

## Post-COVID-19 neuropsychiatric syndrome: Is maladaptive glial recovery to blame?

Prolonged recovery and delayed polysymptomatic complications distinguish the COVID-19, caused by SARS-COV-2 viral infection, from other flu-like illnesses.<sup>1</sup> A growing number of patients report symptoms, including early- and late-onset neurological and psychiatric signs and symptoms, persisting or emerging after initial recovery,<sup>2</sup> suggesting significant potential for retarded sequelae with poorly defined pathogenesis. Although distinct from usual flu-like illnesses, this feature of COVID-19 resembles neurological and mental disorders reported in acute or recovery phases in previous coronavirus (MERS and SARS) outbreaks.<sup>3</sup> We hypothesize that in the aftermath of COVID-19 reactive neuroglia, in a subset of patients, fail to return to the physiological state.

About 30% of patients hospitalized for severe COVID-19 have both acute and delayed neuropsychiatric manifestations<sup>4</sup>; furthermore, even patients with mild or asymptomatic disease presentation often exhibit mood disorders, associated with neurocognitive impairment, delirium, anxiety, traumatic memories, fatigue, and disruption of the sleep–wake rhythm. Post-COVID-19 psychiatric pathology frequently begins with an acute sense of fatigue, apathy, decreased desire for social interaction, impaired concentration, and sleep disturbances, the persistence of which leads towards an overt depression. Fatigue, sleep alterations, changes in eating behaviour, anhedonia, loss of interest in social relationships, are all observed either in overt clinical depression or in neuropsychiatric consequences of systemic infections, whereas hopelessness, pessimism and worthlessness represent aspects more characteristic of major depression.

COVID-19 associated depression appears in many aspects as atypical and distinct from classical manifestations of major depressive disorder. Characteristics of post-COVID-19 depression include a higher incidence of psychotic traits, marked motor agitation, clear neurocognitive deterioration, profound changes in sleep-wake rhythm and resistance to pharmacological treatments.<sup>4</sup> Psychotic abnormalities, manifested by delusions, hallucinations, disorganized thought, speech and behaviour, may initially be associated with delirium at the height of COVID-19 pathology; they however may persist as delirium subsides and the infection resolves. Sometimes psychiatric manifestations emerge

weeks or months after the recovery from the infection, unaccompanied by either delirium or confusion, thus making the differential diagnosis between a primary schizophrenic psychosis and a post-COVID-19 psychosis more difficult. Psychotic aftermath of COVID-19 calls for urgent critical evaluation of its pathobiology necessary for the development of an appropriate therapeutic strategy. Sleep disorders, frequently emerging as the COVID-19 neuropsychiatric sequelae, particularly present atypical characteristics such as difficulty falling asleep, and dissatisfaction with the quality of sleep. These frequently occur in the younger population experiencing asymptomatic COVID-19, without significant levels of anxiety about the outcome and consequences of the disease. Specifically, insomnia, frequently persistent after the disappearance of all other symptoms, and without any obvious anxiety, remains unexplained. The emergence of non-specific delayed neuropsychiatric symptomatology that cannot be attributed to any defined mental disorder, includes fatigue, headache, speech and swallowing dysfunction, concentration difficulties, muscle weakness, dizziness, apathy, generalized hyperalgesia, difficulty thinking/processing (brain fog and confusion), attention difficulties, anguish, and anxiety are frequently observed in COVID-19 convalescents. These clinical manifestations occur after the resolution of acute inflammation, they persevere for many months, and they are resistant to antidepressant or anxiolytic drugs. All these idiosyncrasies may indicate a specific neuropsychiatric entity, which we may define as the post-COVID-19 neuropsychiatric disease.

Evidence of a greater frequency of psychiatric manifestations with atypical characteristics in patients who recovered from COVID 19 infection posits a critical question, whether these disturbances are linked to stress accompanying every systemic infection, or if they are linked to specific neurobiological changes associated with COVID-19. The pathophysiology of COVID-19 is characterized by the combination of systemic inflammation, hypoxia resulting from respiratory failure, and neuroinflammation (either due to viral neurotropism or in response to cytokine storm), which all affect the brain and may trigger or exacerbate psychiatric and cognitive disorders.<sup>5,6</sup>

The defence of the CNS in response to systemic pathologies is mounted by neuroglia, which undergoes complex biochemical, morphological and functional remodelling aimed at strengthening brain-organism barriers, increasing homeostatic support of nervous tissue, removing pathogens, and mobilizing regenerative potential of the CNS. The defensive response of neuroglia is defined as gliosis, which includes reactive astrogliosis, microgliosis and mobilization of oligodendrocyte precursor cells.<sup>6,7</sup> Direct damage to the brain (eg trauma encephalitis or abscess) triggers a specific type of reactive response, which results in the formation of glial scar isolating the lesioned area and preventing communications with the surrounding healthy nervous tissue. In the absence of direct brain damage, resolution of systemic pathology results in restoration of physiological (often defined as homeostatic) status of neuroglial cells. The dynamics and completeness of this process in various diseases remain largely unknown.





Could neuroglia, in a subset of patients, fail to recover after COVID-19 infection? Perturbed glia homeostatic and defensive capabilities can indeed promote the onset and progression of COVID-19 neuropsychiatric disease. Growing evidence from post-mortem examinations of the brains of COVID-19 patients highlight alterations in both astrocytes and microglia, adding credibility to our hypothesis.<sup>8</sup>

Neuroglia contributes to neural plasticity through the regulation of neurogenesis, synaptogenesis, neurotransmitter homeostasis, and brain metabolism. Association between glial cells and psychiatric disorders such as schizophrenia or major depressive disorder are well documented and generally acknowledged. Numerous preclinical and clinical studies demonstrated a reduction in astrocytes densities and morphological and functional asthenia of astrocytes associated with chronic stress and major psychiatric diseases.<sup>9,10</sup> Astrocytic abnormalities include deficient glutamate uptake and K<sup>+</sup> clearance, impaired secretion of neurotrophic factors, reduced metabolic and regenerative support. Neuropsychiatric conditions are accompanied by profound changes in microglial morphology and function leading to secretion of proinflammatory factors, while aberrant phagocytosis affects neuronal circuitry. Conceptually, long-lasting impairment of neuroglia function ultimately impacts synaptic connectivity, excitation/inhibition balance, and information processing, contributing fundamentally to the pathogenesis of neuropsychiatric disorders.

In conclusion, COVID-19 triggers a massive reactive response of neuroglia, the latter acting as the main operator of the inflammatory, protective and regenerative events. However, profound reactive metamorphoses of glia in some patients preclude restoration of neuroglial physiological state, thus compromising glial function and ultimately resulting in homeostatic failure underlying a set of specific neuropsychiatric symptoms that define the post-COVID-19 neuropsychiatric disease.

## CONFLICT OF INTEREST

The authors declared no conflict of interest.

Luca Steardo Jr.<sup>1</sup>   
 Luca Steardo<sup>2,3</sup>   
 Alexei Verkhatsky<sup>4,5</sup>   
 Caterina Scuderi<sup>2</sup> 

<sup>1</sup>Psychiatric Unit, Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy

<sup>2</sup>Department of Physiology and Pharmacology "Vittorio Erspamer", SAPIENZA University of Rome, Rome, Italy

<sup>3</sup>Università Telematica Giustino Fortunato, Benevento, Italy

<sup>4</sup>Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK

<sup>5</sup>Achucarro Center for Neuroscience, IKERBASQUE, Bilbao, Spain

## Correspondence

Luca Steardo Jr., Psychiatric Unit, Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy.


Email: steardo@unicz.it

Caterina Scuderi, Department of Physiology and Pharmacology "Vittorio Erspamer", SAPIENZA University of Rome, Rome, Italy.

Email: caterina.scuderi@uniroma1.it

## ORCID

Luca Steardo Jr.  <https://orcid.org/0000-0002-7077-3506>

Luca Steardo  <https://orcid.org/0000-0003-3570-2195>

Alexei Verkhatsky  <https://orcid.org/0000-0003-2592-9898>

Caterina Scuderi  <https://orcid.org/0000-0002-7314-1539>

## REFERENCES

1. Cortinovis M, Perico N, Remuzzi G. Long-term follow-up of recovered patients with COVID-19. *Lancet*. 2021;397(10270):173-175.
2. Taquet M, Geddes JR, Masud H, Luciano S, Harrison JP. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021;8(5):416-427.
3. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry*. 2020;7(7):611-627.
4. Nalleballe K, Onteddu SR, Sharma R, et al. Spectrum of neuropsychiatric manifestations in COVID-19. *Brain Behav Immun*. 2020;88:71-74.

5. Steardo L, Steardo L Jr, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. *Acta Physiol.* 2020;229(3):e13473.
6. Tremblay ME, Madore C, Bordeleau M, Tian L, Verkhratsky A. Neuropathobiology of COVID-19: the role for glia. *Front Cell Neurosci.* 2020;11(14):592214.
7. Escartin C, Galea E, Lakatos A, et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nat Neurosci.* 2021;24(3):312-325.
8. Lee MH, Perl DP, Govind N, et al. Microvascular injury in the brains of patients with Covid-19. *N Engl J Med.* 2021;384(5):481-483.
9. Verkhratsky A, Rodriguez JJ, Steardo L. Astrogliopathology: a central element of neuropsychiatric diseases? *Neuroscientist.* 2014;20(6):576-588.
10. Dietz AG, Goldman SA, Nedergaard M. Glial cells in schizophrenia: a unified hypothesis. *Lancet Psychiatry.* 2020;7(3):272-281.