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Mapping brain changes in post-COVID-19 cognitive decline via FDG PET hypometabolism and EEG slowing

Paolo Manganotti[1]✉, Katerina Iscra[2], Giovanni Furlanis[1], Marco Michelutti[1], Aleksandar Miladinović[2,3], Alina Menichelli[4], Ivan Cerio[5], Agostino Accardo[2], Franca Dore[5] & Miloš Ajčević[2]

Cognitive decline is a common symptom of post-COVID-19 syndrome. However, the mechanisms underlying this deficit remain poorly understood. This study aims to investigate the relationship between brain metabolic and neurophysiological alteration patterns in patients with persistent subjective cognitive decline after mild COVID-19 using joint FDG-PET and EEG analyses. The study was conducted on 28 post-COVID-19 patients with cognitive decline, who underwent comprehensive clinical evaluation including cognitive testing, FDG-PET imaging, and EEG acquisition. Voxelwise statistical analysis of PET images was performed by comparing post-COVID-19 patients with healthy controls (p-voxel < 0.005 uncorrected, p-cluster < 0.005 FWE-corrected, K > 599 voxels). EEG spectral powers were extracted and compared with age and sex-matched controls. The results showed significant hypometabolism in the bilateral frontal, temporal, and parietal lobes, as well as in the left occipital lobe, along with predominantly frontal EEG slowing in post-COVID-19 patients compared to healthy controls. In particular, the EEG alterations were characterized by a significant increase in relative power in the delta and theta bands, accompanied by a marked reduction in alpha band power in the frontal, temporal, and central regions. The observed PET hypometabolism and EEG slowing patterns in anterior brain regions, may help to elucidate the pathophysiological mechanisms underlying cognitive decline in post-COVID-19 patients.

The global challenge of managing the wide range of symptoms linked to SARS-CoV-2 infection continues, especially in subjects with persistent symptoms. Post COVID-19 condition is characterized by a range of symptoms which usually start within 3 months of the initial COVID-19 illness and last at least 2 months[1] with cognitive difficulties being among the most commonly reported[2,3]. The reported cognitive deficits, often referred to as "brain fog", are particularly concerning, as they significantly impact patients' quality of life and their ability to perform daily activities[4,5]. Indeed, the cognitive deficits emerged as particularly troubling, affecting individuals of all ages including memory deficit, problems with concentration and difficulty focusing.

Recent studies have shown that, even months following COVID-19 acute infection, some individuals continue to experience neurological, psychiatric, and cognitive symptoms associated with detectable brain changes[6–8]. In patients reporting cognitive decline post-COVID-19, multiple PET studies have observed significant hypometabolism, primarily in the frontal and temporoparietal cortical regions[9–14] and less frequently in the occipital and cerebellar regions[9,14–16].

The degree of observed metabolic alterations is reported to be apparently transient and positively correlates with older age, neurological symptoms at the time of neuroimaging assessment, and worse disease severity scores[15]. The hypothesis of large-scale network dysfunction in long COVID patients is further supported by evidence of marked hypoperfusion, predominantly affecting the frontal, parietal, and temporal cortices, assessed by ASL-MRI brain perfusion study[17]. Finally, electroencephalography (EEG) studies have documented EEG

[1]Clinical Unit of Neurology, Department of Medicine, Surgery and Health Sciences, Trieste University Hospital-ASUGI, University of Trieste, Trieste, Italy. [2]Department of Engineering and Architecture, University of Trieste, Trieste, Italy. [3]Institute for Maternal and Child Health - IRCCS Burlo Garofolo, Trieste, Italy. [4]Rehabilitation Unit, Neuropsychological Service Trieste University Hospital- ASUGI, Trieste, Italy. [5]Nuclear Medicine, Imaging Diagnostic Department University Hospital and Health Services of Trieste, Trieste, Italy. ✉email: pmanganotti@units.it

alteration patterns in post-COVID-19 subjects[18–22]. In particular, predominant bilateral EEG slowing in frontal areas was observed in subacute patients with brain fog after COVID-19[21].

However, the underlying mechanisms behind the cognitive symptoms observed in the post-COVID-19, especially after a mild COVID-19 infection, remain a subject of ongoing debate. Given the complexity of these mechanisms, which may include cytokine storms, blood-brain barrier disruption, hypercoagulability, hypoxia, GABAergic and glutamatergic transmission dysfunction, neuroinflammation, immune dysregulation, and the overlap of symptoms with other neurodegenerative diseases[23–25]a multimodal approach may offer greater insight in context of persistent subjective cognitive decline post-covid. Our hypothesis is that a neuroimaging assessment that combines FDG-PET and EEG enables the evaluation of metabolic and neurophysiological dynamics, thus may provide a more comprehensive picture of brain functional dysfunction in post-COVID-19 patients, particularly when considered through the lens of the neurocoupling principle, which emphasizes the functional interconnection between brain electrical activity and cerebral glucose metabolism. Indeed, the combination of EEG and PET may provide a clearer view of the brain functional alterations[26–30]. Studies have shown that using these techniques together in individuals with mild cognitive impairment (MCI) provides insights into the links between synaptic, neurophysiological, and metabolic impairments associated with cognitive decline[26,27,30]. This combined approach may enhance understanding of the broader mechanisms involved, while also may assess the effectiveness of therapeutic interventions.

Our study aimed to investigate brain functional alterations and the underlying mechanisms using PET and EEG in post-COVID-19 subjects with subjective cognitive decline following mild SARS-CoV-2 infection, compared to healthy controls.

Materials and methods

Study population and protocol

This study employed a cross-sectional design to investigate brain alterations in patients with neuro-cognitive sequelae following COVID-19. Participants were recruited from the post-COVID-19 neurological outpatient clinic at the University Hospital of Trieste, Italy, between March 1, 2021, and March 31, 2022. Inclusion criteria required participants to have a confirmed SARS-CoV-2 infection, verified by RT-PCR, and to report persistent subjective cognitive decline that began within 3 months of the initial COVID-19 illness, lasted for at least 2 months, and were still present at the time of inclusion. Eligible participants were older than 18 and had no history of major neurological or psychiatric disorders or cognitive impairments prior to COVID-19 infection. Additionally, participants were required to have neuroimaging without major vascular alterations and to be free from the use of substances affecting the nervous system. Exclusion criteria included any contraindications to PET or EEG procedures, as well as moderate-to-severe COVID-19, defined by clinical and radiographic signs of lower respiratory tract disease or hospitalization due to COVID-19. All participants underwent a comprehensive clinical evaluation, which included medical history, neurological examination, cognitive testing via the Montreal Cognitive Assessment (MoCA), FDG-PET imaging, and EEG recording. EEG and FDG-PET assessments were performed within a maximum interval of 15 days.

As a control group for the FDG-PET analysis, we included twenty-eight healthy controls (HC) randomly selected from the AIMN (Associazione Italiana di Medicina Nucleare ed Imaging Molecolare) database, ensuring they were within the same age range and sex-matched (10 M/18F; 60.0 ± 8.1y). The database, previously validated for extracting SPM-based brain metabolism maps in patients[31–33]is available on the AIMN website (https://aimn.it/brain-fdg/). These subjects exhibited no global cognitive impairment and maintained cognitive stability after an average 4-year clinical follow-up. No significant differences in age and sex were observed.

A total of 28 age- and sex-matched healthy controls were retrospectively selected for the EEG analysis. These subjects had undergone EEG recordings at our University Hospital as part of a prior research project conducted before the SARS-CoV-2 outbreak. None had a history of cognitive impairment or any other neurological disorders.

The research was conducted according to the principles of the Declaration of Helsinki. All participants released their informed consent for treatment of clinical data after all procedures had been fully explained, as for standard institutional procedure. This study was approved by the Local Ethics Committee CEUR (Comitato Etico Unico Regionale, FVG, Italy).

Cognitive assessment

Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA) during the initial visit, administered by a trained neurologist utilizing the validated Italian version[34]. The MoCA evaluates multiple cognitive domains[35]and individual domain scores were calculated based on specific item responses. These domains included orientation (spatial and temporal), attention (digit span, letter A tapping, subtraction), executive function (trail making, abstraction, word fluency), visuo-constructive skills (cube copying, clock drawing), language (naming, sentence repetition), and memory (delayed word recall). The global MoCA score was adjusted for years of education (YoE), with an additional point added for individuals with 12 or fewer years of education. In addition, the MoCA score was also calculated using the correction for the Italian population[36]. Fatigue was assessed using the Fatigue Severity Scale (FSS), a nine-item questionnaire where participants rated the interference of fatigue on daily activities on a 7-point Likert scale, with 1 indicating "strongly disagree" and 7 indicating "strongly agree"[37]. The included subjects were also evaluated with the Prospective-Retrospective Memory Questionnaire (PRMQ)[38]a tool used to assess prospective and retrospective memory abilities in individuals. It includes 16 items measuring the frequency of memory failures in everyday life situations. The questionnaire provides normative data and assesses the latent structure of memory functioning in non-clinical populations. It has been used to assess cognitive decline similar to those reported by long-COVID patients.

Additionally, the patients' psychological well-being was evaluated through the anxiety and depression subscales of the SCL-90-R questionnaire[39].

PET imaging protocol and analysis

The brain glucose metabolism patterns were assessed using [18 F] FDG-PET. Prior to the scan, all patients fasted for at least 6 h. Each patient received an intravenous injection of approximately 200 MBq of FDG, administered 40 min before the scan. To minimize external stimuli during the 40-minute FDG uptake period, participants were placed in a quiet room under resting conditions and wore eye masks. PET scans were acquired using a PET/CT Discovery MI DR scanner (G.E. Healthcare) with an 8-minute acquisition time. Acquisition parameters: for PET Field of View 30 cm, matrix 256 × 256 (pixel 2–4 mm), acquisition time 8 min, TC parameters for attenuation correction 140 kV, 80–150 mA. Scanning time generally 10 s. Image reconstruction was carried out using an ordered subset expectation maximization algorithm with 32 subsets and 5 iterations, and images were displayed on a 128 × 128 matrix with a pixel size of 2.35 mm.

Images were processed and analyzed using SPM12 (http://www.fl.ion.ucl.ac.uk/spm/software/spm12/) run on MATLAB (MathWorks Inc., Sherborn, MA, USA). The preprocessing steps included spatial normalization to a specific [18 F]-FDG-PET template in the MNI space[40]spatial smoothing with an isotropic 8-mm 3D Gaussian kernel of FWHM and a proportional global mean scaling[41]. A comparison between PET images of post-COVID-19 patients and age- and sex-matched healthy controls was conducted using a voxelwise statistical analysis. The statistical threshold was set at T-score 2.63 ($p = 0.005$ uncorrected at the voxel level, familywise error (FWE)-corrected for multiple comparisons at the cluster level, K > 599 voxels).

EEG recording and analysis

EEG recordings were conducted using a Be Plus PRO amplifier (EB NEURO, Florence, Italy) with Ag/AgCl electrodes and a nineteen-channel electro-cap following the International 10/20 System. Electrode impedances were maintained below 5 kΩ, and the sampling rate was set to 128 Hz. Artifacts were identified by visual inspection performed independently by two experienced neurophysiologists (PM and GF). For each subject, the first 120-second artifact-free EEG segment was extracted for analysis. All channels were digitally filtered with the 0.1–30 Hz second-order bandpass filter. Power spectral density (PSD) for each EEG channel was estimated using Welch's method applied to the extracted 120-second artifact-free segment. The signal was divided into successive 10-second Hamming-windowed segments with 50% overlap, resulting in 23 overlapping windows averaged to obtain the final PSD estimate. Relative power for each spectral band (delta: 1–4 Hz; theta: 4–8 Hz; alpha: 8–13 Hz; beta: 13–30 Hz) was calculated by normalizing the power in each band to the total power in the 1–30 Hz range. Relative band power was then averaged across channels within each brain region (frontal, temporal, central, parietal, and occipital). The extracted EEG features were compared to an age- and sex-matched control group. Additionally, average topographic EEG maps were generated for the post-COVID-19 and healthy control groups for each spectral band.

Statistical analysis

Descriptive analysis was used to summarize the results. Continuous variables with a normal distribution are reported as mean and standard deviation (mean ± SD), while those with a skewed distribution are presented as median and interquartile range (IQR), indicating the first and third quartiles. Categorical variables are expressed as counts and percentages (%).

Differences between post-COVID-19 patients and healthy controls were evaluated with the two-sample t-test for continuous parameters or Mann–Whitney U test when the data were not normally distributed, and the chi-square test for proportions. A significance value was selected for $p < 0.05$.

Results

The demographic, clinical, and cognitive characteristics of the 28 post-COVID-19 patients with subjective cognitive decline studied with PET and EEG are summarized in Table 1. Pre-existing comorbidities and risk factors included hypertension (21.4%), obesity (21.4%), smoking (14.3%), dyslipidemia (17.9%), diabetes mellitus (7.1%), atrial fibrillation (7.1%), ischemic heart disease (3.6%), and autoimmune disease (3.6%). During the acute phase of SARS-CoV-2 infection, the most frequently reported symptoms were fever (78.6%), upper respiratory tract involvement (57.1%), asthenia (53.6%), myalgia/arthralgia (46.4%), dyspnea (39.3%), hyposmia (39.3%), headache (35.7%), hypogeusia (28.6%), gastrointestinal distress (14.3%), and palpitations/tachycardia (10.7%). None of the patients required hospitalization or oxygen therapy during the acute phase.

All patients reported persistent subjective cognitive decline, including memory deficits, reduced attention, and executive function impairments, as well as fatigue. The cognitive assessment in post-COVID-19 subjects showed that the median MoCA score was 25 (24–26), with a population-corrected median MoCA score of 22.7 (21.9–24.6) based on Italian norms [34]. No patients scored below the pathological impairment cut-off (< 18) as per the Italian normative data. Domain-specific MoCA scores were as follows: orientation 6 (6–6), attention 5 (4–6), language 5 (5–6), visuospatial function 4 (3–4), memory 3 (1–4), and executive function 4 (3–4). The average Fatigue Severity Scale (FSS) score was 5.64 ± 1.39, with 53.6% of patients exceeding the cut-off for fatigue. Within our cohort, 11 participants exhibited clinically significant depressive symptoms and 8 demonstrated clinically relevant anxiety symptoms during the post-COVID-19 period, as assessed by the Symptom Checklist-90-Revised (SCL-90-R). The Prospective and Retrospective Memory Questionnaire (PRMQ) revealed a high incidence of subjective memory decline: 52.9% of post-COVID-19 patients scored more than 1.5 standard deviations above the normative sample on both the prospective and retrospective memory scales.

In addition to cognitive decline, post-COVID-19 symptoms at the time of evaluation included asthenia (46.4%), persistent dyspnea (35.7%), hyposmia (28.6%), headache (25.0%), myalgia/arthralgia (17.9%),

	(*n* = 28)
Age (years)	56.2 ± 9.9
Sex (M/F)	9 M/19F
Education (years)	13.7 ± 2.6
Δ COVID-19 symptom—Post-COVID-19 assessment (days)	161.0 ± 93.4
Δ Post-COVID-19 assessment—EEG assessment (days)	7.4 ± 2.2
Δ Post-COVID-19 assessment—PET assessment (days)	19.3 ± 8.1
Pre-existing comorbidities and risk factors	
Ischemic heart disease	1 (3.6%)
Hypertension	6 (21.4%)
Atrial fibrillation	2 (7.1%)
Dyslipidemia	5 (17.9%)
Diabetes mellitus	2 (7.1%)
Obesity	6 (21.4%)
Smoke	4 (14.3%)
Autoimmune disease	1 (3.6%)
Clinical features during COVID-19 acute phase	
Fever	22 (78.6%)
Upper respiratory airways involvement	16 (57.1%)
Asthenia	15 (53.6%)
Myalgia/arthralgia	13 (46.4%)
Dyspnea	11 (39.3%)
Headache	10 (35.7%)
Hyposmia	11 (39.3%)
Hypogeusia	8 (28.6%)
Diarrhea/gastrointestinal distress	4 (14.3%)
Palpitations/tachycardia	3 (10.7%)
Post-COVID-19 manifestations	
Number of associated symptoms per patient	2.5 (2–4)
Asthenia	13 (46.4%)
Dyspnea	10 (35.7%)
Hyposmia	8 (28.6%)
Headache	7 (25.0%)
Myalgia/arthralgia	5 (17.9%)
Dizziness/gait instability	5 (17.9%)
Palpitations/tachycardia	3 (10.7%)
Hypogeusia	5 (17.9%)
Diarrhea/gastrointestinal distress	3 (10.7%)
MoCA	25 (24–26)
MoCA domain scores	
Orientation (max 6)	6 (6–6)
Attention (max 6)	5 (4–6)
Language (max 6)	5 (5–6)
Visuospatial function (max 4)	4 (3–4)
Memory (max 5)	3 (1–4)
Executive function (max 4)	4 (3–4)
MoCA corrected according (Aiello et al.)	22.7 (21.9–24.6)
Fatigue Severity Scale (FSS)	5.64 ± 1.39

Table 1. Demographic, clinical and cognitive characteristics of long COVID-19 patents.

hypogeusia (17.9%), dizziness/gait instability (17.9%), palpitations/tachycardia (10.7%), and gastrointestinal distress (10.7%).

The mean time between the onset of COVID-19 symptoms and the post-COVID-19 clinical evaluation, including cognitive assessment, was 5.3 ± 3.1 months. EEG recordings were performed within 15 days of cognitive assessment (mean 7.4 ± 2.2 days), while PET imaging occurred within 1 month of cognitive assessment (mean 19.3 ± 8.1 days).

Compared to healthy controls, patients with post-COVID-19 exhibited significant hypometabolism ($p < 0.005$ uncorrected, $p < 0.005$ FWE corrected) in eight distinct clusters (Fig. 1).

The largest cluster was located in the right frontal lobe (T = 10.49, k = 2917), followed by two clusters in the left frontal lobe (T = 8.48, k = 2195; T = 8.44, k = 1010). Additional clusters were observed in the right temporal lobe (T = 8.79, k = 1087), left temporal lobe (T = 8.00, k = 778), left parietal lobe (T = 6.70, k = 997), right parietal lobe (T = 5.87, k = 618), and left occipital lobe (T = 7.35, k = 599). Detailed anatomical locations of these clusters are provided in Table 2. No areas of hypermetabolism were identified.

Figure 2 presents the average EEG topographic maps of calculated spectral parameters for each group. Higher relative delta and theta power, along with lower relative alpha power, can be observed in post-COVID-19 subjects compared to the healthy control (HC) group, particularly in the frontal, central, and temporal areas. These alterations in brain electrical activity, particularly pronounced in the frontal regions, indicate region-specific changes in oscillatory patterns.

Table 3 reports the median values of delta, theta, alpha, and beta relative power for each group and brain region, along with comparisons between post-COVID-19 subjects and healthy controls. Specifically, post-COVID-19 subjects exhibited significantly higher relative delta power in frontal, central, and temporal EEG channels compared to the HC group. Relative theta power was also significantly higher in post-COVID-19

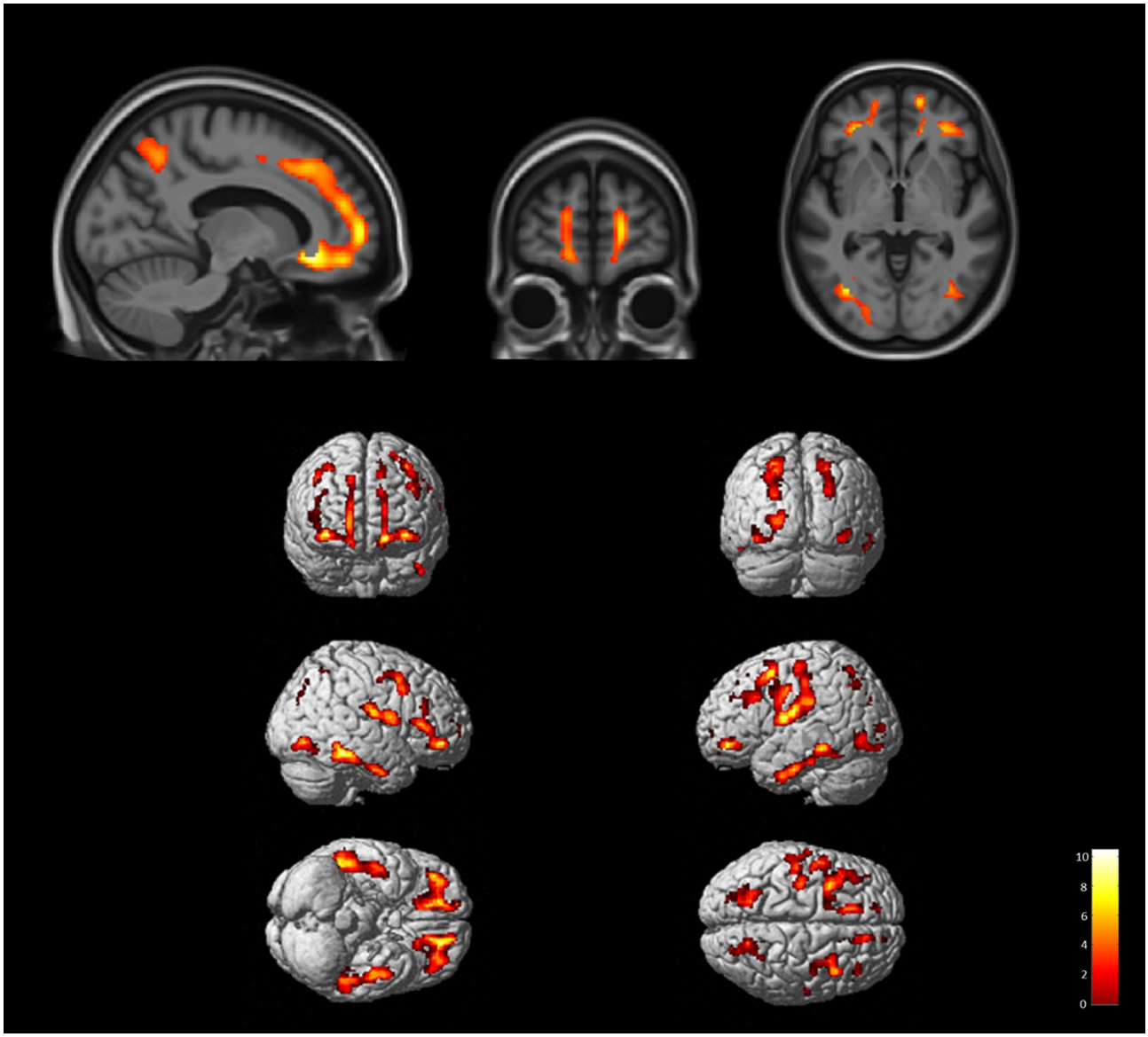

Fig. 1. Brain ^{18}F-FDG PET hypometabolic clusters in patients with post-COVID-19 in comparison to healthy subjects ($p = 0.005$ uncorrected at the voxel level, FWE-corrected at the cluster level, K > 599 voxels). The clusters are projected onto sagittal, coronal, and axial slices (top panel) and onto 3D volume-rendered images (bottom panel).

Area	Side	Voxel	Peak MNI coordinate			T score	*p*-value
			x	y	z		
Frontal lobe	R	2917	20	42	− 8	10.40	< 0.001
Frontal lobe	L	2195	− 34	8	54	8.48	< 0.001
Frontal lobe	L	1010	− 20	44	− 8	8.44	0.001
Temporal lobe	R	1087	52	− 34	− 18	8.79	< 0.001
Temporal lobe	L	778	− 50	− 38	− 14	8.00	0.004
Parietal lobe	L	997	− 24	− 60	54	6.70	0.001
Parietal lobe	R	618	16	− 58	48	5.87	0.015
Occipital lobe	L	599	− 20	− 86	4	7.35	0.018

Table 2. The summary of cluster-level statistics for the identified hypometabolic regions in post-COVID-19 patients, compared to healthy controls, includes anatomical regions, cluster sizes, MNI coordinates of peak locations, t-scores, and p-values.

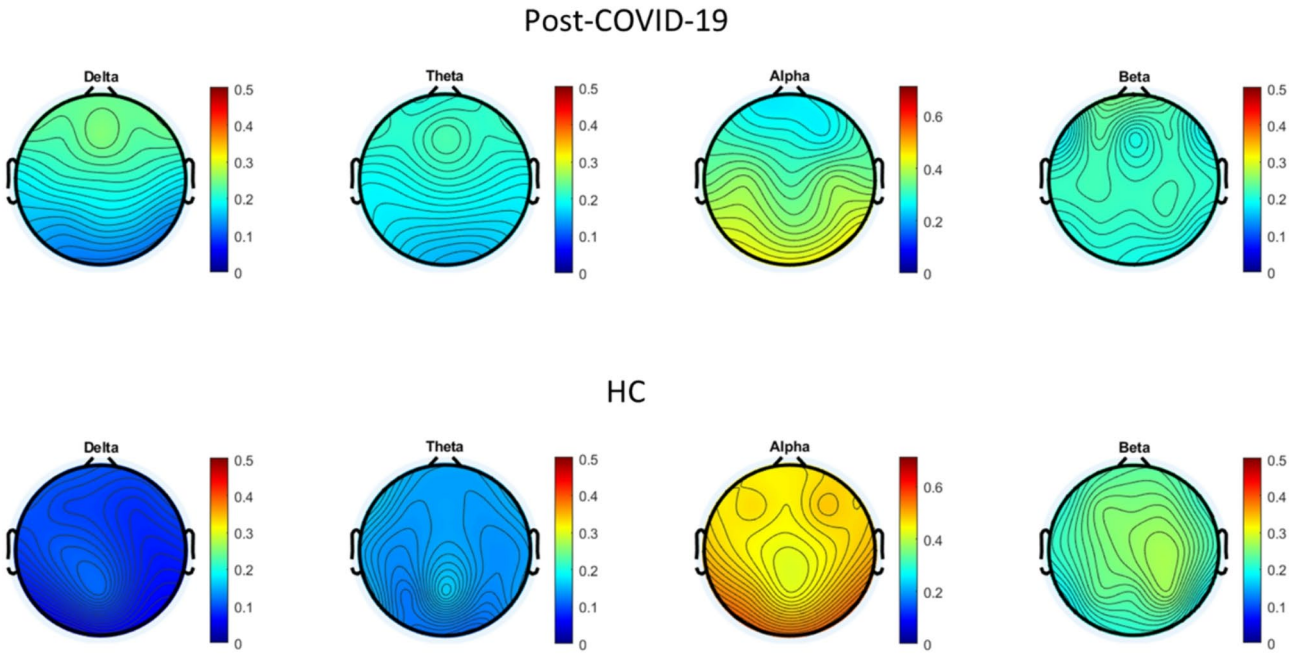

Fig. 2. Average EEG topographic maps of calculated spectral parameters, including relative delta, theta, alpha, and beta power, for each group; (Post-COVID-19—top panel; Healthy Control—bottom panel)

	Delta			Theta			Alpha			Beta		
	Covid-19	HC	*p*-value	Covid-19	HC	*p*-value	Covid-19	HC	*p*-value	Covid-19	HC	*p*-value
Frontal	0.23	0.08	**0.001**	0.21	0.14	**0.009**	0.26	0.42	**0.002**	0.20	0.19	1.000
Temporal	0.13	0.05	**0.004**	0.17	0.13	0.178	0.43	0.54	**0.046**	0.17	0.17	0.728
Central	0.16	0.05	**0.005**	0.19	0.12	**0.027**	0.35	0.51	0.082	0.19	0.22	0.745
Parietal	0.12	0.06	0.112	0.17	0.13	0.186	0.46	0.46	0.307	0.18	0.21	0.626
Occiptal	0.10	0.05	0.083	0.15	0.10	0.057	0.54	0.66	0.120	0.18	0.21	0.781

Table 3. Median values of relative power, including relative delta, theta, alpha, and beta power, calculated for each group (Covid-19: Post-COVID-19 subjects; HC: healthy Control), with comparisons between the two groups for each lobe. Significant p-values are indicated in bold ($p < 0.05$). Significant values are in bold.

subjects in the frontal and central areas. Meanwhile, relative alpha power was significantly lower in post-COVID-19 subjects in the frontal and temporal regions, confirming the predominant frontal EEG slowing trend.

The regional alterations in brain oscillatory activity, expressed as EEG slowing in the frontal, central, and temporal regions (Table 3), align with the hypometabolism patterns identified by significant clusters in the PET analysis (Table 2).

Discussion

Long COVID syndrome can occur regardless of the severity of symptoms during the acute phase[7]with cognitive decline being one of the most prevalent and impactful symptoms on patients' quality of life[5]. Despite the growing recognition of this issue, the underlying mechanisms driving post-COVID-19 cognitive decline remain poorly understood.

The main finding of this study is the identification of significant hypometabolism and EEG slowing in anterior brain regions in patients with persistent subjective cognitive decline after mild COVID-19. Specifically, FDG-PET analysis revealed significant hypometabolism clusters in the bilateral frontal, temporal, and parietal lobes, as well as in the left occipital lobe. EEG analysis showed a significant increase in relative power in the delta and theta bands, along with a marked reduction in alpha band power in the frontal, temporal, and central regions. These findings were observed in patients who experienced mild acute COVID-19 that did not require hospitalization or ventilatory support.

Brain hypometabolism patterns have been identified in several studies analyzing FDG-PET images of both acute and post-COVID-19 patients[9–16,42]. In particular, focal hypometabolism in bilateral frontal, parietal, occipital, and posterior temporal lobes has been observed during the first two months from infection and completely disappeared at 12 months[15]. In cases of long COVID, FDG-PET scans revealed bilateral hypometabolism in regions such as the rectal/orbital gyrus, right temporal lobe, pons/medulla brainstem, and cerebellum, correlating with cognitive and neurological symptoms[9]. Frontoparietal hypometabolism has been reported in hospitalized individuals with neurological symptoms[10]while diffuse hypometabolism affecting the right frontal and temporal lobes was observed in outpatients with post-COVID-19 conditions[13]. Follow-up FDG-PET scans up to six months post-COVID-19 revealed persistent prefrontal hypometabolism[42]as well as frontoparietal and temporal hypometabolism[11]. Persistent hypometabolism in the limbic region, pons, and cerebellum has also been documented up to 16 months post-infection[16]. Cognitive deficits in post-COVID-19, especially in concentration and memory, have been associated with reduced metabolism in the prefrontal and mesial/inferior temporal regions[14]. Moreover, cognitive abnormalities and abnormal brain metabolism were still detectable in nearly half of cases 12 months after COVID-19 infection[12]. Although the aforementioned studies report hypermetabolism in slightly discordant areas, they all converge on the anterior hypometabolism pattern observed in our study, which coincides with EEG alterations which we detected in the same regions.

Recent studies have reported heterogeneous EEG abnormalities in post-COVID-19 patients, without considering other neuroimaging techniques[18,19,21]. Quantitative EEG analysis in subjects experiencing post-COVID-19 brain fog revealed increased right-hemisphere theta, alpha, and sensorimotor rhythm power, elevated beta 2 versus SMR bilaterally, and an increase in beta 1 in the left hemisphere[18]. Fifty recovered COVID-19 patients with cognitive decline had significantly higher theta/beta ratios in central and parietal areas than fifty matched healthy controls[19]. Furthermore, another study reported EEG alterations in 65% of participants, with 69% of them exhibiting slowed activity and 31% showing epileptic discharges, primarily in the frontal regions[21]. These results show that EEG changes in post-COVID-19 subjects are still debated regarding the alteration pattern, though with a predominance of slowing. Our study identified a shift in EEG rhythms from higher frequencies, such as alpha, to lower frequencies like theta and delta, particularly in anterior regions, which aligned with the observed hypometabolism clusters.

The presence of hypometabolism and altered brain electrical activity has been observed in studies that investigated EEG and FDG-PET separately, as well as together, in patients with mild cognitive impairment unrelated to COVID-19[26,30,43–45]. The significant hypometabolism in the temporal lobe was observed in subjects with MCI due to Alzheimer's disease (AD) compared to healthy controls[43,44]. The reduction in alpha and beta activity and an increase in theta power was detected in subjects with mild cognitive impairment due to Alzheimer's or Parkinson's disease[45]. The joint investigation of FDG-PET and EEG showed that may support the differential diagnosis between AD, vascular dementia, and healthy controls, identifying frontal and temporoparietal hypometabolism in AD patients compared to healthy individuals, as well as significantly higher relative theta power in cognitively impaired subjects in the frontal, central, and temporal regions[30]. Moreover, another study has demonstrated that combining FDG-PET and EEG in subjects with MCI allows for a comprehensive evaluation of both the neurochemical and neurophysiological changes that precede the clinical onset of AD, thus improving predictions of disease progression and providing insights into therapeutic efficacy[26].

Hypometabolism clusters and areas with EEG slowing identified in our study, particularly in anterior regions, could justify the reduced post-COVID-19 cognitive performance in executive, attention, language and memory. The observed PET EEG pattern is complementary to identified marked hypoperfusion, assessed by ASL-MRI in cognitively impaired post-COVID-19 subjects, predominantly affecting the frontal, parietal, and temporal cortices[17]. Specifically, the frontal lobes play a pivotal role in functions such as working memory, inhibition, cognitive flexibility, planning, and problem-solving[46,47]. The cognitive issues observed in our cohort are consistent with the common clinical patterns reported in post-COVID-19 studies[10,48,49].

Notably, the neurochemical basis of these findings may be linked to disrupted neurotransmitter systems, particularly involving GABAergic and glutamatergic pathways. FDG-PET hypometabolism in the frontal and temporal cortices may reflect reduced synaptic activity, which could arise from astrocytic dysfunction and impaired glutamate uptake capacity, contributing to excitotoxicity and neuroinflammation[25]. In line with this,

previous TMS study in post-COVID-19 patients performing sub-optimally in the cognitive functions has also shown reduced long-interval intracortical inhibition (LICI, GABAb-mediated) and intracortical facilitation (ICF, glutamatergic), highlighting the impact of COVID-19 on synaptic inhibitory-excitatory balance[24]. Therefore, the glutamatergic dysregulation and a concomitant reduction in GABAergic inhibitory control may create a state of neural dysfunction and metabolic stress. This imbalance could account for both the PET-detected hypometabolism (due to disrupted energy demands of excitatory/inhibitory neurons) and the EEG slowing (as a marker of altered network synchrony and thalamocortical dysrhythmia). The determined metabolic, perfusional and neurophysiological brain changes may help to elucidate the pathophysiological mechanisms underlying cognitive decline in post-COVID-19 patients.

Reduced metabolism often serves as a marker of neuronal dysfunction, where brain cells become less active and consume less glucose[50]. In contrast, a decrease in alpha power, typically associated with relaxed wakefulness and cognitive processing, can signal disrupted brain activity, as often seen in the early stages of cognitive decline[51]. Both hypometabolism and changes in spectral power are indicators of underlying neuronal stress or damage[52,53]. Our results reinforce the idea that cognitive decline in long COVID may be linked to both metabolic and electrical dysfunction in the brain.

The metabolic PET changes and EEG changes observed in post-COVID-19 patients may result from a parainfectious inflammatory process that appears to predominantly affect the frontal lobes and/or frontal networks[54]. Potential pathophysiological mechanisms underlying SARS-CoV-2 infection include neuroinflammation, autoimmunity, must cell activation, vascular changes with blood brain barrier disruption, gut brain axis dysregulation, or direct viral effects on neural tissues[10,55–58]. These mechanisms could plausibly account for cortical and blood-brain barrier dysfunction, leading to hypometabolism, altered EEG spectral power, and cognitive decline.

Our study has some limitations. It is a single-center study with a moderate sample size considering the multimodal nature of the study. A larger sample size would strengthen the generalizability of the findings. Another possible limitation is the temporal gap between the FDG-PET and EEG assessments, which were conducted within a 15-day window. No follow-up was performed, and future longitudinal imaging studies are needed to determine the persistence or resolution of these brain changes. Patients were assessed using the MoCA test, which, although widely used, has limited sensitivity for detecting subtle or domain-specific cognitive deficits. A more comprehensive neuropsychological assessment would provide a more nuanced characterization of the cognitive profile and allow for a stronger linkage between the neuroimaging, neurophysiological findings, and cognitive outcomes. Moreover, a higher incidence of anxiety and depression among post-COVID-19 patients observed in our cohort may have potential psycho-affective contributions to reported cognitive alterations and findings. Another limitation is the heterogeneity in time since COVID-19 infection, ranging from 2 to 8 months after symptom onset, that may affect the interpretation of results. Nevertheless, this reflects the natural variability in patient presentation at post-COVID-19 outpatient clinic. All participants reported persistent cognitive symptoms at the time of evaluation.

Conclusions

In conclusion, in patients with persistent subjective cognitive decline after mild COVID-19 we identified concomitant PET hypometabolism and EEG slowing patterns in anterior brain regions. FDG-PET analysis revealed significant hypometabolism clusters in the bilateral frontal, temporal, and parietal lobes, along with the left occipital lobe. EEG analysis showed a significant increase in relative power in the delta and theta bands, along with a marked reduction in alpha band power in the frontal, temporal, and central regions. The determined metabolic and neurophysiological brain changes may help to elucidate the pathophysiological mechanisms underlying cognitive decline in post-COVID-19 patients.

Data availability

Anonymized data are available upon reasonable request to the corresponding author.

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References

1. *A Clinical Case Definition of Post COVID-19 Condition by a Delphi Consensus*. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 (2021).
2. Crook, H., Raza, S., Nowell, J., Young, M. & Edison, P. Long covid—mechanisms, risk factors, and management. *BMJ* **374**, n1648 (2021).
3. Liu, T. C. et al. Perceived cognitive deficits in patients with symptomatic SARS-CoV-2 and their association with post-COVID-19 condition. *JAMA Netw. Open.* **6**, e2311974 (2023).
4. Nalbandian, A. et al. Post-acute COVID-19 syndrome. *Nat. Med.* **27**, 601–615 (2021).
5. Quan, M. et al. Post-COVID cognitive dysfunction: current status and research recommendations for high risk population. *Lancet Reg. Health West. Pac.* **38**, 100836 (2023).
6. Zhao, S., Toniolo, S., Hampshire, A. & Husain, M. Effects of COVID-19 on cognition and brain health. *Trends Cogn. Sci.* **27**, 1053–1067 (2023).
7. Taquet, M., Geddes, J. R., Husain, M., Luciano, S. & Harrison, P. J. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. **8**, 416–427 (2021).
8. Kausel, L. et al. Patients recovering from COVID-19 who presented with anosmia during their acute episode have behavioral, functional, and structural brain alterations. *Sci. Rep.* **14**, 19049 (2024).
9. Guedj, E. et al. 18F-FDG brain PET hypometabolism in patients with long COVID. *Eur. J. Nucl. Med. Mol. Imaging*. **48**, 2823–2833 (2021).

10. Hosp, J. A. et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain* **144**, 1263–1276 (2021).
11. Blazhenets, G. et al. Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients. *J. Nucl. Med.* **62**, 910–915 (2021).
12. Ferrucci, R. et al. Brain positron emission tomography (PET) and cognitive abnormalities one year after COVID-19. *J. Neurol.* **270**, 1823–1834 (2023).
13. Goehringer, F. et al. Brain 18F-FDG PET imaging in outpatients with post-COVID-19 conditions: findings and associations with clinical characteristics. *Eur. J. Nucl. Med. Mol. Imaging.* **50**, 1084–1089 (2023).
14. Rozenblum, L. et al. Cognitive impairment and brain metabolic changes in post-acute sequelae of COVID-19: insights from an [18 F]FDG PET/CT cohort study. *Clin. Nucl. Med.* **50**, e146–e153 (2025).
15. Debs, P. et al. Post-COVID-19 brain [18F] FDG-PET findings: A retrospective single-center study in the united States. *Am. J. Neuroradiol.* **44**, 517–522 (2023).
16. Horowitz, T. et al. Persistent brain metabolic impairment in long COVID patients with persistent clinical symptoms: a nine-month follow-up [18F]FDG-PET study. *Eur. J. Nucl. Med. Mol. Imaging.* **51**, 3215–3222 (2024).
17. Ajčević, M. et al. Cerebral hypoperfusion in post-COVID-19 cognitively impaired subjects revealed by arterial spin labeling MRI. *Sci. Rep.* **13**, 5808 (2023).
18. Kopańska, M. et al. Comparison of QEEG findings before and after onset of post-COVID-19 brain fog symptoms. *Sens. (Basel).* **22**, 6606 (2022).
19. Gaber, M. M., Hosny, H., Hussein, M., Ashmawy, M. A. & Magdy, R. Cognitive function and quantitative electroencephalogram analysis in subjects recovered from COVID-19 infection. *BMC Neurol.* **24**, 60 (2024).
20. Ortelli, P. et al. Lowered delta activity in post-COVID-19 patients with fatigue and cognitive impairment. *Biomedicines* **11**, 2228 (2023).
21. Furlanis, G. et al. Cognitive deficit in post-acute COVID-19: an opportunity for EEG evaluation? *Neurol. Sci.* **44**, 1491–1498 (2023).
22. Gangemi, A., Suriano, R. & Fabio, R. A. Longitudinal exploration of cortical brain activity in cognitive fog: an EEG study in patients with and without anosmia. *J. Integr. Neurosci.* **23**, 105 (2024).
23. Wang, W., Cui, R., Leng, L., Wang, G. & Peng, G. Cognitive impairment in the post-acute phases of COVID-19 and mechanisms: an introduction and narrative review. *J. Alzheimers Dis. Rep.* **8**, 647–658 (2024).
24. Manganotti, P., Michelutti, M., Furlanis, G. & Deodato, M. Buoite stella, A. Deficient GABABergic and glutamatergic excitability in the motor cortex of patients with long-COVID and cognitive impairment. *Clin. Neurophysiol.* **151**, 83–91 (2023).
25. Horowitz, T., Pellerin, L., Zimmer, E. R. & Guedj, E. Brain fog in long COVID: A glutamatergic hypothesis with astrocyte dysfunction accounting for brain PET glucose hypometabolism. *Med. Hypotheses.* **180**, 111186 (2023).
26. Moretti, D. V. et al. Cerebral PET glucose hypometabolism in subjects with mild cognitive impairment and higher EEG high-alpha/low-alpha frequency power ratio. *Neurobiol. Aging.* **58**, 213–224 (2017).
27. Li, W. et al. Data-driven retrieval of population-level EEG features and their role in neurodegenerative diseases. *Brain Commun.* **6**, 227 (2024).
28. Hermann, B. et al. Multimodal FDG-PET and EEG assessment improves diagnosis and prognostication of disorders of consciousness. *Neuroimage Clin.* **30**, 102601 (2021).
29. Husari, K. S. et al. EEG correlates of qualitative hypermetabolic FDG-PET in patients with neurologic disorders. *Neurol. Clin. Pract.* **13**, e200135 (2023).
30. Szelies, B., Mielke, R., Herholz, K. & Heiss, W. D. Quantitative topographical EEG compared to FDG PET for classification of vascular and degenerative dementia. *Electroencephalogr. Clin. Neurophysiol.* **91**, 131–139 (1994).
31. Varrone, A. et al. EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *Eur. J. Nucl. Med. Mol. Imaging.* **36**, 2103–2110 (2009).
32. Paez, D. et al. COVID-19 pandemic: guidance for nuclear medicine departments. *Eur. J. Nucl. Med. Mol. Imaging.* **47**, 1615–1619 (2020).
33. Caminiti, S. P. et al. Validation of FDG-PET datasets of normal controls for the extraction of SPM-based brain metabolism maps. *Eur. J. Nucl. Med. Mol. Imaging.* **48**, 2486–2499 (2021).
34. Pirrotta, F. et al. Italian validation of Montreal cognitive assessment. *Eur. J. Psychol. Assess.* **31**, 131–137 (2015).
35. Nasreddine, Z. S. et al. The Montreal cognitive assessment, moca: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* **53**, 695–699 (2005).
36. Aiello, E. N. et al. The Montreal cognitive assessment (MoCA): updated norms and psychometric insights into adaptive testing from healthy individuals in Northern Italy. *Aging Clin. Exp. Res.* **34**, 375–382 (2022).
37. Siciliano, M. et al. Fatigue in parkinson's disease: Italian validation of the Parkinson fatigue scale and the fatigue severity scale using a Rasch analysis approach. *Parkinsonism Relat. Disord.* **65**, 105–110 (2019).
38. Crawford, J. R., Smith, G., Maylor, E. A., Della Sala, S. & Logie, R. H. The prospective and retrospective memory questionnaire (PRMQ): normative data and latent structure in a large non-clinical sample. *Memory* **11**, 261–275 (2003).
39. Derogatis, L., Sarno, I., Preti, E., Prunas, A. & Madeddu, F. *Manuale di somministrazione e scoring. Adattamento italiano di SCL-90-R.* https://boa.unimib.it/handle/10281/23234 (2011).
40. Della Rosa, P. A. et al. A standardized [18F]-FDG-PET template for Spatial normalization in statistical parametric mapping of dementia. *Neuroinformatics* **12**, 575–593 (2014).
41. Perani, D. et al. Validation of an optimized SPM procedure for FDG-PET in dementia diagnosis in a clinical setting. *Neuroimage Clin.* **6**, 445–454 (2014).
42. Kas, A. et al. The cerebral network of COVID-19-related encephalopathy: a longitudinal voxel-based 18F-FDG-PET study. *Eur. J. Nucl. Med. Mol. Imaging.* **48**, 2543–2557 (2021).
43. Pagani, M. et al. Early identification of MCI converting to AD: a FDG PET study. *Eur. J. Nucl. Med. Mol. Imaging.* **44**, 2042–2052 (2017).
44. Morbelli, S. et al. 18F-FDG PET diagnostic and prognostic patterns do not overlap in alzheimer's disease (AD) patients at the mild cognitive impairment (MCI) stage. *Eur. J. Nucl. Med. Mol. Imaging.* **44**, 2073–2083 (2017).
45. Polverino, P. et al. Brain oscillatory patterns in mild cognitive impairment due to alzheimer's and parkinson's disease: an exploratory high-density EEG study. *Clin. Neurophysiol.* **138**, 1–8 (2022).
46. Henri-Bhargava, A., Stuss, D. T. & Freedman, M. Clinical assessment of prefrontal lobe functions. *Continuum: Lifelong Learn. Neurol.* **24**, 704 (2018).
47. Jones, D. T. & Graff-Radford, J. Executive dysfunction and the prefrontal cortex. *Continuum (Minneap Minn).* **27**, 1586–1601 (2021).
48. Cecchetti, G. et al. Cognitive, EEG, and MRI features of COVID-19 survivors: a 10-month study. *J. Neurol.* **1**, 1–13. https://doi.org/10.1007/s00415-022-11047-5 (2022).
49. Becker, J. H. et al. Assessment of cognitive function in patients after COVID-19 infection. *JAMA Netw. Open.* **4**, e2130645 (2021).
50. Shichkova, P., Coggan, J. S., Markram, H. & Keller, D. Brain metabolism in health and neurodegeneration: the iinterplay among neurons and astrocytes. *Cells* **13**, 1714 (2024).
51. Lejko, N., Larabi, D. I., Herrmann, C. S., Aleman, A. & Ćurčić-Blake, B. Alpha power and functional connectivity in cognitive decline: a systematic review and meta-analysis. *J. Alzheimers Dis.* **78**, 1047–1088.

52. Raut, S. et al. Hypometabolism, Alzheimer's disease, and possible therapeutic targets: an overview. *Cells* **12**, 2019 (2023).
53. Benwell, C. S. Y. et al. EEG spectral power abnormalities and their relationship with cognitive dysfunction in patients with alzheimer's disease and type 2 diabetes. *Neurobiol. Aging*. **85**, 83–95 (2020).
54. Toniolo, S. et al. Dementia and COVID-19, a bidirectional liaison: risk factors, biomarkers, and optimal health care. *J. Alzheimers Dis.* **82**, 883–898 (2021).
55. Paterson, R. W. et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* **143**, 3104–3120 (2020).
56. Bulla, R. et al. A likely association between low mannan-binding lectin level and brain fog onset in long COVID patients. *Front. Immunol.* **14**, 1 (2023).
57. Medori, M. C. et al. Serum proteomic profiling reveals potential inflammatory biomarkers in long-COVID patients: a comparative analysis with healthy controls. *Eur. Rev. Med. Pharmacol. Sci.* **27**, 1–12 (2023).
58. Talkington, G. M. et al. Neurological sequelae of long COVID: a comprehensive review of diagnostic imaging, underlying mechanisms, and potential therapeutics. *Front. Neurol.* **15**, 1465787 (2024).

Author contributions

P.M., K.I., G.F., and M.A. contributed to the study's conception and design. Methodology was developed by M.A., K.I., and A.A. Data collection was performed by M.A., G.F., M.M., A.Me., I.C. and F.D. Image and signal processing, along with analysis, were conducted by M.A., K.I., and A.Mi. Data analysis was carried out by M.A. and K.I., while results were interpreted by M.A., K.I., G.F., and P.M. P.M., M.A., G.F., and K.I. prepared the manuscript draft. All authors reviewed and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to P.M.

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