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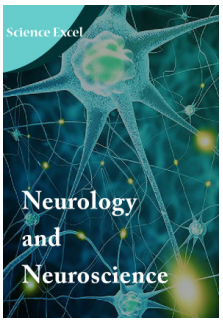
Review Article



EEG -guided Characterization, Monitoring, and Therapy for Neurological and Neurocognitive Sequelae of COVID-19 and Long COVID

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Abstract

The long-term effect of the newly emerged COVID-19 (SARS-CoV-2) virus has not been fully understood. It has been reported that several patients experienced neurological and neurocognitive problems after getting infected by the COVID-19 virus. This paper will review how the COVID-19 virus has impacted the brain, will aim to detect the location of COVID-19 in the brain, and will determine if the neurological complications are a result of "direct" or "indirect" effects of the virus on brain cells. Additionally, we will focus on the neurocognitive impact of COVID-19 and the potential of digital electroencephalography (EEG), quantitative EEG (QEEG) and standardized low resolution brain electromagnetic tomography (sLORETA) to be able to capture, assess, monitor, characterize and facilitate the treatment of both neurological and neurocognitive sequelae seen in COVID-19 and long COVID.

Introduction

The COVID-19 outbreak was caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). As of June 25th, 2021, COVID-19 resulted in 179,686,071 confirmed cases and 3,899,172 deaths [1-3] worldwide. The clinical presentation of COVID-19 ranges from asymptomatic to mild with non-specific symptoms (fever, fatigue, dry cough, headache, malaise, myalgia, dizziness, diarrhea, vomiting, to loss of taste and smell) [4,5]. Approximately 20% require hospitalization, with approximately 25% of those hospitalized (approximately 5%) becoming "critically ill" and progressing to severe pneumonia/acute respiratory distress syndrome (ARDS), strokes, seizures and or multiple organ dysfunction syndrome (MODS) [4-11]. Figure 1 presents a brief snapshot of the symptoms recorded at initial presentation, the spectrum of severity of COVID-19, recovery rates, case fatality rates, risk factors for severe illness and the multi organs damage it affects [12-62]. Studies on risk factors for severe COVID-19 and poor outcomes include high viral load, long virus-shedding period and clinical determinants [12-14,35,63,64]. A meta-analysis (41 studies and 21060 COVID-19 patients) of clinical determinants of COVID-19 severity deduced that older patients (Odds Ratio (OR)=1.73), males (OR=1.51), obese (OR=1.89), smokers (OR=1.40), and those with co-morbidities/complications like; hypertension (OR=2.42), diabetes (OR= 2.40), coronary heart disease (CHD) (OR: 2.87), chronic kidney disease (CKD) (OR=2.97), cerebro-vascular disease (CVD) (OR=2.47), chronic obstructive pulmonary disease (COPD) (OR=2.88), malignancy (OR=2.60), and chronic liver disease (OR=1.51) were more likely to develop severe COVID-19 symptoms [14]. Factors strongly influencing likelihood of recovery included ARDS (OR=39.59), shock (OR=21.50) and acute kidney injury (AKI) (OR=8.84) [14]. If MODS due to COVID-19 is not timely monitored and treated, with multi-target therapeutic approaches keeping in mind the pathogenesis of COVID-19 and its clinical repercussions on the lung, heart, kidney, bowel, liver, and brain; it could be fatal [4,5,15-21,65-69].

Initially, COVID-19 was primarily considered a respiratory infection. Recent evidence has shown that COVID-19 has a major impact on the nervous system either para- or post-infection especially in "long/persistent COVID-19". A retrospective study revealed that 36.4% of 214 COVID-19 patients complained of neurological symptoms like; dizziness (16.8%), headache (13.1%), impaired consciousness (7.5%), dysgeusia (5.6%), and anosmia (5.1%) [62]. Another study reported that 80% of hospitalized COVID-19 positive patients presented with multiple non-specific neurological symptoms ranging from headache, dizziness, fatigue, to myalgia [3,70].

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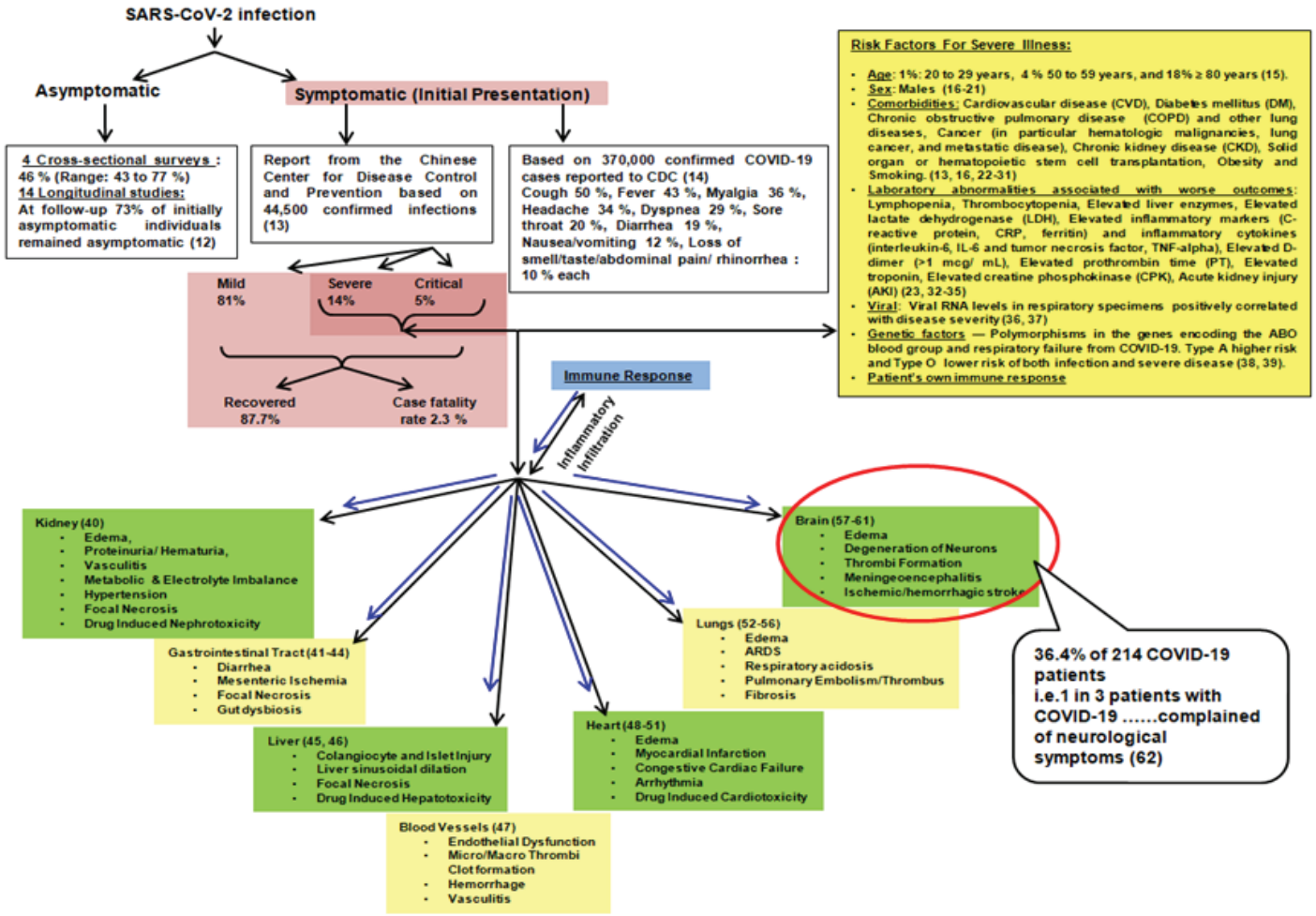

Figure-1. *COVID-19 at a Glance*

Hypogeusia, hyposmia, Guillain–Barré syndrome (GBS), and skeletal muscle injury serve to illustrate COVID-19's impact on the peripheral nervous system (PNS) [5,71]. Mortality and brain damage among individuals that were "critical" was found to correlate with the severity of neurological diseases be it acute necrotizing encephalopathy, encephalitis, epilepsy/seizures, stroke, or ataxia [4,72].

Due to the growing awareness on the neurological involvement and impact of COVID-19 in the para- or post-stages of a COVID infection, it has led to an urgent need to find how COVID-19 impacts the brain. It is not clear whether the neurological changes observed from COVID-19 are the result of "direct" infection and the neurotrophic nature of SARS-CoV-2 or "indirect" due to MODS, cytokine storm due to immune dysregulation and hyperinflammation, the hypercoagulative state, and hyperthrombosis mediating neurological features. Additionally, it is also not well understood how COVID-19 reaches the brain and results in neuropathogenesis. The cross-sectional para-COVID-19 and longitudinal post-COVID-19 studies using electroencephalography (EEG) machines, such as BrainView by Medeia, is another aspect that has also grown in importance to evaluate the neurological and neurocognitive impact of COVID-19. In this paper, we will present an overview of the neurological and neurocognitive impact of COVID-19 and the long-term effects of COVID-19. Here we will focus on the potential of digital EEG, quantitative EEG (QEEG) and standardized low resolution brain electromagnetic tomography (sLORETA) to aid in characterization, monitoring, and guiding therapy. We will first address a) the "Big" questions on the neuropathogenesis of COVID-19, b) Long COVID-19 and c) the evolution of the EEG as an essential tool to guide treatment in certain neurological and neurocognitive issues para- and post-COVID-19 and in long COVID-19.

Methodology

We searched PubMed till June 25th, 2021, for SARS-CoV-2 and Covid-19. Keywords used included: "SARS-CoV-2", "Covid-19", "Long COVID", AND "Neuro", "Brain", "Extra-Pulmonary Infections", "Neurological disorders", "Neurological Complications", "Neuropathogenesis", "Neurological Symptoms", "EEG", "Seizures", "Encephalopathy", "Cognitive Impairments", "Brain FOG", "Executive dysfunction", Language and Speech Impairments, "Processing speed", Parkinson's disease, Alzheimer's disease, Articles written in English were included. Titles and abstracts served as the initial screening checkpoint with the inclusion criteria being studies on humans and adults that evaluated neurological and neurocognitive complications due to Covid-19 and Long-COVID-19. The full text of titles and abstracts that met the inclusion criteria were obtained and included in the study.

Results

The "Big" questions on the neuropathogenesis of COVID-19

a) Does COVID-19 impact/cause changes in the brain?

Several studies reported that many patients were presenting with neurological symptoms. These patients also tested positive for COVID-19/SARS-CoV-2 following the reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays for SARS-CoV-2 using nasopharyngeal/ cerebrospinal fluid (CSF) samples. The consensus early on during the pandemic was that when patients presented with neurological or neurocognitive symptoms and had not yet been tested for COVID-19, COVID-19 testing should be carried out to prevent diagnostic delay or misdiagnosis. Presented below are a few selected studies that illustrate COVID-19's impact on the brain. A retrospective study carried out in Wuhan, China on 214 consecutive hospitalized patients revealed that 78 patients (36.4%) had neurologic manifestations either involving the central nervous system (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure) or PNS (taste impairment, smell impairment, vision impairment, and nerve pain), or skeletal muscular injury manifestations [62]. According to Figure 2, Further individuals with severe COVID-19 versus those with less severe infection also had severe neurological disorders like; acute cerebrovascular diseases (5 [5.7%] versus (vs) 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]) [62,73,74].

Another study conducted in France reported that 58 out of 64 (85%) consecutive patients with COVID-19, admitted to hospital due to ARDS, had neurological symptoms [75]. Neurological features included corticospinal tract dysfunction, encephalopathy, delirium, and agitation 40 patients i.e., 69% when neuromuscular blockade was discontinued). Diffuse corticospinal tract signs (enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes) were present in 39 patients (67%). 15 of 45 (33%) at discharge had dysexecutive syndrome (inattention, disorientation, or poorly organized movements in response to command). Magnetic resonance imaging (MRI) of the brain (n=13) showed enhancement in leptomeningeal spaces (n=8) and bilateral frontotemporal hypo-perfusion (n=11), acute ischemic stroke (n=2) and sub-acute ischemic stroke (n=1). EEG (n=8) results showed nonspecific changes, while a single case of diffuse bifrontal slowing consistent with encephalopathy was observed [75].

In COVID-19 patients, GBS, an autoimmune disorder of the nerves, was observed in a study carried out in three hospitals in Italy. Out of a little over 1000 patients, 5 had GBS 5 to 10 days following the onset of COVID-19 symptoms. GBS manifestations included lower-limb weakness and paresthesia (n=4) and facial diplegia followed by ataxia and paresthesia (n=1) [59,76]. Another study, a case report on a 65-year-old male positive for COVID-19 with acute progressive symmetric ascending quadriparesis and bilateral facial paresis at presentation, was diagnosed as having an acute motor and sensory axonal neuropathy (AMSAN) variant of GBS [77]. It was speculated that molecular mimicry due to COVID-19 played a role in GBS [77]. Another study that stands out is a study on a 24-year-old male from Japan who had never travelled abroad [78]. Fatigue and fever caused him to see a doctor twice, he was found unconsciousness and lying on the floor in his vomit on day 5, and manifested generalized minute long seizures during transport via ambulance. The unique feature of this case is that it was the first case of meningitis due to SARS-CoV-2 and more importantly SARS-CoV-2 RNA was detected in the CSF but not in a nasopharyngeal swab [78].

In two other retrospective studies in Wuhan, 5% of a total of 221 patients developed acute ischemic stroke and 20% of the 113 COVID-19 patients were diagnosed with hypoxic encephalopathy [19,62]. The first nationwide, cross-specialty surveillance study on acute neurological and psychiatric complications in COVID-19 has been conducted in the UK with 125 COVID-19 patients (median age 71 years) with complete clinical datasets [79]. In a cross-specialty surveillance study (n=125) on acute neurological and psychiatric complications in COVID-19 in the UK, 62% were diagnosed with cerebrovascular events (74% ischemic stroke, 23% unspecified encephalopathy, and 1% had CNS Vasculitis), 31% had an altered mental status, comprising (18% encephalitis and 12% intracerebral hemorrhage), 59% exhibited psychiatric disorders (43% new-onset psychosis, 26% neurocognitive syndrome, and 17% affective disorder) [79]. In a study on 184 ICU patients 31% had thrombotic complications and 23 died [80]. Other neurological disorders observed at presentation in COVID-19 positive individuals include acute myelitis, hemorrhagic necrotizing encephalopathy, frequent convulsive seizures [81-83].

b) What is the evidence of SARS-CoV-2's" location in" and" infection of" the brain?

- SARS-CoV-2 in CSF: Liu et al examined 57 case reports where CSF testing for SARS-CoV-2 was carried out and found that 1.28% COVID-19 patients among the pooled 1018 cases tested positive to SARS-CoV-2 in CSF [7,84-91].
- Post-mortem studies on the neuropathology of SARS-CoV-2 in Brain Tissue: Results of 9 autopsy studies on the neuropathology and neuro-invasiveness SARS-CoV-2 were that 58 out of the 87 pooled cases (66.7%) tested positive for SARS-CoV-2 [92-100]. Solomon et al. reported (n=18) hypoxic changes, but no encephalitis or other specific brain changes with 32 sections (n=16), including 3 sections each from the medulla, frontal lobes, and olfactory nerves positive for SARS-CoV-2 nucleocapsid protein [92]. Remmelink et al. found 9 of 11 cerebral samples positive for SARS-CoV-2 RNA in a postmortem study on n=17 patients who died from respiratory failure or multiple organ failure [93]. 8 cases with cerebral hemorrhage or hemorrhagic suffusion, 3 with focal ischemic necrosis, 5 with edema and/or vascular congestion and 10 with diffuse or focal spongiosis were observed. Al-Dalahmah et al. demonstrated presence of SARS-CoV-2 viral transcripts in an autopsy study of one COVID-19 patient performed 3 h after death, in the nasal epithelium and cerebellar clot, olfactory bulb and cerebellum however SARS-CoV-2 transcripts in the medulla were not detectable [94]. Paniz-Mondolfi et al. reported an ultrastructural finding of SARS-CoV-2 viral particles in the CNS, in the neurons and capillary endothelial cells in the frontal cortex [95].

In a landmark autopsy study on 32 COVID-19 patients for the presence of SARS-CoV-2 infection in the CNS, Meinhardt et al. demonstrated SARS-CoV-2 neurotrophic ability [96]. Precise anatomic mapping of oropharyngeal regions and brains resulted in CNS infarction due to cerebral thromboembolism and more importantly highest levels of SARS-CoV-2 copies per cell within the olfactory mucosa sampled directly beneath the cribriform plate (n=13 of 22, 59.1%) being detected, demonstrating SARS-

CoV-2 neurotropism [96]. Further sub genomic RNA showed active virus replication in 4 out of 13, 30.8% of the SARS-CoV-2 RNA-positive olfactory mucosa samples. Viral load in olfactory bulb was: 3 out of 23, trigeminal ganglion: 3 out of 20 and medulla oblongata: 4 out of 23. The findings were further substantiated by immunohistochemistry and electron microscopy [96].

Cantuti-Castelvetri et al. used antibodies against the spike protein of SARS-CoV-2 to detect infection in the olfactory epithelium in 5 out of 6 autopsies on COVID-19 patients. The endothelial cells in small capillaries and medium-sized vessels, the olfactory bulb and tracts also displayed immunoreactivity [97]. Autopsy tissue samples from 22 patients demonstrated the highest levels of SARS-CoV-2 copies per cell in the respiratory tract, kidneys, liver, heart, brain, and blood with 8 patients positive for SARS-CoV-2 in the brain [98]. A postmortem study on 10 COVID-19 patients showed ischaemic changes in the cortex and white matter, moderate to intense microglial activation in the CNS in 5 out of 5 patients 53. Viral load quantified by use of qRT-PCR targeting the viral E gene and the viral polymerase gene was positive in 4 out of 5 patients [99]. Subgenomic viral RNA transcripts were positive in 1 out 5 patients. An autopsy of a five-year-old girl who died from CNS co-infection with SARS-CoV-2 and tuberculosis tested positive for SARS-CoV-2 RNA in cerebellar tissue but negative in CSF [100].

- In Vitro studies on the neuro-invasiveness of SARS-CoV-2: Bullen et al. incubated a human induced pluripotent stem cell (hiPSC)-derived BrainSphere model with SARS-CoV-2 for 6 hours, a fraction of the neural cells were infected, and viral replication was evident at 72 hours post infection [101]. After Ramani et al. exposed 3D human brain organoids to SARS-CoV-2, they were infected by SARS-CoV-2 within two days of exposure. The neurons were the most infected which resulted in altered distribution of Tau from axons to soma, hyperphosphorylation, and apparent neuronal death [102]. Song et al. exposed hiPSC-derived forebrain-specific human neural progenitor cells to SARS-CoV-2. 9-week-old organoids demonstrated infected neurons 24 h post exposure with significantly increased number of SARS-CoV-2 positive cells at 96 h [103].

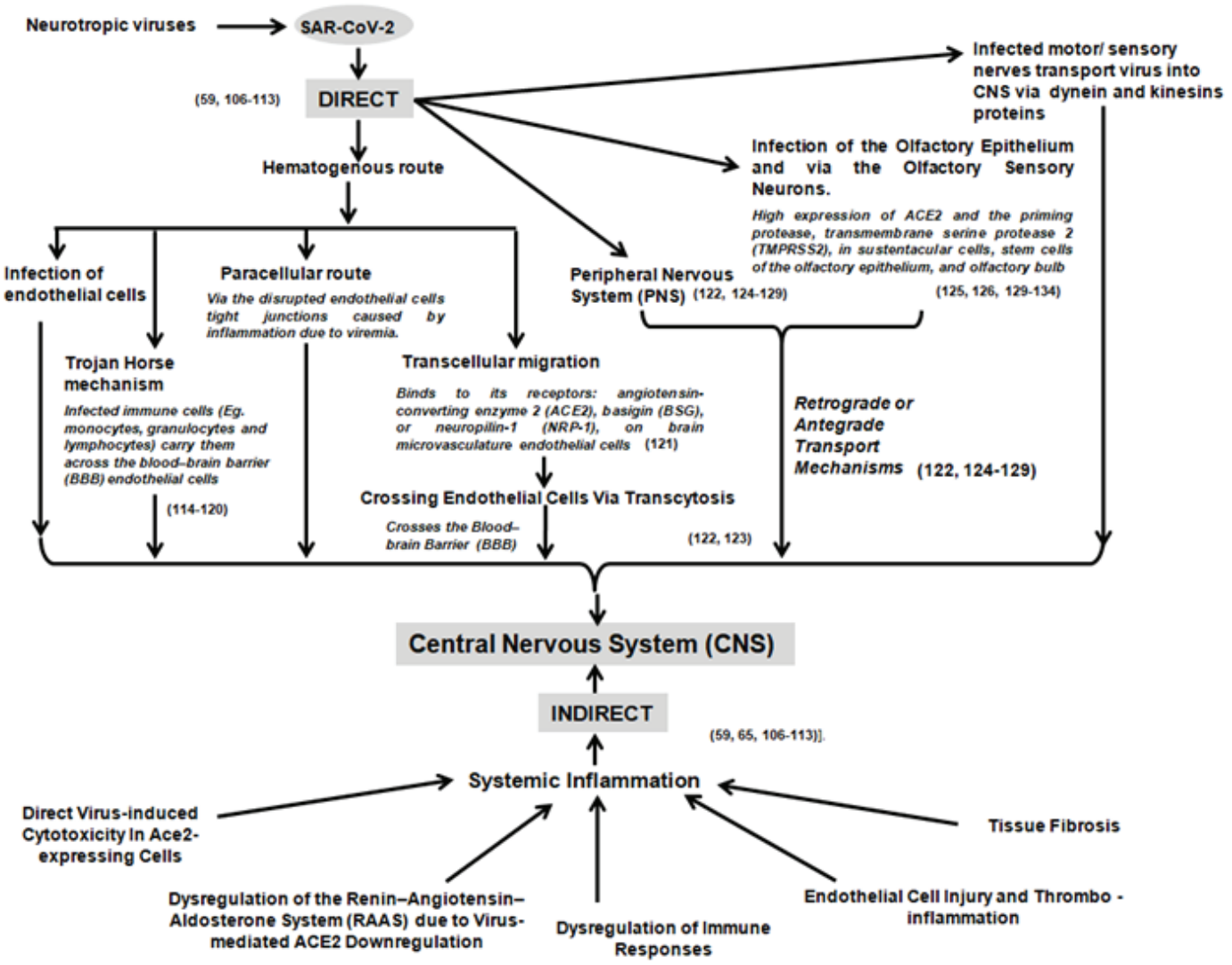

Figure 2. Mechanism by which SARS-CoV-2 reaches the Brain

c) How does COVID or SARS-CoV-2 reach the brain? Are the neurological changes observed the result of "direct" infection or due to "indirect injury" due to MODS, cytokine storm etc?

SARS-CoV-2 belongs to the betacoronaviridae family; it has a single-stranded genomic RNA enveloped by a nucleocapsid core sheathed in a phospholipid bilayer embedded with virulent surface proteins (spike: S, hemagglutininesterase: HE, membrane: M, and envelope: E proteins). SARS-CoV-2 uses its S1 subunit of spike protein to attach to a host's angio-tensin-converting enzyme 2 (ACE2) receptors while the S2 subunit is used for fusion followed by endocytosis. Once inside the cell, uncoated RNA translates various proteins via sub-genomic RNA, followed by assembly of viral particle buds and release from host cells [3,4].

Mechanisms of SARS-CoV-2 Invasion of the CNS

Several theories have been postulated for the virus entry into nervous system. Either direct entry via the ACE2 receptor or indirectly due to systemic inflammation which results from dysfunction and dysregulation by the host immune response (Figure-2) [7,59,104-131].

Direct Invasion of the CNS by SARS-CoV-2

Haematogenous route/entry into the systemic circulation

Airborne SARS-CoV-2 can infect the respiratory tract, in particular the alveolar epithelial cells (type II) and epithelial cells of the gastrointestinal tract both of which are rich in ACE2 receptors. From there via transcellular migration, they could infect the endothelial barrier and enter the systemic circulation via which they can be carried to the brain where SARS-CoV-2 spreads by crossing the blood–brain barrier (BBB) or the blood-cerebrospinal fluid barrier (BCSFB) either via infected endothelial cells or leukocytes [136].

- **Infection of endothelial cells:** Infected vascular endothelium rich in ACE2 receptors facilitate SARS-CoV-2 crossing the BBB from where the virus can spread directly to glial cells, also rich in ACE-2 receptors in the CNS resulting in its neural spread [4, 27,47,48,97,122]. Here too, infected endothelial cells either via transcellular migration or via the paracellular route effect the virus crossing the BBB or the epithelial cells of the BCSFB in the choroid plexus to enter brain tissue [88,94,128].
- **Infiltration through infected immune cells via Trojan Horse mechanism:** Infected leukocytes, granulocytes, monocytes and monocyte that pass through BBB could carry the virus to the brain in a "Trojan horse mechanism" [4, 69, 20].
- **ACE2 receptor via Transcellular migration:** SARS-CoV-2 possesses a twenty times higher affinity for the ACE2 receptor than the original SARS-CoV. SARS-CoV-2 uses these ACE2 receptors to enter host cells. ACE2 receptors are detected in adipose tissue, heart, brain (neurons, astrocytes, and oligodendrocytes with high concentration found in the motor cortex, posterior cingulate cortex, middle temporal gyrus, sympathetic pathways in brainstem, substantia nigra, ventricles, circumventricular organs, thalamus, olfactory bulb neurons and glial cells in the CNS), lung, vascular endothelium, liver, epithelial cells of the digestive and respiratory systems and naso-oral mucosa [3,4,19,70,122,130-134]. The variation of ACE2 receptor expression is one of the key reasons why some organs and tissues are more vulnerable to SARS-CoV-2 [3,8].

Neuronal route

- **Neuronal retrograde dissemination and transneuronal spread:** The virus infects peripheral neurons and uses the transport machinery within the cells in an antegrade or retrograde fashion to gain access to the CNS [45]. The virus thus invades peripheral nerves like the trigeminal and vagus nerves, which innervate different parts of the respiratory tract [132].
- **Infected motor or sensory neurons:** Migration of the viruses is also possible through infection of motor or sensory nerve endings, achieving retrograde or anterograde neuronal transport through the motor proteins, dynein, and kinesins entering via the nerve terminal, replicating and then being transported to the soma to invade the CNS [93,135].
- **Trans-synaptic viral spread:** Inter- and intra-neuronal spread of the virus is brought about by axonal microtubules which facilitate molecular movement across axons either in antegrade or retrograde fashion [46,68,94,136,137]. SARS-CoV-2 can invade the neuron via binding with the ACE2 receptor of neurons, then, the virus passively diffuses and/or is actively transported through axonal transport via axoplasmic flow [46,94,140].
- **Olfactory route:** Entry of SARS-CoV-2 along the olfactory epithelial, ACE-2 receptors in the sustentacular stem cells in the olfactory epithelium, olfactory nerve, the transcribable route are potential routes for the virus to gain entry into the CNS [44,45,49-51,62,63,111,129,137,139]
- **Lymphatic tissue or CSF route:** Lymphatic endothelial cells express the CD209L receptor, another receptor for SARS-CoV-2 [88]. SARS-CoV-2 could thus invade the CNS via the perivascular or lymphatic path abundant in the bronchus and trachea [138]. SARS-CoV-2 could also invade nasal lymphatic tissue and the olfactory nerve perineural spaces.

Indirect Invasion of the CNS by SARS-CoV-2

SARS-CoV-2 may affect the nervous system indirectly due to resulting hypoxia, blood pressure fluctuations, metabolic and electrolyte imbalances (Figure-3) [4]. SARS-CoV-2 can cross BBB by inducing inflammation or hypoxemia through the release of pro-inflammatory chemokines and cytokines [96]. Tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-2, IL-6, and IL-8 have been identified as major pro-inflammatory mediators involved in the cellular invasion of SARS-CoV-2 [3].

Direct viral toxicity could in part account for multiple-organ injury .

Endothelial cell damage and thromboinflammation: Infection-mediated endothelial injury and endothelialitis, in the lungs, kidney, heart, small intestine, and liver in patients with COVID-19, can trigger excessive thrombin production, inhibit fibrinolysis, and activate complement pathways, initiating thromboinflammation and ultimately leading to microthrombi deposition and microvascular dysfunction [31,33–36]. Platelet–neutrophil cross-communication and activation of macrophages in this setting can facilitate a variety of proinflammatory

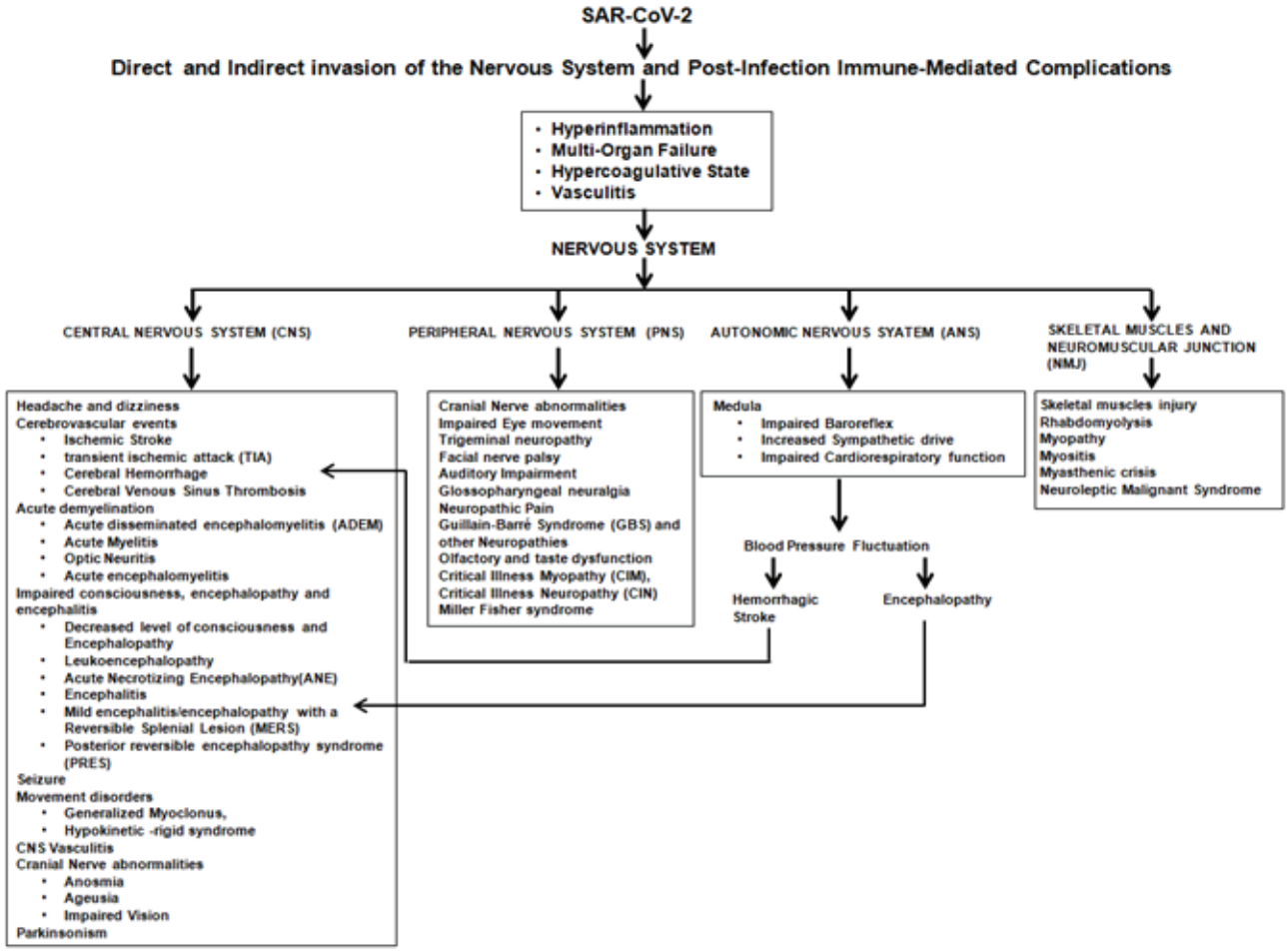

Figure 3. *Neurological Disorders due to SA*

effects, such as cytokine release, the formation of neutrophil extracellular traps (NETs), and fibrin and/or microthrombus formation [37–41].

Dysregulation of the immune response: Dysregulated immune response and cytokine-release syndrome, due to overactivation of innate immunity in the setting of T-cell lympho-depletion, characterize severe COVID-19 [49]. In the CNS infected leukocytes and astrocytes produce pro-inflammatory cytokines such as TNF that can damage oligodendrocytes and/or neurons, and chemokines such as CCL5, CXCL10 and CXCL11 that induce chemoattraction of activated T-cells and/or other leukocytes initiate an aberrant neuroinflammatory loop, which results in neuropathology [47- 49].

Dysregulation of RAAS: The renin-angiotensin-aldosterone system (RAAS) plays a prominent role in vascular tone, vascular permeability, and myocardial remodeling [1-3]. ACE2 counteracting the effects of RAAS, thus as SAR-CoV-2 binds to ACE2 to infect alveolar endothelium in the lung [1-2]. RAAS activation results in acute lung injury that may progress to adult respiratory distress syndrome [1,2,6,7].

Persistent or Long COVID-19

Even weeks and months after getting infected by COVID-19, patients suffer from the lingering side effects of this deadly virus. Here, we are going to focus on brain fog and cognitive impairment in this paper. Many patients reported intermittent brain fog, yet the pathogenesis pathway is unknown, but it may involve neuroinflammation [51]. The inflammation could happen by the pathogenic and stress stimuli that cause the mast cells to release mediators that activate microglia and lead to inflammation in the hypothalamus. Activation of microglia and mast cells could cause cognitive dysfunction and it is most common in patients with Mast Cell Activation Syndrome. There are similar symptoms among people following chemotherapy and people with long COVID syndrome. This condition is called “chemobrain” or “chemofog” and the description is almost like cognitive dysfunction [51].

The National Institute for Health’s definition for Long/persistent COVID includes signs and symptoms that continue or develop after acute COVID-19 i.e., ongoing symptoms of COVID-19 (from 4 to 12 weeks) and post-COVID-19 (12 weeks or more). It can include fatigue, shortness of breath, "brain fog", sleep disorders, intermittent fevers, gastrointestinal symptoms, anxiety, and depression. A study that examined the neurocognitive effects five months post-COVID-19 found that fatigue, overall decreased cognitive speed, led to poor concentration, and memory loss was among the chief complaints [26]. Among 38 patients who had SARS-CoV-2, 42.1% had processing speed deficits, 26.3% delayed verbal recall deficits and 21% percent exhibited both processing speed and verbal memory deficits [26]. Results of another follow-up study six months post-COVID-19 (n=236,379) published in the Lancet

were that the estimated incidence of neurological or psychiatric disorders was 33.62% i.e., 1 in 3 patients post-COVID-19 exhibited neurological or psychiatric disorders [27]. Among the neurological or psychiatric disorders seen post-COVID, 0.56% had intracranial hemorrhage, 2.10% ischemic stroke, 0.11% parkinsonism, 0.67% dementia, 17.39% anxiety disorder, and 1.40% had psychotic disorder. Further, the risk of developing a neurological or psychiatric disorder was increased with the severity of COVID-19 [27].

In an ambidirectional cohort study of associated risk factors of COVID-19 in patients discharged from a hospital in Wuhan, fatigue or muscle weakness was seen in 63%, (1038/1655), sleep difficulties in 26% (437/1655) and anxiety or depression in 23% (367/ 1617) (28). A survey in the US of >1500 respondents post- COVID-19 found that the 4th most reported long-term symptom was difficulty concentrating and focusing further 50% of the respondents had difficulty concentrating and focusing [29]. 29 middle-aged post-COVID-19 patients had impairments in sustained attention and 58 patients approximately 2–3 months post-discharge had executive dysfunction [30,31]. An internet-based test of cognitive functions on recovery of >84,000 probable/confirmed COVID-19 individuals found that impairments in memory, attention and executive functions existed even when adjusting for age, sex, education, and pre-existing co-morbidities [32]. An interventional study started on July 8th, 2020, to evaluate the possibility of a digital game called MentalPlus on rehabilitation and cognitive function. This game is designed to use as an alternative to the psychotherapeutic treatment and rehabilitation of cognitive skills.

Link between Alzheimer's cognitive impairment and COVID-19

Recent research found that the COVID-19 virus can cause long term neurological symptoms including neuroinflammation and microvascular injury that similarly contribute to Alzheimer's and dementia-like symptoms in the brain. The study shows that even when the COVID-19 infection is cleared from the body, people might experience persistent symptoms like brain fog, having a hard time concentrating and thinking. The results show that the altered proteins included RAB7A, VCAM1 and TGFBI are strongly associated with Alzheimer's. Neuroinflammation of the brain cells is a common symptom of Alzheimer's disease, researchers also found this to be a symptom in patients with SARS-coV-2. Upon measuring designed markers in the CSF and blood of patients, they found genetic changes in NKTR, TGFB1, GSTM3, TNFRSF1B, SPP1, and CXCL10 which are linked to Alzheimer's. They also found that neuroinflammation could be the result of increased expression of antiviral defense genes in the endothelial cells like LY6E, IFITM2, IFITM3 and IFNAR1.

The Evolution of EEG- Guided COVID-19 Monitoring and Treatment

COVID-19 lockdown-restrictions: EEG on Hold

When COVID-19 lockdown-restrictions were initiated on 11th March 2020, the government and the Ministry of Health took an initial stand in the first few weeks of the COVID-19 pandemic to post-pone, suspend all elective, "non-urgent" procedures including neurophysiological exams and EEG [33,34]. Remote assistance via telephone, e-mail, and video-audio-conference consultations was instead advocated where appropriate [35-37]. The outcome of these restrictions can be appreciated via the result of an online survey carried out in Italy that found that the number of EEGs carried out went from 46.1 ± 32.5/week (pre-COVID-19 period i.e. prior to March 11th 2020) down to 11 ± 12/week (76 ± 20% reduction) [38]. 93 Video-EEGs were recorded (32% reduction), 40 polysomnography (53% reduction), 14 ambulatory EEGs (78% reduction), and 10 long-term EEG for pre-surgical evaluation (81% reduction) [38]. Among the key reasons behind EEGs being restricted were that the a) EEG technician had to come into close contact with the patient when positioning the electrodes on the scalp and b) if the electrodes were not-disposable they themselves could contribute to the spread of COVID-19. Both of these issues have been overcome with the use of disposable electrode caps that come in a range of sizes.

1 in 3 COVID patients exhibit neurologic complications

Both COVID-19 and the lockdowns that go with this global pandemic have brought in their wake many neurocognitive, neurological, or psychiatric and psychosocial co-morbidities either via de novo induction or by exacerbating preexisting conditions, for example, parkinsonism [39-52]. The results of a study carried out (January 16, 2020, to February 19, 2020) at three special care centers for COVID-19 in Wuhan, China, where; 78 out of 214 patients i.e., 36.4% exhibited neurologic complications [53]. Furthermore, the frequency of neurological complications in patients with severe versus (v/s) mild COVID-19 infections were acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]) [53]. Studies that followed showed that the neurological aftermath of COVID-19 ranged from anosmia/dysgeusia, dizziness, headache, meningitis, to encephalitis, vasculitis, acute disseminated encephalomyelitis, neuropathies, strokes, Guillen-Barre Syndrome, Miller Fisher Syndrome, skeletal muscle injury/myalgia, seizures (new-onset seizure, convulsive seizure, myoclonic seizures, status epilepticus, and new-onset refractory status epilepticus-NORSE, and acute hemorrhagic necrotizing encephalopathy and long COVID-19 or post-COVID-19 sequelae [54-57]. These and other findings resulted in a 360° change in viewpoint with the result that there are various grey, white, and published papers documenting EEG guided therapy in certain complications of COVID-19. Today, EEGs being prescribed to those with an altered mental status, experiencing seizure-like events, have new onset encephalopathy, have slowed reaction to stimuli, speech issues, movement disorders, in guiding of sedation in cases of ARDS, delayed awakening after stopping sedation and cardiac arrest keeping in mind stringent safety guidelines [25,58-70].

EEG guided monitoring and Rx in neurological and neurocognitive complications of COVID-19

To diagnose mild cognitive impairment (MCI) due to COVID-19, there are a few recommended; however, there is no specific test to confirm a cognitive diagnosis as of yet. Depending on the patient's symptoms, physicians may order various tests that can help to clarify the diagnosis of MCI. One example of a diagnostic test used is neurological exam which tests reflexes, eye movements, walking, and the balance of the person who is dealing with MCI. Lab tests such as blood tests to check the vitamin B-12 deficiency or thyroid gland hormone level can also contribute to differential diagnosis. Brain imaging such as MRI or CT scan could be helpful in confirming evidence of tumors, bleeding, or stroke. Lastly, mental status testing has been helpful to provide additional details about mental functions.

BrainView technology, is a novel EEG system that can help

aid in brain health management and diagnostics including the diagnosis of MCI in COVID-19 patients. The BrainView system is a software that acquires, displays, and stores electrical activity of the patient's brain including EEG. EEG recordings are obtained by having patients wear an electrode cap as the patient takes a cognitive assessment test that scores the brain's performance on memory, attention, information processing, and executive function. The system provides a neuro-functional physiology report of the results, data summary, raw data, and images. From the patient's assessment, BrainView is designed to help physicians with their diagnosis by measuring biomarkers related to seizures, memory loss, concussion, cognitive impairment, and other stress-related neurological conditions. Before the BrainView system, EEG technology was not portable, the software was complicated and not practical to use in a busy medical practice. Instead, BrainView is a more ideal EEG method that can be used by both primary care and specialty physicians because the test is short (25 minutes), is portable, easy-to-use, and is non-invasive.

A clinical study using their BrainView QEEG technology to demonstrate both the safety and efficacy of EEG Normative Database measurement technology and its clinical correlation to various clinical conditions. The study is planned to be conducted between 2022-2023. Data will be collected from approximately 4,000 subjects (ages 2 to 95) by various neurology office that use BrainView QEEG as part of their standard diagnostic over the last 5 years. During the BrainView QEEG evaluation, patients wear a 21-channel EEG to document brain activity results and patients answer a neuropsychological questionnaire. Medeia Inc will receive will recieve de-identified questionnaires and the BrainView EEG results from the physician. BrainView EEG results will then be analyzed to demonstrate that BrainView correlates with clinical diagnosis. The purpose of the study is to validate the correlation between clinical diagnosis and treatment progress to data collected from the BrainView QEEG as part of a standard diagnostic regimen. It is expected that the measurements made by BrainView NeuralScan will not vary by more than 15% over the course of a day's measurements and correlate with various clinical conditions, and thus be an accurate, predictive measure of COVID-19 brain health and recovery.

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