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Special Article

Neurocircuitry Hypothesis and Clinical Experience in Treating Neuropsychiatric Symptoms of Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2

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Persistent symptoms following COVID-19 infection have been termed postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection. Many of these symptoms are neuropsychiatric, such as inattention, impaired memory, and executive dysfunction; these are often colloquially termed "brain fog". These symptoms are common and often persist long after the acute phase. The pattern of these deficits combined with laboratory, neuroimaging, electroencephalographic, and neuropsychological data suggest that these symptoms may be driven by direct and indirect damage to the frontal-subcortical neural networks. Here, we review this evidence, share our clinical experience at an academic medical center, and discuss potential treatment implications. While the exact etiology remains unknown, a neurocircuit-informed understanding of postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection can help guide pharmacology, neuromodulation, and physical and psychological therapeutic approaches.

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Key words: neuropsychiatry, neurobiology, COVID-19, long-Covid, PASC, brain fog.

INTRODUCTION

It is well established that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have a broad range of neuropsychiatric symptoms. In the acute infectious period, these can include headaches, anosmia, dysgeusia, inattention, confusion, fatigue, mood disturbances, anxiety, and psychosis. Delirium (encephalopathy or acute brain dysfunction) is a common comorbidity in patients admitted to the hospital with COVID-19.[1] Neuropsychiatric symptoms may persist past the initial infection, exist beyond strict delayed recovery from delirium, and have significant functional implications. The chronic subjective neurocognitive complaints often include poor memory, impaired concentration, and mental fatigue. These are often colloquially referred to as "brain fog" and are common symptoms of postacute sequelae of SARS-CoV-2 infection (PASC), which typically refers to symptoms that occur 4 weeks or longer after the initial onset of illness. This was initially described in the press as "long Covid".

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PASC can include a multitude of symptoms including shortness of breath, decreased exercise tolerance, heart palpitations, and changes in bowel habits. It also frequently includes neuropsychiatric symptoms such as disrupted sleep, headaches, anxiety, depression, impaired attention, and memory. This can occur after severe or mild disease[2] at a frequency of 31%–69%.[3] Female sex, older age, pre-existing asthma, and severity of initial disease have been found to increase the risk of PASC.[4] Elevated levels of inflammatory markers, such as tumor necrosis factor-alpha, interferon-gamma-induced protein 10, and interleukin 6, during early recovery have been correlated with increased risk of PASC.[5] It is less clear what risk factors predispose individuals to neuropsychiatric symptoms of PASC; however, premorbid cognitive risk factors, such as hypertension, sleep apnea, depression, anxiety, and mild traumatic brain injury in addition to abnormal cerebrospinal fluid findings, have been correlated with cognitive symptoms of PASC.[6]

There are multiple hypotheses regarding the pathophysiology of these neuropsychiatric sequelae, many of which posit the indirect effects of SARS-CoV-2 on the frontal and adjacent neural networks. Neuroimaging and electroencephalogram (EEG) have shown structural and functional abnormalities, often in the frontal, temporal, and limbic regions. Neuropsychological testing indicates a frontal-subcortical pattern of cognitive deficits.

Here, we review the pathophysiologic evidence pertinent to PASC and discuss our clinical experience assessing and treating this syndrome.

NEUROPSYCHOLOGICAL TESTING

Neuropsychological testing frequently shows deficits in attention, processing speed, and executive function.[7,8] While a direct causal relationship has not been established, many studies addressing neuropsychological profiles of post-Covid infection had consistent results: significantly lower scores in cognition with the lowest subscores in attention, verbal fluency, and executive function followed by memory and language difficulties.[9,10] These findings can be seen upon measuring digit span, semantic fluency, complex figure drawing, and list memorization, to name a few examples of the battery of tests given during neuropsychological testing. Moreover, an extensive review by Efstathiou et al. found that long Covid is frequently associated with depression, anxiety, posttraumatic stress disorder, sleep disturbances, fatigue, and cognitive deficits specifically related to the frontal network domain.[11]

These findings are consistent with our retrospective cohort study that aimed to characterize the neuropsychiatric symptoms of PASC and their treatment. Briefly, in our cohort of 100 patients with persistent symptoms after a short inpatient stay or who had never been hospitalized, the most prevalent symptoms were fatigue, "brain fog," headache, anxiety, and sleep disturbances. Attention and executive function were also frequently impaired. The mean Montreal Cognitive Assessment score was 26. Many from this study were referred for full neuropsychological testing. While this project did not include a statistical review of these results, the majority were consistent with deficits listed above, often with an overlay of comorbid depression and anxiety symptoms.[10]

This pattern of symptoms is often seen associated with disruption of the frontal subcortical systems. Broadly, this network includes the frontal cortex, striatum, globus pallidus, and thalamus. The frontal subcortical systems not only encompass cognitive functions but also are relevant in mood, language, and motor functioning. These domains can be disrupted preferentially and lead to different clinical presentations. For example, damage to the dorsolateral system (involving the dorsolateral prefrontal cortex, dorsolateral caudate, globus pallidus, and thalamus) can lead to a dysexecutive syndrome with poor problem-solving, lack of motivation, and perseveration. Damage to the orbitofrontal system (involving the ventromedial caudate, globus pallidus, and thalamus) can lead to emotional lability, personality changes, disinhibition, and poor smell discrimination. Damage to the medial frontal system can lead to a syndrome of akinesia and apathy.[12,13] Many of those with PASC report a constellation of these symptoms.

NEUROANATOMICAL EVIDENCE AND HYPOTHESES

Direct invasion of SARS-COV-2 into the central nervous system has not been proven to be common[14]; however, neuroinflammation and break down of the blood-brain barrier have been demonstrated.[15] The

clinical neuropsychiatric syndrome that accompanies acute SARS-CoV-2 infection has suggested to some that direct and/or indirect effects of COVID-19 may reflect a predilection for the frontal lobes and its circuits as the primary target.[16] It is not currently known why certain structures or networks may be particularly susceptible to neuroinflammation in PASC, but a few good leads have emerged.

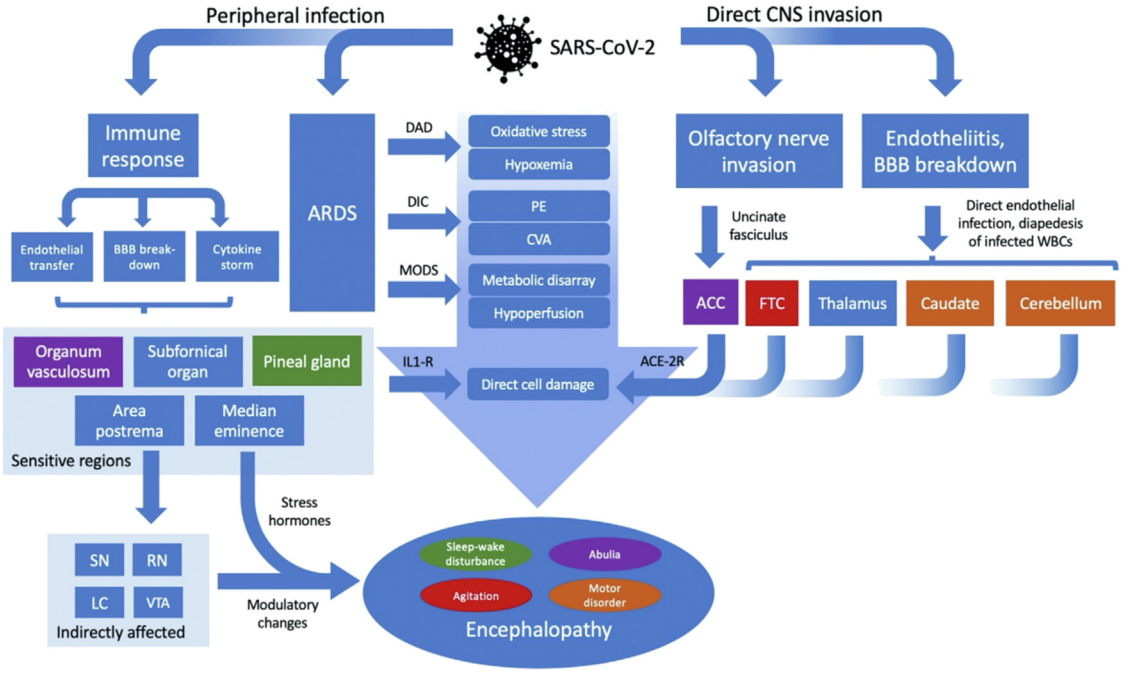
One line of inquiry implicating neuroinflammatory processes reveals why the frontal network may represent a selectively vulnerable area. There is evidence supporting an indirect central nervous system effect of COVID-19: studies reveal a high prevalence of autoantibodies in cerebrospinal fluid of SARS-CoV-2 patients.[17] Many autoantigens are currently unknown, but some have been identified. For instance, in severe COVID-19 patients, autoantibodies in the serum against type I interferons have been reported.[18] Interferons have been implicated in the pathogenesis of Alzheimer disease via neuroinflammation and synapse loss.[19]

Angiotensin-converting enzyme 2 (ACE2) has been established as the functional host receptor for SARS-CoV-2, and there is evidence of development of antibodies against ACE2.[20] Infection with COVID-19 is thought to affect organs and tissues that express ACE2 due to the presence of a spike protein on the viral surface that attaches to this particular receptor. Brain regions that express ACE2 have been studied in the mouse model and include areas involved in brainstem arousal and respiratory networks (ascending reticular activating system). These include the aminergic nuclei involved in brain reward and motor circuitries, such as the locus coeruleus, nucleus raphe, substantia nigra, and ventral tegmental area nuclei. These nuclei modulate the medial prefrontal cortex structures, especially the anterior cingulate cortex, which is relevant in motivation, behavioral activation, and executive function. These nuclei also support the diencephalic homeostatic networks, which include the lateral habenula (that modulates the ventral tegmental area), the mammillary bodies, the hypothalamic paraventricular nucleus, and the supraoptic and supramammillary nuclei. They also are relevant in memory networks with high expression in hippocampal astrocytes and CA1 and CA2 cell layers and in the olfactory bulb, which through the uncinate fasciculus will have modulatory effects on the medial prefrontal cortex, especially the anterior cingulate cortex and its emotion regulation roles.[21,22]

Arthur et al. studied the plasma or serum of 67 SARS-CoV-2 patients and of 13 patient subjects with no history of COVID-19; they reported that ACE2-specific antibodies were detected in 93% of the acutely ill inpatients with COVID-19 compared to none of those without COVID-19.[20] In a different cohort of 32 patients who had had a positive PCR test for SARS-CoV-2 and had been symptom-free for at least 2 weeks prior to donating convalescent plasma, 81% (26/32) had ACE2-specific antibodies. While the authors acknowledge that they do not have data concerning PASC in their study, they hypothesize that ACE2 antibodies that inhibit ACE2 activity, thus elevating angiotensin II levels, may contribute to chronic symptoms.[20] Major effects of elevated angiotensin II, which can be seen in COVID-19 infection, include vasoconstriction, renal sodium reabsorption and potassium excretion, aldosterone synthesis, blood pressure elevation, and induction of profibrotic and inflammatory pathways.[23] The presence of lingering ACE2 antibody titers could initiate a deleterious subchronic innate inflammatory process and result in PASC symptoms.

There are also blood-brain barrier pericytes and endothelial cells which express ACE2.[21] This may be pertinent to a selective vulnerability of the frontal network in PASC especially if one considers the fenestrated endothelial circumventricular regions bordering the medial prefrontal cortex and anterior cingulate cortex (organum vasculosum) and the aminergic nuclei that feed the mesocortical and mesolimbic systems (area postrema).[24] In addition, studies of single-nucleus transcriptomes of frontal cortex and the choroid plexus in 30 SARS-CoV-2 patients reveal cellular changes in COVID-19-associated microglia and astrocytes that share features with pathological cell states in neurodegenerative disorders, such as Alzheimer disease.[15] These include cellular perturbations in choroid plexus barrier cells. The key notion is that widened gap junctions in certain parts of blood-brain barrier and choroid plexus sense and relay peripheral inflammatory signals from macrophages and T cells into the brain in vulnerable areas such as the medial prefrontal cortex resulting in microglial and astrocytic activation and neuroinflammation. Similar pathophysiology has been proposed in schizophrenia, which has been associated with hypofrontality. The choroid plexus of patients with schizophrenia is thought to respond to signals from the periphery by upregulating inflammation-related glial genes to protect the brain and maintain homeostasis, but

FIGURE 1. **Hypotheses of encephalopathy pathogenesis in COVID-19. Note that the model depicted above is hypothetical in nature and is meant to demonstrate the myriad ways in which SARS-CoV-2 infection may induce encephalopathy. For example, while a hallmark of COVID-19 is ARDS and associated hypoxemia, the mechanism of immune dysfunction in COVID-19 and its role in encephalopathy are yet to be established[31] (image reproduced with primary author permission). ACC = anterior cingulate cortex; ARDS = acute respiratory distress syndrome; BBB = blood-brain barrier; CVA = cerebrovascular accident; DAD = diffuse alveolar damage; DIC = disseminated intravascular coagulation; FTC = frontotemporal circuits; IL1-R = interleukin-1 receptor; IRS = immune reconstitution syndrome; LC = locus coeruleus; MODS = multiorgan dysfunction syndrome (sepsis); PE = pulmonary embolism; RN = raphe nucleus; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SN = substantia nigra; VTA = ventral tegmental area.**



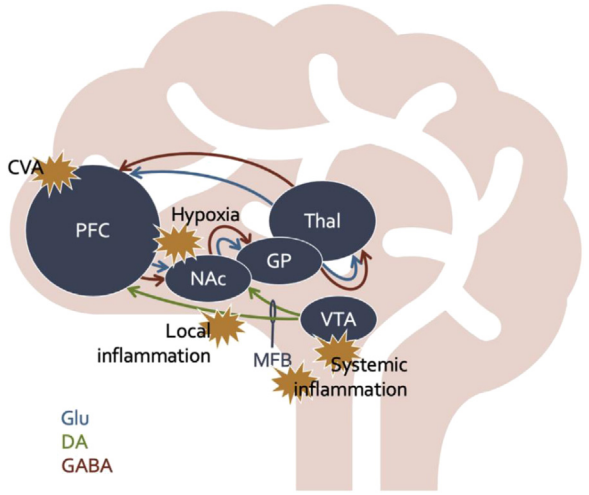
this process fails to prevent immunopathology in the brain.[25] Furthermore, in a case report of a COVID-19 patient with evidence of right orbitofrontal involvement on imaging, it was posited that COVID-19 may produce local inflammation in frontal-subcortical networks via its known invasion of the olfactory bulb.[26]

Proinflammatory cytokines, such as interleukin-1, interleukin-6, and interleukin-10 and tumor necrosis factor-alpha, are frequently elevated in COVID-19 infection cases. These inflammatory cytokines are able to cross the blood-brain barrier and activate microglia and astrocytes.[27,28] This leads to further release of inflammatory mediators in the central nervous system, notably quinolinic acid and glutamate. These can lead to excitotoxicity directly and also upregulate *N*-methyl-D-aspartate receptors, which can contribute to further injury.[27,29] It has been theorized that the cytokine-mediated hyperinflammatory process can lead to a frontal lobe presentation with akinetic mutism, frontal lobe slowing on EEG, and hypometabolism on fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomography.[30] See Figures 1 and 2 for graphical depictions.

NEUROIMAGING

Neuroimaging has demonstrated multiple findings; the most common structural abnormalities have been found within the olfactory network, which includes the limbic and prefrontal structures, and corpus callosum, followed by involvement of the insula, temporal lobe, basal ganglia, brainstem, and cerebellum.[33] More specifically, magnetic resonance imaging before and after SARS-CoV-2 infections has shown a greater reduction in grey matter thickness in the orbitofrontal cortex and parahippocampal gyrus in addition to greater reduction in brain size overall.[34] Studies involving functional

FIGURE 2. **The cortico-striato-thalamo-cortical (CSTC) loops are relevant to the reward and motivation-to-movement pathways. This image shows key sites along this pathway where COVID-19 may cause injury via inflammation and neurotransmitter disruption. DA = dopamine; GABA = gamma aminobutyric acid; GP = globus pallidus; Glu = glutamate; MFB = medial forebrain bundle; NAc = nucleus accumbens; PFC = prefrontal cortex; Thal = thalamus; VTA = ventral tegmental area[32] (image reproduced with primary author permission).**



imaging with FDG-PET have shown frontoparietal hypometabolism.[35]

Associated with PASC dysexecutive and encephalopathic behavioral symptoms, researchers have found frontotemporal hypoperfusion on functional magnetic resonance imaging, frontal EEG slowing, and frontal hypometabolism on 18F-FDG-PET neuroimaging, all of which suggest dysfunction in the frontal lobes or frontal network.[16] In this vein, recent studies may shed light on the etiopathogenesis of PASC. One FDG-PET study in patients suffering from long Covid demonstrated hypometabolism in the olfactory gyrus and associated limbic and paralimbic regions.[36] Another study examined 7 patients with variable clinical presentations of COVID-19-related encephalopathy and performed imaging at 3 longitudinal time points (acute phase, at 1 month, and at 6 months) with brain 18F-FDG-PET/computed tomography in order to study long-Covid impact on the brain metabolism.[37] PET images were analyzed with voxel-wise and regions-of-interest approaches in comparison with 32 healthy controls. All patients at 6 months showed a pattern of hypometabolism in a cerebral network that included prefrontal cortex, anterior cingulate, insula, and caudate nucleus. At 6 months after COVID-19, most patients showed neuropsychiatric improvement but attentional and executive function deficits, anxiety and depressive symptoms, and fatigue and apathy of varying severity persisted coinciding with lasting prefrontal cortex, anterior cingulate cortex, insular, and subcortical 18F-FDG-PET/computed tomography abnormalities.[37] Taken together, neuroimaging evidence indicates that both structural and functional abnormalities occur in patients with persistent neuropsychiatric symptoms of COVID-19, and these deficits primarily implicate the frontal-subcortical system.

ELECTROENCEPHALOGRAPHY

EEG studies have demonstrated a high rate (96%) of abnormal background activity among hospitalized COVID-19 patients,[38] which is consistent with the high incidence of encephalopathy.[39] The most common abnormalities have been identified as generalized slowing, burst attenuation, generalized periodic discharges, and generalized rhythmic delta activity.[40–42] In patients with severe disease, different subgroups have been identified based on EEG patterns. For example, low-amplitude EEG activity and delta range oscillations were associated with unfavorable outcomes (deceased or still in the intensive care unit) at day 14 of hospital admission.[43] These findings could be used as potential predictors of prognosis or to identify those in need of more intensive treatment earlier in their admission. Focal slowing was found predominantly in the frontal lobe,[44] which may underlie some of the persistent dysexecutive deficits in the postacute phase of the illness. More EEG studies investigating both background activity and evoked potentials during both the acute and postacute phase of the illness are needed to identify the neurophysiological biomarkers of these persistent PASC symptoms.

CLINICAL EXPERIENCE

As we have outlined above, pathophysiologic phenomena have been associated with clinical manifestations in some instances. The pathophysiologic-clinical correlation is far from complete however. Often, clinicians are confronted with patients who complain of "brain fog," a phrase which refers to a medley of

symptoms that are not universally defined. The differential diagnoses of this term include mood, anxiety, sleep, attention, and executive function disorders that may be primary in nature or secondary to causes such as vitamin deficiencies, hormonal disturbances, or other medical etiologies. To the extent possible, it is the clinician's role to delineate exactly which cognitive domains are referred to by each patient. Often this ends up being multifactorial. As an example of the difficulties this poses, a patient might use the term "brain fog" to describe difficulty with short-term memory, whereas with further history and upon bedside testing, the deficits actually fall in the realm of attention. Or a patient might use the term "brain fog" to describe an inability to make decisions that upon further questioning seems to stem from impaired sleep and heightened anxiety. Another example would be a patient with previously well-compensated attention deficit disorder, who now has exhausted the utility of previous coping strategies and subsequently struggles with tasks at work.

In our own clinical experience, that is reflected in the abovementioned cohort of 100 patients treated at a large multispecialty hospital, several patterns have begun to emerge.[10] The most common neuropsychiatric symptoms were fatigue, "brain fog," and headache, followed by anxiety, sleep, and depression. "Brain fog" significantly correlated with attention and memory impairment, depression with anxiety, and headache with sleep.[10] We have observed that patients fall broadly into several different "brain fog" subgroups. First, PASC with a predominant executive dysfunction (frontal-subcortical profile) present with attentional and naming difficulties, as well as more generalized confusion. Second, we have seen PASC presenting as an amnestic disorder, but upon examination, the memory issues are driven by encoding and retrieval impairments, related to frontal-subcortical circuitry, rather than hippocampal dysfunction. Some with PASC have exacerbation of existing neuropsychiatric syndromes, such as migraines, other headaches, depression, anxiety, and sleep disorders. Finally, it appears that PASC may also unmask previously unknown subclinical disorders or vulnerabilities, such as early-stage neurodegeneration.

POTENTIAL THERAPIES

Correlation of recently revealed pathophysiologic events with clinical manifestations is, as we have seen, in its very early stages. Development of specific therapies for "brain fog" is at an even more embryonic stage. While there are no Food and Drug Administration-approved treatments for PASC, we have found that taking a symptom-based approach using existing treatments can be useful. For example, if the primary symptoms are headache, other pain, and disrupted sleep, a tricyclic antidepressant could be an early choice. Our recommendation is to pick a tricyclic antidepressant with the least anticholinergic side effects as not to aggravate the cognitive impairment, such as desipramine or nortriptyline. If the primary symptoms are apathy, fatigue, and poor concentration, bupropion may be particularly useful, since it targets the mesocortical dopaminergic system.[45] If depression and anxiety are the most prominent, starting with a selective serotonin reuptake inhibitor may be appropriate. Melatonin or modafinil can be useful when targeting disrupted sleep and circadian rhythm. If attention deficits persist after sleep and mood symptoms are improved, stimulants can be considered. If adrenergic symptoms, such as palpitations, sweating, and anxiety are most prominent, propranolol or clonidine could be considered. Attention to cardiovascular side effects of psychotropic medication is important as COVID-19 has been shown to damage myocardium among other organ systems. While much of this is relatively basic medication management of mood and attention disorders, it can be helpful to use these symptom profiles in deciding upon treatment and in discussions with patients. While there is no "post-Covid pill," many symptoms can be alleviated over time.

Device neuromodulation therapies (particularly noninvasive techniques) may also be considered as an alternative treatment to mitigate neuropsychiatric symptoms in PASC, including dysexecutive deficits.[46,47] In particular, transcranial direct current stimulation, a noninvasive form of neuromodulation, has been shown to improve processing speed in inhibition tasks (e.g., Flanker task) in both healthy individuals and patients with attention deficit/hyperactivity disorder.[48,49] The stimulation also enhanced the amplitude of the EEG P300 component, which is thought to underlie sustained attention and inhibitory control. Moreover, techniques such as transcranial alternating current stimulation, another form of noninvasive electrical stimulation, have proven to improve working memory performance in older adults by synchronizing interregional theta band activity.[50] Clinical trials are needed to test the potential benefit of these paradigms in PASC populations and may provide important insight into the underlying

pathophysiology of cognitive deficits in PASC. Standardized scales to assess symptom burden in PASC, such as 1 recently published quality-of-life instrument, post-acute COVID-19 Quality of Life, will be useful not only in research but also in clinical practice as PASC treatment centers emerge.[51] Finally, a global initiative is underway to determine a consensus set of assessments of PASC symptoms with input from researchers, clinicians, and patients. This international study will help establish a standardized set of outcomes that can be used by all future research studies and clinical practice in individuals with PASC.[52]

Finally, nonsomatic or behavioral treatments, such as psychotherapy, physical therapy, occupational therapy, and cognitive rehabilitation, need to be considered and have shown to be quite useful as a holistic approach to patient care. Exercise has been shown to improve mental health and cognitive function directly as well as indirectly.[53] Prioritizing small physical goals with the long-term outcome of wellness can instill hope and help patients maintain motivation. While treatment development efforts continue, clarifying the clinical phenomenology, symptom targets, and pathophysiology of PASC will be critical to support the expansion of effective therapies. For now, we have seen clinical benefit in utilizing a neurocircuit-informed treatment approach to PASC.

CONCLUSION

The pathophysiology of the symptoms of "brain fog" in PASC, which typically consist of impairments in attention, executive function, and memory, is only beginning to be understood. Evidence suggesting that this syndrome reflects disturbance to the frontal-subcortical networks, which in turn may be due to neuroinflammatory susceptibility of these regions, is beginning to emerge. Our clinical experience is consistent with this theory. Thoughtful pharmacology, neuromodulation, and physical and psychological rehabilitation, in conjunction with time, do seem to benefit these PASC symptoms. As we all gain further understanding and experience, more effective treatments will likely emerge.

Conflicts of Interest: Joan A Camprodon, MD, MPH, PhD, serves on the scientific advisory board of Hyka Therapeutics and Feelmore Labs; he has also been a consultant for Neuronetics. Hamdi Eryilmaz, PhD, receives funding from MGH Mass General Neuroscience (Transformative Scholar Award). Michael D. Kritzer, MD, PhD, receives funding from MGH Training Grant Translational Neuroscience Training for Clinicians (T32 MH112485). Other authors have no potential conflicts of interest to disclose.

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