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The “Tipping Point” : When Electroencephalography (EEG), Quantitative EEG (QEEG) and Standardized Low Resolution Brain Electromagnetic Tomography (sLORETA) in COVID Went From “Ceasure” To “Non-Priority” To “First-Line” Tool in Triage, Diagnosis, Monitoring and Therapy

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Abstract

On the threshold of the COVID outbreak; electroencephalography (EEG) was used in diagnosis, cross-border disease differential diagnosis, disease-staging, monitoring of treatment, sedation and coma, in neuro-therapy and in declaration of brain death. EEG, quantitative EEG (QEEG), and standardized low resolution brain electromagnetic tomography (sLORETA) use entered the doldrums; reaching near “ceasure” due to COVID restrictions. Between 2020-2023, EEG use tipped, going from “Ceasure” to “First-Line” tool in triage, diagnosis, monitoring and therapy due to neurological, neurocognitive, neuropsychiatric, and neuromuscular sequelae of para- or acute- and post-COVID-19. The present paper will discuss this “Tipping point” in EEG, QEEG and sLORETA use.

Introduction

From when the first pandemic warnings were issued globally 773,819,856 individuals have tested COVID-19 positive till date [1-4]. Ascertainment bias aside; the price of COVID-19 and its variants on “global health” include: their wide range of symptoms, rapid spread, lack of preexisting guidelines on treatment and safety protocols, and no FDA approved medications [5-9]. Briefly; in 2019, COVID was new to the medical and public health fraternity, the knowledge on “*how it spread*”, “*how it could be contained*”, “*if immunization was possible*”, “*what was the treatment protocol*” remained an enigma. In acute/para-COVID the drawback was “*one could not predict the outcome*”. It appeared to compromise not only the respiratory system but was also attributed to cause multi organ damage (MOD)” [4,6-10]. Subjects could be:

- asymptomatic, symptomatic with mild, moderate or severe COVID,
- young or old,
- without or without co-morbidities,
- not-vaccinated or vaccinated,
- without prior history of respiratory/cardiac/neurological/neuropsychiatric/renal or other issues,

and yet, one could not predict “*who would recover*” and “*who would become critically ill* with it resulting in 7,010,568 fatalities [4,6-9]. Initially; symptomatic treatment, a learning-on-the-go approach, stringent restrictions that *limited person-to-person contact* were followed. Thus, when the World Health Organization (WHO) declared COVID a pandemic on March 11, 2020 only emergency and acute conditions were treated and all elective procedures were kept on hold or managed via telemedicine where appropriate [4,6-10].

Though much has changed since 2019; in 2023; globally, we are still dealing with the neurological and neuropsychiatric aspects of incident COVID, para-/acute-COVID and post-COVID (Table-1) and the psychosocial and economic aspects of the COVID lockdown [9-12]. We now have vaccines, treatment protocols, and approved medication for asymptomatic, mild and severe COVID and hybrid or work from home measures in place to contain its spread if we face another variant [9-12]. Adding to the psycho-socioeconomic impact of COVID is that some businesses will boom, some will just about survive and others will crumble [13]. Further compounding COVID’s impact is the growing awareness of the wide-ranging and long-lasting neurological

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Table 1. Incident Neurological and Neuropsychological Disorders seen in Acute/Para and Post-COVID-19 Pathophysiology [10]

Incident Neurological and Neuropsychological Disorders seen in			Para- and Post- COVID-19, Post- vaccination Cognitive function and fatigue Pathophysiology
Acute/ Para COVID-19	Post- COVID-19	Due to COVID Treatment	
<p>Psychiatric Disorders Psychosis, Dementia, Anxiety, Depression, Insomnia, Brain Fog</p> <p>Musculoskeletal Disorders Fatigue, Myalgia, Tendinopathy, Muscle Weakness Arthralgia</p> <p>Neurological Disorders Headache, Dizziness, Encephalopathy, Ageusia, Anosmia, Stroke, Microbleeds, Autoimmune response, Seizures</p> <p>Other Organs Affected: Liver, Kidney, Skin, Thyroid, Heart Lung, Endocrine Organs, Gynecological, Gastrointestinal Tract</p>	<p>General sequelae</p> <ul style="list-style-type: none"> Fatigue Heavy Headache Hyposmia Anosmia Memory Loss Cough Shortness of Breath Arxiety/ Depression Heart palpitations parkinsonism Delirium Brain Fog" (poor short-term memory, concentration, problem solving, and executive function), mental fatigue dizziness, vertigo, and anxiety/depression Psychiatric sequelae anxiety, depression, post-traumatic stress disorder (PTSD), brain fog, psychosis, sleep disturbance (unrefreshing sleep, exhaustion, vivid dreams, or nightmares). 	<ul style="list-style-type: none"> Medication toxicity Medication toxicity especially in combination therapy Post-COVID vaccination 	<ul style="list-style-type: none"> Direct Viral Infection Neuroinflammation Congestion be it cerebrospinal fluid (CSF), respiratory, cardiac Hypoxic injury secondary to lung involvement Neuronal Pathway inflammation involvement ACE2 Down regulation Post infection Autoimmunity Hypercoagulability Cytokine Storm Gut Microbiota Tanslocation Neurological consequences Gut Microbiota Translocation secondary sepsis, hypoxia and immune hyperstimulation, elevated cerebrospinal fluid autoantibodies, and white matter change in the brain

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and neuropsychiatric aspects of para-COVID and post-COVID affecting our workforce, our quality of life and therefore our economy [9-13]. Thus, both from a health and economic standpoint, those who test positive for COVID need to be monitored until recovery and "back to normal" is achieved [9-13].

In this context of stringent restrictions due to the COVID pandemic; in March 2020 electroencephalography (EEG) was viewed a "non-priority", an "add-on/dispensable tool" with clinicians, researchers and laboratories reporting near complete stoppage of EEG use [9]. Since then, electroencephalography (EEG) has gone from "ceasure" in 2020, to "reluctant use", to "urgent /first line use" in 2023 [9]. The present paper will explore that journey.

Methods

We searched Google, Google scholar, PubMed till Nov 24th 2023. For initial searches keywords used included: "SARS-CoV-2", "Covid-19", "Long COVID", "Extra-Pulmonary Infections", "Neuro", "Brain", "Neurological disorders", "Neurological Complications", "Neuropathogenesis", "Neurological Symptoms", "Seizures", "Encephalopathy", "Cognitive Impairments", "Brain FOG", "Executive dysfunction", Language and Speech Impairments, "Processing speed", Parkinson's disease, Alzheimer's disease, "EEG", "quantitative EEG (QEEG)", and "Low resolution electromagnetic tomography (sLORETA)". These keywords matched the inclusion criteria, namely; studies that focused on EEG/QEEG/sLORETA use in para-/acute and post-COVID-19.

Studies on COVID guidelines, technological improvements to enhance safety of healthcare providers and patients, neurological neurocognitive, neuropsychiatric, and neuromuscular sequelae of para-/acute and post-COVID-19 were included in the literature review. Following going through the results of the initial searches we elected to use the search engine PubMed and to use the broad title, "COVID + EEG" and "COVID + QEEG" as it gave us a comprehensive overview of our topic of interest and the best fit for the message we wanted to convey. Table-2 presents the results of that search. Articles available in full text + free, that met the inclusion criteria, were in English, were obtained and included in the study.

The EEG

Since July 6th 1924, when the first EEG was recorded, it has evolved from being an add-on tool in the diagnosis of brain health, to an instrument that is used for diagnosis, disease-staging, evaluation of prognosis, monitoring the course of treatment (pharmacotherapy and chemotherapy), and as a therapeutic tool [14-23]. The EEG allows for clinical decision making and non-invasive assessment of the functioning of the 4mm thick cerebral cortex, which governs our mental, neurological, neuromuscular and physiological well-being [14,15]. With a temporal resolution of a millisecond (ms), it captures the brainwaves emitted by the cerebral cortex, namely the Alpha (α , at 8-15 Hz), Beta (β , at 16-30 Hz), Gamma (γ , at 31-100 Hz, low γ , at 30-70 Hz and high γ , at 70-150 Hz) and the sensorimotor rhythm (SMR, at 13-15 Hz) as electrical activity (Figure-1) [14,15]. Figure-1 provides an example of

Table 2. Publications listed on PUBMED on COVID-19 and Electroencephalography (COVID-19 EEG between April 1st 2020 (when the First publications were submitted on COVID and EEG) and Oct 18th 2023.

Broad Topic	Topics	No. of Publications	Broad Topic	Topics	No. of Publications
Guidelines, Safety Measures and Other Publications	Epidemiology	4	Neurological Manifestations	Neurology of COVID and Neurological complications	15
	Guidelines and Policy on Treatment and Safety of Healthcare workers and Researchers	23		Neurologic complications rhabdomyolysis and brain death	1
	Neural Activity + Mask	5		Infants	3
	Safety Measures + PPE suit	1		Children	4
	Waiting Time	1		Elderly patients with neuropsychiatric conditions	2
	Neurology training for COVID	2		Stroke	3
	Work, Psychological, Psychosocial	13		Seizures	20
	Social Isolation	4		Myoclonus	1
	Technology and development	19		Epilepsy	5
	COVID Education and Educational Impact of COVID	8		De Novo Epilepticus (Pediatric /Adult)	11
	Human Brain Resilience	3		Epilepsy Emergency care	1
	Treatment Options	5		Epilepsy and Seizures	2
	Other or unrelated	37		Non convulsive status epilepticus – COVID / medication induced	4
Non-COVID Neurological Neropsychiatric Care during COVID period	Epilepsy	23		Encephalitis	7
	Seizures	1		Encephalopathy and Encephalitis	1
	Epilepsy + Steroid	1		High risk of obstructive sleep apnea (OSA) and COVID encephalopathy	1
	Neurosurgery	1		Acute necrotic hemorrhagic leukoencephalitis	1
	Dementia	3		Cortical Brainstem encephalitis	1
	Dementia and Delirium	1		Encephalopathy	9
	Psychogenic nonepileptic seizures (PNES) and Functional Psychogenic seizures	3		Encephalopathy and Stroke	1
	Multiple Sclerosis (MS)	1		Encephalopathy and Cerebrovascular disease	6
	Major depressive disorder (MDD)	1		Acute disseminated encephalomyelitis like disease	2
	Juvenile Myoclonic Epilepsy	1		Cytomegalovirus (CMV) meningoencephalitis	1
Para- and Post-COVID syndrome	Neurodegenerative Process	1		Meningoencephalitis.	1
	Symptom treatment	2		Acute Cerebral Venous Thrombosis	1
	Impact in children	1		Cerebral venous sinus thrombosis (CVST), pregnancy with hemiplegia	1
	Seizures	1		Large and Small vessel involvement /Borderzone ischemia	2
	Autoimmune Encephalitis	1	Endothelial injury	1	

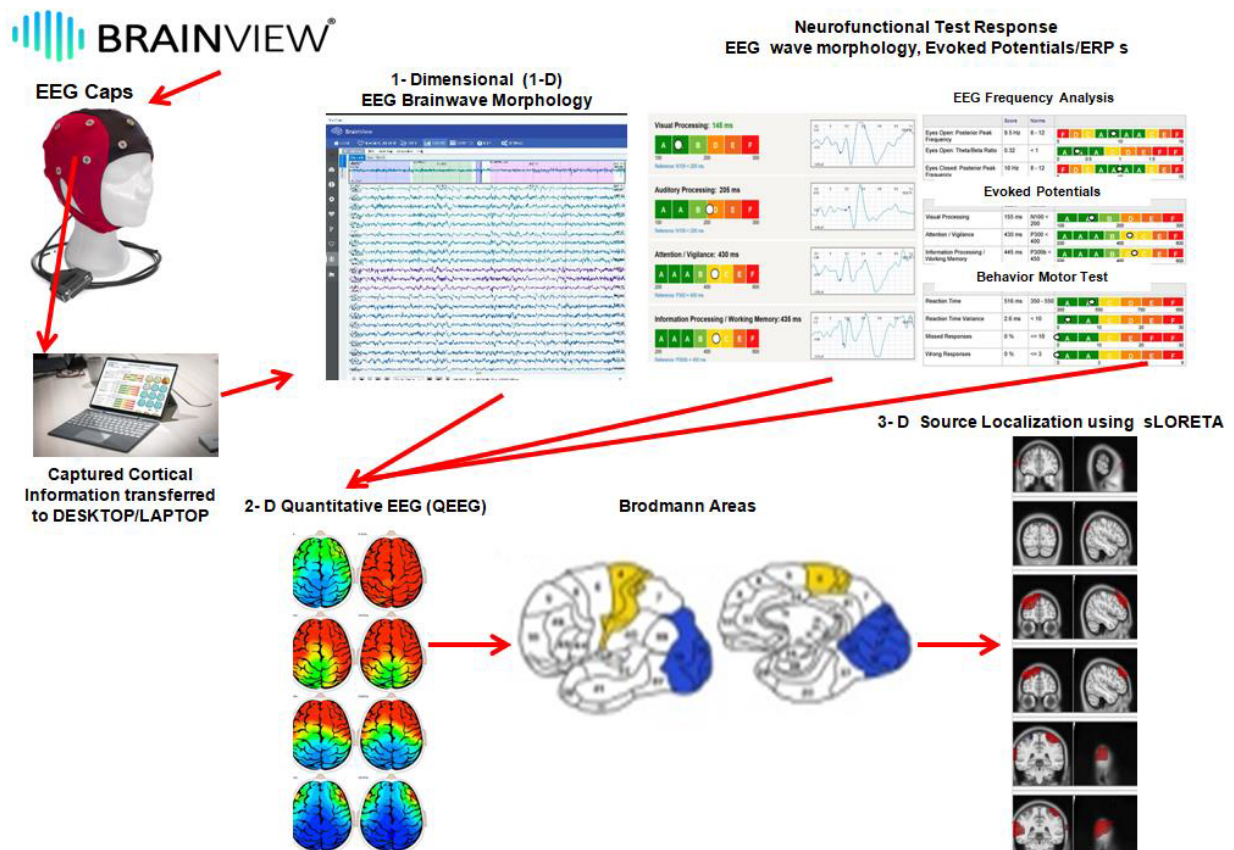
Broad Topic	Topics	No. of Publications	Broad Topic	Topics	No. of Publications
	Sleep	6		Humoral response	1
	Migraine/ Headache	2		Intensive care unit	1
	Delirium and Encephalopathy	2		Cerebral Edema	1
	Confusion	1		Cortical Damage	1
	COVID hyposomia	1		Abrupt Late onset Psychosis	1
	Delirium and Encephalopathy	2		Abnormal Movement	1
	Post COVID Casomia and Cacogeusia	1		Dementia	1
	Cognitive therapy for Severe acquired brain injury(SABI) and caregiver's distress syndrome	1		Sleep	4
	Cognitive Deficits	2		EEG guided Sedation	5
	Reaction Time and Alternative Forced Choice	1		Consciousness recovery	2
	Speech impediments	1		Catastrophic brain injury and death	1
	Brain Fog	1	Post COVID-19 Vaccine	Neonates born to COVID mothers	1
	Post COVID Physical and Cognitive Impairment	1		Encephalopathy, epilepticus	2
	Post COVID preserve perception action integration	1		Encephalopathy , amnesia and seizure	3
	COVID Fatigue and Cognitive impairment	2		Acute Disseminated Encephalomyelitis	1
	Neuropsychiatric syndrome	1		EEG changes	1
	Post traumatic stress symptoms (PTSS)	1		Non epileptic myoclonus status	1
	Depression – Treatment	1		EEG Brainwave morphology – Para-/ Post-COVID	46
	Post traumatic and persistent postural perceptual dizziness (PPPD) in elderly	1	QEEG morphology – Para-/ Post-COVID	14	
	Acute psychosis	1	Review Pertinent to the Topic Para- Post- COVID + EEG	21	
	Hallucinations	1			
COVID + EEG (2019-2023): FULLTEXT : 430; FREE: 374, REVIEW: 47; FREE: 37					
COVID + QEEG (2019-2023): FREE: 10					

Note: Reviews and original articles not relevant to the topic were placed under appropriate broad topic headings

an EEG machine “BrainView” by Medeia wherein brainwave morphology in 1-dimension (1D) is captured either using, classic resting EEG (eyes open and eyes closed) or evoked/event-related potentials (ERPs: visual, auditory, motor, cognitive, or task-related like the odd ball paradigm, Go/Nogo etc). C1 and P1, P200, P300, P3a, P3b, P600, N100, visual N1, N170, N200, N2pc, N400, are some of the ERPs used for 1-dimensional (1D) assessment of cerebral health [15]. The ERP nomenclature, definitions and measures of cortical health namely; brainwave “mean”, “peak” amplitude and “latency” (in ms) have been described by us earlier [16]. EEG wave morphology varies with normal versus disease, age, stimulus used, neurophysiology and neuropsychiatric status [14-20].

Further developments in EEG technology led to conversion of 1-D cortical signals into 2-D topographical color maps. This

was achieved via drawing a comparison between a patient’s brain electric activity and a normative database (Neuroguide, FDA research standard); a specialized software program then calculated Z-scores which are color coded generating quantitative EEG (q-EEG) 2-D topographical color maps [20]. The cerebral cortex divided into four lobes: the frontal, parietal, temporal and occipital; was further mapped out into twenty-six Brodmann’s areas (BA) (Figure-1) based on its cytoarchitecture and function. The demarcation of the Brodmann’s areas (BA), together with independent component analysis (ICA), and standardized low resolution electromagnetic tomography (sLORETA) improved the spatial resolution of EEG converting 1-D and 2-D into 3-D EEG data, and enabled source localization of EEG waves on the cerebral cortex [14-21].



Note: Evoked Potentials/ERPs : stimulus designed to capture/ evaluate auditory, visual, working memory, attention, behavior

“BrainView” by Medeia captures a subject’s brainwaves morphology either “at rest” or following an “event” via ERPs with good temporal resolution ($\approx 1\text{ms}$) in 1-dimension (1-D). Using its “quantitative EEG (q-EEG) component” the subject’s brainwaves are compared with a normative database, generating Z-scores which are color coded and viewable as 2-D topographical color maps. The cerebral cortex mapped into twenty-six Brodmann’s areas (BA) based on cytoarchitecture and function together with independent component analysis (ICA) enable 3-D source localization of the EEG waves on the cerebral cortex via standardized low resolution electromagnetic tomography (sLORETA)

Figure 1. An example of an EEG machine “BrainView” by Medeia

“The Ceasure”

In December 2019, came the first report on a cluster of patients (in Wuhan, China) with a “new” type of pneumonia [2,3]. By March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic [4-7]. COVID and the COVID lockdown compromised access to healthcare. Video-EEG monitoring (VEM) for epilepsy diagnosis and in general inpatient monitoring of epilepsy via EEG were either cancelled or highly restricted or delayed [9,22-29]. For instance, VEM was “restricted” in 38.3% adults and 53.2% children, “stopped” in 6, affecting post-surgery monitoring and choice of anti-seizure medication (ASM) due to seizure misclassification [26-29]. 22% living with epilepsy dealt with the increased stress

of inability to access emergency healthcare when they needed it, resulting in their seizures worsening [22]. Another study revealed that decline in continuous EEG (cEEG) use during the pandemic effected management of hospitalized patient [30]. A study on patients presenting at emergency during the pre-lockdown and lockdown period found that the numbers of patients seeking medical help for non-COVID critical conditions had declined [31]. Further, there was an increase the number of new cases and a decline in known cases of epilepsy/seizures presenting at emergency. The deduction was that the health-seeking behavior of individuals living with epilepsy differed from those experiencing their first seizure [31]. The former felt more confident of managing epilepsy and were more fearful of contracting COVID while the latter felt the converse [31].

The Tipping Point

One centre (Shanghai Jiao Tong University School of Medicine, China) reported a smooth restart of the EEG activity on April 7th 2020, while others reopened in early May (Hospital Sint-Jan Brugge-Oostende, Belgium; National Institute of Mental Health, Klecany, Czech Republic; University of Fribourg, Switzerland) [9]. Between 2020 and 2021 the EEG still hovered between “ceasure” and a “non-priority” in a setting of pre-existing, new onset and COVID-related neurological and neuropsychiatric disorders.

The resumption of EEG began with the A) implementation of guidelines, to help deal with both non-COVID related prior/incident neurological conditions [9,32-45] and B) the neurological sequelae due to para- and post-COVID, medication toxicity related to COVID treatment and post-COVID vaccination sequelae [11,46-64].

A) Implementation of COVID appropriate safety guidelines and EEG protocols are mentioned below: [9,32-45]

- i. Good medical practice (GMP) hygiene guidelines were defined and established
- ii. Testing of patients to rule-out fever, any suspicious respiratory infection and COVID-19 prior to EEG testing was instituted
- iii. Recording of EEG in two separate rooms, one for EEG technical staff and the other for the patient. Thus, allowing for patient isolation from EEG technical staff. Patients were also kept isolated from each other within a ward.
- iv. Guidelines for disinfection and quarantining of material used and the usage of disposables where possible and appropriate were proposed.
- v. The enhancement of existing EEG tools to reduce contact between the EEG technical staff and patient,
 - » disposable EEG caps that allowed for easy application to the patient’s head,
 - » temporary tattoo electrodes (TTEs) that could be laminated directly onto the skin
 - » use of wireless transmission coupled with lightweight amplifiers for recording an EEG
 - » usage of shorter EEG protocols with subjective choice of EEG protocols based on clinical judgment
- vi integrated approach towards triage and early diagnosis and treatment of incident/ post-COVID’s neurological and neuropsychiatric co-morbidities/ sequelae.
- vii continuous education of the various medical teams, early diagnosis/differential diagnosis and treatment of incident/ post-COVID’s neurological and neuropsychiatric co-morbidities was also proposed.

For example, one study presented the guidelines they followed in a case of *de novo* epilepsy post-COVID in a 73-year-old male patient with acute respiratory failure and septic shock. Post-weaning from medication-induced sedation and paralysis, the subject had a convulsive episode with transient left facial droop. They opted to switch from a routine EEG due to the presence of epileptiform abnormalities to a continuous video-EEG (cvEEG). They used disposable EEG electrodes and the EEG machine was placed six feet away. An experienced EEG technician in a personal protective equipment (PPE) suit performed the EEG recording, an N95 face mask

was used for the subject. Decontamination following use of the room, instruments and EEG machine were carried out and the machine was quarantined for 14 days [38,39]. A study on the use of facemasks (FMs) during an EEG found that background frequency (BGF) and background amplitude (BGA) did not differ significantly in with and without FM [40].

Another study stressed the need for awareness among healthcare providers of EEG brainwave morphology in confusion, impaired consciousness, stupor, coma, headaches hypercapnic/hypoxic and anoxic (post-cardiac arrest syndrome) encephalopathies and encephalitides, symptomatic seizures in acute respiratory failure [41]. Emphasis was laid that EEG technical staff, medical students, residents, fellows, clinicians, and neurologists, receive the appropriate training via continuing medical education (CMEs) and webinars in triage, diagnose, differential diagnosis, safety guidelines and treatment protocols to enable them to provide integrated care and to successfully handle incident COVID and neurological sequelae due to para/ acute/post COVID [42-45].

B) The revelation that it’s “All Roads lead to Rome” when COVID hits; 8 / 10 times neuro-injury occurs [11,46-64]:

- i. Though primarily defined as a respiratory infection both para- or post-COVID-19 a.k.a “long haul/ persistent COVID/ Post-Acute COVID-19 Syndrome. (PACS)” appeared to have a major impact on the nervous system. From Table-2 one can deduct that para- or post-COVID-19’s neurological impact on the central nervous system (CNS) and peripheral nervous system (PNS). Para- or post-COVID-19 subjects presented with a range of conditions from anosmia/dysgeusia, dizziness, headache, brain fog, memory loss, cognitive impairment, to encephalitis, meningitis, vasculitis, acute disseminated encephalomyelitis, neuropathies, strokes, seizures (new-onset seizure, convulsive seizure, myoclonic seizures, status epilepticus, and new-onset refractory status epilepticus-NORSE, acute hemorrhagic necrotizing encephalopathy, Guillen-Barre Syndrome, Miller Fisher Syndrome, and skeletal muscle injury/myalgia (Table-1 and Table-2) [46-55]. Another study found 78 out of 214 (36.4%) COVID positive subjects complained of dizziness, headache, impaired consciousness, dysgeusia, and anosmia [46]. The same study also observed that those with severe versus (vs) mild COVID-19 infections were more likely to have neurological complications like acute cerebrovascular diseases 5.7% vs 0.8%, impaired consciousness 14.8% vs 2.4%, and skeletal muscle injury 19.3% vs 64.8% [46]. Another study found that 82.3% (419 out of 509) had neurologic issues (44.8% myalgias, 37.7% headaches, 31.8% encephalopathy, 29.7% dizziness, 15.9% dysgeusia, and 11.4% anosmia) during the course of COVID-19 [47].
- ii. Mechanisms of SARS-CoV-2 invasion of nervous system [11,45-64]:

Several theories have been postulated on the mechanisms of SARS-CoV-2 invasion of nervous system, the CNS and PNS, they include [11,57-61];

Direct Entry

- Following entry into the Angiotensin-converting enzyme 2 (ACE2) receptor rich respiratory and/or gastrointestinal tracts; SARS-CoV-2 via transcellular migration could cross the endothelial/ blood-

cerebrospinal fluid (BCSFB)/ blood–brain barrier (BBB) entering via the haematogenous route/entry into the systemic circulation.

- Infiltration across the BBB with the virus reaching the brain through infected immune cells (leukocytes, granulocytes, monocytes and monocyte) via Trojan Horse mechanism
- SARS-CoV-2 possesses a high affinity for ACE2 receptors. ACE2 are detected in adipose tissue, heart, brain, lung, vascular endothelium, liver, epithelial cells of the digestive and respiratory systems and nasoroal mucosa. Tissue-vulnerability to SARS-CoV-2 is correlated with ACE2 receptor expression. ACE-2 receptors are also found along the transcribable route, along the olfactory epithelial in the sustentacular stem cells and olfactory nerve. Lymphatic endothelial cells express the CD209L receptor which also has an affinity for SARS-CoV-2.
- It infects the motor/sensory neurons/peripheral neurons and their nerve endings via binding to ACE2 receptor. The virus then either passively diffuses and/or is actively transported via axoplasmic flow. Inter- and intra-neuronal spread (Trans-synaptic) is facilitated by axonal microtubules in an antegrade or retrograde fashion.

Indirect Invasion of the CNS by SARS-CoV-2

- Hypoxia, blood pressure fluctuations, metabolic and electrolyte imbalances that occur during COVID may indirectly affect the nervous system.
- Inflammation or hypoxemia releases pro-inflammatory chemokines and cytokines like tumor necrosis factor-alpha (TNF- α), interferon-gamma (IFN- γ), interleukin (IL)-2, IL-6, and IL-8 resulting in cellular invasion by SARS-CoV-2.
- Direct viral toxicity
- Infection-mediated endothelial injury and endothelialitis may trigger excessive thrombin production, inhibit fibrinolysis, and activate complement pathways in turn initiating thromboinflammation, microthrombi deposition and microvascular dysfunction. Cross-talk between activated platelets, neutrophils and macrophages have proinflammatory effects, causing cytokine release, formation of neutrophil extracellular traps (NETs), fibrin and/or microthrombus formation.
- Over-activated innate immunity coupled with T-cell lympho-depletion result in a dysregulated immune response and cytokine-release syndrome. Infected leukocytes and astrocytes in the CNS release TNF which can damage oligodendrocytes and/or neurons. CCL5, CXCL10 and CXCL11 (chemokines) induce chemoattraction of activated T-cells and/or other leukocytes which results in a dysregulated neuroinflammatory loop.
- The renin-angiotensin-aldosterone system (RAAS) is important for vascular tone, vascular permeability, and myocardial remodeling. ACE2 receptors prevent RAAS activation. So when SAR-CoV-2 binds to ACE2 vascular injury occurs.

Medication toxicity

Anti-COVID treatments prescribed range from anti-

retroviral drugs (remdesivir, favipiravir, and lopinavir-ritonavir combination), biologics (tocilizumab), to antibiotics (azithromycin), anti-parasitics (chloroquine and hydroxychloroquine), to corticosteroids (dexamethasone) [63-66]. The potential adverse effects (AEs) of the anti-COVID treatments include [63-66]:

- **Chloroquine (CQ):** psychosis, anxiety, agitation, irritable or blunted mood, seizure, bipolar mood disorder, delirium, reversible vacuolar myopathy, extrapyramidal disorders (Parkinsonism, dystonias and oculogyric crisis), ototoxicity
- **Hydroxychloroquine (HCQ):** Ataxia, loss of hearing, vertigo, dizziness, tinnitus, psychosis, reversible vacuolar myopathy, seizure
- **Azithromycin:** Headache, dizziness, vertigo, catatonia, psychotic depression, delirium, anxiety, somnolence
- **Lopinavir/Ritonavir (LPV-r):** agitation, abnormal dreams, confusion, anxiety, emotional disturbances, neurotoxicity, paresthesias, taste alterations
- **Tocilizumab:** headache, dizziness, peripheral neuropathy, leukoencephalopathy, cognitive impairment, demyelinating disorders, depression
- **Corticosteroids:** agitation, anxiety, depression, delusion, hallucinations, seizure, acute steroid myopathy, myalgia
- **Interferon- α :** anxiety disorders, fatigue, apathy, irritability, mood disorders, cognitive deficits, suicidal tendency, sleep disturbances
- **Umifenovir:** dizziness, acute psychiatric symptoms
- **Favipiravir:** psychiatric reactions

AEs due to the anti-COVID treatments, together with drug-drug interactions between combination therapy used in COVID treatment, concomitant medications, medications prescribed for pre-existing “conditions: neurological or non-neurological or neuropsychiatric or non-psychiatric conditions” further exacerbate neurological and neuropsychiatric sequelae observed. At times, the outcome can range from triggering seizures, lowering seizure thresholds, to serious adverse events (serious AEs), requiring hospitalization or intensive care or death [63-66].

Post Anti-COVID Vaccine

Despite their proven efficacy, vaccines be they inactivated, viral vector-based or mRNA vaccines can cause vaccination-related adverse events following immunization (AEFIs) [63-67]. Till date 13.59 billion individuals have been vaccinated [4] Post anti-COVID-19 vaccines neurological issues observed include; seizures, new-onset refractory status epilepticus (NORSE), acute disseminated encephalomyelitis (ADEM), encephalopathy, acute necrotizing encephalopathy, Guillain-Barre syndrome, transverse myelitis, Bell’s palsy, myocarditis, pericarditis, headache, intracerebral hemorrhage (ICH) and/or Subarachnoid hemorrhage (SAH), “vaccine-induced immune thrombotic thrombocytopenia/ vaccine-induced prothrombotic immune thrombotic thrombocytopenia” (VITT/VIPITTI) [63-67]. Overall EEGs appear to be clinically useful in evaluating and monitoring seizures, encephalopathy of various etiologies, and cognitive issues associated with long COVID [67-71].

A 22-year-old man developed refractory status epilepticus following the second dose of Moderna vaccine [72]. A 69-year-old female following the first dose of Moderna COVID-19

vaccine exhibited intermittent inattention, disorientation, left/right confusion, weakness, gait instability, and decreased speech. She developed acute transient encephalopathy. EEG morphology at 48-hours following manifestation of symptoms showed “diffuse triphasic waves, diffuse theta and delta slowing, and no posterior dominant rhythm [73].

Following the Pfizer vaccine, a 61-year-old woman presented with progressive generalized weakness and difficulty with communication, was encephalopathic and tachypneic and was diagnosed with acute disseminated encephalomyelitis (ADEM) [74]. EEG showed nonspecific diffuse cerebral dysfunction with seizures or epileptiform discharges. On treatment with methylprednisolone and intravenous immunoglobulin her condition improved

A year-long resting EEG follow-up study was carried out on a healthy 50-year-old male following vaccination with Comirnaty vaccine. 12 reference EEG recordings (r1-r12; taken on a monthly basis) and two post-Comirnaty vaccination recordings (p1, p2) were captured. Post-vaccination side effects were fever, headache, and foginess. Though foginess resolved by day five, the changes in EEG morphology remained indicative that the changes were vaccine-related rather than symptom-related. EEG morphology returned to normal by day-12. Decreased theta and alpha rhythm powers, indicators of response to acute stress were also observed. As absolute power deviation in the beta band remained unaltered the deduction was that the vaccine must have served as a biological stressor to the CNS [75].

124 articles directed at the neurological complication of COVID-19 reported that 300 patients had post-COVID Guillain-Barre Syndrome-GBS (PCG), 171 acute inflammatory demyelinating polyneuropathy, 24 with acute motor axonal neuropathy and 16 with sensory axonal neuropathy. Further the number of cases of PCG patients fell from 192 in 2020 to 75 in 2021 indicating a possible association between vaccination administration and PCG decline [76].

A systematic review of EEG changes in subjects vaccinated against COVID-19 (24 case reports + 7 case series=31 studies with a total of 36 participants) revealed generalized slowing and non-convulsive focal status epilepticus, background slowing and epileptiform discharges, were the most common EEG morphology observed post-vaccination. The most common neurological manifestations were headache, fatigue, generalized weakness, vomiting, encephalopathy, encephalitis, encephalopathies, demyelinating disorders post-ictal phases, confusion, encephalitis and, acute disseminated encephalomyelitis (ADEM) [77].

Studies on EEG wave morphology in para- or post-COVID

Table-1 and Table-2 give one a sense of the spectrum of neurological and neuropsychiatric complications due to COVID. Some of the cognitive deficits observed include; compromised simple reaction time (simple RT)/choice reaction time (choice RT)/go/no-go reaction time (go/no-go RT), compromised integration of perception and action, speech impediments, brain fog, post-COVID fatigue, physical and cognitive impairment. While neuropsychiatric disorders seen, ranged from post-traumatic stress symptoms (PTSS), to depression, to post-traumatic and persistent postural perceptual dizziness (PPPD) in elderly, to acute psychosis, to hallucinations etc

A case series of 43 patients served to further illustrate the point, with the spectrum of neurological complications due

to COVID seen categorized into a) encephalopathies (n=10), b) inflammatory central nervous system (CNS) syndromes (n=12) including encephalitis (n=2), acute disseminated encephalomyelitis (n=9), haemorrhagic (n=5), necrotic (n=1), myelitis (n=2), and isolated myelitis (n=1), c) ischaemic strokes (n=8), d) peripheral neurological disorders (n=8), Guillain-Barré syndrome(n=7), one brachial plexopathy (n=1), and e) miscellaneous central disorders (n=5) (78). In such instances EEG studies were performed to classify encephalopathy (61.7–90.4%), assess brainwave morphology for subclinical seizures (27.1–34 %), in critically ill subjects, mechanically ventilated patients, comatose subjects and in general to look for specific patterns in para-/post-COVID [79-82].

EEG abnormalities were classified into the following three broad categories to highlight similar findings and further sub-analyzed as follows [81]:

- **Background Abnormalities**

- Diffuse slowing
- Focal slowing
- Slowing of Posterior Dominant Rhythm (PDR)
- Absent PDR
- Attenuation
- Discontinuous EEG
- Asymmetry
- Decreased reactivity

- **Periodic and Rhythmic patterns**

- Generalized Periodic Discharge (PD)
- Lateralized/ multi-focal PD
- Generalized PD with triphasic morphology.
- Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDS)
- Unclassified PD
- Rhythmic activity

- **Epileptiform changes/discharges**

- Focal Epileptiform Discharges (ED)
- Generalized ED
- Multifocal ED
- Unspecified ED
- Seizures
- Status epilepticus (SE)

Diffuse slowing was the most common background abnormality observed (n = 423, 68.6 %). Rhythmic activity was further sub-categorized into generalized rhythmic delta activity (GRDA), lateralized/ multifocal rhythmic discharges and unclassified (n = 2, 0.3 %). Epileptiform changes/discharges and seizure morphology were also recorded.

COVID-19 related encephalopathy: A 5-year cohort study in 154 patients with altered mental status due to non-COVID encephalopathy revealed 5 distinct EEGs patterns; isolated continuous slowing of background a) theta, b) theta/delta, and c) delta activity, slowing background activity with episodic transients either d) triphasic waves (TWs) or e) frontal intermittent delta activity (FIRDA)]. The findings suggested a link between neuropathophysiology and EEG morphology. Multivariable analyses revealed that theta was associated with brain atrophy, theta/delta with intracerebral hemorrhages, delta

activity with alcohol/drug abuse with or without intoxication, and HIV infection, TWs with liver or multi-organ failure and FIRDA with past-cerebrovascular accidents. TWs were associated with death, theta/delta with unfavorable outcomes, and FIRDA with favorable outcomes [83].

Flamand et al in 2020 presented a case study that stressed the usefulness of EEGs [84]. The group presented a case study on a 80-year-old female who was COVID-negative via polymerase chain reaction (PCR) test, showed no COVID specific features on examination of cerebrospinal fluid (CSF) and brain magnetic resonance imaging (MRI), however full body computerized tomography (CT) revealed COVID-specific lung infection. While responding positively to treatment for bronchial involvement, she subsequently presented with restlessness, coupled with altered consciousness, with progressive worsening of awareness, followed by focal motor seizures.

- EEGs on day-6 and day-8 showed slowing of background activity and repetitive quasi-rhythmic epileptiform discharges in the bilateral frontal areas.
- EEGs on day-11, day-12, day-13, indicated that the outbursts were distinctly triphasic suggestive of toxic/metabolic encephalopathy.
- EEGs on day-18 and day-21 exhibited triphasic activity with a 1–1.5 s periodicity with worsened background activity.

This cross-border periodic triphasic activity EEG morphology is also seen in Creutzfeldt-Jakob disease, West Nile virus neuro-invasive disease and neurosyphilis. Medical history, clinical correlation, lack of metabolic derangement in light of the progressive neurological manifestations with corresponding changes in EEG morphology led the group to conclude that the neurological and EEG changes were associated with COVID-19 infection [84].

Veillieux et al presented two case studies with opposite outcome despite similar EEG patterns. Both COVID-positive subjects exhibited “non-reactive bifrontal monomorphic diphasic periodic delta slow waves”, irrespective of sedative used. They deduced that the EEG patterns might be specific to COVID-associated encephalopathy, capturing the temporal-specific neurological status and less specific of the outcome/prognosis [85].

In 15 (6 were males) subjects with suspected COVID-related encephalopathy, EEGs revealed slowing of the background activity that correlated with the severity of neurological symptoms/clinical manifestations with confusion, aphasia, and impairment of consciousness seen in 11, 1 and 4 subjects respectively [86]. In 13 subjects exhibiting background slowing from 4 to 8 Hz, “theta prevalence” was seen in 5, “theta/delta intrusions” in 4, “focal theta or delta predominance” was seen over the frontal or central regions in 3 and “frontal intermittent rhythmic delta activity (FIRDA)” was seen in 1 subject. Epileptiform wave morphology or triphasic waves were not observed. Repeat EEGs in 3 patients showed marked improvement in posterior activity that paralleled improvement in neurological symptoms. In the 2 cases with post-anoxic coma, Case-14 exhibited suppressed activity EEG morphology on day-1 following return of spontaneous circulation (ROSC) and Case-15 showed discontinued activity that correlated with status epilepticus on day-3 after ROSC [86].

Generalized slowing of EEG background was reported in 91–96.1 % of patients in two large case series and in a meta-

analysis of 12 studies [80,83]. Generalized periodic discharges (GPDs) with triphasic configuration, generalized rhythmic delta activity (GRDA), discontinuous background and burst-suppression pattern indicative of nonspecific encephalopathy [80,81,83]. Focal slowing (17 %) has been reported in a systematic review of 84 studies with 617 patients [81].

EEG, Seizures and Epilepsy: To optimize emergency status epilepticus (SE) management in relation to intensive care unit (ICU), ventilator and staff availability; a multidisciplinary approach is required. The EEG enables differentiation between convulsive and non-convulsive SE, subtle SE from postictal/drug-induced encephalopathy, psychogenic nonepileptic status, convulsive (tonic-clonic) SE, ambulatory forms of nonconvulsive status epilepticus and new-onset refractory SE (NORSE). The EEG is essential in nonconvulsive and convulsive events both in deciding diagnosis and treatment (antiseizure drug, ASD and sedation) in order to prevent systemic or cerebral complications [87]. EEG is also essential in monitoring unexplained encephalopathy in COVID subjects and when clinical symptoms of seizures present due to compromised BBB and/or cytokine reaction due to viral infection [88].

A study aimed at determining the risk factor for seizures examined cEEG findings in 197 COVID-19 patients from 9 centers in the United States and Europe. Ictal or interictal epileptiform abnormalities were present in 48.7 % of patients and seizures in 9.6 %, including status epilepticus in 5.6 % [89]. Hwang et al. reported on EEG findings in 192 patients at 4 hospitals in New York. Epileptiform abnormalities were present in 39.6 %, focal intermittent epileptiform discharges (25%), lateralized periodic discharges (6.3%), generalized periodic discharges (19.3%), and seizures occurred in 8 subjects [90]. Indications for EEG were based on the presence of encephalopathy (54.7%), seizure (18.2%), coma (17.2%), focal deficit (5.2%), and abnormal movements (4.6%). Background EEG activity included generalized slowing in 88.5%, focal slowing (15.6%), burst suppression (3.6%), attenuation (3.1%), with normal EEG observed in 3.1%. EEGs were available in 110/4110 (2.68%) hospitalized COVID-positive-patients from Southeast Michigan out of which 21.8% had new-onset seizure, 7% status epilepticus, and 87.5% had no prior history of epilepsy. Background slowing/attenuation (recovered 60% vs recovered/disabled 96% vs died 96%, $p < 0.001$) and normal EEG (recovered 27% vs recovered/disabled 0% vs died 1%, $p < 0.001$) were associated with outcome.

To answer the questing whether epileptiform abnormalities were more prevalent in COVID-positive (20/26, 76.9%) than -negative (6/26, 23.1%) subjects, 8-channel (Fp1, Fp2, F7, F8, T3, T4, T5, T6, O1, and O2) EEGs were carried out [91]. Indications for EEG among COVID-positive vs -negative subjects, were new onset encephalopathy (68.2% vs 33.3%) and seizure-like events (14/22, 63.6%; 2/6, 33.3%), even among subjects without prior history of seizures (11/17, 64.7%; 2/6, 33.3%). Sporadic epileptiform discharges (EDs) were present in 40.9% vs 16.7%. Frontal sharp waves were present in 8/9 (88.9%) COVID-positive subjects with EDs vs 1/1 of COVID-negative subject with EDs. No seizures were captured via EEG, perhaps because 19/22 vs 6/6 were already on antiseizure medications and/or sedatives [91].

In a retrospective study carried out in France, COVID-positive subjects, underwent EEG (n=78) and MRI (n=57). Clinical, biological, EEG and MRI findings were analyzed to ascertain if COVID-19-related encephalopathy (CORE)

could be predicted using clinical, EEG, and MRI data [92]. A model was developed using receiver operating (ROC) curve characteristics with an area under the curve of 0.94 (95% CI, 0.88-1.00; $p < 0.001$), a sensitivity of 76%, specificity 93%, positive predictive value 65%, negative predictive value 95%, and accuracy 91%. Subjects without CORE vs with CORE had movement disorders (6/9 vs 9/63; $p = 0.002$), frontal syndrome (7/9 vs 8/69; $p < 0.001$), brainstem impairment (4/9 vs 3/69; $p < 0.001$), periodic EEG discharges (4/9 vs 2/69; $p < 0.001$), and white matter-enhancing MRI lesions (3/9 vs 2/48; $p = 0.03$).

In a systematic analysis of 86 studies ($n = 617$, COVID-positive subjects), epileptiform discharges (focal, generalized, multiple and unspecified) were reported in (80/617, 13%), while seizures and status epilepticus were recorded in 1.9% (12/617) and 3.6% (22/617) respectively [81]. Variation in results may be due to a) heterogeneity of the cohorts, b) practice differences and para- and post-COVID sequelae [80,81,88-92].

EEG studies on 26 critically-ill COVID-positive subjects, 30-minute duration, using 9 channels arranged according to the 10–20 system (Cz, FP2, C4, O2, T4, FP1, C3, O1, and T3, with reference in FPz and ground in Oz) [93]. 5/26 had periodic discharges with absence of epileptic activity. 19/26 showed diffuse EEGs with nonspecific theta and alpha wave activity, with diffuse delta wave activity without focal or periodic features in some cases, and 2 had isoelectric EEGs consistent with brain death. Five patients, however, had evidence of generalized periodic discharges. The EEGs (5/26) displayed monomorphic biphasic delta activity or generalized rhythmic delta activity (GRDA) with < 4 -second intervals or lateralized periodic discharges (LPDs) of 1 to 2-second period with right frontal predominance. The EEG abnormalities can be summarized as generalized or LPDs that primarily consist of symmetric slow monomorphic biphasic delta waves of high amplitude occurring in short repetition of < 4 seconds. GRDA and LPD EEG findings with the presence of the monomorphic biphasic high-amplitude delta waves associated with occasional myoclonic muscular activity and they concluded could indicate brain injury due to anoxia, severe hypoxia, anesthesia, or the direct effects of COVID (vasculopathy and coagulopathy). Background slowing and theta activity in EEGs could be due to sedation, somnolence, coma, anoxia or hypoxia, and other CNS-depressive entities.

Creutzfeldt-Jakob Disease (CJD) is difficult to diagnose. With a survival expectancy of 1-year from symptoms onset and 4-months post-diagnosis, it is lethal [94]. Its hallmark; initial subtle psychiatric and neurological symptoms, (depression, anxiety, nervousness, autonomic disturbances, disruption of sleep–wakefulness rhythm, gait alterations) followed by rapidly progressing dementia with myoclonus, visual disturbances leading to cortical blindness, ataxia, and akinetic mutism [94]. Seizures, SE, non-convulsive status epilepticus (NCSE) though rare can manifest leading to a wrong diagnosis. Diagnosis is via clinical features, imaging, EEG, and cerebrospinal fluid (CSF) analysis [94]. Another study presented a case report of fulminant CJD in a COVID-positive individual presenting as NORSE followed by his death 15 days from admission [95]. A healthy 80-year-old man COVID-positive, diagnosed with probable sporadic CJD on admission, rapidly progressed to dementia, gait abnormalities and myoclonus. EEG findings showed diffuse activity slowing with high amplitude sharp/slow-wave complexes [96]. A 70-year-old COVID-positive lady with rapidly progressing dementia diagnosed as CJD, EEG

showed triphasic periodic sharp wave complexes [97]. A subtype of immune-mediated encephalitis associated with COVID, mimics acute-onset sporadic CJD. A 64-year-old man positive for COVID presented with confusion, aphasia, myoclonus, and silent interstitial pneumonia. Cognition and myoclonus rapidly deteriorated with EEG evolving to generalized periodic discharges [98]. Treatment with steroids and intravenous immunoglobulins produced EEG, clinical and neurological improvement at 6-month follow-up [98]. A previously healthy 60-year-old man developed fever days after the family members he was staying with were diagnosed with COVID. He became confused, slow, forgetful, and tested COVID positive. Over two weeks his disorientation worsened, he developed paucity of speech with paraphasic errors, and unsteady gait with intermittent right-hand clenching. On admission he was inattentive and perseverative, with non-fluent discourse, anomia, impaired comprehension, phonemic paraphasias, and intermittent myoclonic jerks of the right arm. EEG revealed abundant 1–1.5 Hz left lateralized periodic discharges and diffuse delta-theta slowing. He was treated with intravenous immune globulin (IVIG) and steroids (methylprednisolone) until CJD was confirmed. Neurologic status progressed to mutism, right hemiplegia, spontaneous multifocal myoclonus, somnolence and agitation culminating in his death 2-months after symptom onset.

A 19-channel-EEG study on “post/long-COVID Cognitive” and EEG abnormalities at 2-months (baseline, $n = 49$) and 10 months (follow-up, $n = 33$) with matched healthy controls inferred that cognitive and EEG abnormalities observed at 2-months improved at 10-months follow-up [99]. At baseline, 53% were impaired in at least one cognitive domain, with 16% “with pure” executive function, 6% with memory and 6% with visual-spatial impairments, and 25% with multidomain impairment. 28% showed psychopathological disturbances (10% depressive symptoms, 12% PTSD features, 6% both) and in general fared worse than healthy controls. EEG and exact low-resolution brain electromagnetic tomography (eLORETA) results showed lower individual alpha frequency (IAF), greater cortical current source densities (CSD) at delta frequency band in the bilateral frontal and central-temporal regions compared to healthy controls. As the connectivity analysis showed significant higher linear lagged connectivity (LLC), values at delta band for all pairs of regions of interest (ROI) i.e. bilateral frontal, central-temporal, and parieto-occipital regions the delta frequency band was further analysed via eLORETA. A reduction of LLC values between “left” -frontal and -parieto-occipital regions, and “right” -frontal and -central-temporal regions as well as between right frontal and left central-temporal regions, was seen.

Another study focused on cognitive function and EEG brain waves at baseline (15 days after diagnosis), 3-6 months and 6-12 months “post/long-acute-COVID” ($n = 53$) and healthy volunteers ($n = 30$) without COVID (100). EEG data at F3-F7, Fz-F3, Fz-F4, and F4-F8 channels at rest, and while performing the Trail Making Test Part-A (TMT-A, low cognitive demand), and the TMT-B (high cognitive demand) tests were obtained. Cognitive tests included the Montreal cognitive assessment (MoCA); digit span forward numbers (DSFN). DSBN = digit span backward number (DSBN), digit span forward line (DSFL). digit-span backward line (DSBL). Among the health volunteers, reduction in EEG activity was associated with an increase in time taken for the cognitive task (TMT-A and TMT-B). While in the post/long COVID-19 group reduction in EEG activity and complexity during the cognitive task was

associated with increase in time with worsening of cognitive tests scores and were indicative of cognitive deterioration. Reduction of electrical activity and signal complexity “at rest” and “during high cognitive demands” at F3-F7 and Fz-F4 areas at 6-12 months was also observed.

Studies on psychiatric and central nervous system (CNS) disorders “post-COVID-19 vaccination” (eg. encephalitis, ADEM, acute encephalopathy, acute necrotizing encephalopathy, seizures, and NORSE) found no specific association; with EEG patterns either normal, or displaying nonspecific generalized slow activity [3-8,101-106]. A case study on post-COVID-vaccination disorders reported on a case of bilateral optic neuritis following ChAdOx1 COVID-19 vaccination [107].

Changes in “Evoked potential” (EP, visual, auditory, somatosensory, and olfactory) para-COVID and post/long-COVID were also studied. No significant differences were seen between individuals post/long-COVID (n=76) versus 44 normal/control subjects (n=44) controls in terms of visual evoked potentials (VEP). However, prolonged P100 latencies were observed in 12 patients post/long-COVID [108]. A 62-year-old male presented with asymptomatic left optic neuropathy and prolonged left P100 latency. However, he had left eye amblyopia since childhood [109]. Brainstem auditory evoked responses (BAERs) in asymptomatic post-COVID-19 subjects (n=8) versus age-matched controls showed no differences between the two groups [110]. BAERs evaluated in subjects with severe-COVID who displayed difficulty in weaning off the ventilator (n=10) found four with increased interpeak III-V wave latency [111]. BAERs carried out in critically ill COVID subjects (n=17) was normal (n=6), displayed peripheral disorganization (n=9) and were uninterpretable due to agitation in n=2 [112]. The non-specific results suggest preservation of central somatosensory and auditory systems post-severe-COVID. Of 17 ICU patients tested for median somatosensory evoked potentials (SSEPs), n=2 were uninterpretable, peripheral abnormalities of N9 in latency or amplitude (n=2), 1 patient with Guillain-Barré syndrome showed no response and n=12 displayed normal N20 [112].

QEEG and sLORETA

A QEEG study comparing 12 pilots post-COVID and reported having impairments in concentration and vision and other medical issues, versus 8 pilots post-COVID who did not report having any such post-COVID issues. During the QEEG examination, values were read from all points (Cz, C4, C3, Fz, F3, F4, P3, and P4). A standard GSES questionnaire [113], that assesses self-efficacy i.e. a person's belief in dealing with difficult situations and obstacles [113].

Figure-2a presents a QEEG study that evaluated “brain waves associated with relaxation and concentration in pilots post-COVID”. The study group consisted of pilots post-COVID reporting impairments in concentration, vision, being tired, irritable and disoriented when receiving multiple auditory and visual input in the cockpit, etc. The control group comprised of pilots who did not have any such impairments post-COVID. Both control (n=12) and study (n=8) groups were administered the standard general self-efficacy scale (GSE) questionnaire and resting EEG-eyes open was performed [113]. QEEG examination at electrodes Cz, C4, C3, Fz, F3, F4, P3, and P4 revealed that the amplitude of alpha, theta, and beta2 waves (mean±standard deviation, μV) were significantly higher (at $p<0.001$) while sensorimotor rhythm (SMR) was significantly lower (at $p<0.001$) in study versus control group.

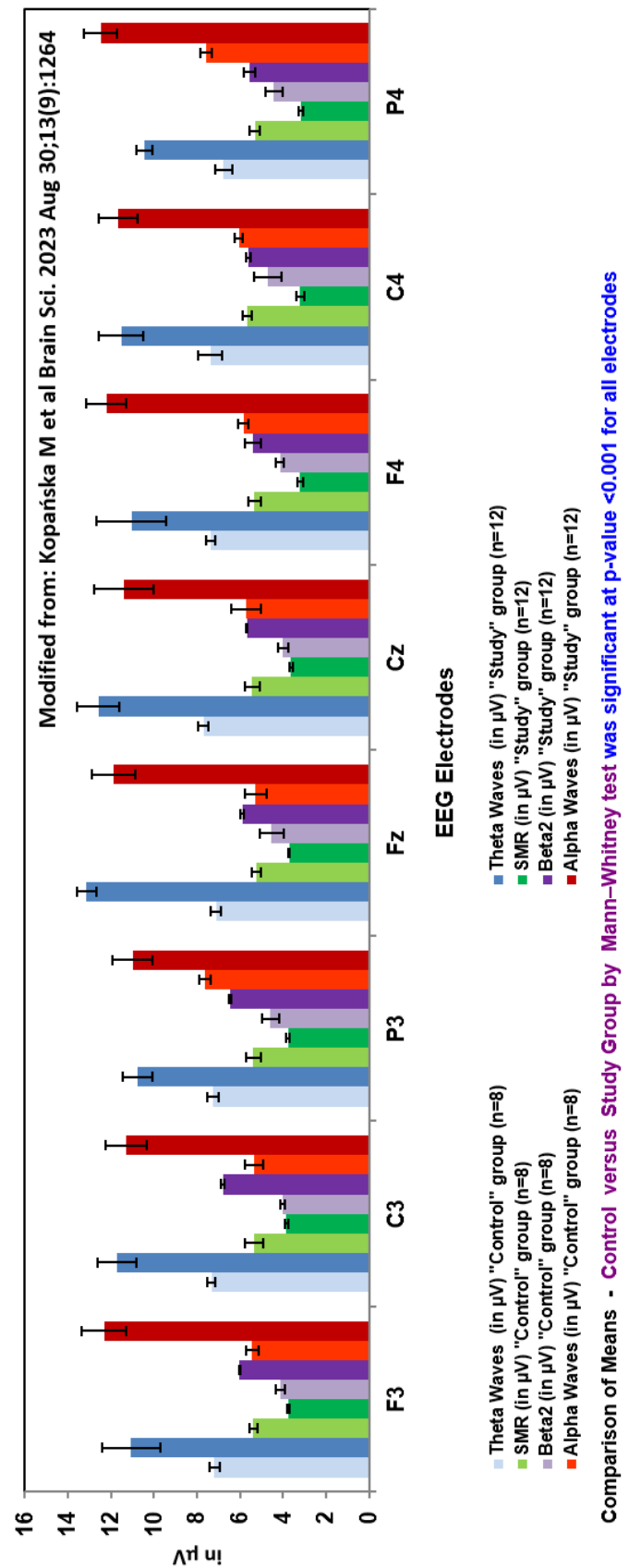
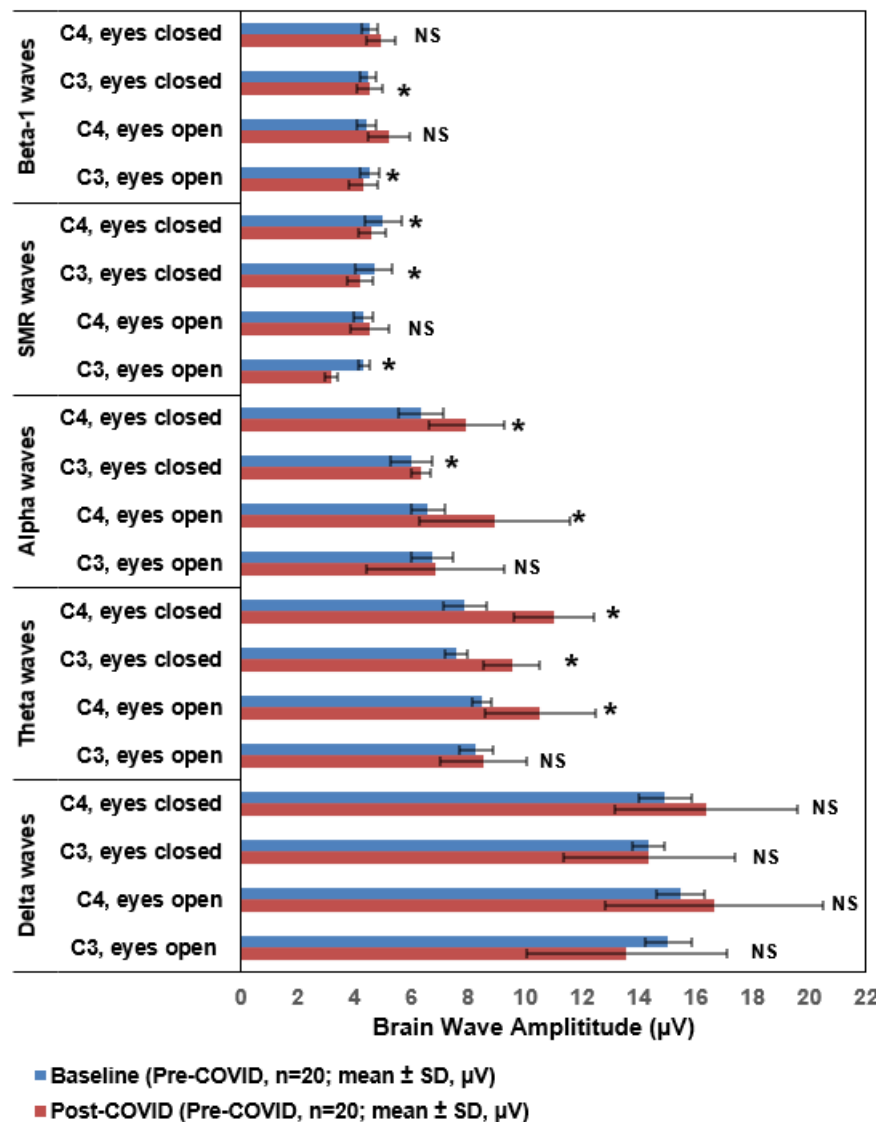


Figure 2a. Quantitative Electroencephalography (QEEG) to Assess Post-COVID-19 Concentration Disorders in Professional Pilots



Modified from: Kopańska M et al, *Sensors (Basel)*. 2022 Sep 1;22(17):6606

Figure-2b: Quantitative Electroencephalography (QEEG) to Assess Baseline Versus Post-COVID Brain Wave Amplitudes among University Academic Staff

Another study focused on, “whether subjectively described post-COVID symptoms of brain fog, cognitive impairment, disorganization of behaviour etc., were associated/correlated with corresponding changes in QEEG profile”. The study compared “at baseline (pre-COVID)” versus “post-COVID” amplitude (µV) of delta, theta, alpha, SMR, and beta-1 waves amplitudes at C3 (left hemisphere) and C4 (right hemisphere), 10/20 system, eyes open/closed using the Cz montage and the Cz electrode as the common reference in 20 out of 145 university academic staff (on whom prior baseline EEG values were available) who had ≥5 cognitive issues [114]. Study findings (Figure-2b) provide clear evidence that quantitative comparison of C3 and C4, eyes open/closed, QEEG-based “baseline” versus “post-COVID” brain wave amplitudes proved significantly different, and are reflective of the post-COVID symptoms reported.

Brain injury due to COVID-related acute encephalopathy or hypoxic-ischemic encephalopathy or in critically ill comatose

COVID patients is commonly observed. One study “looked at the ability of continuous EEG (cEEG) to predict neurological outcome”. Three-channel-bipolar-montage (P3-O1, Fz-Cz, P4-O2) with 40 second epochs capturing EEG reactivity to vocal-, noxious- and tactile-sensory stimuli in 10 patients (good outcome%=50%), over 37 patient-days, following sedative and paralytic medication withdrawal were analyzed [115]. “Baseline” i.e. prior to sensory stimuli versus “EEG reactivity” to: vocal (calling patients’ by name and clapping), tactile (sternal rub and trapezius pressure) and noxious (via nose stimulation with a swab) stimuli were compared. QEEG/EEG-reactivity measures included spectral power changes and temporal-variance in delta, theta, alpha, spindle, and beta waves at “baseline” and following the above “stimuli”. The multiple independent t-test with false discovery rate (FDR) correction was used to detect differences in spectral power between those with good versus poor outcome. Theta power and theta temporal-variance at “baseline” versus “EEG reactivity to stimuli” were

Modified from: Kopańska M et al, Clin Neurophysiol. 2021 Mar;132(3):730-736

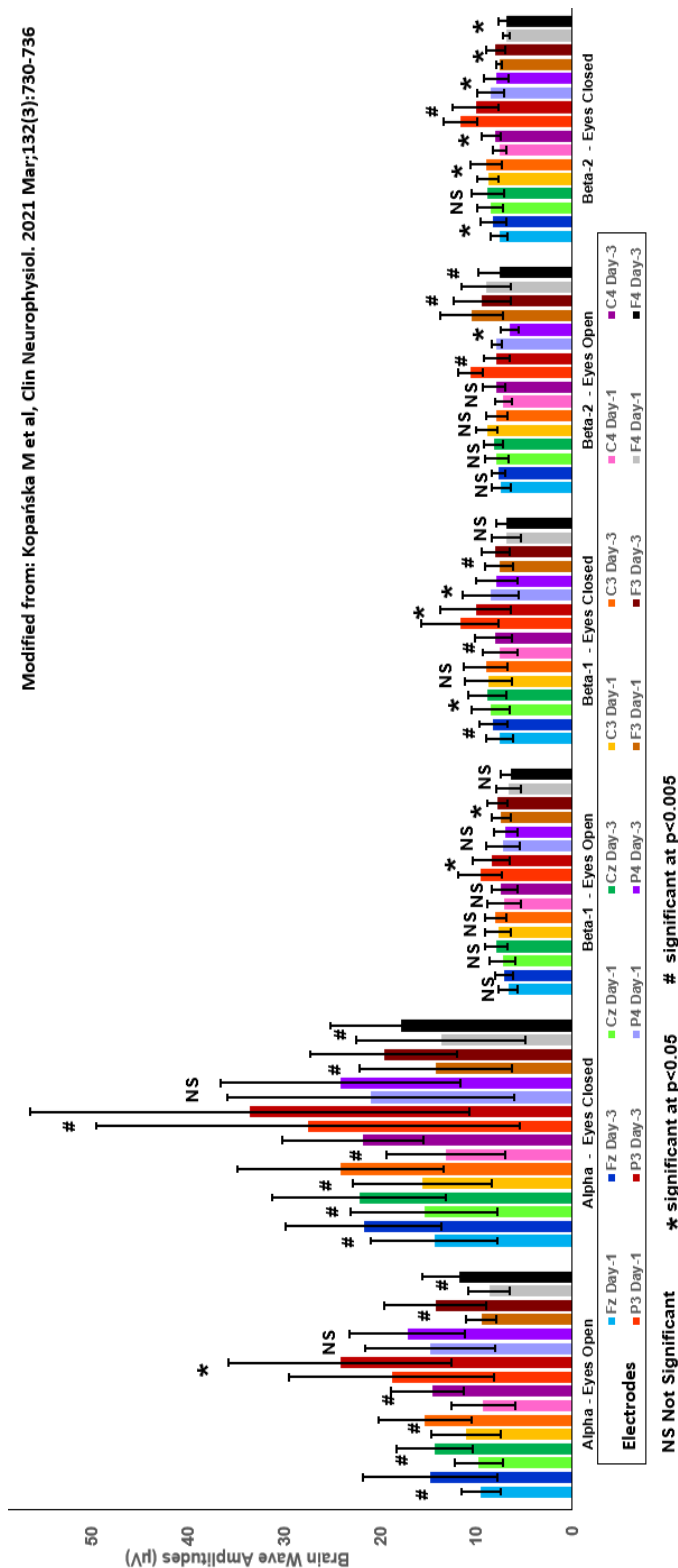


Figure-2c: QEEG Study Comparing Differences in Mean ± SD Brain Wave Amplitudes (µV): Before (Day-1) Versus After (Day-3) the SKY relaxation course (n=15) using the Wilcoxon paired test

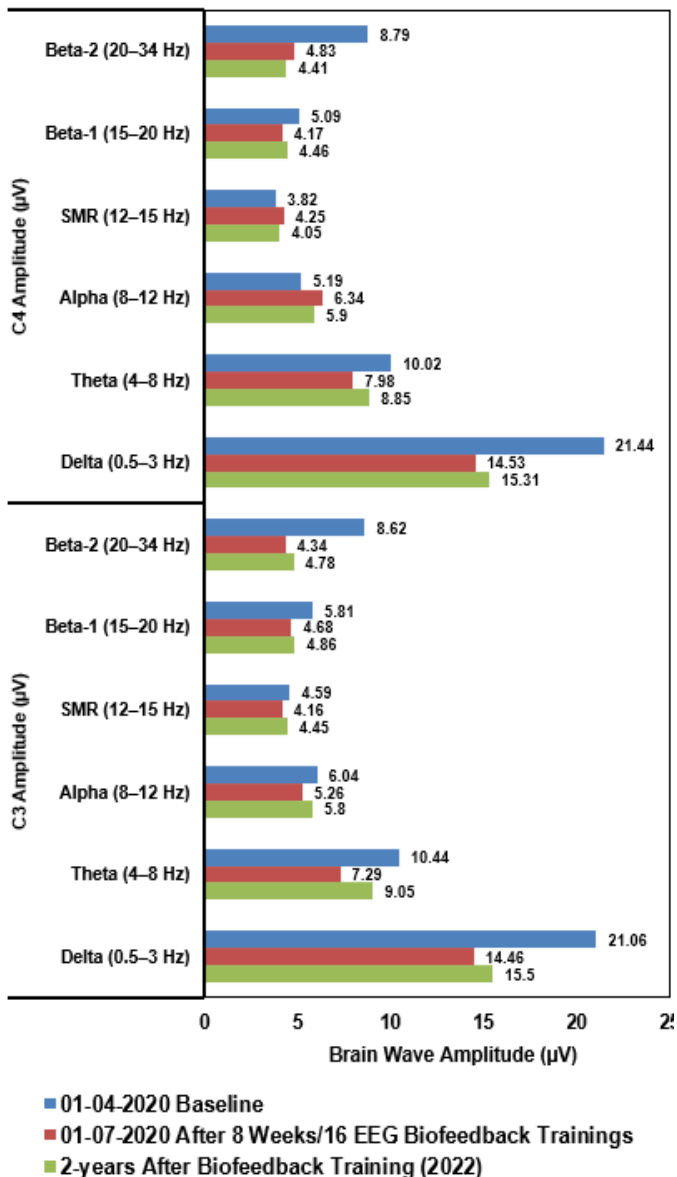
the best predictors of good neurological outcome (odds ratio > 2.39; pFDR < 0.005). Spectral-heat maps comparing good (n=2) versus poor (n=2) outcome also indicated that higher EEG activity in the theta-alpha range especially in “EEG reactivity

to stimuli” was a good predictor of good outcome. Delta-theta spectral power was also a significant predictor (t's > 2.93, pFDR < 0.005, effect-sizes > 0.33) of good outcome (n=5) for all three channels, both at baseline and during EEG reactivity to stimuli. Higher temporal-variance with greater diversity in frequency bands and spatial extents (Levene's F > 6.32, pFDR < 0.005) was another strong predictor of good outcome.

“Frontotemporal 98-days EEG-guided sedation” (5 frontotemporal EEG leads (Fp1, Fp2, F7, F8, Fpz/reference and a ground electrode, 10/20 system) was used in 11 consecutive critically ill COVID positive patients [116]. EEG-guided sedation has the advantage of ensuring shorter duration of exposure to intensive care unit (ICU) and mechanical ventilation as well as effective use of sedatives. Sedation status was classified using random forest algorithm with an accuracy of 80% ± 17% using Power Spectral Density (PSD) in the specified frequency bands. Sedation was considered adequate if the EEG displayed predominantly continuous background activity while markedly attenuated or discontinuous EEGs (≥3 seconds), was classified as high level of sedation. The study limitations cautioned that attenuation and discontinuity in EEG patterns also occurred in hypoxic-ischemic injury or cerebral infarction and that clinical correlation was required in such cases.

QEEG was used in defining brainwave patterns in “critically-ill subjects” post-ICU post-COVID related encephalopathy [117]. The clinical characteristics of subjects with infectious toxic encephalopathy (ENC) were n=31, male%=51.6%, age (years) 74.2±16.6, level of alertness (%): Fully alert 22.6%, Confused 38.7%, Stuporous 32.3% and Comatose 6.5%. Subjects with SARS-CoV-2 (COVID) were n=20, male%=85%, age (years) 63.9±12.1, level of alertness (%): Fully alert 10%, Confused 50%, Stuporous 40%, and none were Comatose. Subjects with encephalopathy after cardiorespiratory arrest (CRA) were n=21, male%=95.2%, age (years) 62.8±11.4, level of alertness (%): none were fully alert, Confused 14.3%, Stuporous 4.8% and Comatose 81%. The grading for 120-300 s epoch length EEGs (divided into 1-second (s) windows with 10% overlap) followed in this study were EEG grade-I: excess of slow posterior activity; EEG grade- II: predominant theta activity in more than 50% of recording; EEG grade-III: predominant delta activity in more than 50% of recording; and EEG grade-IV: burst-suppression pattern. EEG findings for ENC were: grade-I =12.9%, grade-II =32.3%, grade-III = 51.6%, grade-IV =3.2%) versus EEG findings for COVID: grade-I=25%, grade-II=20%, grade-III=60%, none were grade-IV; versus EEG findings for CRA: where none were grade-I, grade-II=9.5%, grade-III 28.6%, and grade-IV=61.9%. EEGs of COVID patients were near-physiological in pattern. EEG bands of the COVID group were midway ENC and CRA in terms of distributions. However, Shannon's spectral entropy (SSE) was higher and hemispheric connectivity lower for COVID subjects.

A QEEG study evaluated the efficacy of a “Breathing-based meditation technique in treating post-COVID cognitive issues”. Sudarshan Kriya Yoga (SKY), is a breathing and meditation technique that involves controlled, rhythmic, and cyclic breathing and is known to improve concentration and relaxation [118]. The technique was taught to 15 individuals 2-months post-COVID by trained professionals from the Art of Living (AOL); a non-profit organization. Pre- (day-1) and post- (day-3) the “SKY course”, brainwaves (delta, theta, alpha, SMR, beta1, and beta2 waves) were captured from the central (Cz, C3, and C4), frontal (Fz, F3, and F4), and parietal (P3,



Modified from: Kopańska M et al, Brain Sci. 2022 Nov 14;12(11):1541

Figure-2d: A QEEG Case study: Brainwaves at Baseline, after 8-weeks Neurofeedback and 2-years Post- Neurofeedback Treatment of COVID-19-Related Panic Attacks

P4) channels, 10–20 system using resting EEG (eyes open/closed). Pre-“SKY course” (day-1) delta, theta, alpha, SMR, beta1, and beta2 brainwaves at eyes open and eyes closed were compared with post-“SKY course” (day-3) brain wave values. Figure 2-c provides a graphical illustration of the results of that comparison.

EEG-based Neurofeedback (EEG-NF) has been used to treat behavior, mood, depression and anxiety [119]. Figure 2d presents the results of a “case study on the potential of QEEG and Neurofeedback for assessment and treatment of panic attacks (PA)” [120]. The subject’s clinical history was as follows; a 47-year-old man, with an academic degree, working in a management position and married for 15 years with 2 children was affected by PA. He had no prior history of either panic attacks or receiving any psychological treatment. He

presented with severe panic attacks, vegetative symptoms and both destructive and negative thoughts. The PA followed him testing COVID-19 positive, his fear of contracting COVID, his perception of how it affected his overall health, and his fear of unemployment. “Baseline” EEG recordings (central strip Cz-C3-C4) were obtained prior to commencement of “EEG/QEEG-based Neurofeedback”.

Sixteen, “EEG/QEEG-based Neurofeedback” 30-minute sessions (two sessions per week for two consecutive months), i.e. 15 minutes feedback on each point for both hemispheres, with 1-3 min long treatment-units were carried out. The “SMR/Theta training protocol” was used for neurofeedback training as was a described below:

- **“SMR training protocol”:** The goal was to maintain the SMR wave amplitude and equalize SMR, Beta-1 and Beta-2 wave amplitudes. This was achieved by reducing Beta-2 wave amplitude to SMR wave amplitudes. This would mimic the normal process of inhibition of stimuli i.e. one’s ability to self-regulate and restore calm when one is anxious. From Figure-2d one can appreciate that as SMR values at “Baseline” were $<5\mu\text{V}$ the threshold for inhibiting Beta1 and Beta2 wave amplitudes was set at and brought to $\leq 4.5\mu\text{V}$ at both C3 and C4 channels when measured at “2-months neurofeedback treatment i.e. treatment end-point”. The threshold for inhibiting the amplitude of Beta2 waves decreased from a peak of activity—from about $9.5\mu\text{V}$ to $6.5\mu\text{V}$.
- **The Theta protocol”:** By inhibiting Theta waves at $<15\mu\text{V}$, Delta waves went from $21\mu\text{V}$ to $\leq 15.5\mu\text{V}$ thus resulting in the restoration of the ratio of Theta power is to Delta power (1:1 ratio, power equalization).

Figure-2d presents the brain wave amplitudes “at baseline”, “following 2-months neurofeedback treatment” and “2-years after treatment”. Delta, Beta1 and Beta2 waves amplitude reduction are indicative of increased cortical activity and restoration of the “normal” sequence of “stimulation” and “rest”. The authors also emphasized that the educational level of the study subject was key to the study outcome i.e. he could comprehend and follow his own neurophysiological activity and attempt to influence it (119).

These findings serve to reiterate the possible objective, justifiable and adjunct usefulness of EEG, QEEG and sLORETA in triage and when clinically assessing, treating and monitoring treatment efficacy of pertinent para-COVID and post-COVID sequelae. However, main challenges anticipated are:

- The ability to differentiate between pre-existing EEG morphological abnormalities i.e. prior to COVID infection.
- The ability to differentiate neurotrophic related specific changes from those that possibly result from pulmonary/systemic deterioration observed in para- and post-COVID-19.
- Overinterpretation of changes in brain function due to the multi-domain impairment/multi-organ damage and non-specific symptoms observed in para- and post-COVID-19.
- Intact cerebral morphology indicated by unremarkable CTs or MRIs alone do not always indicate good clinical status/outcome. Thus, it would be prudent to assess the impact of the COVID-19 infection on the EEG spectrum/records in the context of structural changes to

the brain.

- At the present time, there is no definite evidence to support the presence of a specific EEG pattern associated with COVID-19 encephalopathy and other COVID-related neuro disorders. There is a need for a large sample size to decide on para- and post-COVID causative and associative changes in EEG morphology, the frontal preponderance of EEG abnormalities, the alpha coma pattern observed in certain instances in severe encephalopathy [80,81,83,85,91-93,121].
- Maximizing the potential of QEEG-based neurofeedback therapy in treating cognitive issue and EEG-, QEEG- and sLORETA-based medication/sedation prescription and dose titration

Conclusion

The COVID pandemic in its wake with its para- and post-COVID sequelae has added to the burden of neurological, neurocognitive, and neuropsychiatric disorders and behavioral issues. The general global consensus is that of “preparedness” should another pandemic occur; especially pertaining to the para-, and post-repercussions of infections be they viral or bacterial. Increasing global connectedness due to social networking for commerce, science and technology, art, education, and travel; mean that infection control measures need to remain the “new norm”. Otherwise, we could be looking at an infection reaching pandemic proportions even prior to its detection. When the COVID pandemic was declared, it was thought to only affect the respiratory system resulting in near “ceasure” of EEG-based assessment of cortical health due to pandemic restrictions. It soon became clear that the healthcare system was dealing with epilepsy, encephalopathy, encephalitis, delirium, seizures, insomnia, brain fog, cognitive issues, memory loss, cognitive issues, depression, panic attacks, anxiety etc of both non-COVID and COVID origin. Conditions for which the EEG is pivotal as one of the battery of assessment tools. EEG-based brainwave morphology, qEEG-based brain mapping and sLORETA-based source location today serve as cost-effective “first-line” tools in triage, screening, diagnosis, monitoring, guiding therapy and as therapy. In the context of “present need and future requirement”, the focus in the field of EEG-based neuro care is on:

- development of EEG-, QEEG- and sLORETA-based markers of cortical health and para- and post-COVID sequelae
- development and use of EEG- and QEEG-based neurofeedback for use in treatment of para- and post-COVID sequelae where possible and appropriate
- better, accurate and more sensitive EEG, qEEG and sLORETA equipment and software,
- substitution of reusables with disposables where possible,
- use of wireless or remote testing,
- better hygiene and safety measure like; cost-effective protective clothing, reducing exposure time, that would ensure safety of both healthcare providers and patients alike.
- Measures to contain infection spread if we should face another variant need to be in place and ready to deploy
- Neurological complications caused by COVID-19 are frequent and represent a risk that compromises

the functional capacity and the life of patients. The suspicion of these conditions, the strict control of metabolic alterations and cardiovascular risk factors, the effective and safe treatment of these entities, are a current challenge and have been throughout the pandemic. The rehabilitation process in these patients remains a challenge. This is due to the limitations generated by multi-organ damage, risk of brain death and multi-domain brain/cognitive impairment observed.

Abbreviations

1-dimension: **1-D**; 2-dimension: **2-D**; 3-dimension: **3-D**;
 Acute Disseminated Encephalomyelitis: **ADEM**; Adverse Events: **AEs**; Adverse Events Following Immunization: **AEFIS** (Also Known As: **A.K.A**); Angiotensin-converting enzyme 2: **ACE2**; Anti-Seizure Medication: **ASM**; Antiseizure Drug: **ASD**; Art Of Living: **AOL**; Background Amplitude: **BGA**; Background Frequency: **BGF**; Blood-Brain Barrier: **BBB**; Blood-Cerebrospinal Fluid: **BCSFB**; Brain Magnetic Resonance Imaging: **MRI**; Brodmann's areas: **BA**; Cardiorespiratory Arrest: **CRA**; Central Nervous System: **CNS**; Central Points, EEG Electrodes Positions, 10/20 System: Cz, C3, And C4; Cerebrospinal Fluid: **CSF**; Chloroquine: **CQ**; Choice Reaction Time: **Choice RT**; Computerized Tomography: **CT**; Continuous EEG: **cEEG**; Continuous Video-EEG: **cvEEG**; CORONAVIRUS DISEASE: **COVID-19**; Post-Acute COVID-19 Syndrome: **PACS**; Electroencephalogram-neurofeedback: **EEG-NF**; Electroencephalography: **EEG**; Epileptiform Discharges: **ED**; ERP Nomenclature: C1, P1, P200, P300, P3a, P3b, P600, N100, Visual N1, N170, N200, N2pc, N400; Event-Related Oscillations: **EROs**; Event-Related Potentials: **ERPs**; Facemasks: **FMs**; False Discovery Rate: **FDR Correction**; Frontal Intermittent Delta Activity: **FIRDA** (Frontal Points, EEG Electrodes Positions, 10/20 System: Fz, F3, And F4; General Self-Efficacy Scale: **GSE** Questionnaire; Go/No-Go Reaction Time: Go/No-Go RT; Hydroxychloroquine: **HCQ**; Independent Component Analysis: **ICA**; Infectious Toxic Encephalopathy: **ENC**; Intensive Care Unit: **ICU**; Intracerebral Hemorrhage: **ICH**; Lopinavir/Ritonavir: **LPV-R**; Magnetic Resonance Imaging: **MRI**; Messenger Ribo-Nucleic Acid: **mRNA**; Micro Volts: **μV**; Multi Organ Damage: **MOD**; Neutrophil Extracellular Traps: **NETs**; New-Onset Refractory Status Epilepticus: **NORSE**; Nonconvulsive status epilepticus: **NCSE**; Occipital Points, EEG Electrodes Positions, 10/20 System: O1, O2; Panic Attack: **PA**; Parietal Points, EEG Electrodes Positions, 10/20 System: P3, P4; Periodic Discharge: **PD**; Peripheral Nervous System: **PNS**; Persistent Postural Perceptual Dizziness: **PPPD**; personal protective equipment: **PPE**; polymerase chain reaction: **PCR**; Post-Acute COVID-19 Syndrome: **PACS**; Post-COVID Guillain-Barre Syndrome-**GBS**: **PCG**; Posterior Dominant Rhythm: **PDR**; Post-Traumatic and Persistent Postural Perceptual Dizziness: **PPPD**; Post-Traumatic Stress Symptoms: **PTSS**; Power Spectral Density: **PSD**; p-Value: **p**; Quantitative Electroencephalography: **QEEG**; Renin-Angiotensin-Aldosterone System: **RAAS**; Resting State Electroencephalography: **rsEEG**; Return Of Spontaneous Circulation: **ROSC**; Rhythmic Discharges: **RD**; Second: **s**; Sensorimotor Rhythm: **SMR**; Serious Adverse Events: **Serious AEs**; Severe Acute Respiratory Syndrome Coronavirus: **SARS-Cov-2**; Shannon's Spectral Entropy: **SSE**; Simple Reaction Time: **Simple RT**; Standardized Low Resolution Brain Electromagnetic Tomography: **sLORETA**; Status Epilepticus: **SE**; Stimulus-induced rhythmic, periodic, or ictal discharges: **SIRPIDS**; Subarachnoid Hemorrhage: **SAH**;

Sudarshan Kriya Yoga: SKY; Temporary Tattoo Electrodes: TTEs; Triphasic Waves: TWs; Vaccine-Induced Immune Thrombotic Thrombocytopenia: VITT; Vaccine-Induced Immune Thrombotic Thrombocytopenia/ Vaccine-Induced Prothrombotic Immune Thrombotic Thrombocytopenia: VITT/VIPITTI; Vaccine-Induced Prothrombotic Immune Thrombotic Thrombocytopenia: VIPITTL; Versus: vs; Video-EEG Monitoring: VEM; World Health Organization: WHO

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