memory. The olfactory bulb is rich in the chemical dopamine, which is important for pleasure, motivation and action. It may be that Covid-19 alters the levels of dopamine (DA) and other chemicals, such as serotonin (5-HT).

DA and 5-HT are monoamine neurotransmitters in the human brain that are involved in several physiological processes of the CNS. 5-HT is involved in the regulation of several physiological functions, including the sleep-wake cycles, body temperature, blood pressure, perception of pain, hormonal functions of the hypothalamus and psychological functions, such as depression and anxiety [23, 24]. Peripheral 5-HT is also able to modulate several mechanisms of different viral infections through its receptors. A recent study by Anderson et al. [25] revealed that viral infections with subsequent cytokine storm syndrome, which is an important sign of the breakdown of the blood-brain barrier. Studies conducted in individuals with major depressive disorder following antidepressant treatment, mostly including selective serotonin reuptake inhibitors (SSRIs), supports that, overall, antidepressants may be associated with decreased plasma levels associated with COVID-19 severity [26]. On the other hand, SSRIs have anti-inflammatory effects and they achieve this effect through the decrease of pro-inflammatory cytokine production and increase of anti-inflammatory cytokines. SSRIs are the most widely prescribed class of antidepressants and are often used as a first-choice medication for depression and numerous other anxiety disorders (e.g., panic disorder and obsessive-compulsive disorder) due to their efficacy, safety, and tolerability.

The levels of both these neurotransmitters are regulated in the brain by reuptake and metabolism. The functions of DA have been linked to Parkinson's disease, schizophrenia, depression and the regulation of motoric movements [27, 28, 29]. Recently, Attademo et al. [30] reported that alterations of both the serotonin and dopamine synthetic pathways might be involved in the pathophysiology of COVID-19 infection. The virus may manipulate the immune system by increasing the levels of dopamine to increase the possibility of

viral entry. Dopaminergic receptors can enhance the chance of binding some viruses to the CNS. The increased dopamine reduces oxygen levels, especially when considering the hypoxic condition associated with COVID-19. This happens as dopamine has a known ability to blunt the ventilatory response of the human basal carotid body activity to hypoxia [31]. This hypoxic state is coupled with hypercapnia, peripheral vasodilatation, anaerobic metabolism and accumulation of toxic metabolites. Prolonged hypoxia can induce persistent and uncontrolled neuroinflammation which is responsible for the damage of the hippocampus and cortical areas associated with cognitive functions and behavioural alterations [32]. The possible involvement of these neurotransmitters is suggested by a significant link between ACE-2 and DOPA decarboxylase (a major enzyme of both the DA and the 5-HT synthetic pathways) that catalyses the biosynthesis of dopamine. These changes in neurotransmitter levels in the brain are likely responsible for the mood, fatigue and cognitive changes that are commonly experienced by Covid-19

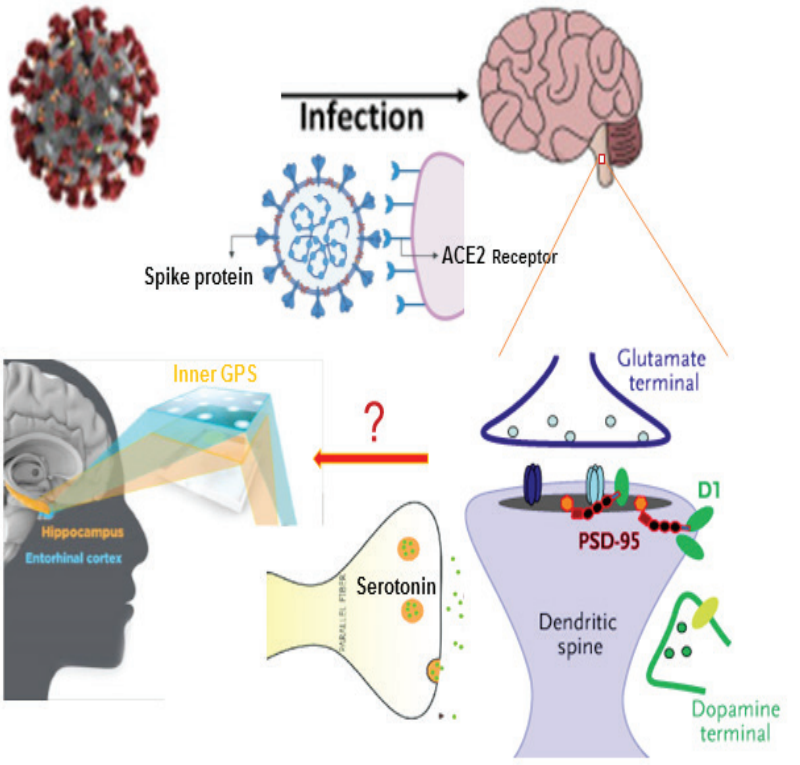

Fig 1. Graphical abstract

patients. Thus, these findings suggest that dopamine plays a primary role in reducing host immunity and increasing the chance for severe complications.

The repeated stress caused due to Covid 19 pandemic over contracting or spreading the virus to other family members, as well as isolation and loneliness, can also change the brain chemistry. That is a major trigger for persistent inflammation in the body, which can also affect the brain and shrink the hippocampus and therefore affect emotions. Stress can also affect levels of brain 5-HT and DA, which can affect the mood of Covid 19 patients. Eventually, these changes can cause symptoms of depression and anxiety. However, the brain is incredibly plastic, which means it is changeable and can compensate for damage.

In the current study, the article aims to provide a to-the-point review of the current literature regarding the efficacy of selective serotonin reuptake inhibitors (SSRIs) as a therapeutic option for COVID-19. Early intervention for emerging cognitive problems will be critical for independent functioning and improved quality of life for many COVID-19 survivors. However, further experimental research works are needed to evaluate this hypothesis.

References

1. Dahmani, L., Bohbot, V.D. Habitual use of GPS negatively impacts spatial memory during self-guided navigation. Sci Rep 10, 6310 (2020). https://doi.org/10.1038/s41598-020- 62877-0.
2. Xiang, Y.-T. Yang, Y. Li, W. Zhang, L. Zhang, Q. Cheung, T. et al. Timely mental health care for the 2019 novel coronavirus outbreak is urgently needed Lancet Psychiatry, 7 (3) (2020), pp. 228-229, 10.1016/S2215-0366(20)30046-8.
3. MHC Key Laboratory of Biosafety, National Institute for Viral Disease Control and Prevention, China CDC, Beijing, China
4. Li Q, Guan X, Wu P, Wang X, Zhou L, et al. (2020) Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med 382:1199 1207.
5. Zhu N, Zhang D, Wang W, Li X, Yang B, et al. (2020) A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 382: 727-733.
6. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, Graham BS, McLellan JS (2020) Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367:1260
7. M.K. Chung, S. Karnik, J. Saef, C. Bergmann, J. Barnard, M.M. Lederman, et al. E. Bio Medicine, 58 (2020), Article 102907, 10.1016/j.ebiom.2020.102907.
8. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020 doi: 10.1001/jamaneurol.2020.1127.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019

novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi:10.1016/S0140- 6736(20)30183-5 2.
10. 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):7264-7275. doi:10.1128/JVI.00737-08.
11. Kim JE, Heo JH, Kim HO, et al. Neurological complications during treatment of Middle East respiratory syndrome. J Clin Neurol. 2017;13(3):227- 233. doi:10.3988/jcn.2017.13.3.227
12. Lau SKP, Lee P, Tsang AKL, et al. Molecular epidemiology of human coronavirus OC43 reveals the evolution of different genotypes over time and the recent emergence of a novel genotype due to natural recombination. J Virol. 2011;85(21):11325- 11337. doi:10.1128/JVI.05512-11.
13. Liu T, Yang N et al (2020a) Neurological manifestations of patients with COVID-19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain [published online ahead of print, 2020 May 4]. Front Med. https ://doi.org/10.1007/s1168 4-020-0786-5.
14. Zhang Y, Geng X, Tan Y et al (2020) New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomed Pharmacother 127:110195. https ://doi.org/10.1016/j.bioph a.2020.11019 5.
15. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis. 2020;ciaa330. doi:10.1093/cid/ciaa330.
16. Wu Y, Xu X, Chen Z et al (2020a) Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 87:18–22. https ://doi.org/10.1016/j.bbi.2020.03.031.
17. Nicholls J, Peiris M (2005) Good ACE, bad ACE do battle in lung injury. SARS Nat Med 11(8):821–822. https ://doi.org/10.1038/nm080 5-821.
18. Tauber SC, Eiffert H, Brück W, Nau R (2017) Septic encephalopathy and septic encephalitis. Expert Rev Anti Infect Ther 15(2):121–132. https ://doi. org/10.1080/14787 210.2017.12654 48.
19. Balachandar V, Mahalaxmi I, Subramaniam M et al (2020) Follow-up studies in COVID- 19 recovered patients—is it mandatory? Sci Total Environ 729:139021. https ://doi.org/10.1016/j.scito tenv.2020.13902 1.
20. Li Z, Liu T, Yang N et al (2020a) Neurological manifestations of patients with COVID- 19: potential routes of SARS-CoV-2 neuroinvasion from the periphery to the brain [published online ahead of print, 2020 May 4]. Front Med. https ://doi.org/10.1007/s1168 4-020-0786-5.
21. Politi LS, Salsano E, Grimaldi M (2020) Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (COVID-19) and anosmia. JAMA Neurol 77(8):1028–1029. https ://doi.org/10.1001/jaman eurol .2020.2125.
22. Hampton, T. (2016) How depressed mood may develop after viral infection JAMA, 315, p. 2267, 10.1001/jama.2016.6852
23. Owens MJ, Nesenoff CB (1994) Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. Clin. Chem. 40: 288–295.
24. Berger M, Gray JA, Roth BL (2009) The Expanded Biology of Serotonin. Annu. Rev. Med. 60: 355–366. doi: 10.1146/annurev.med.60.042307.110802.
25. Anderson, G. Reiter, R.J. (2020) Melatonin: roles in influenza, Covid-19, and other viral infections Rev Med Virol, 30, 10.1002/rmv.2109

26. Hojyo S, Uchida M, Tanaka K, Hasebe R, Tanaka Y, Murakami M, et al. How COVID- 19 induces cytokine storm with high mortality. Inflamm Regen. 2020;40:1–7
27. Barbeau A (1969) L-Dopa Therapy in Parkinson's Disease. Can Med Assoc J 101: 59– 68.
28. Dunlop BW, Nemeroff CB (2007) The role of dopamine in the pathophysiology of depression. Arch. Gen. Psychiatry 64: 327–337.
29. Webster RA, Dopamine DA, In Webster RA, editor (2002) Neurotransmitters, Drugs and Brain Function, 137–161.
30. Attademo, L., Bernardini F. (2021) Are dopamine and serotonin involved in COVID-19 pathophysiology? Eur J Psychiatry, 35, pp. 62-63, 10.1016/j.ejpsy.2020.10.004.
31. Bainbridge CW, Heistad DD. Effect of haloperidol on ventilatory responses to dopamine in man. J Pharmacol Exp Ther 1980; 213(1): 13.
32. Sasannejad C, Ely EW, Lahiri S (2019) Long-term cognitive impairment after acute respiratory distress syndrome: a review of clinical impact and pathophysiological mechanisms. *Crit Care*. 2019 Nov 12; 23(1):352.