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Tatiana Horowitz, Luc Pellerin, Eduardo Zimmer, Eric Guedj. Brain fog in long COVID: A glutamatergic hypothesis with astrocyte dysfunction accounting for brain PET glucose hypometabolism. *Medical Hypotheses*, 2023, 180, pp.111186. 10.1016/j.mehy.2023.111186 . hal-04406602

HAL Id: hal-04406602

<https://amu.hal.science/hal-04406602>

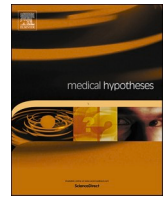
Submitted on 7 Feb 2024

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Brain fog in long COVID: A glutamatergic hypothesis with astrocyte dysfunction accounting for brain PET glucose hypometabolism

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ARTICLE INFO

Keywords:

PET
Long COVID
Post-COVID condition
PASC
Glutamate
Metabolism
Brain fog
Astrocyte

ABSTRACT

Brain [¹⁸F]FDG-PET scans have revealed a glucose hypometabolic pattern in patients with long COVID. This hypometabolism might reflect primary astrocyte dysfunction. Astrocytes play a key role in regulating energy metabolism to support neuronal and synaptic activity, especially activity involving glutamate as the main neurotransmitter. Neuroinflammation is one of the purported mechanisms to explain brain damage caused by infection with SARS-CoV-2. Microglial activation can trigger reactive astrogliosis, contributing to neuro-inflammatory changes. These changes can disturb glutamatergic homeostasis, ultimately leading to cognitive fatigue, which has been described in other clinical situations. We hypothesize that glutamatergic dysregulation related to astrocyte dysfunction could be the substrate of brain PET hypometabolism in long COVID patients with brain fog. Based on these elements, we propose that therapeutics targeting astrocytic glutamate regulation could help mitigate long COVID neurological manifestations.

Introduction

Long COVID, also called post-COVID condition (PCC) or post-acute sequelae of SARS-CoV-2 infection (PASC), is defined by the persistence of symptoms for at least 2 months, usually 3 months from the onset of COVID-19, that cannot be explained by an alternative diagnosis in the context of a probable or confirmed SARS-CoV-2 infection [1]. These symptoms encompass various manifestations, including cognitive fatigue and brain fog. [¹⁸F]Fluorodeoxyglucose (FDG) positron emission tomography (PET) brain imaging has been proposed as a tool to demonstrate brain impairment in this condition [2].

[¹⁸F]FDG is a safe fluorine-18 radiolabelled analog of glucose that takes part like glucose in its metabolism. It is the most used radiotracer for brain PET imaging. The brain is a major glucose consumer, as glucose is needed to support cerebral function [3,4]. Brain [¹⁸F]FDG-PET imaging is commonly employed for the diagnosis of neurological disorders, as alterations in brain metabolism can occur under many pathological conditions. In neurodegenerative diseases, a reduced brain [¹⁸F]FDG-PET signal has been associated with neuronal loss, although there is

clear evidence that [¹⁸F]FDG-PET hypometabolism can precede significant neuronal death by several years [5]. In long COVID, specific regions of the brain have been found to be hypometabolic using [¹⁸F]FDG-PET imaging, such as the limbic/paralimbic circuit (including the olfactory grooves, cingulate, temporal cortex, amygdala, hippocampus, insular cortex, and hypothalamus), the brainstem, and the cerebellum [2,6,7].

Glucose metabolism assessed using [¹⁸F]FDG-PET is thought to reflect synaptic activity, the regulation of which depends on functional interactions between neurons and astrocytes [8]. Astrocytes are abundant glial cells of the central nervous system that crucially adapt energy metabolism to synaptic activity and regulate glutamatergic synapses. Glutamatergic neurons heavily rely on astrocytes to support the synthesis and release of glutamate, which is the neurotransmitter responsible for 90 % of excitatory neurotransmissions in the human brain [9]. Astrocytes play a pivotal role in this metabolic cooperation by taking up glutamate from the synaptic cleft and converting it into glutamine through the enzyme glutamine synthetase. This process not only facilitates efficient glutamate recycling but also ensures the replenishment of

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glutamine, which can be transported back to the neurons to serve as a precursor for the synthesis of amino acid neurotransmitters, including glutamate. Additionally, astrocytes provide energy substrates to neurons through the astrocyte-neuron lactate shuttle, through which astrocytes metabolize glucose into lactate and release it to be used as a prominent fuel for neuronal metabolism [4,9,10]. This exchange of metabolites between astrocytes and neurons is essential for maintaining synaptic homeostasis and supporting neuronal activity. Disruption of this metabolic coupling, such as reduced astrocytic glutamate uptake or impaired lactate supply to neurons, can lead to glutamatergic excitotoxicity and impaired neurotransmission and ultimately contribute to brain dysfunction [11].

Astrocytes are also key responders to neuroinflammatory changes via pro- and anti-inflammatory actions [12]. Under certain conditions, astrocytes undergo molecular, morphological and functional changes and gain a reactive state, termed reactive astrogliosis [13]. Astrocytes become hypertrophic or atrophic [14], exhibiting an altered release of signalling molecules and changes in their ability to support neuronal function. Neuroinflammation, along with microglial activation and mitochondrial dysfunction, plays a role in numerous neurological disorders, and all three conditions are thought to be involved in long COVID [15].

Overall, brain hypometabolism reported using [^{18}F]FDG-PET imaging may be interpreted as arising from two underlying mechanisms, based on recent advances in the field [8,16,17]:

- (i) Astrocytes undergo reduced glucose utilization secondary to decreased activity of neurons/synapses, which are primarily impaired. This functional mechanism is nonspecific and commonly observed in various cerebral diseases, independent of the pathological process affecting the brain.
- (ii) Astrocytes undergo a more specific process primarily linked to their reduced capacity to take up glutamate, subsequently resulting in decreased lactate supply to neurons as a key energy source [9]. This leads to the accumulation of glutamate in the extracellular space, causing interference with normal neurotransmission and eventually resulting in glutamatergic excitotoxicity and neuronal death [16,18]. In these cases, astrocyte reactivity might be both a sign of their dysfunction and a contributing factor to the deleterious effects on neurons.

The hypothesis for long COVID

We hypothesize that the hypometabolism pattern observed in long COVID patients with brain fog using [^{18}F]FDG-PET might primarily be a signature of astrocyte-related glutamatergic dysregulation (Fig. 1).

Evaluation of the hypothesis and empirical data

Long COVID is classically associated with cognitive dysfunction described as brain fog [19], characterized by a lack of mental clarity,

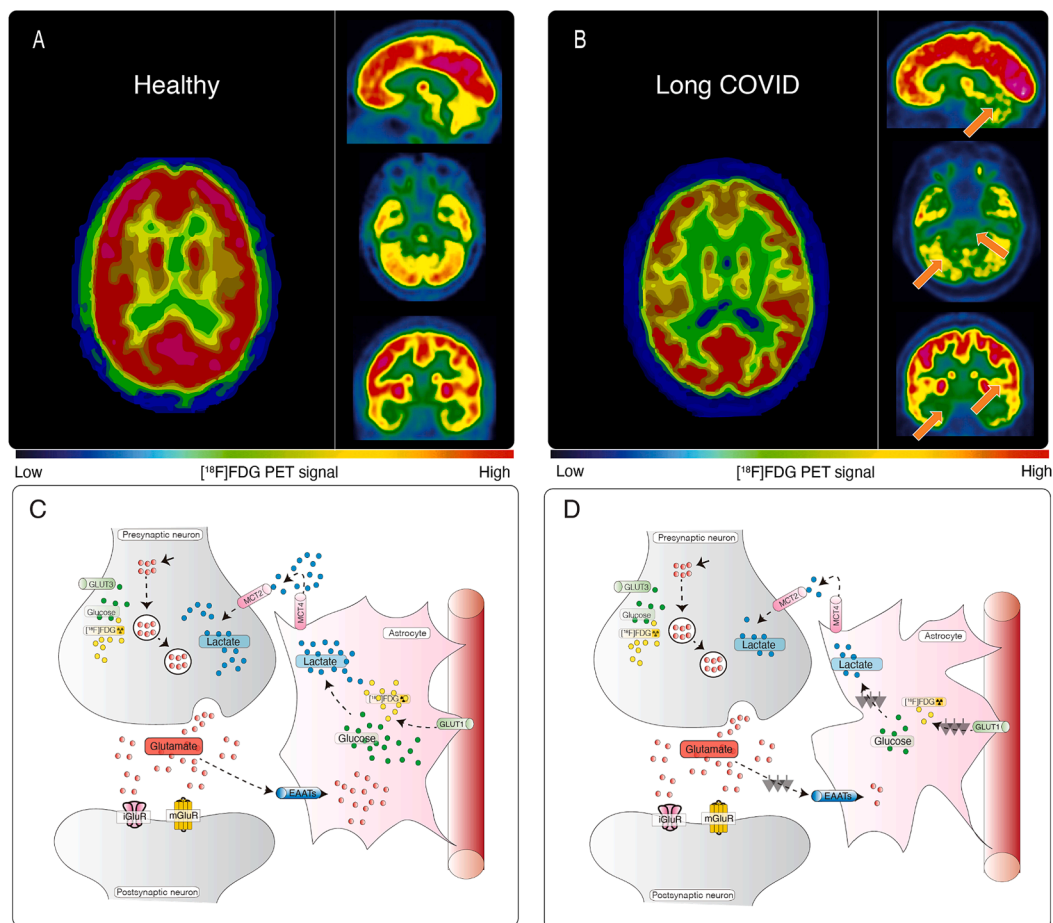


Fig. 1. Hypometabolism detected with 18F[FDG]-PET in long COVID patients: putative astrocyte dysfunction and glutamatergic dysregulation. (A) 18F[FDG]-PET scan of a healthy subject. (B) 18F[FDG]-PET scan of a long COVID patient. Hypometabolic areas are indicated with arrows. (C) A diagram showing a healthy condition in which an astrocyte has a normal capacity to take up glutamate and recycle it to sustain glutamatergic neurotransmission, giving rise to normal glucose utilization and lactate production to ensure adequate neuronal energy supply. (D) A diagram showing a long COVID condition in which an astrocyte has reduced glutamate uptake capacity, leading to reduced glutamate recycling, lower glucose utilization (observed with 18F[FDG]-PET as hypometabolism) and lower lactate production, dysregulating glutamatergic neurotransmission and possibly endangering neuronal survival.

difficulty concentrating, and an inability to focus, with cognitive activities becoming effortful. Interestingly, a link between cognitive fatigue and glutamate dysregulation has been suggested in other clinical conditions [20]. In a recent magnetic resonance spectroscopy study, Wiehler and colleagues proposed a neurometabolic basis for cognitive fatigue [20]. They found an increase in the accumulation of substances requiring clearance, including glutamate, during high-demand cognitive tasks compared to low-demand tasks. This elevated level of glutamate suggests that the activation of certain brain regions is more energetically demanding and susceptible to astrocyte dysfunction. Moreover, this brain fog seems similar to that reported as “chemo-fog” in patients with cancer, with possible common immunological mechanisms induced by the tumour or its treatment [21,22], also involving astrocytes and microglial activation [23]. Interestingly, a similar brain FDG-PET frontal hypometabolic pattern to that of long COVID has been recently reported in patients with immune-effector cell-associated neurotoxicity syndrome after chimeric antigen receptor T-cell therapy, suggesting shared cytokine-induced inflammation [24]. Furthermore, fatigue has previously been linked to apathy, olfactory dysfunction, and cognitive impairment in other clinical conditions, such as Parkinson’s disease [25]. In this disease, the symptoms are interestingly supported by a similar brain network to that of long COVID [26] involving the same two presumptive models of propagation, descending (“top-down”) from the nose to the brain and ascending (“bottom-up”) from the autonomic nervous system to the brain.

Concerning the connections between the potential mechanism pertaining to cognitive fatigue and cytokine-induced inflammation with the observed hypometabolism in patients with long COVID, we hypothesize that the reduction in astrocytic glutamate uptake capacity causing extracellular glutamate accumulation could contribute to brain fog.

Implications of the hypothesis and discussion

Hypometabolism revealed in brain [18F]FDG-PET scan is a usual pathological finding, for example in the interictal state of focal epilepsy which is associated with cognitive deficits [27]. In this case, the hypometabolism is reversible after antiepileptic treatment and parallels the regression of possible interictal symptoms, especially cognitive impairment, as illustrated in transient epileptic amnesia [28]. We notice that the potential benefits of ketogenic medium-chain triglyceride (MCT) supplementation have been similarly proposed both in epilepsy and to refuel the post-COVID-19 brain by compensating for defects in glucose metabolism in astrocytes and neurons [29].

More globally, therapeutics acting on glutamatergic neurotransmission are available and may reduce symptoms related to glutamatergic excitotoxicity [30], possibly attenuating the consequences of primary astrocyte dysfunction, with for example the α_2A -adrenoceptor agonist guanfacine and N-acetylcysteine (NAC) which are currently under investigation in long COVID [31]. In a recent study, a promising combination of guanfacine and NAC improved cognitive function in 8/12 long COVID patients with brain fog. Researchers have proposed hypotheses to explain this possible drug-association mechanism, namely, that some regions in the brain may be more vulnerable to long COVID with brain fog [32]. This vulnerability could be due to unusual features of synapses in these regions that mostly rely on NMDA receptors, as these glutamatergic synapses are excitatory, and glutamate acts on postsynaptic NMDA receptors to activate neurons. NAC reduces oxidative stress associated with excessive activation of NMDA receptors, and guanfacine reduces deleterious potassium-mediated channel signalling in neurons and enhances neuronal firing [31]. Another option to be considered is memantine, an NMDA channel blocker used to treat moderate-to-severe Alzheimer’s disease, which reduces glutamate-induced prolonged Ca^{2+} influx in neurons and may help to mitigate the detrimental effects of impaired astrocytic glutamate uptake [33].

Another therapeutic option would be to target astrocytes directly. As mentioned, these cells are responsible for the maintenance of glutamate

homeostasis. They recycle glutamate via its uptake by high-affinity Na^{+} -dependent glutamate transporters (e.g., excitatory amino acid transporter 2 - EAAT2) and its conversion into glutamine [34]. A class of β -lactam antibiotics has been identified as promoting the expression of glutamate transporters and enhancing glutamate uptake by astrocytes [35]. Ceftriaxone was shown to not only stimulate glutamate uptake but also boost glucose utilization (and the concomitant [^{18}F]FDG-PET signal) in astrocytes [8]. Ceftriaxone has been investigated as a potential treatment for excitatory events that occur in the brain of amyotrophic lateral sclerosis patients (NCT00349622; NCT00718393) [36]. Multiple EAAT2 activators/inducers have been identified and could be tested as potential glutamate uptake enhancers. These EAAT2 activators/inducers are also potential candidates for PET radiopharmaceutical development of novel radiotracers, which would greatly help us advance our understanding of brain metabolic changes in long COVID and other brain conditions, especially other postinfectious disorders [37]. Finally, metformin has been recently suggested to prevent long COVID [38]. Metformin is well known for its effects on peripheral metabolism, but it also works in the central nervous system by stimulating glycolysis and lactate production by astrocytes [39].

It is important to acknowledge that our hypothesis does not discriminate among upstream mechanisms that are likely involved in astrocyte dysfunction. Indeed, three main mechanisms, possibly concomitant, have been proposed in long COVID, as follows: direct astrocyte infection by SARS-CoV-2, a pathogen-triggered immune reaction, and cytokine-mediated inflammation [22,40,41]. According to the first mechanism, SARS-CoV-2 infects astrocytes, interestingly causing metabolic changes consistent with our hypothesis, and leading to neuronal dysfunction that contributes to the structural and functional alterations observed in the brains of COVID-19 patients [40]. This viral persistence has already been reported in other phagocytic lineages, such as monocytes [42], and has been suggested in the human body and brain after SARS-CoV-2 infection [43,44]. A preprint study using innovative PET target imaging reported that long COVID symptoms were associated with activated T lymphocytes in the spinal cord and gut wall [45], with concomitant detection of cellular SARS-CoV-2 RNA in the rectosigmoid lamina propria tissue of all patients. According to the second mechanism, a structural protein derived from SARS-CoV-2 may act as a pathogen-associated molecular contributor to dysimmune reactions and lead to vascular damage and neuroinflammation [41]. According to the third mechanism, SARS-CoV-2 infection ultimately increases microglial/macrophage reactivity [22,46] and proinflammatory cytokines in microglia and is associated with mitochondrial dysfunction [47,48]. It is important to note that astrocytes are potentially becoming reactive in these three proposed hypotheses. It is especially possible that the prolonged inflammatory response and neuroinflammation observed in long COVID could lead to astrocyte reactivity and possible metabolic dysfunctions. The presence of reactive astrocytes in long COVID suggests the involvement of astrocytes in the disease process and could potentially contribute to the neurological symptoms experienced by some individuals with long COVID.

Next contributions expected from molecular imaging to consolidate the hypothesis

Further research is needed to establish a definitive link between reactive astrocytes and long COVID. Additional studies utilizing more specific markers or techniques targeting astrocyte function and glutamate homeostasis will be necessary for a comprehensive understanding of the underlying mechanisms and for the development of effective treatments for long COVID-related brain fog. In this context, multitracer PET studies to explore neuroinflammation could be a useful strategy to understand long COVID, with concordant preliminary results [6,15,49–52]. Specifically, PET imaging with a TSPO tracer, used as an index of microglial activation, has revealed widespread longitudinal neuroinflammation in SARS-CoV-2-infected rhesus macaques [52], and

elevated TSPO binding was associated with persistent depressive and cognitive symptoms after initially mild to moderate COVID-19 illness. To our knowledge, no studies with MAO-B or I2BS PET tracers, used as indices of astrocyte reactivity, have been conducted yet.

In conclusion, we hypothesize that the [¹⁸F]FDG-PET hypometabolism pattern observed in long COVID patients with brain fog is indicative of astrocyte-related glutamatergic dysfunction. In this line, therapeutic approaches targeting glutamate neurotransmission and astrocyte function could help to alleviate astrocyte dysfunction in long COVID, improve cognitive fatigue, and potentially prevent further brain lesions.

Disclosure

ERZ serves on the scientific advisory board of next innovative therapeutics (Nintx). ERZ is a co-founder and is on the scientific advisory board of MASIMA

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics

Consent statement/Ethical approval: Not required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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