

OUT OF FOCUS

The Science of Brain Fog

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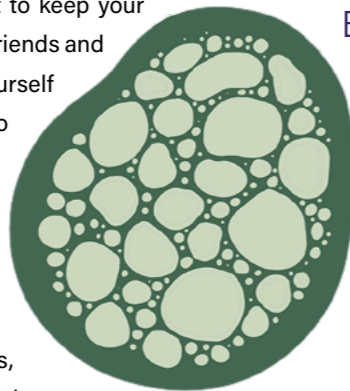
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WHAT IS BRAIN FOG?

On March 11th, 2020, the COVID-19 pandemic was officially declared by the World Health Organization. Precautions such as masks and social distancing were unheard of at the time; health organizations around the world scrambled to figure out more about how the virus spread, and how to stop it. A couple of days later, you begin to come down with a fever and notice that you can't smell the air freshener in your car. You learn after work that a fellow is sick with symptoms like loss of smell and having a high fever. Currently, getting a test for COVID-19 is extremely difficult, so while you can't confirm you have the virus, you decide to call out of work anyways. You end up being sick for a week, and it is the worst you have ever felt in your entire life. You run a high fever, feel like it is impossible to stay focused on anything, and cannot taste or smell anything that you eat. Two weeks after your sickness, you are officially "COVID free". However, you still find it difficult to keep your mind focused on anything. Conversations with friends and family are hard to keep up with now. You find yourself forgetting things at work often, and you feel so tired all the time. You're not sick anymore, so why do you still feel this way?

It is now July 2020, 4 months after you contracted the virus, yet you still feel the same mentally as when you first got sick. Multiple times, you've almost gotten fired from work for forgetting an important document or yelled at for being unable to keep up in work meetings. You don't talk to people as much as you used to, due to how much effort it takes to pay attention to a two minute conversation. You can't remember anything that's happened in the past week. You've tried talking with doctors, but all the tests come back normal, and there's nothing they can do. You feel so alone in this endless fog of misery, and you wonder if you'll ever get better.



For some that were infected with coronavirus disease 2019 (COVID-19), symptoms of the virus remain long after their initial illness, in what is known as 'long COVID'. The term 'long COVID' was first coined by Elisa Perego, who talked about her experiences with lingering COVID-19 symptoms after her recovery on Twitter [1]. Medically, a person is given the diagnosis of long COVID-19 if their symptoms last for four weeks and cannot be explained by any other cause [2]. Currently, it is unknown why this illness occurs in some patients, but not others. Those with long COVID tend to experience a variety of symptoms, including brain fog. Brain fog, medically known as clouding of consciousness [3], is used to describe difficulties focusing and thinking that is sluggish [4]. While the relation between COVID and brain fog is currently unknown, what we know now about brain fog can help us to figure out why this link occurs and ways to treat this.

BIOLOGY OF BRAIN FOG

Biologically, clouding of consciousness is believed to be caused by cells in the brain that cause inflammation [5]. These cells are known as mast cells, and they help control the permeability of the blood-brain barrier [5]. The blood-brain barrier is important for controlling the flow of molecules in and out of the brain to keep the organ functioning normally, and prevents toxins and pathogens from entering the brain [6]. Additionally, mast cells are used as alarms to alert the immune system when it encounters something that will cause an allergic reaction in the body [5]. Different molecules activate mast cells to trigger the alarm system, causing the release of a variety of chemicals, such as histamine [5]. Histamine is important for learning and motivation, but excess histamine in the brain can cause clouding of consciousness by activating histamine auto-inhibitory receptors that stop the functions of mast cells [5].



WHAT CAUSES BRAIN FOG?

A variety of sources seem to cause brain fog, so what goes on in the brain to create that foggy feeling you just can't shake? Typically, clouding of consciousness occurs in those that have disorders such as celiac disease, chronic fatigue syndrome, autism, and more [7]. This can also occur as a result of anxiety, stress, or a lack of sleep [8]. Aside from neurological disorders, evidence shows that factors such as stress and obesity can play a role [5]. Obesity is related to an increase in inflammation from mast cells, which can lead to brain fog and related disorders such as Alzheimer's Disease [5]. Stress causes mast cells to release inflammatory mediators that trigger inflammation to occur [9].

Additionally, exposure to air pollution and mold may also cause brain fog. In an experiment conducted by Joseph Allen, participants were randomly assigned to rooms in an office that differed in pollution levels and ventilation levels [10]. The pollution in the study was defined as volatile organic compounds (VOCs), chemicals that are harmful to humans [10]. The participants stayed in the room until the end of the day and were then asked to complete a cognition test, in the

form of answering surveys [10]. Participants in rooms with lower VOCs levels scored higher on the cognition test [10]. The results of the study suggest that there is a correlation between pollution and cognitive function.

Certain treatments can also cause clouding of consciousness. The term "chemo-fog" is used to describe how patients with cancer feel cognitively after going through chemotherapy [5]. Chemo-fog can affect various parts of a patient's cognition, such as attention, concentration, ability to organize information, and more [7]. The treatment causes an increased release of cytokines, which cause inflammation in the brain [7]. Cytokines are proteins that are released from cells that can affect other cells in the body, and can either be pro-inflammatory or anti-inflammatory [11].

COVID-19 AND BRAIN FOG

Recently, the topic of brain fog has been a popular subject due to COVID-19. For many that are sick with the virus, the effects outlast the amount of time they experienced symptoms related to the disease. This is known as "long-haul" COVID, and symptoms such as fatigue, coughing, and brain fog are commonly

associated with the illness [1]. It is unknown why some people who are sick with the virus experience long COVID, and why the clouding of consciousness is a common symptom for those that do have long COVID.

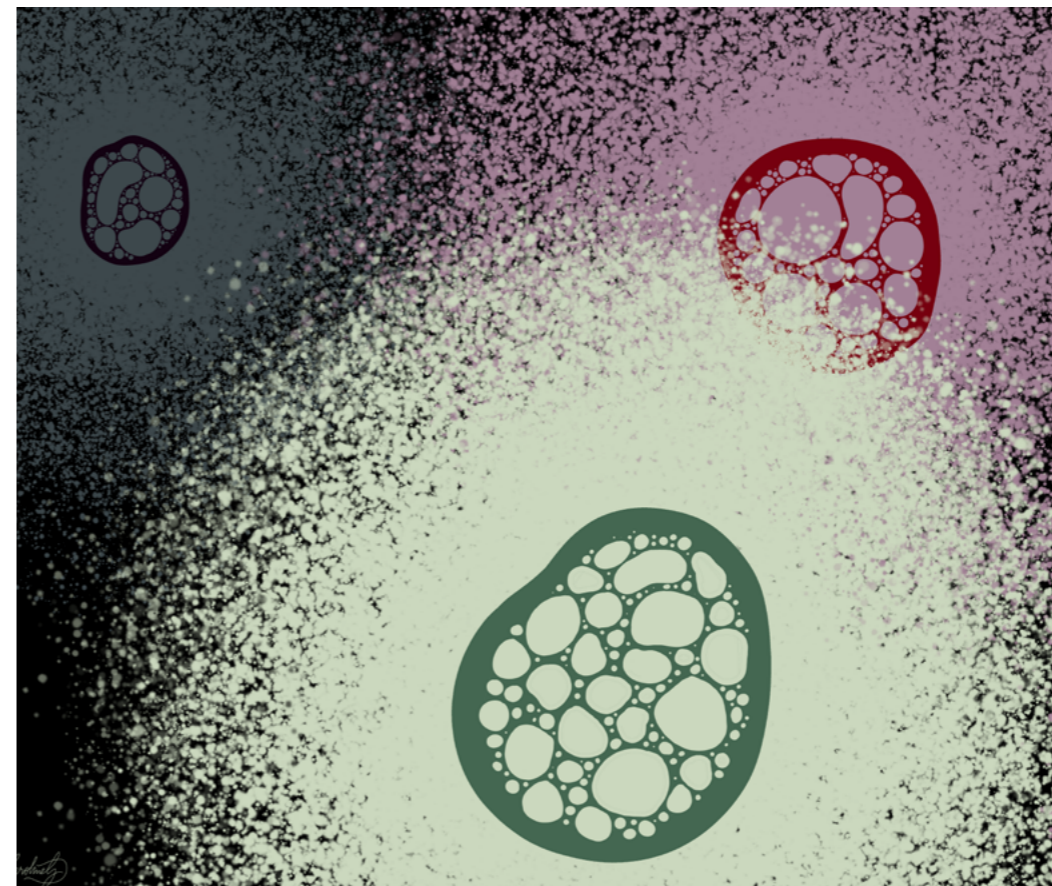
Currently, the link between the virus and this symptom is being researched. When looking at the symptoms of long COVID that patients tend to report, many are related to the brain, such as headaches, difficulties sleeping, and of course, brain fog [4]. This suggests that the virus may affect the brain in some way. A study from researchers in the United Kingdom, while not peer-reviewed yet, shows strong evidence that the disease causes structural damage to the brain [1]. Scans of more than 40,000 participants were taken before the pandemic, and the participants were invited to be scanned again in 2021 [1]. The study looked at 785 participants; 401 participants had contracted the virus between the scans, while 384 participants had not [1]. When looking at the brain scans of participants that had contracted the virus, grey matter thickness in the brain was reduced, and damage was seen in areas relating to smell [1]. How would COVID-19 reach the brain? Research shows that the virus might be able to reach the brain by traveling up the

nose, and passing through the olfactory mucosa, which is the lining of the nose that is near the brain [12]. This would explain why patients that were sick show damage in areas relating to smell, as it affects not only the nose, but also the area of the brain that processes signals from the nose.

Once the virus is inside the brain, how does brain fog occur? One study suggests that when COVID-19 infects neurons in the brain, the virus essentially “hijacks” the neuron in order to use energy stores found inside [13]. The virus then uses the energy stores in the neuron in order to replicate and continue to spread throughout the brain [13]. This requires the neuron to need more oxygen to create more energy to make up for what the virus took, which leads to inflammation in the brain that causes the clouding of consciousness [13]. A lack of oxygen in the brain causes the release of cytokines from neurons, which also promotes inflammation in the brain [14].

TREATMENTS

Currently, there are no known medications for brain fog [15]. However, there are treatments that do not involve medication. Brain fog can be caused by sleeping too little or too much, so



getting seven to nine hours of rest every night may help reduce these symptoms [16]. Exercising is proven to improve brain health, and it is recommended to exercise for 30 minutes a day, five days a week [4]. Taking care of your mental health can help to alleviate stress, as chronic stress can lead to the development of brain fog [16]. Additionally, avoiding alcohol and drugs, and having a healthy diet can help to combat the development of brain fog [4].

A treatment known as enhanced external counterpulsation (EECP) therapy, could potentially be used to help patients with the disease deal with clouding of consciousness. EECP therapy is primarily used for patients that have cardiovascular diseases as it helps to fix the issue with the flow of blood coming back to the heart [17]. The therapy works by placing three sets of inflatable cuffs on the arm [17]. As the heart stops contracting, the puffs, which also contract, help to increase pressure in the aorta and blood flow in the arteries and heart [17]. The first recorded treatment of EECP used for COVID-related brain fog was on a 38-year-old woman who was sick with the virus in October 2020 [18]. The patient had long COVID symptoms, such as brain fog and fatigue, for months before starting treatment [18]. EECP was chosen for her due to the compression from the treatment causing an increase in blood flow that helps to regulate proinflammatory molecules [19]. The patient reported that her brain fog improved after the first week of therapy, and after five weeks, she reported feeling as healthy as she was prior to getting sick [6]. While the results from the study

supports the use of luteolin as a treatment, as brain fog is commonly related to disorders and illnesses such as depression and autism.

CONCLUSION

Brain fog occurs for a variety of reasons, with some as minor as not getting enough sleep, or some as major as being caused by a disorder. Inflammation in the brain contributes to the difficulties in thinking and focusing that are commonly seen in patients infected with coronavirus. Currently, we believe COVID-19 to be linked to brain fog because of signs that the virus causes structural damage in the brain, and the theory that the virus hijacks neurons to use their energy to replicate. This causes neurons to try to compensate for the loss in energy by using more oxygen, which causes inflammation to occur. While there is no definite cure for this occurrence, activities such as getting enough rest every night, or having a healthy diet may help clear the fog from your mind. Medical treatments, such as EECP and luteolin are being studied at the moment to try to help long COVID patients who suffer from brain fog.

While we do not know much about COVID-19 now, work is being done every day to learn more about the virus. Hopefully, with new information, we will find an effective treatment for those with long COVID related brain fog, and perhaps apply this knowledge to treating brain fog that is caused by other factors not related to this disease. 🧠

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RUNNING ON EMPTY: HOW COVID HAS AFFECTED OUR SOCIAL SKILLS

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