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LETTER TO THE EDITOR

About the source and consequences of ^{18}F-FDG brain PET hypometabolism in short and long COVID-19

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Dear Sir,

We have read with great interest the article recently published by Guedj et al., titled ^{18}F-FDG brain PET hypometabolism in patients with long COVID [1]. We recently proposed that PET imaging versatility might hold the key for understanding pathophysiological changes in the brain of COVID-19 patients [2]. The article by Guedj and colleagues is a great demonstration of how powerful PET imaging can be in this regard.

This article provides evidence that COVID-19 patients with persistent functional complaints, more than 3 weeks after the first symptoms, present continuous ^{18}F-FDG PET hypometabolism in multiple brain regions, including the olfactory gyrus, hippocampus and cerebellum.

Few months ago, small-scale studies provided initial evidence of brain glucose hypometabolism in COVID-19 individuals [3, 4] sharing similar findings concerning the hypometabolic brain regions, such as the pre-frontal cortex and the gyrus rectus. Our letter intends to raise awareness on (1) the biological interpretation of decreased brain ^{18}F-FDG PET signal in COVID-19 and (2) potential sequelae due to brain glucose hypometabolism in long COVID.

This article is part of the Topical Collection on Letter to the Editor

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Cellular origins of ^{18}F-FDG PET hypometabolism in COVID-19

In 1977, Sokoloff developed and validated a kinetic model for estimating brain glucose metabolism using PET ^{18}F-FDG [5]. Sokoloff's two-tissue compartment model comprises ^{18}F-FDG in plasma, free ^{18}F-FDG and phosphorylated ^{18}F-FDG in brain tissue [5]. For more than 4 decades, the biological interpretation of brain PET ^{18}F-FDG signal was considered a direct index of neuronal activity [6]. Nevertheless, over the last years, a more integrative view in which astrocytes, an abundant type of glial cells, are also prominent contributors to the ^{18}F-FDG PET signal has emerged [7]. Indeed, it seems that astrocytes substantially contribute to ^{18}F-FDG PET signal [8–10]. Moreover, it is known that astrocytes play pivotal roles in the brain defence against peripheral inflammatory changes [11]. Guedj and colleagues [1] mentioned that acute systemic inflammation and SARS-CoV-2 neurotropism could be related to brain inflammatory alterations. Complementary, other groups identified signs of reactive astrogliosis in post-mortem tissue of COVID-19 patients [12], in cellular models and in brain organoids [13]. In keeping with this, one could not neglect astrocyte dysfunction as the possible cellular origin of brain ^{18}F-FDG PET hypometabolism in COVID-19. In vivo brain imaging of COVID-19 individuals using specific PET radiotracers targeting reactive astrocytes (e.g. ^{11}C-DED and ^{11}C-BU99008) could help settling this matter.

Persistent brain hypometabolism measured by ^{18}F-FDG PET - a risk for developing neurodegenerative diseases

While the cellular origins of brain ^{18}F-FDG PET hypometabolism in COVID-19 remain to be defined, it seems clear that we are dealing with persistent synaptic dysfunction. Guedj et al. [1] demonstrated that multiple brain regions are hypometabolic in long COVID. In addition, it seems that there

is a link between clinical manifestations and regional glucose hypometabolism. For instance, decreased glucose consumption in the cerebellum was linked to hyposmia/anosmia and cognitive impairment. Another recent study followed up the ^{18}F-FDG brain profile of seven patients in the early phase of infection, 1 month and 6 months after COVID-19 onset. Interestingly, the abnormal cognitive function associated with pre-frontal cortex hypometabolism persisted in all patients for ~6 months [14]. Remarkably, ^{18}F-FDG brain hypometabolism in the pre-frontal cortex is present in multiple neurodegenerative disorders [15] and neuropsychiatric conditions [16], sometimes even preceding the first symptoms.

Thus, the cellular origins of COVID-19 ^{18}F-FDG PET hypometabolism in short- and long-term scenario remain to be explored, with mounting evidence suggesting an astroglial contribution. Furthermore, persistent ^{18}F-FDG PET hypometabolism in long COVID patients should be carefully monitored in terms of potential sequelae, such as the development of brain disorders.

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Declarations

Conflict of interest The authors declare no competing interests.

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