Received: 14 December 2023 | Revised: 16 May 2024 | Accepted: 31 May 2024

DOI: 10.1002/alz.14089

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Parallel electrophysiological abnormalities due to COVID-19 infection and to Alzheimer's disease and related dementia

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Funding information
United States National Institute of Health; National Institute of Aging, Grant/Award Numbers: P01AG078116, P30AG072946, R01AG063857, R01AG057234, R01AG054484, R56AG060608,

Abstract

Many coronavirus disease 2019 (COVID-19) positive individuals exhibit abnormal electroencephalographic (EEG) activity reflecting "brain fog" and mild cognitive impairments even months after the acute phase of infection. Resting-state EEG abnormalities include EEG slowing (reduced alpha rhythm; increased slow waves) and epileptiform activity. An expert panel conducted a systematic review to present compelling evidence that cognitive deficits due to COVID-19 and to Alzheimer's disease and related dementia (ADRD) are driven by overlapping pathologies and neurophysiological abnormalities. EEG abnormalities seen in COVID-19 patients resemble those observed in early stages of neurodegenerative diseases, particularly ADRD. It is proposed that similar EEG abnormalities in Long COVID and ADRD are due

1R21AG046637; United States Department of Veterans Affairs, Grant/Award Number: 5I21RX003173; Alzheimer's Association, Grant/Award Numbers: SG-20-725707, HAT-07-60437, AARF-21-848281; ANID/FONDECYT Regular, Grant/Award Numbers: 1210195, 1210176, 1220995; ANID/PIA/ANILLOS, Grant/Award Number: ACT210096; FONDEF, Grant/Award Numbers: ID20I10152, ID22I10029; ANID/FONDAP, Grant/Award Numbers: 15150012, 15150012; Takeda, Grant/Award Number: CW2680521; MULTI-PARTNER CONSORTIUM TO EXPAND DEMENTIA RESEARCH IN LATIN AMERICA; Tau Consortium; Global Brain Health Institute; HORIZON 2021, Grant/Award Number: H2021-MSCA-DN-2021; Marie Skłodowska-Curie Doctoral Networks, Grant/Award Numbers: 101071485, PNRR-MAD-2022-12376415; Italian Ministry of University, Scientific and Technological Research, Grant/Award Number: 2010SH7H3F

to parallel neuroinflammation, astrocyte reactivity, hypoxia, and neurovascular injury. These neurophysiological abnormalities underpinning cognitive decline in COVID-19 can be detected by routine EEG exams. Future research will explore the value of EEG monitoring of COVID-19 patients for predicting long-term outcomes and monitoring efficacy of therapeutic interventions.

KEYWORDS
ACE2, Alzheimer's disease and related dementia, astrocytes, background frequency, brain fog, coronavirus and EEG, COVID-19, encephalopathy, inflammatory cytokine storm, Long COVID, long COVID, resting EEG, SARS-CoV-2

Highlights

- Abnormal intrinsic electrophysiological brain activity, such as slowing of EEG, reduced alpha wave, and epileptiform are characteristic findings in COVID-19 patients. EEG abnormalities have the potential as neural biomarkers to identify neurological complications at the early stage of the disease, to assist clinical assessment, and to assess cognitive decline risk in Long COVID patients.
- Similar slowing of intrinsic brain activity to that of COVID-19 patients is typically seen in patients with mild cognitive impairments, ADRD. Evidence presented supports the idea that cognitive deficits in Long COVID and ADRD are driven by overlapping neurophysiological abnormalities resulting, at least in part, from neuroinflammatory mechanisms and astrocyte reactivity.
- Identifying common biological mechanisms in Long COVID-19 and ADRD can highlight critical pathologies underlying brain disorders and cognitive decline. It elucidates research questions regarding cognitive EEG and mild cognitive impairment in Long COVID that have not yet been adequately investigated.

1 | INTRODUCTION

This review is written to highlight the relevance of neurophysiological evaluation of coronavirus disease 2019 (COVID-19) patients in support of their clinical care and to highlight similarities between potential pathological mechanisms that contribute to the neurological consequences of COVID-19 infection and neurodegenerative diseases, including Alzheimer's disease (AD). Abnormal electrophysiological brain activity is a characteristic finding in COVID-19 patients who exhibit reduced power in the resting state electroencephalographic (rsEEG) alpha rhythm (8–12 Hz; arousal state and attention). Additionally, both COVID-19 and ADRD patients show widespread increases in power of delta (<4 Hz) rhythms.

These changes are often accompanied by mild cognitive impairment (MCI) such as memory problems and brain fog. Similar slowing of resting brain activity is typically seen in patients with MCI and Alzheimer's disease and related dementias (ADRD). Here we present evidence that abnormal EEG and related cognitive deficits in COVID-19 and ADRD are driven by overlapping neurophysiological abnormalities. These neurophysiological abnormalities can be detected by routine EEG exams.

2 | LONG COVID, NEUROLOGICAL AND COGNITIVE SYMPTOMS, AND EEG SIGNATURES

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can induce "Long COVID," a postacute sequela of COVID-19 that refers to persistent symptoms continuing for months or longer after the initial SARS-CoV-2 infection. The persistent symptoms affect multiple physiological systems with respiratory, cardiovascular, neurological, and psychological symptoms.[1] One study found that 76% of individuals with mild-to-moderate COVID-19 experienced at least one persistent symptom 6 months after their initial infection.[2] Another study found that 52% of COVID-19 survivors experienced persistent symptoms 3 months after infection. These persistent symptoms can significantly impair individuals' quality of life and result in higher healthcare costs.[3]

RESEARCH IN CONTEXT

1. **Systematic review**: We have applied all aspects of a systematic review in the writing process. The expert panel of electrophysiological professional interest area, which is connected to Alzheimer Association has previously published a review on pathological slowing of resting-state electroencephalographic (EEG) in Alzheimer's disease and related dementias (ADRD) patients. After we identified the research questions on the connection between coronavirus disease 2019 (COVID-19) and EEG, we conducted the key words search from multiple sources, for example, PubMed, Google scholar, NIH, CDC, and literature software. We set the criteria for the present review on EEG signatures of Long COVID literature to curate relevant references specific to EEG studies in COVID-19 positive individuals. Additionally, we enhanced our expert panel of electrophysiological experts of ADRD and COVID-19 by inviting additional experts in neurophysiology and astrocyte reactivity and neuroinflammation. Additional references were identified by the authors on the expert panel especially new publications through 2024. Aimed to cover all related EEG and Long-COVID studies, the review was also benefited from co-authors' research on COVID-19 and EEG, publication recommendations, and personal communications from the experts.
2. **Interpretation**: Similar slowing of resting brain activity to that of COVID-19 is typically seen in patients with mild cognitive impairments. Our review presents new evidence and supports the idea that cognitive deficits due to COVID-19 and ADRD are driven by overlapping pathologies, also reflected by similar neurophysiological abnormalities. Both neural inflammation and cytokine/complement activation in COVID-19, amyloid and tau pathologies in ADRD contribute to astrocyte over reactivity, leading to synaptic dysfunction in neurodegenerative diseases. Astrocytes are likely a primary target of COVID-19 because of the close interaction with the vasculature. Evidence presented here suggests that astrocytes are indeed injured/activated by COVID-19 infection or infection with similar viruses resulting in neuroinflammation. Parallel changes in astrocyte reactivity are found in ADRD and are suspected to cause synapse loss and neurodegeneration. What we have learned in the ADRD field may give us clues to how reactive astrocytes contribute to the neural morbidities seen in COVID-19, for example, astrocyte reactivity leads to the production of Complement C3 and loss of glutamate transport, both of which can damage synapses. Postsynaptic current and synchrony of oscillations is what EEG measures.
3. **Future directions**: (1) Determine the value of EEG monitoring of COVID-19 severity and prediction of long-term consequences and cognitive decline risk. (2) Investigate EEG measurements as proxy for synaptic dysfunction due to astrocyte-microglia reactivity and pathology. (3) Establish specific EEG features closely associated with COVID-19 disease and cognitive dysfunctions. (4) Identify common EEG features in both COVID-19 and ADRD. (5) Evaluate EEG network features as neural biomarkers for clinical trials of pharmacological and nonpharmacological interventions in COVID-19 patients. (6) Assess variations of COVID-19 related EEG indicators in diverse populations.

2.1 | Neurological and cognitive symptoms of Long COVID

Neurological symptoms are a significant part of Long COVID, and understanding the underlying mechanisms is crucial for better diagnosis and treatment. In a meta-analysis of 18 studies on 10,530 patients 3 months after COVID-19 onset, overall prevalence of neurological symptoms was 32% for brain fog, 28% for memory problems, and 22% for attention disorder.[4] Another report with clinical observations of neurological complications in 236,379 patients in the 6 months after a COVID-19 diagnosis found that 33.62% of patients had demonstrated clinically significant neurological or psychiatric dysfunction.[5]

Neurological symptoms of Long COVID reflect the COVID-19 neuroinvasion and include headache, tremors, problems with attention and concentration, sluggish cognitive function, dysfunction in the peripheral nerves, and mental health problems.[6,7] Beyond these typical brain fog symptoms, systematic evidence suggests frequent associations with depression[4] and post-traumatic stress disorder (PTSD).[8] Together, these symptoms can be characterized as "brain fog." The American Medical Association defines brain fog as some persistent neurological symptoms, including slowed cognition, concentration difficulties, confusion, and forgetfulness.[9] Most people with Long COVID report instances of severe fatigue and brain fog several months after their initial infection.[10] Those symptoms may fluctuate or relapse over time.[11]

The relationship between SARS-CoV-2 infection and cognitive impairment is another important topic.[12] Long-term effects of COVID-19 on cognition are illustrated by a recent case study, reporting a 62-year-old woman suffering from persistent cognitive deficits 8 months after COVID-19 infection with no preinfection history of cognitive impairment. At follow-up observation, the individual showed symptoms of memory loss, confusion, slowed motor function, and difficulty in language production and comprehension.[13] Similarly, a recent study examining cognitive functioning in adults following a COVID-19 infection found that those with persistent unresolved symptoms exhibited larger deficits than those with quickly resolved symptoms and those in the non-COVID-19 control group.[14] Those deficits included poor memory and reasoning, as well as increased brain fog.

These studies present a model for potential neurophysiological and neurological dysfunctions due to COVID-19 neuroinvasion.[13,15–17]

As research has progressed throughout the pandemic, a growing number of studies have reported cases of Long COVID patients suffering from similar impairments in focus and attention, memory retrieval, executive functioning, language production, and visuospatial abilities.[1,17–20] This cognitive impairment did not occur only in the acute disease phase and in severe cases.[21,22] Possible causes of emergence of ADRD included microglial inflammation,[23] ischemic changes associated with COVID-19,[24] and endothelial lesions that can impair the clearance of brain metabolites including beta-amyloid peptides, which are involved in AD.[25] Structurally, there was reduced brain grey and white matter in individuals with brain fog and in recovered patients, along with cortical thinning in frontal and temporal lobes.[26] In brain organoids, astrocytic subclusters with enrichment for genes that are implicated in neurodegenerative diseases revealed differentially expressed genes (DEGs) related to upregulation of pathways found commonly in Alzheimer's disease (AD) and Parkinson's disease (PD) in response to SARS-CoV-2.[27] Furthermore, patients with COVID-19 encephalopathy have higher plasma neurofilament light chain (pNfL) and plasma glial fibrillary acidic protein (pGFAP) concentrations which indicate neuronal dysfunction and CNS injury in their blood, like many other types of dementias.[28]

2.2 | Long COVID and EEG activity

EEG markers may be of interest for the clinical research carried out in patients with cognitive impairment, as they are noninvasive, repeatable without significant learning effects, globally available, and cost-effective.[29] Scalp-recorded EEG recordings allow the investigation of underlying cortical neural activities, including ionic current flows and related voltages, with a great time resolution (less than 1 msec).[30] It is also well known that EEG markers provide evidence of nonspecific alterations in neuronal network activities caused by underlying neurodegenerative or vascular changes[31–33] in the early stages of cognitive impairments.[34,35] Furthermore, topographical and spectral features of EEG measured at rest reflect neurophysiological oscillatory mechanisms underpinning the (dys)regulation of vigilance, mood, and cognition. The ability to measure these features at rest (i.e., while the individual is sitting with their eyes open or closed) is a particular strength, as it allows for the study of brain function and connectivity in healthy individuals and in those with ADRD alike.[36]

Previous studies have reported that rsEEG rhythms are abnormal in patients suffering from persistent or Long COVID brain fog; specifically, individuals exhibit topographically focal or diffuse "slowing" of rsEEG rhythms.[16,37] This slowing can be quantified by the spectral analysis of rsEEG rhythms as diffuse power density increase in rsEEG activity at low frequencies, such as delta (<4 Hz) and theta (4–7 Hz) frequency bands, and power density decrease at alpha (8–12 Hz) and beta (13–30 Hz) frequencies. In the healthy aging brain, rsEEG activity at alpha frequencies reflects spontaneous synchronization of cortical and thalamic neurons as a main neurophysiological mechanism regulating global cortical arousal states and vigilance.[34,36]

2.2.1 | Epileptiform-like activity

In severe cases of COVID-19, EEG has been found to be a valuable method to assess early neurological changes, including encephalopathy, seizures, and status epilepticus.[38] In COVID-19 patients, EEG displays several abnormalities including epileptiform activity and generalized slowing, especially in frontal regions, despite normal brain MRI.[39–41] During the early phase of the pandemic, two meta-analyses reported abnormal background EEG activity in COVID-19 patients, showing EEG pathologies between 69% and 96% of patients.[39,41] In these reports, epileptiform activity was observed in lower proportions (20% and 23% respectively). EEG seizures in COVID-19 patients were associated with higher mortality rates.[42] However, this finding may be related to the fact that patients with diagnosis of previously existing epilepsy or comorbid conditions tend to display higher rates of EEG abnormalities.[39,42,43]

In summary, Long COVID involves complex interactions between cognitive functions, structural and molecular mechanisms, and neurophysiological alterations related to underlying activities of neuronal networks. While much remains to be explored, these recent findings provide valuable insights for future research and suggest potential assessment, monitoring, and therapeutic strategies using EEG recordings.

3 | METHODOLOGY OF THE REVIEW

Two reviews of EEG findings in COVID-19 patients in 2020 and 2021 demonstrated slowing of EEG waveforms with COVID-19.[39,44] The expert panel of electrophysiological professional interest area (EPIA) associated with Alzheimer Association has previously published a review on slowing of resting-state EEG features for clinical trials in AD/ADRD. After formulating the research question regarding COVID-19 and EEG, we conducted key word searches from multiple sources, for example, PubMed, Google Scholar, National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and literature software. Keywords used in the search were: "resting EEG," "background frequency," "Alzheimer's disease and related dementia", "Neurovascular," "COVID-19 and EEG," "Long COVID and EEG," COVID-19, SARS-CoV-2, encephalopathy, angiotensin-converting enzyme 2 (ACE2), astrocytes, Inflammatory cytokine storm, "Cognitive Decline," and "Long COVID OR coronavirus OR SARS AND EEG."

After setting the criteria for the present review on EEG signatures of Long COVID, a literature search was performed to curate relevant references specific to EEG studies in COVID-19 positive individuals. Two authors (Y.J. and J.N.) reviewed each article to determine relevance to EEG and cognitive decline and brain fog. New citations of several encompassing reviews on COVID-19 or cognitive decline were identified and reviewed for further follow up of sources.[17,18,20,45,46] From this, additional studies were identified pertaining to the effect of COVID-19 on cognitive decline, with a specific focus on EEG correlates. After further review of these articles, those deemed relevant, novel, and impactful in relation to EEG correlation in persons with (Long) COVID-19 were included (Figure 1).

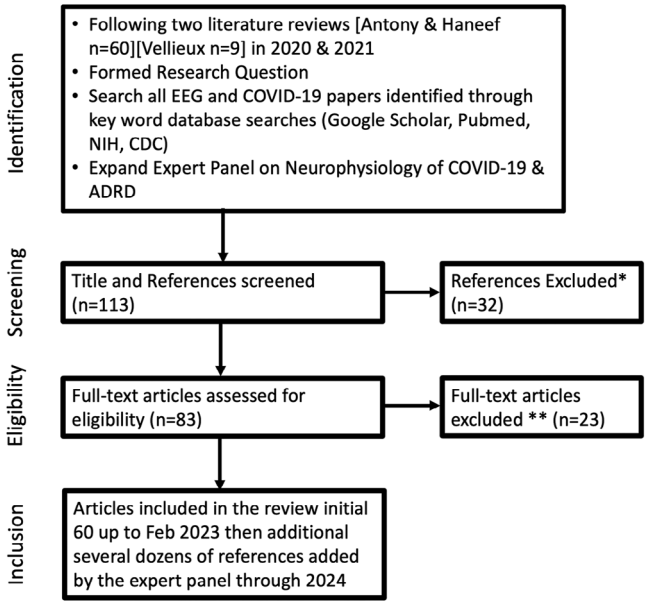

FIGURE 1 Diagram detailing the process of systematic literature review. *Reasons for exclusion of references were duplicates, absence of electroencephalogram (EEG), and lack of access. **Reasons for full-text article exclusion were lack of EEG finding reports, focus on adolescent subjects, and descriptive articles on EEG collection

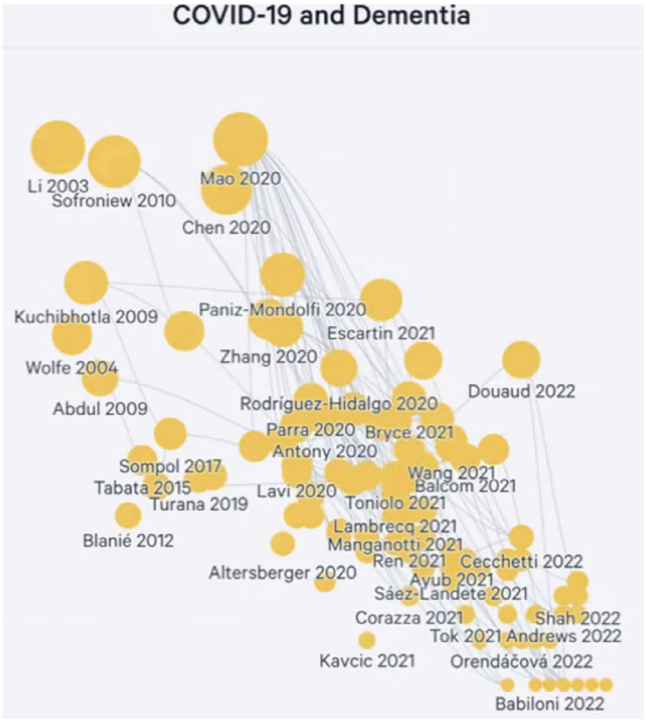

FIGURE 2 Overlap in coronavirus disease 2019 (COVID-19) and Alzheimer's disease and related dementias (ADRD) literatures. A diagram demonstrating the significant overlap and interconnectedness of the literature in dementia and COVID-19 literature. Larger circles indicate a bigger impact of a paper in the field based on citations (created by LitMaps)

Meanwhile, we enhanced our expert panel of electrophysiological experts on AD/ADRD and COVID-19 by inviting additional specialists in neurophysiology, astrocyte reactivity, and neuroinflammation. We also internally debated various hypotheses about underlying pathological changes related to neurophysiological findings. Additional references were identified by the authors on the expert panel, especially new publications through 2024. Aiming to cover all related EEG and long-COVID studies, we also benefited from co-authors' research on COVID-19 and EEG, publication recommendations, and personal communications from the experts. Figure 2 shows the interconnectedness of literatures of COVID-19 and those in AD/ADRD.

We identified two caveats of this methodology, including (1) the broad diagnostic criteria in the enrollment of patients with Long COVID brain fog after testing negative (e.g., type, duration, and severity of the symptoms) from the reviewed studies and (2) the heterogeneous procedures used during rsEEG data analysis (e.g., removal of artifacts) and for computing the rsEEG spectral measures. Ideally, future studies should aim at standardizing these criteria.

4 | EEG STUDIES IN COVID-19 PATIENTS

4.1 | rsEEG activity in acute COVID-19

Several studies discussed characteristics of abnormal rsEEG activity recorded in COVID-19 patients ranging from acute individual case reports[47] to larger longitudinal studies.[48] Results showed disrupted brain activity,[38,49] but normal EEG activity was also reported.[50] The EEG abnormalities observed were correlated with severity of the general health condition, COVID-19 assessment, length of surveillance, and any pre-existing neurological problems like epilepsy.[39] Slowed or aberrant electrical brain activity, mainly in the frontal lobe, was the most frequent EEG finding.[41,51,52]

EEG abnormalities seen in COVID-19 individuals could indicate potential brain damage that may persist after acute infection. In this context, frontal lobe-specific EEG abnormalities may be qualified as a possible biomarker if consistently observed in COVID-19 encephalopathy.[53] Some previous studies performed a visual analysis of ongoing EEG waveforms in critically ill COVID-19 patients with long-lasting neurological symptoms, including encephalopathy, for example, confusion, fluctuating alertness, or delayed awakening after stopping sedation in the intensive care unit.[54] In the following paragraphs, we compare the EEG activity recorded during and months after COVID-19.

Acute COVID-19 causes characteristic rsEEG patterns (Table 1) with a generalized "slowing" in the rsEEG activity.[39,48,54,55] In these studies, most acute COVID-19 patients (60%–90%) were characterized by abnormal rsEEG activity, such as dominant background rsEEG delta-theta rhythms (<7 Hz) or intermittent delta (<4 Hz) rhythmic activity instead of typical posterior dominance in rsEEG alpha rhythms, and nonconvulsive epileptiform activity or alpha (8–12 Hz) coma in a minority of cases.[39,48,54–56] Concerning frequency features, abnormal power densities at rsEEG delta, theta, and alpha rhythms

TABLE 1 Acute COVID-19 EEG studies

Authors and title of the studies	Study type	Affected brain site	Neurological abnormalities	EEG findings	EEG markers
Antony and Haneef (2020), Systematic review of EEG findings in 617 patients diagnosed with COVID-19	Literature review	Frontal	- stroke - headache - seizure - altered mental status - speech difficulties	- diffuse slowing (68%) - focal slowing (17%) - slow posterior dominant rhythm (2.3%) - absent posterior dominant rhythm (10.2%) - background attenuation/suppression (1.3%) - discontinuous EEG/burst suppression (2.1%) - asymmetry (2.1%) - decreased reactivity (3.2%)	- frontal epileptiform discharges - frontal monomorphic biphasic slow waves - periodic discharges with triphasic morphology - generalized rhythmic delta activity
Haykal, M. A., and Menkes, D. L. (2023), The clinical neurophysiology of COVID-19-direct infection, long-term sequelae and para-immunization responses: A literature review	Literature review	Frontal	- nonspecific encephalopathy	- generalized periodic discharges - generalized slowing	- epileptiform discharges - alpha coma pattern
Koutroumanidis et al. (2021), Alpha coma EEG pattern in patients with severe COVID-19 related encephalopathy	Observational study	Frontal	- headache - dizziness - impaired consciousness - seizure	- encephalopathic features - generalized slowing - general low voltage - spontaneous fluctuations	- anterior theta - anterior delta - bilateral delta bursts - alpha coma
Pati et al. (2020), Quantitative EEG markers to prognosticate critically ill patients with COVID-19: A retrospective cohort study	Retrospective cohort study	Unspecified	Unspecified encephalopathy	- low voltage	- low spectral delta-theta power - low theta-alpha activity
Pellinen et al. (2020), Continuous EEG findings in patients with COVID-19 infection admitted to a New York academic hospital system	Retrospective study	Unspecified	- coma - encephalopathy - seizure	- seizures - generalized slowing - periodic discharges - nonperiodic epileptiform discharges	- generalized rhythmic delta activity
Petrescu et al. (2020), Electroencephalogram (EEG) in COVID-19: A systematic retrospective study	Retrospective study	Left temporal	- headache - confusion	- sporadic triphasic waves - multifocal or generalized periodic discharges - left temporal sharp contoured waves	- generalized rhythmic delta activity - diffuse delta and theta slowing
Vespignani et al. (2020), Report on electroencephalographic findings in critically ill patients with COVID-19	Report	Frontal	- altered mental status - headache - loss of consciousness - poor arousal - poor responsiveness	- periodic discharges - generalized slowing	- high amplitude frontal monomorphic delta waves - diffuse nonspecific theta and alpha activity - theta consistent with sedation

were reported in severe cases of acute COVID-19.[56,57] Regarding spatial characteristics, frontal rsEEG abnormalities were often prominent.[39,54–57]

More severe rsEEG alterations (summarized in Tables 1–2) in COVID-19 patients were associated with prior pathological conditions.[56] Both seizure and epileptiform activity were seen in those with history of epilepsy or seizures, while those with a prior history of cognitive impairment exhibited stronger changes relative to those with normal cognitive history.[48] Unfortunately, there is no systematic comparison between these findings and abnormalities reported in patients with other brain disorders. However, multiple studies have shown that acute infections impact CNS function, leading to seizures, epileptiform activity, and alpha coma (AC) patterns.[48,54–56] AC is a distinctive EEG pattern observed in unconscious patients in a state of clinical coma. It is a predominant, generalized, and symmetrical rhythm within the alpha frequency band (8–13 Hz) associated with brain stem lesions. Patients may transition to theta coma caused by cortical dysfunctions.[58]

4.2 | rsEEG findings in Long COVID

EEG studies highlighting the features of rsEEG abnormalities in Long COVID patients showed interesting results summarized in Table 2.[15,17,40,59,60] Background "slowing" of rsEEG rhythms was a common finding.[15,17] Specifically, the posterior dominance in rsEEG alpha rhythms (typical in noninfected individuals) was observed in only 42% of patients with Long COVID, while the others are characterized by dominant power in theta (42%) or theta-delta (14%) bands.[15] Furthermore, hemispherical asymmetries in rsEEG amplitude were abnormally high at delta, theta, alpha, and beta bands in Long COVID patients.[17,61] Abnormally high rsEEG delta rhythms on widespread scalp regions were the most common abnormality in Long COVID patients.[15,17,40,61] Notably, Brutto et al. (2021) reported that individuals with a history of mild COVID-19 infection are 18 times more likely to develop long term brain disorder and cognitive decline than controls based on 6-month follow-up rsEEG.[17] Both verbal memory deficits and frontal executive functioning issues were also correlated with rsEEG abnormalities in Long COVID patients 2 months after the infection.[40]

5 | EEG SLOWING IN COVID-19

Some abnormalities in rsEEG activity reported in Long COVID patients were observed in patients with ADRD. For example, abnormally high rsEEG delta-theta power density over widespread scalp regions was reported in AD patients, in comparison to healthy controls.[62,63] Furthermore, early AD patients typically showed a shift to lower frequency in rsEEG rhythms[29] and altered task-evoked EEG potentials, which led to gradual loss of cognitive functions, especially working memory and executive functions, as well as slower reaction times.[64] Such slowing of rsEEG rhythms is thought to reflect a thalamocortical "disconnection mode" during disease progression from preclinical to clinical stages of ADRD.[29] Along these lines, similar abnormally prominent rsEEG activity was reported in patients with MCI, partially induced by vascular or metabolic dysfunctions, for example, high blood pressure and type 2 diabetes.[63] Overall, a continuum of alterations in rsEEG was associated with pathological aging, generally characterized by reduced alpha and beta power and increased delta and theta power in ADRD compared to healthy controls, with some variation across brain regions. There were also reductions in the frequency and power density of the posterior dominant rhythm in AD.

5.1 | COVID-19 EEG abnormality and known AD pathologies

It is not entirely clear how COVID-19 contributes to a shift to lower frequencies in the rsEEG activity, parallel to that observed in ADRD patients.[65] New magnetoencephalographic (MEG) evidence supports the link between "slowing" in the brain rhythms and cellular mechanisms of impaired cerebral excitatory and inhibitory (E/I) synaptic functions associated with tau and A-beta (Aβ) in AD patients.[66,67] In these seminal studies, increased excitatory activity was related to high tau levels, while increased inhibitory time-constants correlated with higher Aβ depositions.[66] Linking these effects to the abnormal rsEEG activity seen in Long COVID patients, it can be speculated that similar accumulation of amyloid and tau may co-occur with the neuroinflammatory, autoimmune, hypoxia, and cerebrovascular alterations that are often observed in ADRD patients.[67]

Understanding a potential relationship between COVID-19 and the amyloid and tau pathologies could also be insightful. Studies show that COVID-19 patients having neurological symptoms had amyloid pathologies. For instance, patients with amyloidosis are at a higher risk for severe COVID-19 infection and mortality.[68] Furthermore, total-tau and neurofilament light (NfL) chain in cerebrospinal fluid (CSF) were elevated in one in four COVID-19 patients with acute neurological syndromes compared to non-COVID-19 control patients.[69] Both in vivo and in vitro studies showed that amyloid precursor protein promotes the entry of SARS-CoV-2 virus into cells and further aggravates AD pathology.[70]

At the molecular level, microarray and RNAseq dataset analysis suggest common enriched genes in COVID-19 and AD. These include hub genes, specific miRNA targets associated with COVID-19 and AD, and several enriched cell-signaling pathways, such as PI3K-AKT, Neurotrophin, Rap1, and Ras, which may induce amyloid precursor protein and tau hyperphosphorylation associated with neurodegeneration.[71,72] The structure of SARS-CoV-2 includes four proteins: spike, envelope, membrane, and nucleocapsid proteins, which form amyloid fibrils intracellularly or extracellularly (spike protein).[73] Besides direct viral induction of Aβ, indirect connections between COVID-19 and Aβ are also reported. For example, COVID-19 as a respiratory disease causes hypoxia that has been linked with increased Aβ burden and dementia.[74] Alternative indirect COVID-19-Aβ burden connection mechanisms were also reported, including inflammation,[75] blood-brain barrier breakdown,[76,77] glucose metabolism dysregulation,[78] and commonly associated genetic risk

TABLE 2 Postacute Long COVID studies

Authors and title of the studies	Study type	Affected brain site	Neurological abnormalities	EEG findings	EEG markers
Cecchetti et al. (2022), Cognitive, EEG, and MRI features of COVID-19 survivors: A 10-month study	Longitudinal study	- Bilateral frontal - Central temporal	- chronic malaise - diffuse myalgia - sleep disturbances - migraine-like headaches - ageusia - anosmia	- frontal slow waves	- high individual alpha frequency - cortical current source density - high delta linear lagged connectivity - delta oscillations
Brutto et al. (2021), Cognitive decline among individuals with history of mild symptomatic SARS-CoV-2 infection: A longitudinal prospective study nested to a population cohort	Longitudinal prospective study	- Right temporal - Frontal	- anosmia - ageusia - headache	- generalized background slowing - focal slowing - epileptiform discharges - sporadic sharp waves	- posterior dominant alpha rhythm - rhythmic delta waves
Furlanis et al. (2023), Cognitive deficit in post-acute COVID-19: An opportunity for EEG evaluation?	Cross-sectional study	- Bilateral frontal - temporal	- hyposmia - myalgia - headache - dizziness - tinnitus	- epileptiform discharges - generalized slowing - seizures	diffuse theta-delta slowing
Kopanska et al. (2022), Attempted brain wave modeling in participants under severe chronic stress using quantitative electroencephalogram	Longitudinal comparative study	- Frontal - Parietal	- chronic stress	- high frequency right hemispheric waves - low level sensorimotor rhythm	- reduced alpha - decreased theta
Saez-Landete et al. (2021), Retrospective Analysis of EEG in Patients With COVID-19: EEG Recording in Acute and Follow-up Phase	Longitudinal Retrospective Analysis	- Frontal - Temporal	- low awareness - disorientation - mood disturbance - confusion - inattention	- absence of posterior dominant rhythm - reduced voltage	- reduced alpha - reduced theta
Babiloni et al. (2024), Resting-state EEG rhythms are abnormal in post COVID-19 patients with brain fog	Cross-sectional study	- Occipital - Parietal	- chronic fatigue - postexertional malaise - myalgia - headaches - confusion	- lowered posterior resting state dominant rhythm	- reduced alpha 2 - reduced alpha 3

factors such as apolipoprotein E4 (APOE4).[79] For example, one study reported increased proinflammatory cytokines in the CSF of COVID-19 patients, which negatively correlated with decreased CSF soluble amyloid precursor protein.[80] Intriguingly, SARS-CoV-2 induced Aβ burden can serve dual functions, both in a protective role and by activating Aβ expression and toxicity underlying AD progression.[81–83] More knowledge needs to be gained to understand the unprecedented condition that we will be facing in the next few decades. Taken together, these preliminary findings suggest that the links between amyloid, tau pathology, and COVID-19 may explain the slowing EEG waves in COVID-patients.

5.2 | Hypoxia, heart rate variability, and rsEEG activity in Long COVID

Hypoxia, which is associated with ADRD, including AD and cerebrovascular dementia,[84] is another possible cause of abnormalities in rsEEG activity and neurological symptoms in Long COVID patients. Hypoxia serves as a vital connection between lung and heart deficits that are linked to cerebrovascular dysfunction in the brain. Here, we present well established evidence that hypoxia contributes to rsEEG activity and likely to Long COVID. COVID-19 infection impacts brain blood perfusion and oxygenation by several mechanisms. SARS-CoV-2 neuroinvasion through the cerebral vasculature may affect regional brain blood flow and metabolism, thus affecting the synchronization of oscillatory activity in cortical and thalamic neurons, which underlie dominant rsEEG alpha rhythms and regulation of cortical arousal and vigilance.[29,85,86] Lower oxygen saturation levels have been linked with more severe rsEEG abnormalities, indicating that higher levels of hypoxemia could contribute to brain dysfunction. Related EEG abnormalities include mostly diffuse and focal slowing, and absence of posterior dominant rhythm.[87]

COVID-19 is associated with respiratory symptoms and often requires treatment via ventilation in severe cases connected to acute respiratory distress syndrome (ARDS). ARDS can induce hypoxia, which results in hypoxic encephalopathy, particularly in older individuals with high vulnerability to oxidative stress.[45] Respiratory damage can even give rise to silent hypoxia, defined as a condition where an individual has alarmingly lower oxygen saturation levels than anticipated (~50%–80% saturation, while the anticipated saturation level is 95% or higher) in the absence of any breathing difficulty.[88] As illustrated by Rahman et al. (2021), silent hypoxia has been associated with several COVID-19 related symptoms.[89] Silent hypoxia can result in overexpression of ACE2 receptors thereby increasing the risk of damage through COVID-19 infection. The condition can also further contribute to the mechanism of the "cytokine storm" by recruiting different mediators of inflammation. Moreover, silent hypoxia can cause serious endothelial damage through nuclear factor kappa B (NF-kB) transcription factor activation. Finally, silent hypoxia can signal a different immune-metabolism pathway and cause secondary organ damage. All these factors lead to the critical condition of COVID-19 patients along with an increased mortality rate.[89]

Hypoxia could result from abnormal heart-brain connections as well. The heart provides oxygen for the brain through cardiovascular blood flow that is regulated by the balance of two branches of autonomic activity (symptomatic and parasympathetic/vagal nerves). The autonomic activity is proxied by heart-rate variability (HRV), which has been reported to change in COVID-19 patients. For example, in a recent study, resting HRV predicted survival in patients aged 70 and older.[90] COVID-19 was shown to be related to decreased HRV,[91] suggesting COVID-19 may link with autonomic dysfunction. Autonomic dysfunction may be reflected by orthostatic intolerance, which has been experienced by some COVID-19 patients.[92] Orthostatic intolerance or autonomic dysfunction can be associated with hypoperfusion in the brain and may contribute to hypoxia and cognitive symptoms (e.g., brain fog). Besides HRV, the change of cardiovascular activity can also result from COVID-19 infection in the heart itself.[93,94] Changes in cardiac tissue will affect the pumping activity and eventually link to hypoperfusion of the brain. Allostatic interoceptive overload, commonly observed in dementia via autonomic-cardiac-brain interaction, could also represent a complex and multilevel mechanism involved in COVID-19.

An EEG signature in some COVID-19 patients who are slow to recover consciousness includes burst suppression.[95] Burst suppression is an EEG pattern during which active and isoelectric (flat) periods alternate. The characteristics of burst suppression suggest that it can be a dynamic process, affecting nearly the entire cortex, and that it is associated with a decreased cerebral metabolic rate of oxygen consumption. Electrophysiological modeling has shown that burst suppression is likely a signature of a neurometabolic state that preserves basic cellular function "during states of lowered energy availability." These brain states likely serve as a neuroprotective mechanism. Prolonged coma and recovery accompanied with hypoxia and markedly reduced brain metabolism with similar EEG patterns are present in certain patients after cardiac arrest and in certain anoxia-tolerant vertebrates.[95] In some severe COVID-19 encephalopathy patients, an AC pattern may be observed. The predominant, generalized, and symmetrical rhythm within the alpha frequency band[58] is rare in other encephalopathies but has a relatively high incidence in COVID-19 encephalopathy, which may imply neurotropism with a predilection for the brainstem ascending reticular system.[54]

Hypoxia related EEG patterns in COVID-19 patients may mimic those seen in sleep apneas (OSA). In a study of men with obstructive sleep apnea (OSA), severity of hypoxia was significantly associated with EEG slowing and reduced power across all frequency bands, predominantly in rapid eye movement (REM) sleep, and with beta power during non-REM (NREM) sleep.[96] Reduced P300 amplitudes in severe OSA (SOSA) patients suggest impaired attentional resources during stimulus evaluation processes, while prolonged P300 latency is linked to altered stimulus classification and cognitive processing speed.[97] The alterations in brain electrical activity in regions associated with emotional regulation, long-term memory, and the default mode network may be caused by chronic global hypoxic state.[98]

Previous studies indicate that transient experimental hypoxia induces abnormal posterior resting state delta and alpha rhythms in

healthy volunteers.[99] A study comparing EEGs of subjects who inhaled an acute hypoxic mixture at sea level or who reached a high-altitude area under chronic hypoxia, showed that severe hypoxia caused more obvious abnormalities on EEGs, and that acute hypoxia caused more obvious abnormalities but faster recovery than chronic hypoxia.[100,101] Other studies indicate that during systemic hypoxia, the spectral power of rsEEG with closed eyes increases, except for in the alpha band.[101] In the alpha band, a rapid decrease in power is observed, which is greater at mild desaturation,[102] especially in the first 150 s of hypoxia.[103] Regarding event-related potentials (ERPs), significant reduction can be observed in the amplitude of the visual mismatch negativity (MMN) under hypoxic conditions.[104] Acute hypoxia has been found to impair neural activity in motor executive and inhibitory processing, cause a reduction in the peak amplitudes of Go-P300 and No-go-P300, and delay peak latency of Go-P300[105] and P300 latency,[106] with no change in earlier components (i.e., P200 or N100).[107] Thus, cognitive ERPs can be sensitive to hypoxia induced cognitive impairments. Regarding modality, auditory responses are believed to be less sensitive to hypoxia compared to visual responses, resulting in relatively less slowing with auditory stimuli.[107] Regarding topography of hypoxic changes in the brain, a MEG study localized an increase in beta-1 activity to the right superior frontal gyrus, indicating a relationship between prefrontal activation and performance deficits.[108] Further research is needed to understand the relationship between EEG/MEG alterations and hypoxic conditions directly resulting from COVID-19.

COVID-19 can lead to CNS hypometabolism as well. Brain hypometabolism, measured by positron emission tomography (PET), has been observed in Long COVID patients with persistent memory impairment.[109] Furthermore, Martini et al. (2022) reported a diffuse brain hypometabolism in COVID-19 patients followed longitudinally, which recovered after 5 months along with blood saturation and inflammatory biomarker levels, and cognitive status.[110] In these patients, EEG monitoring showed general "slowing" of frontal rsEEG rhythms, along with a spread in frontal hypometabolism.[16] Arica-Polat et al. (2022) reported that cognitive impairment due to COVID-19 infection may be caused by ACE receptor density in the pial, hippocampal, and amygdala areas.[111] Furthermore, individuals with severe dementia having a milder COVID-19 infection could be explained by gray matter atrophy in those brain areas.

Building on emerging evidence of EEG abnormality in COVID-19, the expanded Expert Panel endorsed the present narrative review to clarify the likely relationships between EEG abnormalities related to Long COVID (Figure 3). Next, the hypotheses of possible overlapping pathophysiological and neurophysiological mechanisms underlying Long COVID and ADRD are examined.

6 | POSSIBLE NEUROPHYSIOLOGICAL ABNORMALITIES IN LONG COVID: PARALLEL TO ADRD

Recent studies have discussed how Long COVID infection can affect neuronal activity and cognitive status, though the exact pathophysiological mechanisms leading to the neurological and psychiatric consequences of Long COVID have not been determined conclusively.[112] Early in the pandemic, it was debated whether the SARS-Co-V2 virus can directly infect central (CNS) and peripheral (PNS) nervous systems, or if the "neurotoxicity" may result from indirect immune-mediated mechanisms.[110] The CNS was found to be substantially involved in COVID-19 based on several neurological and pathophysiological symptoms,[113] although there are varying degrees of CNS involvement in the acute phase of COVID-19 patients.[87] Patients with transient COVID-19 effects may have a substantially preserved neuronal function illustrated by normal background rsEEG alpha activity; in contrast, those with more severe prognoses exhibited significant rsEEG abnormalities.[87] A few causative neurobiological and neurophysiological mechanisms for Long COVID and abnormal rsEEG activity are outlined below. These mechanisms will be also discussed in relation to ADRD for the similarities in the rsEEG abnormalities in Long COVID and ADRD.

6.1 | Neuronal abnormalities in Long COVID and ADRD arising from neuroinflammation and chronic glial reactivity

One of the most likely mechanisms of COVID-19 neuroinvasion explaining the "slowing" of rsEEG activity is the inflammatory response to the SARS-COVID-19 virus, leading to cytokine-mediated neuroinflammation.[114] Binding of coronavirus spike proteins to ACE2 in the bloodstream[115] can affect ACE2 expression throughout cerebral vasculature, resulting in vascular inflammation and possibly the disruption of the blood-brain barrier (BBB). Infiltration of bloodborne particles into the brain is a well-known trigger for the activation of microglia and astrocytes associated with elevated neuroinflammatory signaling.[116] Moreover, inflammation-mediated disruption of the BBB can make astrocytes and other resident brain cells directly accessible to SARS-CoV-2 viral particles.

Astrocytes are metabolic liaisons between cerebral vessels and neurons. Nearly every cerebral vessel is sheathed by specialized processes called astrocyte endfeet (circles in Figure 4). Other astrocyte processes cradle many, if not most, excitatory connections in the brain. Astrocytes can uptake viral particles directly through coronavirus coreceptors (e.g., CD147 or DPP4), or through interactions with other perivascular cells like pericytes. Not surprisingly, astrocytic injury has been reported to occur early in acute phases of COVID-19 infection.[117] Once injured (or activated), astrocytes can release a wide array of cytokines and chemokines. Astrocytes were suggested to play a major role in the generation of an inflammatory cytokine storm response following infection with a murine coronavirus that mirrors COVID-19. Viral infection of astrocytes has been linked to encephalitis and other acute inflammation-related morbidities.[118]

Astrocyte reactivity is a prominent feature of AD and most ADRDs (e.g. in response toxic Ab and Tau species) where it is suspected as a proximal cause of neuroinflammation, cerebrovascular dysfunction, impaired synapse function, and neuronal hyperexcitability.[119,120]

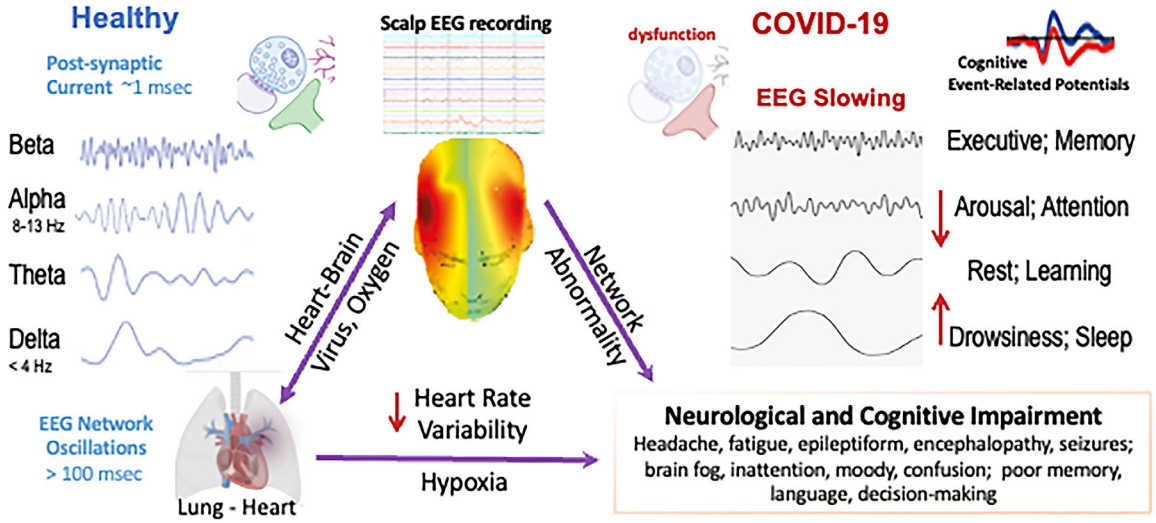

FIGURE 3 Electroencephalographic (EEG) abnormality in healthy versus coronavirus disease 2019 (COVID-19) positive individuals. Scalp EEG signals measure synchronized postsynaptic current and neurovascular network activity. EEG abnormalities observed in COVID-19 patients display increased slow-wave and epileptiform-like EEG signals in mostly frontal sites, as seen in Table 1 (acute) and Table 2 (Long COVID). Cognitive and neurological dysfunctions reported in COVID-19 patients resemble those with mild cognitive impairment due to neurodegenerative diseases.

Like AD and ADRDs, changes in COVID-19-associated astrocytic inflammatory signatures are regulated by canonical NF-kB signal transduction.[121,122] Interestingly, neurotropism and neurotoxicity are higher after COVID-19 infection in neurons and astrocytes expressing the AD risk gene APOE4,[123] suggesting that astrocytes may be a source of confluence for pathophysiologic changes observed in individuals with COVID-19 and dementia. As outlined above, reactive astrocytes may contribute to neurologic dysfunction arising with COVID-19 and dementias through the initiation and/or maintenance of harmful neuroinflammatory responses. Below, we consider how reactive astrocyte signaling and neuroinflammation can directly affect synapses (and EEG patterns) based on findings from the AD/ADRD literature.

6.1.1 | Astrocytes, complement C3 factors, and synapse loss

The complement cascade (Figure 4) is a critical defense mechanism against invading pathogens (both outside and inside the CNS) but can cause extensive damage to host tissues when chronically engaged and/or dysregulated.[124] As compared to controls, the brain tissues of patients who died from COVID-19 have shown a significant increase in multiple complement components including C1q, C4d, C5b-9, and C3. These effects have been shown to occur with vascular endothelial cells and are associated with the extravasation of fibrinogen and apparent leakage of the BBB.[125] These findings implicate both the classical and alternative complement pathways and suggest that C3b and the C5b-9 terminal complement complex (membrane attack complex, MAC) may act in concert with neuroinflammatory and immune factors to contribute to the neurological sequelae seen in patients with COVID-19.

Among their many functions in brain tissue, the complement system plays an important role in eliminating unnecessary or dysfunctional synaptic structures. The essential players in synapse elimination are C1q, coming primarily from neurons, and C3, derived primarily from astrocytes. Under neuroinflammatory conditions (and elevated complement signaling), the release of C3 from reactive astrocytes is converted to proteolytic fragments upon interaction with C1q from nearby neurons. These C3 fragments, especially C3b, opsonize inactive or dysfunctional synapses leading to microglial mediated phagocytic clearance. C3 has been proposed as a primary mechanism for synapse loss and dysfunction in AD.[126] C3 is robustly elevated in reactive astrocytes in aging and most ADRDs and is strongly induced in astrocytes by exposure to pathogenic Aβ peptides.[127] In mouse models of AD-like pathology, C3 and C1q tend to localize with synapses to a much greater extent than what is observed in age-matched wild-type littermates. Moreover, genetic knockdown of C3 has been shown to preserve synaptic density and improve neural function in amyloidogenic mice. Whether COVID 19 mediates synapse loss and/or neurodegeneration through a similar release of C3 from reactive astrocytes remains to be determined.

In addition to releasing C3 and other synapse-related proteins, reactive astrocytes in ADRDs also lose properties that help protect or maintain healthy synapses. One of the fundamental protective roles of astrocytes is the uptake of glutamate from synapses via high-capacity glutamate transporters, like EAAT2 (GLT1 in rodents) and EAAT1 (GLAST in rodents). Glutamate transport from the synapse into the astrocyte not only preserves excitatory/inhibitory balance and protects against exocytotic damage, but it also regulates the delivery of energy substrates (e.g. lactate) to neurons.[120] Potent neuroinflammatory mediators, including cytokines (e.g., interleukin 1 beta [IL-1β] and tumor necrosis factor alpha [TNFα]) and Aβ peptides arising with neuroinflammation and/or ADRDs lead to the downregulation of

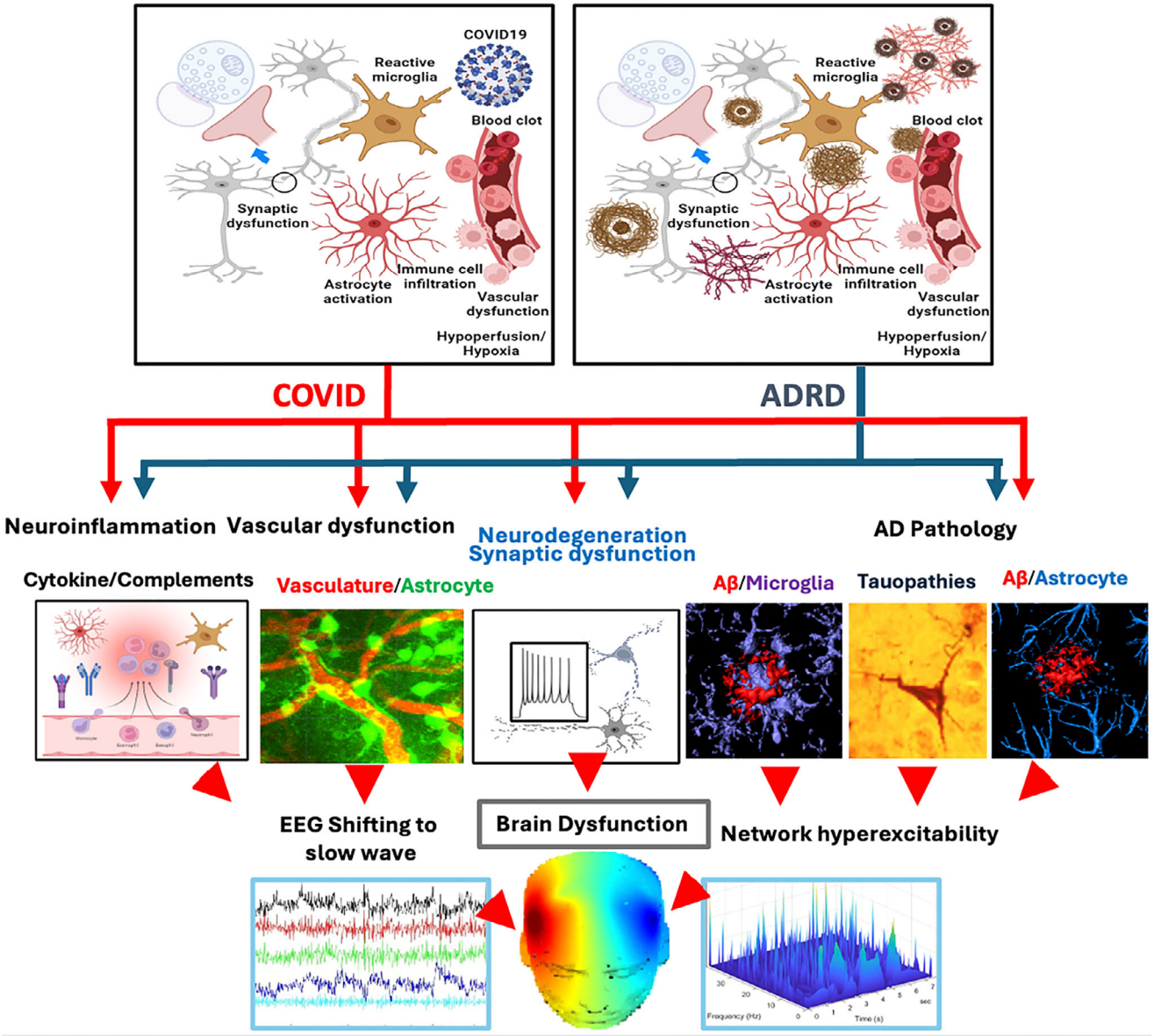

FIGURE 4 Complex brain pathophysiology and pathology of coronavirus disease 2019 (COVID-19) infection and Alzheimer's disease and related dementias (ADRDs). COVID-19 is a viral pathogen that systemically induces blood immune cell activation, glycocalyx damage, blood clotting, vascular damage and dysfunction observed in heart attack and stroke. This causes blood component infiltration, hypoperfusion and glia cell activation in brain tissue. The circles illustrate endfeet of astrocyte in modulation of synaptic functions. Alternatively, this viral particle could directly enter and trigger parenchymal astrocyte and microglia activation. Proinflammatory cytotoxic cytokines and complements produced from both blood and glia cells cause neuroinflammation and neuronal injury. Dysregulation of glutamate, calcium signaling, and oxidative stress further complicates physiological function of synapses and neurons. This complex pathophysiology is similarly found in AD and ADRDs where vascular pathology and neuronal loss are commonly observed. Hypoxia, oxygen, and heart-brain dysfunction contribute to EEG signals. Consequently, signs and symptoms of confusion, inability to concentrate, learning and memory impairment are concurrently found with reduced electroencephalographic (EEG) signals and abnormal EEG synchrony in cortical, subcortical, and deep brain regions.

astrocytic glutamate transporters,[128–131] resulting in delayed glutamate clearance, dendritic degeneration, and synapse hyperexcitability.

Glutamate transporter levels are regulated by classic inflammatory pathways, like NFκB, and closely intertwined Ca^{2+} dependent pathways like calcineurin/NFAT (nuclear factor of activated T cells). Astrocytes pre-exposed to a variety of cytokines and other inflammatory mediators lead to hyperactivated Ca^{2+}-signaling,[132] which may, in turn, stop the development of synchronized neuronal calcium oscillations[133] and/or promote deficits in Ca^{2+} dependent synaptic plasticity.[134] Hyperactivation of astrocytic calcineurin and NFATs is a common feature of several ADRDs including AD,[135,136] vascular cognitive impairment and dementia,[137,138] and traumatic brain injury.[139,140] Targeted blockade of calcineurin/NFAT signaling in astrocytes prevents downregulation of glutamate transporters in primary astrocyte culture models of neuroinflammation, and in mouse models of amyloid pathology, leading to improved glutamate uptake, reduced neuronal

hyperexcitability, increased synaptic strength and dendritic integrity, and improved cognitive function.[130,131,135] However, the role of astrocytic calcium signaling or glutamate dysregulation as contributing factors in COVID-19 related neurologic dysfunction and degeneration has yet to be investigated.

6.1.2 | Abnormal EEG reflects synaptic dysfunction

It has been well established that EEG signals measure synchronized postsynaptic neural activity and neuron networks that reflect altered synaptic functions underlying cognitive changes.[141] Abnormal EEG signals arise mainly from postsynaptic currents and not action potentials in the brain. Synaptic losses were observed early on in both the temporal and parietal cortexes of brains of patients with MCIs and AD.[142]

Decades of literature has shown cognitive event-related EEG potentials (averaged EEG activity related to a cognitive event such as attention or memory retrieval) correlate to various cognitive functions in healthy humans and dysfunctions in aging and mental disorders[141] including ADRD.[31] However, cognitive EEG studies in COVID-19 patients appear to be a missing piece.

6.2 | Autoimmune response in Long COVID and ADRD

A second potential common mechanism of COVID-19 neuroinvasion and ADRD explaining the "slowing" of rsEEG activity may be an autoimmune driven response. Some factors such as proinflammatory cytokines and chemokines, damage-associated molecular patterns (DAMPs), molecular mimicry, cross-reactive antibodies, and auto-antibodies may contribute to autoimmune dysregulation in Long COVID patients. The analysis of a COVID-19 positive patient showed neurological improvement to steroid treatment, indicating that the viral mechanism could be tied to an autoimmune neuroinflammation.[143] A cytokine storm induced by COVID-19 caused neuroinflammatory encephalitis via immune effector cell-associated neurotoxicity syndrome (ICANS).[18,45] ICANS presents with generalized EEG "slowing" as well as clinical manifestations including confusion, short-term memory impairment, expressive deficits, and behavior disturbances including impulsivity, emotional lability, abulia, and akinetic mutism.[18,45]

It has also been revealed that autoimmune disease related encephalitis, due to antibodies acting against the N-methyl-D-aspartate (NMDA) receptors, can lead to diverse neurological and psychiatric symptoms.[144] Similarly, COVID-19 patients showed dysregulated autoantibody levels correlating with the virus severity, including antibodies against the dopamine-1 receptor, NMDA receptor, brain-derived neurotrophic factor, myelin oligodendrocyte glycoprotein (MOG), and acetylcholine receptor when compared with healthy controls.[145] Overall, the complex pathophysiology seen in Figure 4 is similarly found in AD and ADRDs where vascular pathology and neuronal loss are commonly observed. Consequently, signs and symptoms of confusion, inability to concentrate, and learning and memory impairment are concurrently found with reduced EEG signals and abnormal EEG synchrony in cortical, subcortical, and deep brain regions.

6.3 | Cerebrovascular injury and atrophy in COVID-19 and ADRD are linked to abnormal EEG

Cerebrovascular injury and atrophy are signals of relative long-term brain damage and have been linked to abnormal rsEEG activity in COVID-19 and ADRD. A UK Biobank study investigating brain scans before and after COVID-19 infection compared with matched controls with no previous infection showed significant loss of gray matter with (1) greater reduction in global brain size, (2) greater reduction in the orbitofrontal cortex and para-hippocampal gyrus, and (3) greater changes in regions that are functionally connected to the primary olfactory cortex.[146] In another study exploring if the spatial distribution of the anatomical events follows a cortical or subcortical pattern, the authors found the epicenters of this spread may be the cerebellum and putamen.[147] Furthermore, white matter events were identified most frequently in the corticospinal tract and corpus callosum. The corticospinal tract is the main pathway connecting subcortical brain regions such as the thalamus and basal ganglia. Along with this, the corpus callosum has an important role in interhemispheric communication, which can lead to a disconnection syndrome and a wide variety of neurocognitive deficits.[147]

To summarize the contrasts and commonalities in COVID-19 and AD/ADRD, we built a model from pathology, EEG, and cognitive impairment (Figure 5). Evidence in Section 6 suggests that astrocytes are indeed injured/activated by COVID-19 infection, or infection with similar viruses, resulting in neuroinflammation. Parallel changes in astrocyte reactivity are found in ADRDs. In ADRD, astrocyte reactivity is suspected to cause synaptic hyperactivity, synapse loss, and neurodegeneration. Astrocyte reactivity leads to the production of complement C3 and loss of glutamate transport, both of which can damage synapses. EEG measures postsynaptic activity in neuronal networks that reflect synaptic injury underpinning cognitive dysfunction. What we have learned in the ADRD field gives us clues to how reactive astrocytes and neuroinflammation contribute to the neural morbidities seen in COVID-19.

7 | UNRESOLVED ISSUES AND POTENTIAL EEG NEURAL BIOMARKERS FOR INTERVENTION

Some substantial open questions remain. One question is whether there is converging evidence on spatial and frequency features of abnormal rsEEG rhythms in Long COVID patients. Another question is whether these abnormal features are specific to Long COVID patients or reminiscent of those with vigilance and cognitive deficits due to other pathological processes. Indeed, some abnormalities in rsEEG

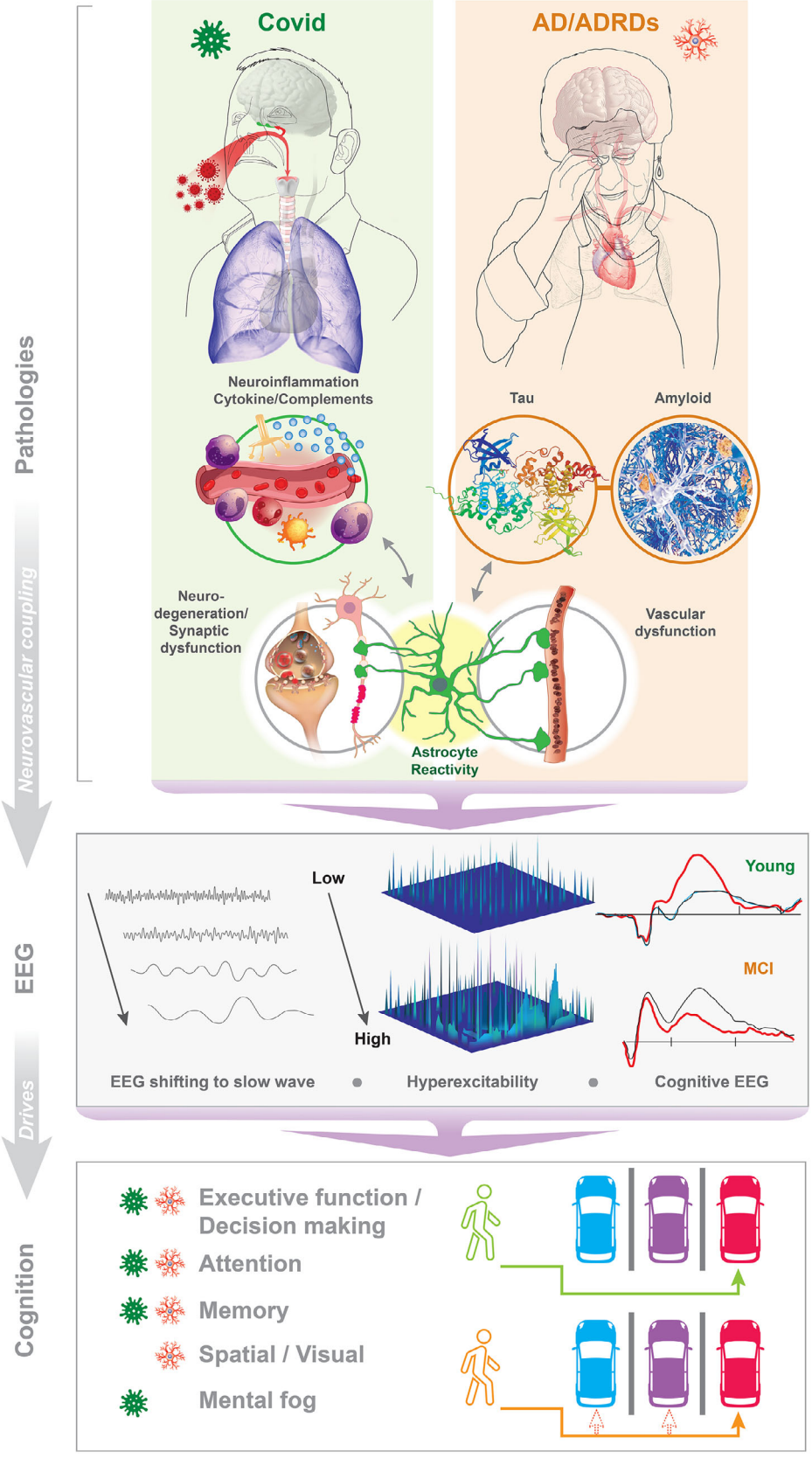

FIGURE 5 Proposed model: Parallel pathology underlying shared electroencephalographic (EEG) abnormality, and cognitive dysfunction in coronavirus disease 2019 (COVID-19) and Alzheimer's disease/Alzheimer's disease and related dementias (AD/ADRD). (A) Similar pathologies between COVID-19 and ADRD. Both neural inflammation and cytokine/complement activation in COVID-19, amyloid and tau pathologies in ADRD contribute to astrocyte over-reactivity, leading to synaptic dysfunction in neurodegenerative diseases. Astrocytes are likely a primary target of COVID because of the close interaction with the vasculature. Evidence in Section 6 suggests that astrocytes are indeed injured/activated

by COVID infection or infection with similar viruses resulting in neuroinflammation. Parallel changes in astrocyte reactivity are found in ADRDs. In ADRD, astrocyte reactivity is suspected to cause synapse loss and neurodegeneration. What we have learned in the ADRD field may give us clues to how reactive astrocytes contribute to the neural morbidities seen in COVID 19, for example, astrocyte reactivity leads to the production of Complement C3 and loss of glutamate transport, both of which can damage synapses. (B) EEG signals represent synchronized postsynaptic neural activity and neurovascular coupling networks measured at the scalp. Common abnormalities observed include increased slow-wave EEG signals and network hyperexcitability in EEG of both COVID-19 and ADRD patients. Although cognitive event-related potentials (e.g., searching for a car as working memory target) exhibit consistent brainwave patterns in Young heathy individuals versus those with mild cognitive impairment (MCI), cognitive EEG has not yet been explored in COVID-19 patients. (C) Highlights of key cognitive dysfunctions, e.g., poorer frontal executive functions, decision-making, reduced attention focus, and short-term memory, along with slowed reaction times, reported in both COVID-19 and MCI patients. Decades of literature documents that cognitive event-related potentials underserve various cognitive functions. Although attention, memory, and frontal decision-making dysfunctions are common in both COVID-19 and ADRD patients, COVID-19 patients commonly report more brain or mental fog, while spatial and visual disorientation, predominantly affecting the posterior brain regions, are more frequently observed in dementia patients

delta, theta, and alpha rhythms have been reported in patients with cognitive deficits due to AD or cerebrovascular diseases. The cause of brain fog in Long COVID has not been fully understood.[148,149] Similar symptoms have been observed in people living with other brain conditions (e.g., stroke, epilepsy) without previous COVID-19 infection.[1,150] Several important issues are currently unresolved or understudied in COVID-19 related EEG indicators.

7.1 | Fatigue, severity of Long COVID, and contribution to EEG signals

Fatigue, which is frequent in older adults and ADRD patients, is one of the most consistently reported symptoms of COVID-19, both initially and after infection.[10] The exact source of this persistent fatigue is disputed, but it is proposed that fatigue suffered by those infected with COVID-19 is related to the inflammatory nature of the virus. Chronic fatigue is linked to many diseases, including autoimmune diseases like rheumatoid arthritis.[151] It is proposed that long-term, low-grade inflammation maintains consistent fatigue by creating an imbalance between cellular energy availability and behavioral energy expenditure.[152] It is contribution to EEG signals is no clear. The inflammatory cytokine storms that the body undergoes during infection of COVID-19 create a consistent energy expenditure of the immune system, causing the infected individual to experience fatigue.

Challenges regarding mixed EEG index of severity of symptoms of Long COVID were found in aging individuals, along with severe effects found in younger individuals in the acute phase of the virus.[153,154] Intermittent frontal rhythmic dischargers were reported as an EEG biomarker of acute SARS-CoV-2 infection in children.[155] Valsamis et al. (2023) reported more severe effects of EEG slowing in acute COVID-19 subjects below age 70.[154] The average power spectrum was significantly enhanced in the delta band and attenuated in the alpha and beta bands compared to aged-matched control patients in the intensive care unit (ICU) with a negative COVID-19 polymerase chain reaction (PCR) test.[154] These observations raise several questions, including the main mechanisms contributing to CNS symptoms in COVID-19 infection, which might be different in young and older patients (e.g., magnitude of cytokine storm). Another debate is whether preexisting cognitive impairment does not cause higher morbidity rates in COVID-19 individuals, but rather those with preexisting cognitive impairment are more likely to suffer from other comorbidities that cause more severe cases of COVID-19.[156]

Cognitive functions and anxiety were significantly affected by an acute omicron infection in 2023, which demonstrates its association with nervous system symptoms (gray matter thickness/subcortical nuclear volume). Yet, there is evidence that cognitive deficits subside after some time in mild COVID-19 patients.[157] However, measuring associations between mild COVID-19 infection and long-term cognitive deficits is challenging due to the scarcity of longitudinal data, as infection is unpredictable and reinfection rates are high.[158]

7.2 | EEG monitoring in COVID-19 recovery and treatment

There are various methods of treatment for COVID-19. Many of the remedies for COVID-19 include antiviral medications or a monoclonal antibody intravenous treatment. More serious cases of individuals hospitalized with COVID-19 warrant treatment focused on different elements of the virus, including immunotherapy drugs like tocilizumab.[52] In the case of an individual hospitalized with COVID-19, presenting with excessive aphasia and inattentiveness, progressing to severe encephalopathy, treatment with tocilizumab resolved neurological symptoms within 2 days.[59] Initial EEG after hospitalization revealed background slowing and sharp frontal waves, while the 2-month follow-up EEG post-treatment with tocilizumab showed no remarkable abnormalities.[59] The fact that tocilizumab disrupts the inflammatory cytokine storm response demonstrates a potential treatment for neurological symptoms of COVID-19. In the case of a 77-year-old female presenting with neurological deficits following COVID-19 infection, intravenous methylprednisolone treatment resulted in a gradual improvement of speech and cognition as well as a reduction of the background slowing of the EEG signal.[16] These cases of COVID-19 successfully treated using drugs offer hope.

Pharmacological treatments of COVID-19 tend to be a broad approach to treat the illness rather than specifically targeting the cognitive symptoms that result from the infection. Though not in broad clinical practice, a proposed method of treatment to specifically target these neurological deficits is quantitative EEG (QEEG) neurofeedback

therapy. This method of coaching individuals to influence their own EEG frequencies has been utilized to mitigate some behavioral symptoms of other conditions.[59] QEEG may be a useful tool to monitor the recovery of brain functioning as it is easily applicable and repeatable over time, even in large cohorts of subjects with COVID-19, from asymptomatic to critical illness. In using a treatment method that specifically targets cognitive function, there may be greater potential to remedy neurological symptoms of COVID-19 and ameliorate the effects of long-term brain fog. However, research is needed to directly test this hypothesis, and EEG studies could provide objective measurements of the integrative functional state of the brain.

7.3 | Modulation of COVID-19 related abnormal EEG by age, sex, and education

Age is a primary risk factor for both ADRD and COVID-19. Age and sex made significant differences in the survival rates for COVID-19 in Wuhan China. Deceased patients are typically older than recovered patients,[159] recovered patients are more likely to be male. Resting-state EEG alpha rhythms in MCI patients are also differently affected by age and sex, as well as education attainment.[160] Posterior alpha sources are more abnormal in male MCI patients due to AD.[66,161] The psychiatric manifestations are varied between many identifying factors, such as presence of a pre-existing psychiatric disorder, critical illness, intensive care, and systemic inflammation.[162]

Fear of the disease has an interesting age effect. COVID-19 related stress is expressed differently across sexes and is not consistent across varied populations.[163] Contrary to expectations, some evidence suggest that younger individuals are more susceptible to stress, and psychological manifestations compared to older generations.[164] Similar increases of worry and risk perception are observed in women from low-income settings.[165] In contrast, there were no noticeable sex differences in instances of anxiety, depression, and stress.[166] Prosocial activity and cooperation are important factors influencing the adequate responses to the pandemic.[165,167,168] Forced lockdowns left many aging people without social structure and support, resulting in more significant cognitive decline.[169] This exemplifies the detriment of isolation on individuals because of the COVID-19 pandemic.

The sex or gender differences in electrophysiology of COVID-19 infection or underlying mechanisms are not well investigated, however it is well known that gender distribution of cognitive symptoms was clearly visible.[170] In a study including patients with COVID-19 infection and associated neurological symptoms, post-COVID-19 syndrome was found to be more common in women than men, with the most common symptoms being headache and cognitive impairment. In addition, PTSD was more prevalent in women during the COVID-19 pandemic. In a longitudinal study on PTSD, greater *Late Positive Potential* (LPP) EEG response predicted PTSD, indicating that this might be useful as a marker for prevention and treatment. To continue, assessing anxiety symptoms and pretrauma LPP to emotional stimuli may be helpful for identifying vulnerable individuals before the onset of symptoms.[171] Furthermore, prior research suggests that gender is an important factor in hypoxia resilience. There is identifiable brain wave suppression for both men and women with hypoxic exposure, and there are significant differences in this suppression between genders, such as significant decreases in theta and gamma frequency power for women compared to men.[172]

Several rsEEG studies investigated the effect of the sex factor in ADRD patients, which offers insights of future COVID-19 related EEG studies in men and women. One study showed higher values of posterior delta and theta power in females over male patients (56–79 years).[173] Additionally, another study showed that in AD patients, the male sex combined with early disease onset and increased severity of behavioral impairment predicted mortality.[174] A third study showed that, in those patients, mortality was predicted by the combination of the male sex with the following conditions: older age, poor cognitive function, low rsEEG alpha and beta power density, and temporoparietal atrophy.[175] These findings agree with previous evidence showing that brains of women over men may benefit from a sort of neuroprotection related to larger normalized volumes of the hippocampus, basal ganglia, and thalamus.[176] This neuroprotective effect may depend on both constitutional and environmental factors and might interact with the AD-related amyloid and tau neuropathology and/or the cortical neurodegeneration,[177,178] stabilizing the rsEEG alpha source activities in the normal elderly and prodromal AD females.[160] Finally, sex differences in astrocyte and complement C3 have not yet been examined in the context of COVID-19 EEG evaluation.

Educational level may also be related to healthcare access,[179] particularly for older people who experienced difficulties in accessing such services due to a lack of familiarity or skill with digital applications. Educational level is strictly related to the concept of cognitive reserve, allowing those individuals with high education attainment and whose life is typically characterized by many occasions and opportunities to learn new knowledge and exercise cognitive functions in their job and social environment to be resilient concerning their cognitive status along physiological and pathological aging.[180,181] The neuroprotective effect of education becomes compensatory while ADRD neuropathological processes occur, as revealed by more resilient cognitive neural systems to the neuropathological and neurodegenerative burden.[181] Previous results on rsEEG biomarkers in cognitively intact adults showed that early AD amyloidosis contrast the beneficial effects of cognitive reserve on neurophysiological oscillatory mechanisms at alpha frequencies[86] and connectivity between the thalamus and visual cortical networks.[182] The functional compensatory mechanisms unrelated to brain structure alterations were observed also at the prodromal stage of the disease.[29] Whether education will have protective effect for cognitive impairment due to Long COVID is not known.

7.4 | Racial disparities in COVID-19 EEG

Many bio-social factors influence COVID-19 symptoms like ADRD, for example, genetics of an individual brain, and cognitive reserve. The effects of COVID-19 on the brain have not only been related to general cognitive function, but also psychiatric symptoms. Both the

neurological consequences of the virus and the stresses of solitude during lockdown can contribute to increased cognitive decline, particularly in those with predementia.[169] Recovered individuals post-COVID-19 infection have reported worse mental health issues, including anxiety, depression, and PTSD for up to 10 months after infection.[40] The continued cognitive impairment coupled with persistent psychiatric symptoms could indicate a link between the effects of COVID-19 on the brain in various areas of function. EEG abnormalities include high individual alpha frequency, cortical current source density, high delta linear lagged connectivity, and delta oscillations.

The expectation for severe psychiatric symptoms associated with COVID-19 infection would be that the stress of hospitalization and treatment causes higher rates of mental illness. However, this is not always the case. In a study that compared hospitalized and home-treated COVID-19 infected individuals, members in both groups showed symptoms of PTSD postinfection recovery, illustrating that the stress of ventilation and sedation in hospital treatment cannot be the only cause of psychiatric symptoms of COVID-19.[40] Suicidal thoughts were also more prevalent in home-isolated individuals compared to hospitalized individuals. In addition, depression screening showed that home-isolated individuals had scores over twice as high as those who were hospitalized, indicating severe depressive symptoms.[183] Comparison of home versus hospital treated individuals highlights the impact of isolation on mental health of those infected with COVID-19.

Environmental stress associated with COVID-19 can increase multilevel allostatic overload, which in turn increases the risk of developing AD[184] and other dementias.[185] Having to face the uncertainty of the infection in isolation contributes to fear and worsening mental state without the support of direct medical intervention that is seen in hospital treatment.[183]

To the best of our effort, we could not find any studies specifically focusing on EEG markers of COVID-19 in Black or African American participants. Lack of research is surprising since it is well documented that the pandemic disproportionately affected Black or African American individuals. African American/Black and Hispanic populations have been reported to experience higher rates of COVID-19 infection and mortality. Differences in exposure risk and healthcare access could lead to higher mortality and infection rates.[186] Among the EEG research community, which strives to gather good quality data, there is unintentional bias, which can include avoidance of recruitment and retention of Black and African American participants due to common hair types (e.g., curlier) and hairstyles (e.g., braids).[187]

As stated in a recent special issue in diversity in neuroscience research, there is growing evidence of racial disparities within the field.[188] The systemic lack of data from Black and African American participants significantly limits the generalizability of findings. This is especially concerning considering in the context of dementia as Black and African American individuals are twice as likely as White individuals to have ADRD.[189] Complex mechanisms can be involved. For example, the associations between APOE4 and ADRD are weaker in populations of African descent than in other populations.[190] However, we believe that the COVID-19 pandemic and reverberating negative effects represent a unique opportunity for EEG researchers to commit additional efforts to recruit and retain sizable diverse samples. We also require novel EEG solutions that can better accommodate different hair types. While these are being developed, gaps still exist, particularly for dense EEG topographies (e.g., 64- and 128-channel systems).[191]

Neuroimaging studies have documented racial and ethnic disparities in brain health in mid- and late life. For example, a recent MRI study found that, compared to White and Latinx adults, Black adults showed an accelerated pattern of brain aging (i.e., cortical thickness and white matter hyperintensity volume) in middle age.[192] Similar studies using EEG markers can significantly add to this evidence base and thus further highlight the impacts of social, physical, and economic adversities that are often faced by individuals from excluded populations.[192] Unsurprisingly, these effects are purported to be higher in populations with negative social determinants of health and who face inequities.[37,193] Unlike expensive neuroimaging methods, EEG recordings are affordable and can be done wirelessly and remotely,[194,195] which indicates it to be a good candidate for reducing health disparity in rural and underprivileged populations around the world.

8 | FUTURE DIRECTIONS AND CONCLUSION

With an aging population worldwide, the persistence of neurological effects such as brain fog with Long COVID represents a massive societal and biomedical challenge. In particular, the potential role of Long COVID as a risk factor for ADRD in older populations warrants further investigation. Growing research has focused on elucidating common neurophysiological substrates underlying vigilance and cognitive symptoms in Long COVID and ADRD risk. EEG is ideal to address these questions, as it is cost-effective, minimally invasive, and widely accessible.

9 | FUTURE DIRECTIONS

Future studies should capture both similarities and differences in the pathophysiology of cerebral oscillations in COVID-19 and ADRD. There are multiple unresolved issues that are important to explore including: (1) Determine the value of EEG monitoring of COVID-19 severity and prediction of long-term consequences and cognitive decline risk. (2) Investigate EEG measurements as proxy for synaptic dysfunction due to astrocyte-microglia reactivity and pathology. (3) Establish specific EEG features closely associated with COVID-19 disease and cognitive dysfunctions. (4) Identify common EEG features in both COVID-19 and ADRD. (5) Evaluate EEG network features as neural biomarkers for clinical trials of pharmacological and nonpharmacological interventions in COVID-19 patients. (6) Assess variations of COVID-19 related EEG indicators in diverse populations.

10 | CONCLUSION

In this review, we try to communicate three take-home messages. First, EEG abnormalities have potential for identifying neurological complications and assisting clinical assessment and cognitive decline risk in

Long COVID patients. Second, identifying overlapping pathophysiology, such as neuroinflammatory mechanisms and astrocyte reactivity, will advance our understanding of critical pathways of both ADRD and COVID-19 underlying cognitive and functional decline. Third, what we have learned in the neurophysiology and ADRD field provides insights as to how reactive astrocytes may contribute to the neurovascular comorbidities seen in COVID-19. Also, it elucidates research questions regarding cognitive EEG and MCI in Long COVID that have not yet been adequately investigated.

In conclusion, some individuals with COVID-19 display abnormal intrinsic brain activity and cognitive impairments that resemble those seen in neurodegenerative diseases, particularly ADRD. The evidence presented indicates that COVID-19 and ADRD pathologies share common impacts on synaptic and neurovascular dysfunctions involving astrocyte reactivity and neuroinflammation. Furthermore, cognitive symptoms due to COVID-19 are underpinned by neurophysiological abnormalities typically seen in ADRD, which can be detected by routine EEG exams.

ACKNOWLEDGMENTS

This manuscript was facilitated by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), through the Electrophysiology Professional Interest Area (EPIA). The views and opinions expressed by authors in this publication represent those of the authors and do not necessarily reflect those of the EPIA membership, ISTAART or the Alzheimer's Association. The following authors serve as current or past members of the EPIA executive committee: Drs. Claudio Babiloni, Mihály Hajós, Bahar Güntekin, Görsev Yener, Xianghong Arakaki, Agustin Ibanez, Francesca R Farina, Susanna Lopez, and Yang Jiang. EPIA is committed to (1) exploiting EEG biomarkers for improving the understanding of neurophysiological mechanisms underlying Alzheimer's disease and age-related brain disorders at various spatial and temporal scales and (2) promoting clinical applications. The authors thank Thomas Dolan for medical illustration of Figure 5 and Mariena Passidomo for proof-reading and editing assistance. The review was partially supported by United States National Institute of Health (NIH), National Institute of Aging (NIA) Funding P01AG078116, P30AG072946, R01AG063857, R01AG057234, R01AG054484, R56AG060608, and 1R21AG046637; United States Department of Veterans Affairs Funding 5I21RX003173; Alzheimer's Association grants SG-20-725707, AAR-F2-1848281, and HAT-07-60437; by Funding from ANID/FONDECYT Regular (1210195 and 1210176 and 1220995); ANID/FONDAP/15150012; ANID/PIA/ANILLOS ACT210096; FONDEF ID20I10152, ID22I10029; ANID/FONDAP 15150012; Takeda CW2680521 and the MULTI-PARTNER CONSORTIUM TO EXPAND DEMENTIA RESEARCH IN LATIN AMERICA. Rainwater Charitable foundation – Tau Consortium, and Global Brain Health Institute); HORIZON 2021, H2021-MSCA-DN-2021 (Marie Skłodowska-Curie Doctoral Networks) grant 101071485; PNRR-MAD-2022-12376415 and Italian Ministry of University, Scientific and Technological Research funding 2010SH7H3F. The contents of this publication are solely the responsibility of the authors and do not represent the official views of these Institutions. The funders played no role in preparation of the manuscript or decision to publish.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Jiang Y, Neal J, Sompol P, et al. Parallel electrophysiological abnormalities due to COVID-19 infection and to Alzheimer's disease and related dementia. *Alzheimer's Dement*. 2024;:1-24. https://doi.org/10.1002/alz.14089