Dopaminergic vulnerability in long COVID: striatal PET imaging at the brain-body interface

Eric Guedj[a,*] and Danielle Beckman[b]

[a]Aix Marseille University, APHM, CNRS, Centrale Marseille, Institut Fresnel, Timone Hospital, CERIMED, Nuclear Medicine Department, Marseille, France
[b]Institute for Intelligent Biotechnologies, Helmholtz Munich & Research Center for Environmental Health, Neuherberg, Germany

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What cannot be seen is too often considered uncertain. Long COVID illustrates this difficulty. Many patients report disabling fatigue, brain fog, cognitive inefficiency, apathy and psychomotor slowing; yet conventional investigations, including structural MRI, often fail to capture the biology underlying these symptoms. This invisibility matters clinically: when no structural lesion is seen, neuropsychiatric manifestations remain vulnerable to being interpreted as nonspecific, functional, or reactive.

Absence of a conventional MRI signature, however, does not imply absence of brain pathology. Parkinson's disease, for example, has no reliable individual diagnostic signature on routine MRI; yet is recognised as a neurochemical disorder in which molecular SPECT and PET imaging can reveal dopaminergic loss beyond what structural imaging can show. More broadly, psychiatric and neuropsychiatric symptoms arise from brain networks and neurochemical systems that may require molecular, metabolic, or connectivity-based tools to become visible.

In this issue of *eBioMedicine*, Liu and colleagues report a PET study that translates a clinically elusive neuropsychiatric phenotype of long COVID into a measurable dopaminergic signal. Using (+)[^{11}C]DTBZ, targeting vesicular monoamine transporter 2 (VMAT2), they report reduced striatal VMAT2 binding in adults with long COVID compared with healthy controls, involving the ventral striatum, dorsal putamen, and dorsal caudate. Lower regional VMAT2 binding was associated with greater apathy, slower motor performance, and, in exploratory analyses, worse memory performance.[1]

This work shifts the discussion from symptom description to mechanistic stratification. By linking neuropsychiatric symptoms to a presynaptic dopaminergic marker, it reframes part of the long COVID spectrum as a measurable brain-network phenotype, while acknowledging that subjective experience and psychiatric phenomenology can have measurable neurobiological correlates.

Interpretation nevertheless requires precision. Although VMAT2 PET is a robust marker of presynaptic monoaminergic, predominantly dopaminergic, terminal integrity in the striatum, reduced binding does not necessarily imply irreversible neuronal loss. It may reflect altered vesicular storage capacity, regulatory changes in transporter expression, or adaptive presynaptic changes. In long COVID, where the temporal evolution and potential reversibility of these abnormalities remain largely unresolved, longitudinal studies and appropriate disease-control groups will be needed to determine their specificity and clinical significance.

The findings should also be interpreted beyond a striatal signal. Apathy, psychomotor slowing and cognitive inefficiency involve distributed nigrostriatal, mesolimbic, and mesocortical circuits. Molecular connectivity approaches have shown that PET and SPECT can move beyond regional uptake measures to map neurotransmission-based networks, including dopaminergic pathways.[2] Future studies could determine whether reduced VMAT2 binding reflects an isolated striatal abnormality or a broader disruption of dopaminergic network organisation.

Moreover, this network-level interpretation intersects with neuroglial and neurometabolic hypotheses. [18F]FDG PET studies have reported cerebral hypometabolism in long COVID,[3] potentially reflecting astrocyte-mediated glutamatergic dysregulation and impaired metabolic support to neurons.[4,5] Reduced VMAT2 binding may therefore represent one downstream manifestation of broader neuroglial dysfunction. Consistent with this possibility, experimental studies suggest that SARS-CoV-2 can affect dopaminergic neurons and trigger inflammatory, stress-response, and senescence-like pathways.[6,7] Together, these findings provide a plausible biological framework linking viral exposure to persistent dopaminergic dysfunction.

This framework also places long COVID at the brain-body interface, within the broader context of post-infectious neurology and exposome-related brain vulnerability. Large-scale biobank analyses have associated several viral exposures with increased long-term risk of neurological diseases, reinforcing the need to consider infections as potential modifiers of long-term brain health.[8] Long COVID may represent a model in which systemic exposures converge on vulnerable dopaminergic circuits through immune, vascular,

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*Corresponding author. Laboratoire de Médecine Nucléaire, Hôpital de la Timone, 264 rue Saint Pierre, 13005, Marseille, France.
E-mail address: eric.guedj@univ-amu.fr (E. Guedj).

metabolic, and neuroglial pathways. Reduced VMAT2 binding then becomes more than a regional imaging abnormality: it is a molecular entry point into the brain-body biology of persistent neuropsychiatric symptoms.

Therapeutically, these findings are promising but hypothesis-generating. Dopaminergic interventions may ultimately prove beneficial in selected patients with objective evidence of dopaminergic dysfunction, while molecular imaging could help identify biologically coherent subgroups and monitor treatment responses.

More broadly, the study by Liu and colleagues illustrates the transition of long COVID research from symptom description to biological stratification.[9] The most important message is not that long COVID is a dopaminergic disease, but that a distinct neuropsychiatric endotype may become visible when examined with appropriate molecular tools. The dopaminergic striatum should now be viewed not as an isolated target, but as a window into the brain-body mechanisms through which infection can leave enduring neuropsychiatric consequences.

Contributors

EG and DB contributed to literature search, data collection, data interpretation, and writing—original draft. Both authors contributed to writing—review & editing. Both authors directly accessed and verified the underlying data reported in this manuscript. All authors had full access to the data and accept responsibility to submit the manuscript for publication.

Declaration of interests

The authors declare no conflict of interest.

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