The Neurological Sites Impacted Post-COVID-19 Infection

Submitted by

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Health Sciences

To

The Honors College

Oakland University

In partial fulfillment of the

requirement to graduate from

The Honors College

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April 7th, 2023

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Abstract

This literature review intends to prove that there is a correlation between anatomical and physiological effects of the brain that the patient exhibits post COVID-19. This will be achieved through identification and comparison of anatomical, biochemical, histological, and physiological sources of *long COVID*-related memory impairment as well as cognitive, motor, and visual deficits within the brain. From that information, this literature review will correlate each symptom to a set of structures that may produce *long-COVID*-associated symptoms in patients. With this knowledge, we may be able to formulate successful treatment plans based on the sites of infection. A strong understanding of areas of the brain generally worsened post *long-COVID-19 infection* could improve the accuracy of treatment and enhance its effects. Most favorably, treatment could one day better the daily lives of individuals suffering from cognitive, memory, motor, or visual deficits by reducing their symptoms.

This literature review intends to find missing areas within today's research about *post-COVID-19 syndrome* and subsequently prove that it is unadded knowledge to the field. The research will proceed with a specific set of research terms to incorporate the most relevant findings. All articles listed in this proposal are acquired from Oakland University's Kresge Library or Google Scholar. Articles related to the disease in question are written within the past three years, and all articles included in this literature review are peer-reviewed and originally written in English.

Current Research

Post-COVID-19 syndrome and *long COVID syndrome* are terms used to describe the residual symptoms of a COVID-19 viral infection. Such symptoms last from a couple of weeks to a few years depending on the patient's gender and pre-existing conditions. Recent studies acknowledge the manifestations of *long-COVID-19* due to a large population of patients experiencing lingering symptoms (Duggan et al. 2022; Stefanou et al. 2022). The common symptoms observed in one study are cognitive decline, fatigue, "brain fog," myalgia, dizziness, word-finding difficulties, and memory impairment (Duggan et al. 2022). In regard to where the neurological infection takes place and what tissues are affected, it has yet to be determined. Therefore, the general purpose of this study is to establish and correlate the specific sites of neurological damage to symptoms from the COVID-19 virus.

In addition to the acknowledgment of *long-COVID-19* symptoms, scientists have discovered variables contributing to the severity and quantity of symptoms in patients. Two primary factors mentioned are age (Del Brutto et al. 2021) and the severity of the COVID-19 disease state (Akbari et al. 2021). In the age-related study, elderly patients demonstrated greater reductions in cognitive function in comparison to their younger counterparts. Similarly, the average hospitalized COVID patient had more severe symptoms than non-hospitalized COVID participants. Within these studies, however, specific areas in the cerebrum suffering from cognitive decline were not determined as researchers were unable to pinpoint an area leading to brain fog and memory impairment. Thankfully, there is a possibility that the residual effects of post-COVID syndrome may not be permanent. A particular study used Montreal Cognitive Assessment (MoCA) scores over the duration of 1 year to discover that the cognitive

performance in *long-COVID-19* patients ultimately improved over time without specific treatment (Del Brutto et al. 2021).

What is known thus far only scratches the surface of what is known about *post-COVID-19 syndrome* as there is little known about the sites of neurological infection. As of now, only a few studies have speculated on COVID-19's frequent targets in the brain. One analysis stated that the COVID-19 virus happens to stimulate mast cells in the hypothalamus thus causing massive stress in the patient. The result of this chronic stress could leave residual symptoms of cognitive dysfunction and brain fog (Cholevas et al. 2021). Another study, through the use of cerebral FDG PET scans, examined the brains of neurological *long-COVID-19* patients and proposes that the cingulate cortex, a separate structure from the hypothalamus, is also a target of the infection due to one of the participants displaying cortical hypometabolism (Farid et al. 2021). The source also compared the case of hypometabolism in former COVID patients to those who suffer from Alzheimer's disease. Interestingly enough, a second study by Dr. Shimohata made a similar connection between neurological *long-COVID* patients and neurodegenerative disorder patients (2022). According to these studies, the virus harbors within the brain and destroys brain cells as compared to neurodegenerative disorders. However, despite the wealth of information acquired, the studies were only able to determine areas of the cerebrum unrelated to the motor, sensory, and cognitive deficiencies.

As we can see, the aforementioned studies neglected to ascertain numerous sites affected by COVID-19 infection in the brain. Due to the limited information presented in the current conversation, the following study will map out and compare specific locations in which COVID-19 attacks the cerebrum and what parts of the brain are damaged post-COVID infection.

Establishing the sites of viral infection could prompt medical professionals to search for and enhance COVID-related treatments against the effects of cognitive decline. Consequently, treatments rendered to patients who could potentially suffer from neurological COVID-19 symptoms could assist with faster recovery, thus improving their quality of life.

Aims and Objectives

The overall objective of this review is to determine and compare what specific structures of the cerebrum produce *long-COVID-19* symptoms. The project will review the series of memory, motor, sensory, and visual symptoms demonstrated by patients and reason through the several areas of the brain that could relate to such manifestations. The end goal will be to obtain a solidified map of brain structures contributing to their respective residual effects and determine what characteristics these structures have in common.

Aims

1. To obtain a general understanding of the types of cognitive, memory, motor, and visual impairments that many patients experience as a result of post-COVID infection.

2. To make an anatomical correlation between brain structures and their respective neurological *long-COVID-19* symptoms exhibited by the average patient.

3. To discover specific synaptic pathways connecting various long-COVID-infected brain structures.

Objectives

1. At this time, there is no agreement on what symptoms are related or unrelated to *long-COVID syndrome.* For this reason, this project will establish the commonalities of symptoms between prominent research articles and journals. The similarities will serve as the foundation for determining what symptoms are related to specific brain structures, possibly improving what we know about COVID-19 and how it creates long-term effects in the brain.
2. The association of brain structures to the onset of symptoms could help us understand what COVID-19 is capable of doing to the brain temporarily and permanently. Obtaining a general idea of which structures are transformed post-COVID-19 infection could encourage therapeutic strategies to restore such areas. It could also spread awareness of what symptoms necessitate careful attention after recovering from the illness.
3. By using what is already known about the brain's anatomy and its neurological properties, we could learn about the pathogenesis of COVID-19 within the brain. Understanding how the virus enters the brain may allow for the field of medicine to combat viral entry into the brain for patients diagnosed with COVID-19.

Methodology

This literature review intends to prove that there is a gap in research by collecting a series of articles and journals reflecting what is already known about the residual symptoms in COVID patients. Then, it will highlight the similarities between said contents as well as the areas yet to

be covered about *long-COVID-19*; particularly *long-COVID-19* within the cerebrum. By pinpointing specific gaps in research regarding *long-COVID-19*, the project will prove that there is a need to investigate that area in the future.

The database used to select all research articles and journals mentioned in this review is Oakland University's Kresge Library OneSearch and Google Scholar search engine. Key terms entered into the search engine are "brain," "neurological," "brain fog," "motor," and "sensory." The purpose of entering key terms and selecting peer-reviewed articles alone is to ensure that all results are related to the in-depth current research of long-COVID in the brain only. All data will be collected from English articles published between the years 2020 and 2022. Content that is not peer-reviewed will be excluded from the project to dismiss information that is not relevant to the current literature. However, this literature review accepts all forms of peer review processes.

Results

Multiple studies regarded attention, processing speed, language comprehension, word-finding abilities, and reduced verbal and visuospatial memory to be commonly reduced in patients suffering from *long-COVID-19*. All symptoms were a direct result of fatigue. Unlike other neurodegenerative disorders such as Alzheimer's disease, *long-COVID-19* is not the direct cause of disabled motor movements. However, it does correlate to chronic joint and muscular pain. Such pain gives rise to motor deficiencies often found. A very limited set of studies reported visual impairments as a notable symptom of *long-COVID-19* and therefore will not be considered one that the majority of patients experience.

COVID-19 Cytokine Storm Phenomenon

Similar to other organs of the body, the brain possesses a highly-regulated system capable of responding to unwanted materials (i.e. pathogens). The microenvironment consists of various glial cells responsible for maintaining homeostasis within the brain and its junction with the bloodstream. Many resident cells are naturally activated in cases of inflammation in the body and near the brain. A few of those cells are microglia, astrocytes, mast cells, and oligodendrocytes. Neuroinflammation is the brain's natural response to a pathogen and is moderated by chemokines, cytokines, and free radicals.

Microglia are a subset of glial cells found in the central nervous system. They are macrophages that consume dead brain cells, repair damaged areas, and respond to inflammation. They are also capable of interacting with astrocytes and oligodendrocytes in certain disease conditions (Bachiller et al. 2018). Microglia possess two phenotypes: M1 and M2. M1 is a state in which they release pro-inflammatory cytokines to contact neighboring glial cells and perform phagocytosis (consumption) of foreign bodies (Mosser and Edwards 2008). When a pathogen is detected in the central nervous system, microglia will change their phenotype from M2 to M1 and trigger astrocytes response through the release of specialized proteins: pro-inflammatory cytokines (IL-6, TNF-α, etc.) and ATP (Smith et al. 2011).

Astrocytes are star-shaped glial cells in the CNS that are designed to cycle neurotransmitters and maintain a strong blood-brain barrier (Sofroniew and Vintners, 2010). The blood-brain barrier is made of tight endothelial junctions and essentially regulates the exchange of molecules between the bloodstream and the brain to maintain homeostasis (Cabezas et al. 2014). They can release growth factors such as (VEGF, glial cell line-derived neurotrophic factor

(GDNF), basic fibroblast growth factor (bFGF), and ANG-1) which facilitate the formation of tight endothelial cell junctions (Alvarez et al. 2013; Wong et al. 2013). Structurally, astrocytes are the first line of defense in preventing pathogens from entering the brain.

The released ATP and cytokines from microglia bind to the G protein-coupled receptors of astrocytes (Buffo et al. 2010). After the reception of cytokines from microglia, astrocytes will release nitrogen monoxide and glutamate or decrease the uptake of neurotransmitters outside of their cell bodies. Both of these cases cause apoptosis of neighboring cells such as oligodendrocytes. Astrocytes will also secrete cytokines of their own to recruit more oligodendrocytes and white blood cells as well as respond to pro-inflammatory cytokines from activated oligodendrocytes (Linnerbauer et al. 2020). In additional response to pro-inflammatory neuronal activity from microglia, astrocytes will release potassium ions and prostaglandins onto blood vessels from their end feet which then decrease the structural integrity of the blood-brain barrier (Paulson and Newman 1987; Linnerbauer et al. 2020). The crosstalk between the astrocytes and the endothelial cells allows for white blood cells and pathogens to enter the cerebral spinal fluid. Astrocytes detect the changes from peripheral neurons and blood vessels and relay the message back to microglia and oligodendrocytes with the aim to prevent any further damage to CNS tissue. This continuous bidirectional process between microglia and astrocytes promotes inflammation. Mast cells, which are residents of the blood-brain barrier, also increase the permeability of the blood-brain barrier through the release of histamine. The main goal of mast cells is to bind to pathogens and release cytokines to crosstalk with other neurons in hopes of eliminating the invader (Marshall JS 2004).

While the process of neuroinflammation is natural and helpful, prolonged exposure to these inflammatory responses can lead to neuronal death from the toxicity of cytokines; this is often the case for chronic diseases and even COVID-19. In such scenarios, an excessive number of cytokines are released into the blood in a short period of time. Many call this uncontrolled and chronic neuroinflammation a "cytokine storm."

COVID-19 Neuroinvasion

A particular study (Zhang et al. 2021) reveals that the COVID-19 virus disrupts the basement membrane of the blood-brain barrier, allowing the virus to infect brain tissue. Neuroinvasion is accomplished by direct infection and replication of primary basement membrane endothelial cells as well as up-regulation of MMP9 to degrade the basement membrane. There also tends to be an elevation in tumor necrosis factor-α (TNF-α) during the onset of COVID-19. This tendency for COVID-19 patients to have high levels of TNF-α mirrors the upregulation of the same cytokine in chronic fatigue patients (Yang et al. 2019). It has also been shown that the level of fatigue may show a direct correlation with the overproduction of TNF-α and other inflammatory signals (Berenetschot et al. 2022). In summary, the COVID-19 virus is often detected by microglia as shown by the increased release of TNF-α which, in turn, activates astrocytes and mast cells that ultimately increase the permeability of the blood-brain barrier. The entrance and prolonged stay of the virus allows for a consistent production of TNF-α which is suggested to produce fatigue.

Cognitive and Memory Impairments

Various studies show that cognitive impairment is a recurring symptom among patients with *long-COVID-19*. Specifically, working memory (Edith et. al 2021; Albu et al. 2022; Almeria et al. 2020; Hosp et. al. 2021; Zhou, et al. 2020), executive functioning (Versace et al. 2021; Alemanno et al. 2021) attention (Mattioli et al. 2021), and spatial confusion (Matos et al. 2021) are the most commonly reported cognitive symptoms. In terms of memory, the majority of research articles report that memory impairment is incredibly common with typically more than half of samples exhibiting this. This symptom is even said to have a direct correlation with increased depression and anxiety (Albu et al. 2021; Almeria et al. 2020; Hampshire et al. 2021; Llanna et al., 2022; Venkataramani and Winkler, 2022; Zhao et al. 2022). There are two primary forms of memory impairment shown: Verbal memory – word-finding and recognition – and visuospatial memory – identifying an object and its location relative to other objects. Tests conducted on patients show a common theme of delayed object recognition among those who tested COVID-19 positive (Aiello et al. 2022; Albu et al. 2022; Ferrucci et al. 2022; Hosp et. al. 2021; Zhao et al. 2022). In terms of verbal memory, various sources record a trend of delayed word recall (Albu et al. 2022; Ferrucci et al. 2021; Mendez et al. 2021).

Motor and Visual Impairments

Impaired voluntary movement is not commonly claimed to be a direct outcome of *long-COVID-19*, rather it is said to be a result of fatigue and joint pain. Additionally, visual disorders are not reported as common symptoms of acute or *long-COVID-19* (Galal et al. 2021; Sykes et al. 2021; Hadad et al. 2022). In general, both forms of impairment are considered anomalies and were said to arise from pre-existing conditions.

Discussion

A number of studies compare the symptoms of *long-COVID-19* to the typical symptoms of chronic fatigue syndrome (Venkataramani and Winkler 2022; Wostyn 2021), neurodegenerative disorders (Venkataramani & Winkler, 2022), and executive function disorder (Ardila & Lahiri, 2020). From this information alone, we can speculate which areas of the brain are altered in a typical patient. One 2008 research article notes that patients with chronic fatigue syndrome (CFS) often had a highly activated occipito-parietal cortex, posterior cingulate cortex, and parahippocampal gyrus (Caseras et al. 2008). The occipital lobe is generally responsible for visual processing and spatial recognition and may be overstimulated *long-COVID-19* patients who demonstrate signs of delayed object recognition. The posterior cingulate cortex is involved in memory, like the hippocampus, and is involved in visuospatial processing similar to the occipital-parietal cortex (Rolls 2019). We can therefore suggest that the hippocampus and posterior cingulate cortex correlate with delayed object recognition and poor visual perception in patients.

The same study that connected *long-COVID-19* to neurodegenerative disorders (Alzheimer's disease, Huntington's disease, Parkinson's disease, etc.) and CFS (Venkataramani and Winkler 2022) finds that *long-COVID-19* microglial activation is prevalent in subcortical and microglial white-matter regions and suggests that the inflammatory response is associated with inhibited hippocampal neurogenesis. It also claims that inflammation in the hippocampal area may explain why patients tend to have poorer memory. CFS, which is functionally similar to

COVID-19, occurs as a result of nerve cells in the central or peripheral systems losing their function over time and eventually dying. By means of the entorhinal cortex, which connects the hippocampus and parahippocampus, the information can be combined with object and reward-related information to form episodic memories (Rolls and Wirth 2018). From both of these studies, we can conclude that the hippocampus's infection is responsible for poor memory and lack of perception due to inhibited neurogenesis and rapid hippocampal cell death.

Executive dysfunction syndrome is defined as a disorder in the frontal lobe that lessens one's ability to plan and manage their own thoughts, emotions, and actions. In summary, "brain fog" is one of the most prevalent symptoms. Patients with dementia and chronic fatigue syndrome more often than not demonstrate poor executive function and we see this in a great number of post-COVID-19 patients. With executive function being a primary issue for this patient population, there is a likelihood that the thalamus, and by extension, the prefrontal cortex of the brain (Ardila 2019) are targeted by the virus. Interestingly enough, the thalamus, cingulate cortex, and hippocampus all share a similar neuronal tract. The thalamus is connected to the cingulate cortex by the thalamocingulate tract. This pathway then travels along the cingulum and eventually enters the parahippocampal gyrus and hippocampus (Weininger et al 2019). The parahippocampus provides an additional route to the hippocampus via the entorhinal cortex and provides the hippocampus with visuospatial information. Due to the fact that the thalamus, cingulate cortex, and hippocampus all correlate to symptoms exhibited by *long-COVID-19* patients, it is likely that the virus targets the thalamocingulate tract and entorhinal cortex.

Language comprehension impairment is a shared symptom among *long-COVID-19* and chronic fatigue syndrome (CSF) patients as well. Ergo, there is a probable similarity in the

changes of white and gray matter for both populations. A particular study (Zeineh et al. 2014) notices that those with CSF showed changes in the arcuate fasciculus structure – a bundle of axons within the hypothalamus connecting the temporal and inferior parietal cortices. The arcuate fasciculus is made up of the Wernicke and Broca structures – both of which are made of gray matter. It was found that a greater number of abnormalities in the arcuate fasciculus increased the level of fatigue and memory impairments demonstrated in CFS patients (Zeineh et al. 2014). The very same could be true in *long-COVID-19* patients as well. A damaged arcuate fasciculus is also described to lead to slower language processing and comprehension skills (Ivanova et al. 2021). From this, we can propose that the hypothalamus, specifically the arcuate fasciculus, correlates with higher levels of fatigue and possibly some deficiencies in language processing among those with *long-COVID-19*.

In conclusion, we suspect that the hippocampus, thalamus, hypothalamus (paraventricular nucleus and arcuate nucleus), prefrontal cortex, and cingulate cortex are all the targets of the *COVID-19* virus and suffer long term damage after recovery. The virus affects these areas of the cerebrum by means of the arcuate fasciculus bundle, thalamocingulate tracts, and entorhinal cortex. For the previous information, I may extrapolate that cytokines travel across the thalamus, cingulate cortex, parahippocampal gyrus, and hippocampus by the thalamocingulate tract. The thalamus is connected to the cingulate cortex by the thalamocingulate tract which then travels along the cingulum, parahippocampal gyrus and hippocampus. Since the posterior cingulate gyrus is connected to the hippocampal memory system and parietal cortex by dorsal streams (Rolls 2019) while the mediodorsal thalamus connects to the prefrontal cortex via thalamocortical tracts (Ferguson & Gao 2015), we can presume that all of these structures are

affected due to their vicinity and connections. We can suggest that the hippocampus, prefrontal cortex, and posterior cingulate cortex are three structures capable of altering a patient's cognitive abilities. Infection of the hippocampus and prefrontal cortex manifests in forms of poor memory and perception. Inflammatory response in the posterior cingulate cortex contributes to delayed object recognition and poor perception as well. Lastly, the hypothalamus may be responsible for reduced language comprehension and memory impairment while the thalamus and prefrontal cortex is proposed to be the culprit of poor executive function. The increase of similar pro-inflammatory cytokines presents a unique relationship between chronic fatigue syndrome and COVID-19. It is possible that CFS is a direct result of COVID-19 due to possessing similar regions of infection, mirroring patterns of protein release, and both demonstrating symptoms of executive dysfunction, poor memory, delayed object recognition, and language comprehension.

Outcomes

The overall objective of this study, to find out and compare what areas of the cerebrum are associated with the *long-COVID-19* symptoms patients experience, will come with a varying set of results. This study intends to associate various parts of the cerebrum with their respective symptoms produced by *long-COVID-19* patients. Given what is already known about the brain and what they perform under normal and pathological conditions, there is a potential to narrow down what parts of the brain are culprits for the symptoms witnessed. Additionally, research conducted in this study will summarize the symptoms of *long-COVID-19* based on journals published with concrete evidence from multiple sources. Summarizing the key results of recent

and in-depth research could benefit the scientific community in that it will help scientists come to a firm conclusion about what symptoms are often caused by *long-COVID-19* and what symptoms can be excluded in typical cases.

A portion of this project aspires to pinpoint one or multiple synaptic pathways that permit electrical and chemical signals to enter into two or more *long-COVID-19*-infected brain structures. Establishing key connections such as these could one day improve what we currently know about COVID-19 and its pathogenesis. Consequently, obtaining such knowledge may assist us in utilizing specific blocking agents of neural pathways based on where the sites of entry are located. Since many individuals such as myself have become increasingly curious about the capacities *long-COVID-19* and to what extent it harms the brain, this project attempts to repeatedly inquire about it in detail and in the long term. This is also a wonderful opportunity for a young student like myself to obtain key knowledge that is currently undiscovered by the scientific community for the first time. The information obtained from this project could greatly enhance the forms of treatments and medications I, in the future, will perform and dispense to patients suffering from *long-COVID-19* and similar viral illnesses.

Biographical Note

I am a student majoring in Health Sciences with a strong interest in gross human anatomy. Currently, I am pursuing a degree with a concentration in Pre-Pharmacy and aspire to attend a pharmacy institution in the near future. The primary role of a pharmacist is to ensure that the correct prescription is allotted as it will greatly impact a patient's experience. Since I desire

to prioritize my career in curative patient care, discovering the sources of memory, motor, sensory, and visual impairments exhibited by various disease states will assist me in deciding what medications could improve symptoms.

For the reasons mentioned above, I believe that this project may help me develop a strong understanding of the characteristics severe diseases possess and possibly provide me, and the rest of the scientific community, with great insight into what can be done to mitigate the symptoms of *long-COVID* and similar viruses. Knowing that I must continually broaden my knowledge of new diseases, gaining background on what occurs on a physiological level will make me an active combatant against illnesses within the realm of pharmacy. With that in mind, I plan to use this project as the first step in taking an in-depth look at what a disease does at a physiological level to one day develop new cures for such an illness.

Acknowledgments

I give my deepest thanks to Professor Kauhn, to whom I owe an immense debt of gratitude for guiding me throughout this project. I would also like to acknowledge the Oakland University Honors College for turning my dreams of research into a reality.

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