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Commentary

Long COVID and the brain network of Proust's madeleine: targeting the olfactory pathway

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Long COVID is defined by the persistence or recurrence of symptoms after initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This condition affects 20% of patients at 5 weeks and 10% at 3 months, with a major impact on health care and social systems [1]. Long COVID has been described in all countries facing the pandemic. It corresponds to different realities, which can be associated [1]. On the one hand, patients may present with sequelae of acute coronavirus disease 2019 (COVID-19) (e.g. pulmonary fibrosis or stroke) as well as physical/psychological impairments following long stays in intensive care units. On the other hand, a group of often younger patients has emerged with mainly mild to moderate initial presentations and persistent or recurrent symptoms, dominated by fatigue and dyspnoea; loss of olfactory and gustatory function; subjective or mild cognitive impairment; sleep disturbances; and pain complaints (headache, chest pain or diffuse pain).

These persistent or recurrent symptoms after SARS-CoV-2 infection in patients who have no morphological lesions on conventional imaging (CT scan or MRI) could correspond to dysfunction of brain regions, as suggested by [^{18}F]fluorodeoxyglucose metabolic positron emission tomography (PET) imaging studies [2,3]. Recent work has especially shown metabolic impairment of the olfactory bulbs within the fronto-basal region and dysfunction of a network of connected cerebral regions including limbic/paralimbic regions (especially the amygdala and hippocampus), the brainstem (pons/medulla) and cerebellum [2]. Beyond olfaction, these hypometabolic brain regions are well known to be involved in memory, emotion, autonomous behaviours, motor skills and pain pathways. Among the 35 patients in this PET study (mean age 55 years) and after a mean delay of 3 months, 80% had dyspnoea, 66% had pain, 49% had memory/cognitive impairment, 46% had insomnia, 29% had hyposmia/anosmia and 26% had dysgeusia/ageusia [2].

Interestingly, the identified pathway seems to describe the limbic network of Proust's famous madeleine: the smell is quickly followed by the taste, recognition (and, more broadly, the memory)

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and associated emotions. This limbic system is known to be closely linked on brainstem nuclei to the autonomic nervous system, which is also involved during emotional memory processing and whose dysregulation can lead to cardiovascular, muscular, gastrointestinal and respiratory symptoms (e.g. diarrhoea, dizziness, hypertension, palpitations or tremor) [4]. Additional analysis of the 35 patients in the PET study has confirmed an association between olfactory loss and memory complaints in this group ($p = 0.027$, Fisher's exact test; memory complaints in 80% of patients with olfactory loss versus 36% of patients without olfactory loss) [2]. Olfactory function loss at the time of infection has also been reported to be among the main risk factors for subsequent memory impairment [5]. The fronto-basal cortex is involved in attention and short-term memory linked to the olfactory sense. After being processed and refined in the olfactory bulb and piriform cortex, the olfactory sensory input is processed in the amygdala and hippocampus (two key brain areas involved in emotion and memory), making olfaction a privileged sense for accessing memories. Perturbations of the olfactory circuit and functioning can therefore result in emotional and cognitive dysfunctions, as described in animal models such as olfactory bulbectomy, a relevant model of depression. Accordingly, loss of olfaction is associated with depressed mood and anxiety in long COVID more strongly than are life-threatening symptoms such as shortness of breath [6].

Impairments in both cognitive and olfactory functioning are prevalent in several brain disorders, for example in Parkinson's disease, Alzheimer's disease, mild cognitive impairment, and also in aging [7]. Along these lines, olfactory dysfunction negatively impacts the structural volumetry of the medial temporal lobe in early stages of Alzheimer's disease, and deafferentation of the hippocampus from olfactory inputs worsens memory decline [8]. As a consequence, strategies to enhance olfactory function have been suggested to improve cognitive decline [8], and alleviate anterograde and retrograde amnesia on recent and remote memories in these patients [9]. The olfactory system has also been proposed to be targeted as a therapeutic pathway through intranasal delivery of various drugs [7]. Interestingly, olfactory and memory impairments have been recently linked in Alzheimer's disease and COVID-19 through similar neurobiochemical features, especially involving angiotensin-converting enzyme 2 receptors and pro-inflammatory markers such as interleukin-1, interleukin-6, cytoskeleton-associated protein 4, galectin-9, and apolipoprotein E4 allele [10].

The areas of brain hypometabolism that have been found in long COVID are visually obvious on PET scans of many patients, and have been quantitatively identified at the group and individual levels [2]. Their severity is associated with the severity of symptoms [2]. The relationship of metabolism with clinical presentation is however complex because olfactory hypometabolism was also reported in patients without obvious loss of olfactory function. Nevertheless, absence of functional complaints does not exclude more subtle clinical alterations.

The profile of hypometabolism identified in patients with long COVID does not seem to correspond to those in patients with depression, post-traumatic stress disorder or even fibromyalgia. If limbic alterations have also been described in these conditions, the association with concomitant hypometabolism of the brainstem and cerebellum is more atypical [11].

The metabolic impairment of the olfactory bulbs is an important phenomenon to consider for further therapeutic interventions. COVID-19-related anosmia has been associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters [12]. The olfactory clefts could therefore constitute the gateway through which SARS-CoV-2 accesses the brain, reaching the olfactory bulb and other contiguous and deep brain regions through angiotensin-converting enzyme 2 receptors [2]. In the absence of known remote lesions, the impairment of the olfactory bulb could then represent the origin of the more posteriorly located effects on cerebral function of other limbic regions (including amygdala and hippocampus), and also the brainstem and cerebellum, through diaschisis (decreased functional activity of cerebral regions from connected brain-damaged areas) as a result of deafferentation (loss of input).

It is not known at this stage whether the infection or the inflammation could diffuse to more posterior regions in long COVID, from nose and olfactory bulbs to the deepest regions of the brain, causing irritation and dysregulation. Viral trans-synaptic progression has previously been demonstrated with other coronaviruses [13]. Both RNA and protein of the virus have been found in the neurons of patients who died from severe SARS-CoV-2 infection [14] and accompanied T-cell infiltration and microglial activation in euthanized macaques after apparent remission of COVID-19 [15]. Such neuroinflammation requires long-term follow up, considering the known relationships of neuroinflammation with the onset and progression of neurological and psychiatric diseases. These relationships are multifactorial, with several other determinants. They could nevertheless be found in a significant number of patients given the magnitude of the global pandemic.

We cannot exclude the possibility that hypometabolism in the fronto-basal cortex could be a sign of a premorbid neural phenotype associated with increased vulnerability to long COVID. Nevertheless, we believe that the functional aspect of this remote effect is important because most patients recover after a few months in the absence of obvious brain lesions on brain MRI. This functional recovery could be accelerated by different strategies of rehabilitation [7,9]. In patients with persistent olfactory dysfunction, olfactory rehabilitation may act on the whole network and possibly on other symptoms, in addition to other approaches such as respiratory and cognitive rehabilitation or adapted physical activity. In this line, olfactory training markedly improved post-infectious olfactory dysfunction compared with no training by inducing neuroplastic changes in regional functional connectivity beyond olfactory pathways [16].

In the future, the inflammatory and/or viral brain component of long COVID could be explored *in vivo* with more specific targets, for example, with PET imaging of neuroinflammation and microglial activation using translocator protein (TSPO) ligands. In the same way, follow-up metabolic PET studies are required to specify the correct relationship between the PET abnormalities and the temporal sequence of functional complaints, and especially earlier [^{18}F] fluorodeoxyglucose PET examinations to investigate the hypothesis of brain hypometabolic dysfunction secondary to earlier brain hypermetabolic inflammation. If the hypothesis is borne out, the development of new therapeutic strategies should target the olfactory clefts in the most severely impaired patients who will have little or no recovery after rehabilitation, for example, by using intranasally administered anti-inflammatory or antiviral drugs to act [7], beyond functional effects, on the pathological impairment of Proust's madeleine brain network.

Author contributions

EG wrote the first draft based on previous discussions with all co-authors. All co-authors contributed to improving the first draft until the validation of this final version.

Transparency declaration

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