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Neurological Manifestations Associated with SARS-CoV-2 Invasion of the Autonomous Nervous System

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Abstract

Although pneumonia and acute respiratory failure are the most frequent and severe complications of patients with SARS-CoV-2 infection, many of them also develop neurological signs and symptoms. From sickness behavior to coma, neurological disorders are associated with impairment of consciousness and dysautonomia, resulting from brainstem dysfunction. We propose here that SARS-CoV-2 invasion via the olfactory and trigeminal nerves generates a local neuro-inflammatory process aggravated by systemic inflammatory responses and micro-circulatory ischemic process. In addition to its short and long-term neurological consequences, the COVID-19-related brainstem dysfunction compromises the adaptive response to stress and contributes to organ failure and death. The detection of brainstem dysfunction mainly relies on neurological examination and non-invasive methods, such as pupillometer and spectral analyses of heart rate and blood pressure. We review the existing evidence of brainstem involvement in the course of Covid-19, its main mechanisms, diagnostic strategies, and potential outcomes.

Keywords: Brainstem; Neurotropism; COVID-19; Nucleus Tractus Solitarius; Olfaction, Neuroinflammation

Abbreviations: ACE2: Angiotensin Converting Enzyme-2; ADEM: Acute Disseminated Encephalomyelitis; ANS: Autonomic Nervous System; ARAS: Activating Reticular Ascending System; ARDS: Acute Respiratory Distress Syndrome; BBB: Blood-Brain Barrier; BP: Blood Pressure; CNS: Central Nervous System; COVID-19: Coronavirus Disease 2019; CSF: Cerebrospinal Fluid; DWI: Diffusion-Weighted Imaging; ECG: Electrocardiogram; EGG: Encephalogram ; GBS: Guillain-Barré Syndrome; HF: High Frequency; HR: Heart Rhythm; ICU: Intensive Care Unit; LF: Low Frequency; MRI: Magnetic Resonance Imaging; MSSNA: Muscle Skin Sympathetic Nerve Activity; NTS: Nucleus Tractus Solitarius; OSNs: Olfactory Sensory Neurons; PD: Pupillary Diameter; PLR: Pupillary Light Reflex; QSTART: Quantitative Axonal Sweat Reflex Test; RR: Respiratory Rhythm; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; SSNA: Skin Sympathetic Nerve Activity; SSR: Sympathetic Skin Response; TMPRS2: Transmembrane Serine Protease 2

Background

COVID-19 patients can develop various central neurological disorders, including loss of smell and taste (anosmia and ageusia, respectively), ischemic injury (stroke), encephalopathy (delirium), and encephalitis [1,2], but also peripheral damages such as Guillain-Barré Syndrome (GBS) [3]. If the severity of respiratory failure remains the major determinant of the COVID-19 patient outcome, neurological disorders are also associated with increased mortality and morbidity [4]. In addition, to the role of COVID-19 severity markers, neurological disorders

are also determinants of the COVID-19 course, as they can compromise the adaptive response to the systemic inflammation and may account for long-term psychological and cognitive impairments in those who survive COVID infections (i.e., the Long-COVID). In this context, the brainstem is likely the most vulnerable structure from the circuits potentially involved with both short- and long-term consequences. The brainstem controls arousal via the activating reticular ascending system (ARAS) and vital functions and immune responses integrity via autonomic centers. COVID-19 has severely challenged health care systems worldwide, with the urgent need for medical countermeasures, including the development of efficacious therapeutics. Here, we present the clinical spectrum, the diagnostic methods, and the potential pathogenesis of the COVID-19 that result from brainstem dysfunctions.

Neurological Manifestations and ICU-related Complications

The neurological manifestations are considered relevant components of the clinical spectrum of the COVID-19. They can be classified from acute neurological manifestations as anosmia, ageusia or sickness behavior, to long-term consequences such as cognitive decline or mood disorders. In retrospective cohort studies, neurological symptoms were reported in one-third to half of the patients [5,6]. The incidence of neurological disorders increases with the severity of the COVID-19, from 45% in severe pneumonia to 85% in acute respiratory distress syndrome (ARDS) [6]. Moreover, the severity of COVID-19-related neurological disorders is associated with the presence of encephalopathy, encephalitis, stroke, or myopathy as reported in Intensive Care Unit (ICU) [4-6]. However, some of these dysfunctions can be complications of critical illness, rather than COVID-19 itself. Nevertheless, all these neurological disorders are associated with increased mortality and morbidity, notably by inducing long-term functional, psychological, and cognitive impairments.

Non-specific neurological symptoms include dizziness, headache, and malaise are reported especially at the onset of the infection [3]. Hypo/anosmia and hypo/dysgeusia have been rapidly identified as early specific neurological symptoms, which occur in 80% of the cases [7]. Importantly, these symptoms are considered as clinical evidence for a potential SARS-CoV-2 neurotropism [8].

Any infection can induce stereotyped behavioral changes, the so-called sickness behavior [9] that includes among others, loss of appetite, asthenia, lethargy, social withdrawal, apathy, and impaired attention and concentration. Sickness behavior has been shown to be associated with long-term psychological disorders, notably depression [9]. It is likely that many neurological and psychological symptoms that COVID-19 patients complain about belong to the sickness behavior syndrome (that can mimic hypoactive delirium). Conversely, encephalopathy is a pathophysiological condition that results from a global brain dysfunction. It is characterized by impairment of consciousness, ranging from delirium to coma, with electroencephalographic changes from slowness activity of electrical discharge to *status epilepticus*. It can be associated with seizure, extrapyramidal and pyramidal signs, but also neuropsychiatric manifestations including psychosis in 8% of the cases [10]. Brain imaging is usually normal. The rate of encephalopathy is higher with severity of COVID-19, as 13% to 38% of ICU COVID-19 patients will develop a disorder of consciousness [11]. Some risk factors include patient's age and pre-existing neurological disease [12]. One of the main specificities of COVID-19-related encephalopathy is the EEG pattern characterized by periodic discharges located in the frontal region (Table 1). MRI reveals hypersignals of white matter in T2/FLAIR sequence of cortical or subcortical localization [13,14]. Encephalopathy results also from critical illness and the adverse effects of ICU management, including hypoxemia, metabolic electrolyte disturbances, drug toxicity or withdrawal hemodynamic, and renal or liver failures. However, SARS-CoV-2-induced vasculopathy, endothelial dysfunction, hypercoagulability/antifibrinolysis, and systemic inflammation might contribute to the pathogenesis. Disorders of consciousness can be secondary to encephalitis reported in 10% to 30% of COVID-19 patients according to the study design, diagnosis methods, and severity of COVID-19 [11]. They can be revealed by impaired consciousness, seizure, or focal neurological signs. According to clinical and MRI findings, encephalitis is classified as acute disseminated encephalomyelitis (ADEM)-like or auto-immune like disorders [15-17] (Table 1).

Acute ischemic stroke, or transient ischemic attack, are diagnosed in 26% of non-ICU COVID-19 patients [11]. Severe COVID-19 patients are at high-risk of ischemic and hemorrhagic strokes, and the potential mechanisms includes hypercoagulabilty, antifibrinolysis and endothelial activation/dysfunction, potentially leading to vasculitis and thrombo-embolism. Among the peripheral nervous system disorders, so far, GBS has been the most reported one [3]. GBS must be differentiated from ICU-acquired paresis, which spare cranial nerves, and is related to a myopathy and/or axonal polyneuropathy [18].

Skeletal striated muscles are also a privileged target of SARS-CoV-2 which can be explained by the surface expression of the TMPRSS2 receptor [19] or by the consequences of the actors of systemic inflammation on the tissues (IFN-gamma, TNF-alpha, IL-1ß, IL-6, IL-17) inducing an increase in protein catabolism, a decrease

Table 1: Description of case reports of neurological syndromes in COVID-19 patients.

Main Clinical neurological syndromes	Neurological symptoms and manifestations	Finded biological data	Electroencephalogram	Neuroimaging (Brain MRI)	References
Encephalopathy	Fever, coma, myoclonus, impairment of brainstem reflexes, absent withdrawal to pain and diminished deep tendon reflexes.	Increased levels of IL-6, IL-8, IL-10, IP-10 and TNF-alpha in CSF. RT-PCR for viral analysis in CSF negative. Increased levels of plasma anti-S1 IgG Increased levels of anti-S1 and anti-E IgM in CSF.	Diffuse slowing.	Cerebral edema with hypoxic ischemic changes and abnormalities with restricted diffusion concerning right hemisphere, grey matter, deep grey nuclei, splenium and temporal lobe, carotid artery thrombus.	(Benameur et al., 2020)
Encephalitis/ Encephalomyelitis	Asthenia, disorientation with attention deficit, verbal and motor perseverations with grasping, myalgia, tonico-clonic seizure and psychotic symptoms, hemianopsia, hemineglect. Delirium and altered consciousness. Headache, fever, lethargy, stiff neck, photophobia and new onset seizure. Headache, generalized fatigue and fever, consciousness disturbances, neck stiffness and multiple generalized seizure.	Biochemical arguments for meningoencephalitis with lymphocytic pleiocytosis. Negative RT PCR SARS-CoV-2 in CSF. high CSF protein levels without pleocytosis and PCR negative for viruses. Elevated albumin quotient without oligoclonal bands. CSF with lymphocytic pleiocytosis, proteinase. RT PCR for SARS-CoV-2 in CSF non available. CSF cell count was 12/ mL–10 mononuclear and 2 polymorphonuclear cells without red blood cells. Positive RT PCR SARS-CoV-2 in CSF.	non-convulsive, focal status epilepticus (abundant bursts of anterior low- to medium- voltage irregular spike and waves super-imposed on an irregularly slowed theta background) then moderate theta background slowing without epileptiform features. Non available. Generalized slowing with no epileptic discharges. Epileptic discharges.	Normal Cortical or white matter hyperintensities, contrast enhancement, and sulcal he- morrhagic features. Normal Hyperintensity along the wall of inferior horn of right lateral ventricle in DWI. FLAIR hyperintense signals changes in the right mesial temporal lobe and hippocampus with slight hippocampal atrophy. Right lateral ventriculitis and encephalitis.	(Bernard-Valnet et al., 2020) (Dogan et al., 2020) (Duong et al., 2020) (Moriguchi et al., 2020)

Sickness Behavior	Sadness, fatigue, depression with passive suicidal statements, fever, sleep disturbances, poor appetite, anxiety and panic attacks.	Elevated IL-6 levels (> 25 pg/ml)	Seizure like activity with brain dysfunction on EEG consistent with metabolic encephalopathy.	Only head CT performed (negative).		(Alpert et al., 2020)
Acute Ischemic stroke	Dysarthria, left hemiplegia, and alteration of consciousness Nonfluent aphasia. Word-finding difficulties, bilateral incoordination, homonymous hemianopia, confusion and altered consciousness, incoordination. Dysarthria or aphasia and facial droop and weakness.	Non available. Elevated D-dimer levels (> 7000 µg/L) with positive lupus anticoagulant.	Non available. Non available.	Hyperintensive lesions of bilateral cerebellar hemispheres, right occipital cortex, bilateral centrum semiovale and bilateral parietal cortex in DWI with hyperintensities in FLAIR. Multiple small ischemic infarctions with hyperintensive lesions (arrows) in bilateral cerebellar hemispheres. Vertebral artery thrombus and acute cerebellar artery territory infarction with petechial haemorrhagic transformation. acute infarction in the right corpus striatum and an established infarct in the same region with moderate background cerebral small vessel disease acute infarction in the right thalamus, left pons, right occipital lobe and right cerebellar hemisphere with thrombotic material in the basilar artery and bilateral mild-to-moderate P2 segment stenosis.	(Zayet et al., 2020) (Beyrouti et al., 2020)

				Bilateral subcortical and deep nuclei lesions	
ADEM	Dysarthria, Dysphagia (bulbar impairment), expressive aphasia, headache and myalgia. Coma, impaired oculocephalic response and left hemiparesis, reflex impairment. Fever and altered mental status.	CSF analysis with normal cell counts, protein and glucose RT-PCR for SARS-CoV-2 in CSF non available. RT PCR SARS-CoV-2 in CSF non available.	No electrical arguments for seizure. Non available.	Multifocal patchy areas of abnormal signs, diffusion weighted lesions and ADC changes in bilateral frontoparietal, anterior temporal lobes, ganglia, external capsules and thalami. Hyperintense lesions on T2 FLAIR sequence in deep hemispheric and juxtacortical white matter Signs of Acute Necrotizing encephalopathy i.e hemorrhagic rim-enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions.	(Zhang et al., 2020) (Poyiadji et al., 2020)

in synthesis capacities and inhibiting repair mechanisms (decrease in differentiation and pro- fibrosing and atrophying) on a clinical and experimental point of view [20,21]. The prevalence of myalgia, if it does not appear to be constantly associated with severe clinical pictures, nevertheless represents up to 50% of cases and is predictive of a pejorative evolution [22,23]. Muscle involvement may either be related to direct muscle injury, characterized by an increase in creatine kinase proportional to severity with arrays of rhabdomyolysis [24], or to motor neuron involvement [21]. This muscle dysfunction can persist 3 to 6 months after hospital discharge representing up to 63% of cases, manifested by reduced muscle strength of the distal muscles, adaptation to effort, and functional capacity [25].

A brainstem dysfunction can be a component of this COVID-19 neurological spectrum and may negatively impact the COVID-19 course. Together, these clinical observations strongly support the neurotropism of SARS-CoV-2 and, in particular, the brainstem hypothesis that we now describe in more detail.

Can the Brain be a Key Target of SARS-CoV2?

The viral brain invasion

Because COVID-19 is not a restricted respiratory infection but rather a multisystem disease resulting from a complex interplay of viral, immunological, inflammatory and coagulative cascades, a variety of potential biomarkers have been identified (reviewed in [26]). These biological markers are manifold, including biochemical (e.g., albumin, LDH), immunological (e.g., CD4+ cells, CD8+ cells, B cells and natural killers (NK) cells), inflammatory (e.g., CRP, cytokines), coagulation or hematological (e.g., ferritin/transferrin ratio, Procalcitonin).

Regarding brain dysfunctions, increased concentration of Neurofilament light chain protein (NfL) and glial fibrillary acidic protein (GFAp) in COVID-19 patients on admission correlates with increased mortality risk [27]. A study on 47 mild, moderate and severe COVID-19 revealed that patients with severe COVID-19 exhibited higher plasma concentrations of GFAp and NfL than controls, while GFAp was also increased in patients with moderate disease [28]. In patients with severe disease, an early peak in plasma GFAp decreased on follow-up, while NfL showed a sustained increase from first to last follow-up [28]. Thus monitoring blood biomarkers for nervous system injury is useful in early suspicion, diagnosis, monitoring, and recognition of complications, management and disposition of COVID-19 patients with CNS injury. During the former SARS epidemic outburst, studies have reported the presence of SARS-CoV particles in brain samples from infected individuals [29-31]. Yet, the mechanism by which neuroinvasion occurs remains unclear, even if the neurotropism of SARS-CoV-2 is not surprising, bearing in mind its structural homology with SARS-CoV. The humoral and the neuronal retrograde routes have been proposed for respiratory viruses to reach the CNS [32,33]. Once in the brain, SARS-CoV-2 might reach the brainstem and compromise autonomous functions (Figure 1).

Is the Olfactory Route a Potential Path for SARS-CoV-2?

Previous studies have reported smell and taste disturbances in the course of SARS-CoV-2 infection [5, 34]. Anosmia and dysgeusia were more frequent in less severe cases, and dysautonomia had been noticed in 3% of patients [34]. Though less frequent, it has been reported some cases of oculomotricity anomalies [35] and trigeminal nerve damage [36]. The peripheral nervous system may thus constitute one of the entries for SARS-CoV-2 to infect the CNS.

A meta-analysis from case series, cohort studies and case control studies, reports that predominant involvement of the olfactory system with disruptions across olfactory structures, including the olfactory bulb/tract and the primary olfactory cortex [37]. Interestingly, these abnormalities also extended to the corpus callosum, cingulate cortex, and insula, jointly enabling propagation of SARS-CoV-2 toward secondary olfactory areas. In particular, some related cytotoxic lesions of the corpus callosum have been reported from presumed COVID-19 [38].

SARS-CoV-2 is detected in the brain of 53% of COVID-19 patients, with SARS-CoV-2 viral proteins found in cranial nerves originating from the lower brainstem and in isolated cells of the brainstem [39]. The nerves V, VII, and IX, which ultimately lead to the nucleus tractus solitarius (NTS) are prime suspects since gustatory dysfunction have been reported from COVID-19 patients [34]. The virus may also use the olfactory nerve as an alternative retrograde route to access the brain [40]. The olfactory sensory neurons (OSNs) of the olfactory epithelium, including immature neurons, project to the olfactory bulb [41]. From there, the virus can broadly spread within different brain areas as the primary projections of the olfactory bulb are the olfactory nucleus, olfactory tubercle, piriform cortex, the anterior part of the parahippocampal gyrus (entorhinal cortex) and the peri-amygdaloid cortex of the amygdala [42]. Human brain tissues express SARS-CoV-2 cell receptor ACE2 (angiotensin converting enzyme-2) [43], including the ventricles or the substantia nigra, but also brain areas directly or indirectly associated

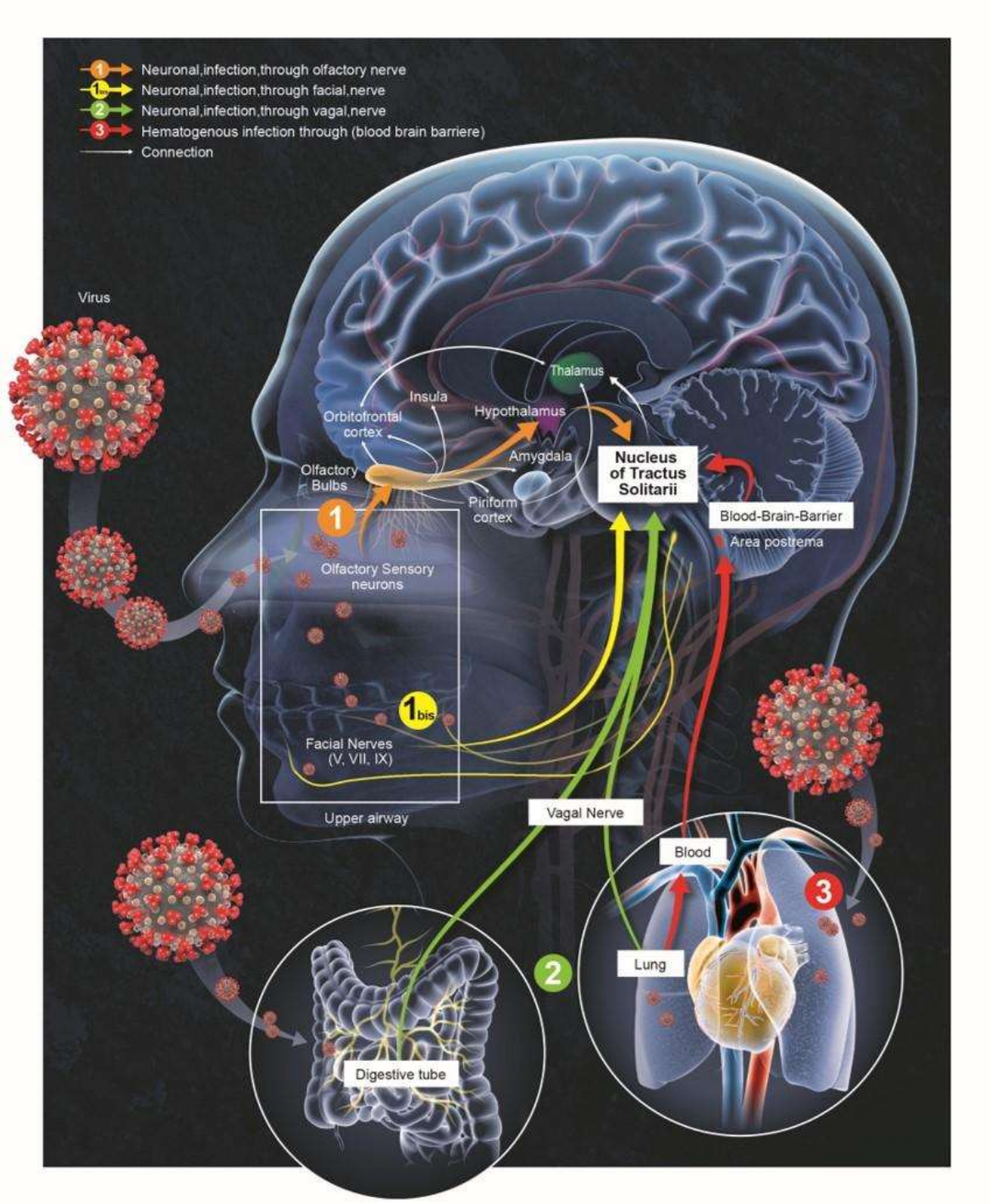

Figure 1: Is NTS a target of SARS-CoV-2? The *Nucleus* of *Trachus Solitarii* (NTS) is a key structure of the autonomous nervous system that receives information from both the central and peripheral systems to regulate vital body functions. There is three different, but non-exclusive, pathways for the SARS-CoV-2 to reach the NTS: Through retrograde neuronal infection of: **1)** the olfactory nerve to the olfactory bulb and then down the olfactory cortex to the NTS, or/and **1 Bis)** the fifth, seventh and ninth cranial nerves (V, VII, IX). Alternatively, **2)** the vagal nerve (X) may also transport to the NTS the virus or inflammatory mediators. This hypothesis could explain the digestive and respiratory symptoms reported by patients with Covid-19. Finally, **3)** The hematogenous route may also transport the SARS-Cov-2 or inflammatory proteins to the NTS through the Area Postrema.

with the olfactory pathway, including the amygdala, the hippocampus, hypothalamic nuclei and the frontal cortex [44]. Furthermore, it is likely that ACE2 is not the sole host factor associated with neuroinvasion of SARS-CoV-2 and Neuropilin-1 represents a strong alternative candidate [45].

The hypothesis of a viral invasion through the olfactory route is supported by RNA-seq analyses reporting expression of ACE2 and TMPRSS2 (Transmembrane Serine Protease-2) [46] in the olfactory sustentacular cells, microvillar cells, Bowman's glands, and horizontal basal cells [47,48], and at lower level in the OSNs [49]. Also, SARS-CoV-2 has been shown to invade olfactory nerves in hamsters [50,51] and brains of COVID-19 patients [52,53]. SARS-CoV-2-induced acute anosmia and ageusia in golden Syrian hamsters, are notably reported to last as long as the virus remained in the olfactory epithelium and the olfactory bulb [54]. Moreover, olfactory mucosa sampling from patients showing long-term persistence of COVID-19-associated anosmia 196 day after infection still revealed the presence of virus transcripts and of SARS-CoV-2-infected cells, together with protracted inflammation [54]. SARS-CoV-2 persistence and associated inflammation in the olfactory neuroepithelium may account for prolonged or relapsing symptoms of COVID-19 such as loss of smell. The way OSNs are infected by SARS-CoV-2 remains still unknown, but as horizontal basal cells are progenitors that continually divide to replace OSNs [55], it is possible that infected horizontal basal cells could produce newly formed OSNs infected by SARS-CoV-2, and by axonal transportation allow the virus to migrate from the sensory epithelium to the olfactory bulb [41], and from there spreads into further central targets [40] (Figure 1).

The vagus nerve: a genuine pathway for neuroinvasion or an effector of brainstem dysfunction?

One important common point between the pulmonary and digestive systems concerns their innervation by the vagus nerve (Figure 1). It has bidirectional connections to both the neuroepithelial and smooth muscle cells of both respiratory and gastrointestinal tracts [56,57], and exhibits motor, sensory, and immuno-modulating functions [58,59]. To exert such pleiotropic effects, the vagus nerve exhibits both afferences and efferences with actions mediated by neurotransmitters on several subtypes of tissue immune cells [60,61]. As such, a stimulation of the vagus nerve can reduce the neuroinflammation both experimentally by the lipopolysaccharide as well as in more naturalistic conditions [59,62]. The vagus nerve is also involved in the reflex mechanisms regulating physiological respiratory adaptation to stress, heart rate, and the digestion processes. Most of the afferents from the vagus nerve project onto the NTS in the medulla of the brainstem. The vagus nerve appears therefore as a gateway from the respiratory or digestive systems to the CNS. In turn, it could be a target on its own leading to deleterious consequences, particularly respiratory, when the NTS is damaged (Figure 2). A possible alternative option embraced by our 'vagal hypothesis would be that the vagus nerve constitutes the way by which the brainstem dysfunction can be transmitted to organs innervated by this nerve (lungs, heart, etc.). Along these lines, it should be mentioned that the vagus nerve indeed exerts an important function in regulating inflammation by controlling innate immune responses during pathogen invasion or tissue injury. The nature of the efferent vagus nerve-mediated immunoregulatory output is cholinergic. Via the so-called inflammatory reflex, the vagus nerve controls immune activation and suppresses proinflammatory cytokine release. Further preclinical or clinical investigations should clarify whether the vagus nerve allows the viral neuroinvasion or rather it constitutes an effector of brainstem dysfunction responsible for inflammatory dysregulation in COVID-19 patients.

The hematogenous route

The virus might also enter the brainstem via the humoral route, through endotheliitis [63]. Indeed, SARS-CoV-2 could gain access to the CNS by infecting endothelial cells of the blood–brain barrier (BBB), epithelial cells of the blood-cerebrospinal fluid barrier in the choroid plexus, or from a "Trojan Horse" strategy by hacking inflammatory cells [64]. A special entrance in the humoral route is embodied by features of the area postrema: *i.e.*, a highly vascular paired structure in the medulla oblongata of the brainstem. While the detection of the virus in the cerebrospinal fluid (CSF) is still controversial [1,17,65], antibodies against SARS-CoV-2 were however detected in the CSF of COVID-19 patient [66]. Similarly, a transmission electron microscopy study has evidenced the presence of viral-like proteins inside brain microvascular endothelial cells in the frontal lobe of a COVID-19 patient and confirmed the presence of SARS-CoV-2 within the tissue using RT-PCR assays [67]. This observation provided the evidence that SARS-CoV-2 can infect the brain microvascular endothelial cells of the BBB. Nonetheless, whether the infection originated from the brain, blood, or CSF remains still unclear. As CSF communicates with nasal lymph through the cribriform plate [68,69], inoculation of the CSF through this channel seems pertinent with the olfactory impairments reported in COVID-19 patients.

Biomarkers and Dysregulated Inflammatory Response in COVID-19

A neuro-inflammation is mainly the consequence of BBB impairment and endothelial activation induced by

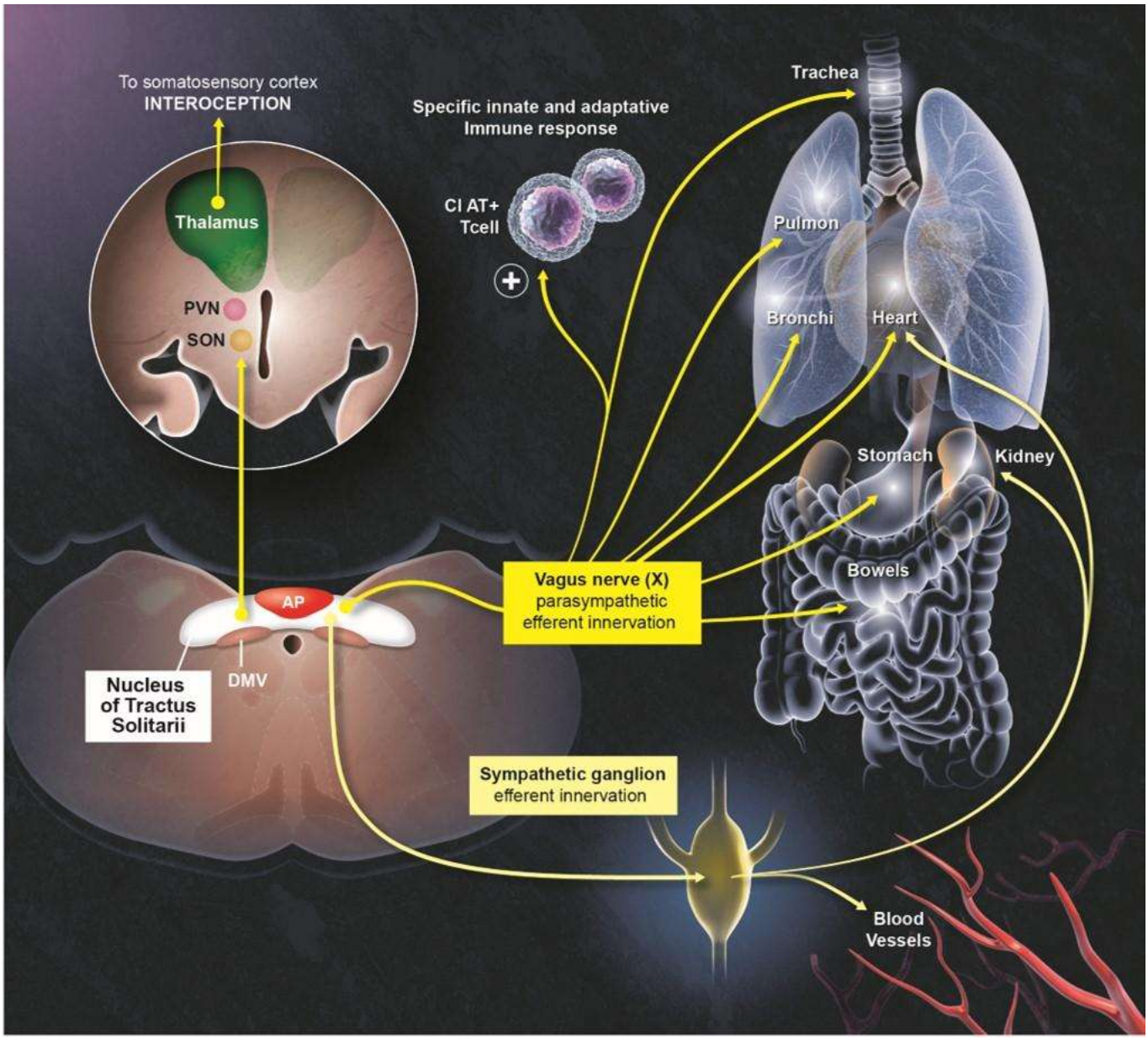

Figure 2: NTS efferences to the peripheral system and dysautonomia. Dysautonomia could be defined as a failure, or an overactivity, of sympathetic and/or parasympathetic components of the autonomous nervous system. Patients with COVID-19 show very broad symptoms, including body temperature and heart rate impairment, digestive disorder and breathlessness. The impairment of the sympathetic system, in particular the NTS by SARS-CoV-2, could explain these symptoms and contribute to the "inflammation storm" observed in patients. *ChAT+ Tcell: Choline Acetyltransferase expressing T-Cell.*

circulating pro-inflammatory cytokines and chemokines, whose levels correlate with severity of COVID-19 [70]. It is characterized mostly by an activation of microglial cells or the presence of T-lymphocytes that acquire a neurotoxic immune profile. The neuro-inflammatory process is common in various infectious conditions, such as sepsis, however the overproduction of IL-17 by T-helper 17 (Th17) cells would be particularly involved in coronavirus infections [71]. This up-regulation is also responsible for chemokines induction of expression, such as CCL2 (MCP-1) and CXCL1, by the cerebral vascular endothelium with increase in the migration of activated Th17 cells within the brain parenchyma [72]. The presence of IL-17 in abundance in the brain is responsible for triggering numerous pro-inflammatory cytokines, chemokines, and protein mediators (*e.g.*, COX-2, PGE-2) pathways [73]. The activation of these various inflammatory pathways during SARS-CoV-2 infection leads to higher production of cytotoxic T-lymphocytes and activation of the NFκB pathway with consequences for neuronal toxicity [74,75].

A recent review established and classified an up-to date list of biomarkers in COVID-19 according to organ/system involved, their temporal trends, and their association with clinical phenotype and therapeutic responses [26]. Abers et al. analyzed levels of 66 soluble biomarkers in 175 Italian patients with COVID-19 ranging from mild/moderate to critical severity and assessed type I IFN–, type II IFN–, and NF-κB–dependent whole-blood transcriptional signatures [76]. They identified 14 biomarkers (CCL2, IL-15, soluble ST2 [sST2], NGAL, sTNFRSF1A, ferritin, IL-6, S100A9, MMP-9, IL-2, sVEGFR1, IL-10, lactoferrin, CXCL9) that when increased were independently associated with mortality, while IL-1α was associated with mortality when decreased. Among these, sST2, sTNFRSF1A, IL-10, and IL-15 were consistently higher throughout the hospitalization in patients who died versus those who recovered, suggesting that these biomarkers may provide an early warning of eventual disease outcome [76].

By investigating the brain tissue of patients who died from COVID-19, Matschke et al. detected SARS-CoV-2 in the brains of 21 (53%) out of 40 examined patients [39], with SARS-CoV-2 viral proteins found in cranial nerves originating from the lower brainstem and in isolated cells of the brainstem. Neuroimmune activation was observed in all examined brains, with prominent involvement of the brainstem and neuroimmune reaction, in line with our 'brainstem hypothesis'. The presence of SARS-CoV-2 did not seem to be associated with the severity of neuroimmune activation. Remarkably, diffuse activation of microglia, with occasional microglial nodules, and presence of cytotoxic T lymphocytes were pronounced in the brainstem.

The Brainstem Hypothesis

Previous coronaviruses have been proven to invade the brainstem in humans [77,78]. As discussed above, SARS-CoV-2 could propagate within infected patients through the humoral route or might spread by the mean of trans-synaptic and exo-synaptic propagation [79-81], along the vagus nerve or the olfactory system, eventually reaching respiratory centers in the brainstem, adding a neurogenic component to the respiratory failure [81,82]. Indeed, the SARS-CoV-2 neurotropism and expression of ACE2 receptors (or Neuropilin-1) in the brainstem make this structure a well-qualified target for SARS-CoV-2 [80,83,84]. By connecting the diencephalon to the spinal cord and the cerebellum, the brainstem is located at the interface between the limbic system, and the efferent signaling pathways to peripheral organs [85,86]. It controls oculomotricity, facial sensory and motor functions, hearing, balance, and oropharyngeal function via cranial nerves. The brainstem regulates the sleep/wake cycles via the ARAS, thereby it is involved in alertness and awareness [87]. It plays a major role in hemostasis via the autonomic nervous system (ANS) [88,89]. Schematically, the ANS controls the pupillary size and light reflex, heart rate (HR), blood pressure, the tidal volume and respiratory rate (RR), gastrointestinal motility, and bladder tone as well as the immune response [90]. The brainstem autonomic centers integrate bottom-up body signals and efferent top-down signals from the cortex (Figure 3).

Located at the level of the dorso-medial medulla, the NTS is a key center in the autonomic control as it processes: 1) taste information from the facial, glossopharyngeals, and vagal nerves (the latter is the main nerve of the parasympathetic division of the autonomic nervous system); 2) mechano- and chemo-receptors inputs from the carotid, aorta, and sinoatrial node, and also from the respiratory tract and lungs, via the glossopharyngeal and vagal nerves; 3) gastrointestinal and liver inputs via the vagal nerve. Through its direct projection to the vagal efferent neurons in the dorsal motor nucleus of the vagus nerve, the NTS mediates several reflexes including the gag reflex, the carotid sinus reflex, the aortic reflex, the cough reflex, the baroreceptor and chemoreceptor reflexes, several respiratory reflexes, and reflexes within the gastrointestinal system regulating motility and secretion. The rostral (rNTS) and caudal (cNTS) parts participate in cough reflex mechanisms, modulation of inspiratory frequency and amplitude, and heart rate and blood pressure [91]. The NTS also innervates the sympathetic neurons of the ventrolateral region of medulla oblongata, a major site controlling sympathetic preganglionic neurons and involved in the control of cardiovascular functions [92,93].

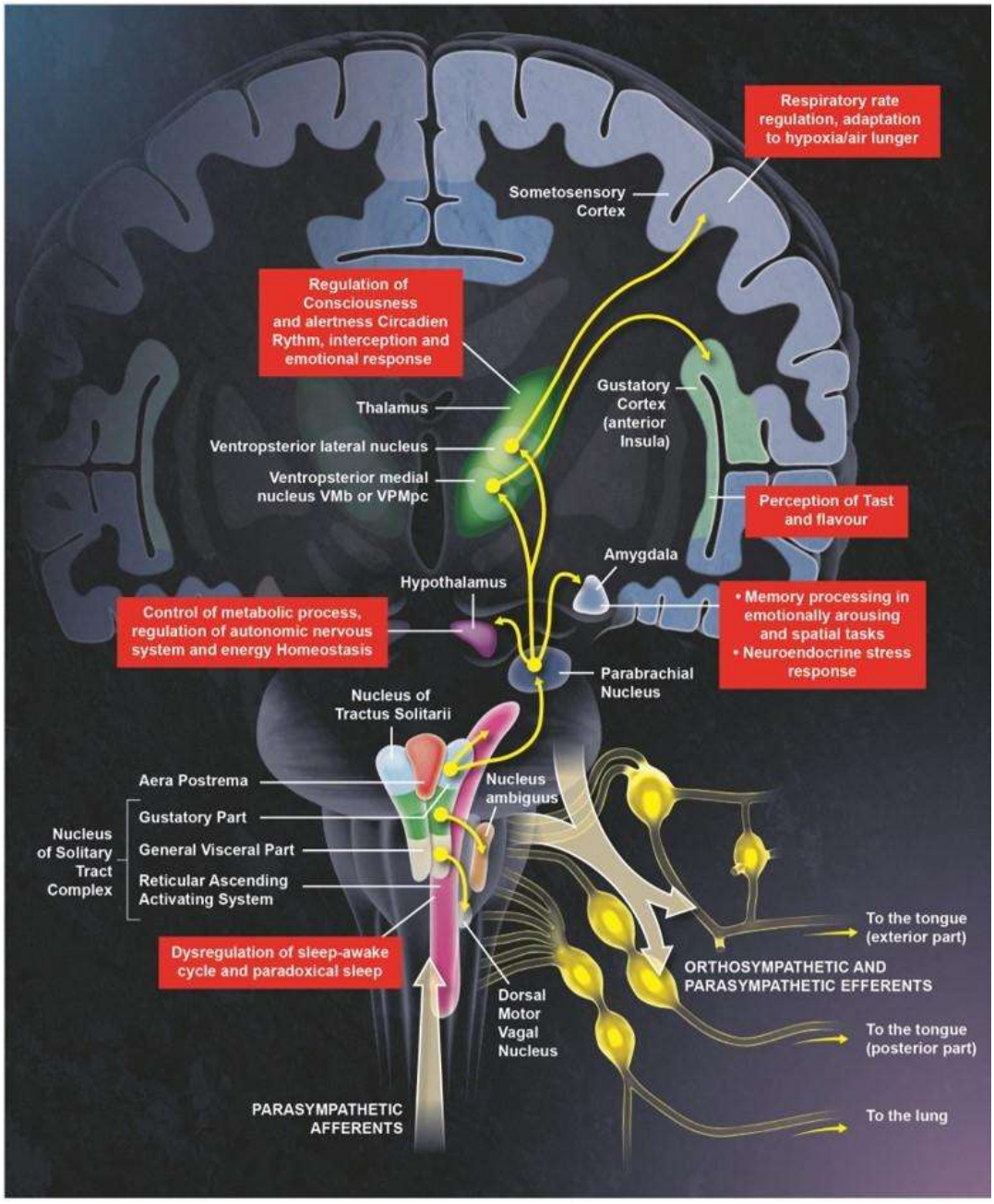

Figure 3: Interactions between NTS, brain efferences, cortical structures and brainstem nuclei. The *Nucleus of Tractus Solitarii* (NTS) is located at the interface between afferents from the peripheral ANS and the efferent pathways to the basal ganglia including the thalamus and nuclei located in the brainstem (BS). NTS shares many neuronal connections with these structures, involved in the control of the homeostatic, somatosensory, emotional and stress adaptation, memory, interoceptive functions and related to the state of consciousness. An affection of the NTS by direct SARS-CoV-2 invasion, or in connection with the infection-induced inflammation transmitted to the brainstem via the Area Postrema, could lead to a dysfunction of these different systems. The disruption of these pathways could explain the various neurological clinical manifestations observed during SARS-CoV-2 infection, especially in the most severe cases, but also the persistence of long-term complications in patients with Covid-19.

Because of its connections to various brain regions, the NTS is a hub connecting reciprocal signaling between visceral organs and the neuroendocrine and limbic centers [94,95]. Its caudo-medial part (cmNTS) receives signals from the vagus nerve and regulates food intake by negative feedback [96]. It also integrates hormonal and non-hormonal signals (circulating nutrients) related to the energy status of the organism [97,98] (Figure 3). The NTS plays an indirect yet essential role in the individual's ability to adapt to emotionally stressful situations and set-up avoidance behaviors when facing a danger [99,100]. Due to its connections with the amygdala's central and baso-lateral nuclei [101,102], the NTS contributes to behavioral responses to stress. The NTS can influence vasopressin release and activate the hypothalamic-pituitary-adrenal axis by its direct connections with the hypothalamus's paraventricular nucleus. The NTS is a central relay of the interoceptive network that allows the perception and integration of signals originating from the inner body and it is essential to trigger responses to stress, emotional behavior, attention, alertness, and self-consciousness.

Dysautonomia could be defined as a failure or, in some cases, an overactivity of the sympathetic and/or parasympathetic nervous systems [90,103]. Dysautonomia has been described in various central and peripheral neurological diseases, either acute or chronic. NTS dysfunction can lead to major dysfunction of the cardiorespiratory centers and the metabolic homeostasis [104]. NTS dysfunction can be a cause of neurogenic hypertension, obstructive sleep apnea, and metabolic disorders [105,106]. Experimental studies have shown that it induces severe disturbances of eating behavior and energy balance (Figure 3). NTS dysfunction impairs the interoceptive-dependent functions, such as the perception of danger, emotional behavior, attention, and self-consciousness.

Numerous clinical manifestations result from brainstem dysfunction in COVID-19 patients. First, anosmia and dysgeusia can be related to NTS dysfunction. From a direct viral invasion to the olfactory bulb or by inflammation at the lamina propria, an NTS dysfunction might interrupt the link between the insular and temporal taste and the afferent pathways conveying signals from specialized chemoreceptors [107] via facial (cranial nerve (CN) VII), glossopharyngeal (CN IX) and vagus (CN X) nerves (Figure 3). Second, impairment of consciousness, ranging from delirium to coma, could result from the brainstem dysfunction at the ARAS or NTS level, which controls the sleep-wake cycle and contributes to interoceptive-dependent attention and self-consciousness. Thus, brainstem dysfunction could contribute to the COVID-19-associated encephalopathy and sleep disturbances, which are reported in up to 15% of hospitalized COVID-19 patients [6], and up to 40% in recovered COVID-19 patients [108]. Impairment of interoception is illustrated by the low level, or even the absence, of anxiety and fear responses often observed in COVID-19 patients who will shortly require mechanical ventilation [109]. This phenomenon is called "happy hypoxia" since very low blood oxygenation does not trigger dyspnea [110]. In a retrospective cohort of COVID-19 patients in Wuhan, only 20% complained of shortness of breath. Moreover, 62% of patients with severe COVID-19 and 46% of those who required intubation did not complain of any dyspnea [111].

The NTS sends efferences with synapses of the noradrenergic type to the amygdala's central and basolateral nuclei [101,102]. Adrenergic stimulation of NTS contributes to increasing the retention of spatial or emotional memories [112]. Beyond the phenomenon described in COVID-19 patients as a dysregulated response to hypoxia, a lesion of the NTS could play a role in modulating this stress response. In addition, it seems that certain efferences from the tonsils are, in turn, involved in reaction mechanisms to hypoxia and acute exacerbation of respiratory diseases such as asthma involves the paraventricular nucleus [113]. The abnormal response of COVID-19 patients to hypoxia supports our brainstem hypothesis since this region plays a vital role in respiratory regulation.

Frequent clinical manifestations present in COVID-19 patients, as cardiac arrhythmias, maladaptive response to hypoxia, digestive disorders, or, more generally, lability in blood pressure, could also be linked with brainstem autonomic dysfunctions [81]. Finally, the brainstem dysfunctions can be associated with a pre-existing neurological disease, such as neurodegeneration in elderly patients and critical illness by itself [87]. A brainstem autonomic dysfunction can contribute to COVID-19 related mortality and morbidity by compromising the perception and integration of homeostatic disturbances, impairing the adaptive neuroendocrine, autonomic and behavioral response to stress, thus jeopardizing immune responses. More importantly, brainstem dysfunction in critically ill patients infected with SARS-CoV-2 could contribute to symptoms associated with long-term psycho-cognitive disorders [114, 115].

The nervous system regulates immune responses and inflammation through sensory neurons capable of detecting pathogen fragments, cytokines, and other immune signals. This detection generates immunoregulatory responses through efferent autonomic neuron signaling in a manner of reflex regulation that involves the vagus nerve, among others [116]. Along this line, the brain can integrate neuro-immune communication, and its functions could be altered by peripheral immune dysregulation and inflammation in the context of COVID-19, as described during other infectious diseases [89].

It is noteworthy that the NTS is a potential target of SARS-CoV-2, because it is connected to the olfactory tract, the trigeminal nerve, and the vagus nerve, thereby facilitating axonal propagation of the virus [117,118]. The NTS is also located at the vicinity of the area postrema, thus favoring the inflammatory response through the humoral pathway [87,119]. Figure 2 illustrates the brainstem's potential role in the pathophysiology of SARS-CoV-2 infection, which is also suggested during other viral infections, notably by retrovirus (HIV and human T-lymphotropic virus), herpes viruses, flavivirus, enterovirus 71 and lyssavirus [87].

Assessing Brainstem and Autonomic Nervous System Dysfunctions in Critically Ill patients

As we previously described [87], assessment of brainstem dysfunctions relies essentially on non-invasive neurophysiological tests, including evoked potentials, blink-reflex and EEG. enables to assess brainstem conduction time, of which increase can result from structural or functional impairment, the somatosensory and brainstem auditory evoked potentials (i.e., SSEP and BAEP) could be recorded [120, 121]. Interestingly, it has been shown that SSEP P14-N20 inter-latency and BAEP III-Waves inter-latency are associated respectively with increased mortality and post-sedation delayed awakening or delirium in deeply sedated critically ill patients [122]. The electrophysiological testing of the blink reflex explores the trigeminal facial loop but its prognosis value in comatose patients needs to be confirmed. Interestingly, it has been recently shown that the response R2 of the blink reflex is impaired in mechanically ventilated COVID-19 patients [123], suggesting a dysfunction at the level of the ponto-medullary circuitry involving the reticular formation. The EEG reactivity to auditory, visual or nociceptive stimuli involves also, but not exclusively, the ascending reticular activating system [124]. Its absence is associated with adverse outcomes, in various causes of coma, including deeply sedated critically ill patients [125].

The diagnosis of brainstem autonomic dysfunction relies on various methods, more or less invasive and feasible at bedside in ICU patients [33,126]. These methods and their application in COVID-19 patients have been recently addressed by the American Autonomic Society [127]. The pupillary diameter (PD) and pupillary light reflex (PLR) are regulated by both sympathetic and parasympathetic synergistic control in response to light intensity. The measurement of PD and dynamic changes of the PLR (latency and velocity of the response) with pupillometry enables to non-invasively assess the sympatho-vagal balance [128]. The analysis of the respiratory rate (RR), the tidal-volume variability, the diaphragm functions and patient-ventilator asynchronies [129,130] are useful for detecting impaired central control of the respiratory system.

Regarding the cardiovascular system, the assessments of the hemodynamic changes during a Valsalva test [131], a deep inspiration [132], anisometric grip, a cold test [133] or during orthostatism [134,135] are not easily performable in critically ill patients. Conversely, the measurement of heart rate variability (HRV) enables to non-invasively and at bedside assess the autonomic control of the cardiovascular system. This method is based on the analysis of the fluctuations of the RR intervals in the different frequency domains of ECG using, for instance, a Fast Fourier Transform. Each frequency domain is finely regulated and influenced by physiological functions such as respiratory rate, circadian rate, blood pressure or neuroendocrine system [136]. The HRV analysis is usually performed in the time or frequency domains, most often over a period of 24 hours or sometimes over a shorter period of 5 minutes to assess the influence of various external factors. For instance, the analysis in the frequency domains allows to identify the low frequencies (LF: 0.04-0.15 Hz) that depends on the activity of baroreceptors and high frequencies (HF: 0.15-0.4 Hz) that depends on the variations of breathing and blood pressure. The LF/HF ratio is therefore a marker of the sympathetic and parasympathetic activity balance [137,138].

Thermoregulatory activity can also be assessed by measuring sweating and sudomotor function, mediated by cholinergic postganglionic fibers of the sympathetic system. Several evaluation methods are available, including the sweating test that evaluates the change in color of powders (most often quinizarin) during sweating [139], the quantitative axonal sweat reflex test (QSART) [133], the sympathetic skin response (SSR) and the Sudoscan, the latter being the least invasive method based on measuring the cutaneous conductance [140]. Sudoscan is a recently developed technique using an applied electric current that induces a shift of chloride ions from the sweat glands to the skin surface. The conductance measured between the anode and a reference electrode is proportional to the chloride concentration, itself a reflection of the sweat capacity [141].

The co-monitoring of EEG characteristics in sleep or awake states and HR variability represents the "heart-brain coupling" which is controlled by the ANS afferences and efferences [142]. There are other methods for assessing the ANS, but they are more difficult to perform, to interpret, or they are more invasive. Thus, the measurement of circulating catecholamines [143] is feasible but their physiological significance questionable. Their measurement with radionucleotides like 123-meta-iodobenzyl-guanidine [139] is more accurate but not feasible in routine. Microneurography is a quantitative

method of the sympathetic activity of the post-ganglionic innervation of the muscle or skin vessels (*i.e.*, MSSNA and SSNA for Muscle Skin Sympathetic Nerve Activity and Skin Sympathetic Nerve Activity, respectively), with the help of two electrodes inserted into the muscles or the skin fascia. The MSSNA reflects the vasoconstrictor signal that depends on baroreflex activity and arterial pressure level, while SSNA depends on skin vasomotor activity.

Conclusions and Perspectives

An increasing number of observations related to neurological manifestations bring compelling evidence about SARS-CoV-2 neurotropism. It is clear that not only SARS-CoV-2 has developed several strategies for neural system invasion, but also that certain key structures of the CNS, particularly the brainstem, are related to the onset, and maintenance, of some of the COVID-19 symptoms. Beyond the clinical consequences related to the CNS disorders, the capacity of SARS-CoV-2 (and its new variants) to affect brainstem might be a cornerstone to decipher their pathogenicity. The brainstem dysfunctions might result from a direct viral invasion and/or non-viral neuro-inflammatory or ischemic processes. Therefore, clinical examination and non-invasive methods such as pupillometer and spectral analyses of cardiovascular signals should be used more routinely at bedside in COVID-19 ICU patients. Speculatively, antiviral and immunomodulatory therapeutics could be proposed for targeting the underlying mechanisms of brain dysfunction. Plasma exchanges and high-doses of steroids should be proposed in COVID-19 patients in a similar way they are frequently used during auto-immune-like encephalitis. If for obvious reasons, pulmonary and vascular manifestations had received a lot of attention at onset of the outbreak, neurological-associated symptoms of the COVID-19, especially those concerning the structural and functional integrity of the autonomous nervous system, should receive further attention because of their direct or indirect impacts on the maintenance of homeostasis of many systems.

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Competing Interest

The authors declare having no competing interests.

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