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Resting-state EEG rhythms are abnormal in post COVID-19 patients with brain fog without cognitive and affective disorders

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HIGHLIGHTS

- More than 90% of post-COVID participants showed no cognitive or psychiatric disorders, and 75% showed $\geq$ 2 fatigue symptoms.
- Compared to the Control group, the post-COVID group showed lower posterior resting state EEG alpha source activities.
- This effect was more significant in the post-COVID patients with $\geq$ 2 fatigue symptoms, possibly related to vigilance and allostatic dysfunctions.

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ABSTRACT

Objectives: Several persons experiencing post-covid-19 (post-COVID) with "brain fog" (e.g., fatigue, cognitive and psychiatric disorders, etc.) show abnormal resting-state electroencephalographic (rsEEG) rhythms reflecting a vigilance dysfunction. Here, we tested the hypothesis that in those post-COVID persons, abnormal rsEEG rhythms may occur even when cognitive and psychiatric disorders are absent.
Methods: The experiments were performed on post-COVID participants about one year after hospitalization for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Inclusion criteria included a "brain fog" claim, no pre-infection, and actual organic chronic disease. Matched controls (no COVID) were also enrolled. All participants underwent clinical/neuropsychological assessment (including fatigue assessment) and rsEEG recordings. The eLORETA freeware estimated regional rsEEG cortical sources at individual delta (<4 Hz), theta (4–7 Hz), and alpha (8–13 Hz) bands. Beta (14–30 Hz) and gamma (30–40 Hz) bands were pre-fixed.
Results: More than 90% of all post-COVID participants showed no cognitive or psychiatric disorders, and 75% showed $\geq$ 2 fatigue symptoms. The post-COVID group globally presented lower posterior rsEEG alpha source activities than the Control group. This effect was more significant in the long COVID-19 patients with $\geq$ 2 fatigue symptoms.
Conclusions: In post-COVID patients with no chronic diseases and cognitive/psychiatric disorders, "brain fog" can be associated with abnormal posterior rsEEG alpha rhythms and subjective fatigue.
Significance: These abnormalities may be related to vigilance and allostatic dysfunctions.

1. Introduction

It is well-known that COVID-19 is a respiratory disease caused by SARS-CoV-2, which provoked death in millions of patients in

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2020–2023. In about 10% of COVID-19 patients, clinical symptoms can persist or even increase beyond the acute phase with a sequela often named "post-acute COVID-19" or "long COVID" (Nalbandian et al., 2021; Allard et al., 2022). Those symptoms include myalgia, chronic fatigue syndrome (CFS), dyspnea, sleep disorder, migraine-like headaches, ageusia, anosmia, mental symptoms, autonomic dysfunctions, and other less common manifestations (Jennings et al., 2021; Del Brutto et al., 2021; Mazza et al., 2021; Raveendran et al., 2021). Concerning its clinical definition, the World Health Organization stated that long COVID occurs "*in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually three months from the onset, with symptoms that last for at least two months and cannot be explained by an alternative diagnosis*" (Soriano et al., 2022). Similarly, the UK National Institute of Clinical Excellence defined the symptoms lasting 4–12 weeks as "*ongoing symptomatic*" long COVID (National Institute for Health and Care Excellence, 2022).

COVID-19 may impair brain integrity, inducing encephalitis and cerebrovascular accidents (Asadi-Pooya et al., 2022). Impaired brain integrity would be responsible for some clinical manifestations collectively termed "brain fog"; these manifestations include the person's subjective feeling of being mentally slow, fuzzy and confused, forgetful, spaced out, and with deficits in visual-spatial, naming, attention, executive functions, and mood (Asadi-Pooya et al., 2022). Among these symptoms, the subjective sensation of chronic fatigue (i.e., also named chronic fatigue syndrome) is one of the most frequent. Specifically, 20%-30% of long COVID patients investigated > 6 months after infection onset showed fatigue symptoms (Mantovani et al., 2021; Simani et al., 2021). Furthermore, long COVID persons with chronic fatigue showed worse scores in sleep quality, depressive symptoms, subjective cognitive complaints, and Borg baseline (Mantovani et al., 2021). Notably, fatigue symptoms reached a prevalence of 45% in long COVID patients when assessed a bit earlier (>4) months after the infection onset (Salari et al., 2022). That variability of the long COVID with chronic fatigue in the literature is probably due to the subjective nature of the patient's claims.

The neural basis of long COVID and "brain fog" has been explored with several brain research techniques. Some insightful examples are reported in the following. In a previous study (Dressing et al., 2022), 2-deoxy-2-[fluorine-18]fluoro-D-glucose positron emission tomography (18-F-FDG PET) was administered in long COVID persons with claimed neurocognitive deficits for > 3 months after the infection. Although cognitive deficits were confirmed in about 25% of them, no significant abnormality in 18-F-FDG PET scans was observed at the group level (Dressing et al., 2022). In another study (Bispo et al., 2022), magnetic resonance imaging (MRI) tractography was investigated in long COVID persons three months after the infection. They were characterized by chronic fatigue but without cognitive deficits and showed microstructural alterations in several tracts connecting associative areas of both hemispheres (Bispo et al., 2022). Other studies used electroencephalographic (EEG) techniques to explore the abnormal neurophysiological oscillatory mechanisms underpinning the regulation of quiet vigilance/consciousness levels in long COVID persons evaluated during a resting-state condition. In a longitudinal study, it was reported that compared to the pre-infection recordings, long COVID persons showed increased power at theta (4–7 Hz), alpha (8–12 Hz), and beta (13–30 Hz) rhythms from resting-state EEG (rsEEG) data recorded at the few scalp electrodes explored, i.e., C3, Cz, and C4 (Kopańska et al., 2022). In another study (Cecchetti et al., 2022), long COVID persons showed greater cortical rsEEG delta source activation and connectivity two months after the infection over control individuals. These effects were positively associated with performances to neuropsychological tests probing frontal executive functions and with subcortical white-matter lesions as revealed by MRI. At the same time, they were negatively related to verbal memory deficits (Cecchetti et al., 2022). Notably, the mentioned cognitive impairment and abnormalities in rsEEG delta source connectivity were partially reduced at the 10-month follow-ups (Cecchetti et al., 2022). In another study (Furlanis et al., 2023), long COVID persons with "brain fog" at about four months from the infection showed abnormal EEG (i.e., slow, asymmetric, or epileptiform activity and significant rsEEG delta power) in about 60% of them and several cases with poor cognitive status.

The above data suggest that long COVID patients with "brain fog" may be associated with abnormalities in the rsEEG rhythms underpinning the regulation of quiet vigilance and consciousness levels. However, the mentioned heterogeneity of the symptoms in the definition of "brain fog" (Asadi-Pooya et al., 2022) prevented an association between spatial and frequency features of the abnormal rsEEG rhythms and the specific clinical manifestations of that syndrome. For example, many long COVID patients enrolled in previous rsEEG studies showed cognitive or psychiatric disorders as symptoms of the "brain fog" syndrome (Kopańska et al., 2022; Cecchetti et al., 2022). This is not surprising as objective cognitive deficits can be observed in about 20–40% of long COVID persons after > 2 months from the infection and are more prevalent when they suffer from pre-infection chronic diseases (van den Borst et al., 2020; Blazhenets et al., 2021; Walitt and Bartrum, 2021; Rahmati et al., 2023). Furthermore, it should be remarked that even when neuropsychological tests and clinical scales do not confirm an objective cognitive or psychiatric disorder, subjective mental symptoms alone, including chronic fatigue or vigilance-sleep dysfunctions, can have a significant deleterious impact on the quality of life in post-COVID persons and should be considered (Townsend et al., 2020, 2021). These subjective mental symptoms without objective cognitive and psychiatric disorders may be underestimated, even stigmatized as "functional" and untreated (Nath, 2020).

Here, we tested the hypothesis that in long COVID seniors subjectively claiming "brain fog," abnormal rsEEG rhythms may substantiate their clinical condition even when objective cognitive and psychiatric disorders are ***absent***. To minimize the cases of objective cognitive or psychiatric disorders, we enrolled seniors hospitalized for COVID-19 about one year before, and that subjectively claimed the persistence of "brain fog" (post-COVID) at the time of the enrollment. Furthermore, they did not have pre-infection or actual chronic diseases as risk factors for cognitive and psychiatric disorders. In the study design, cognitive and psychiatric status, fatigue, other subject mental complaints, and cortical rsEEG rhythms were compared (1) ***between*** the post-COVID and the control (no COVID) participants and (2) ***within*** the post-COVID participants as a function of the clinical manifestations of the confirmed "brain fog" by the experimental procedure. To enhance the spatial information content of rsEEG rhythms, we used a methodological approach validated in persons with cognitive deficits due to HIV infection (Babiloni et al., 2016, 2018).

2. Materials and methods

2.1. Participants and diagnostic criteria

All post-COVID and control participants were enrolled in 2021–2022. They were examined to ascertain their physical, clinical, and cognitive status. All participants were asked to complete questionnaires or brief interviews assessing medical history, medication use, parental psychopathology, demographics, psychiatric symptoms, alcohol and drug use, and general cognitive status.

The post-COVID (experimental) group was constituted of 36 adult participants (both sexes, mean age of 59.8 years ± 1.0 standard error of the mean, SE), selected from a group of 1,250 patients. They were enrolled based on the following inclusion criteria: (1) admission to the Division of Infectious Diseases, Department of Public Health and Infectious Diseases of the Sapienza University of Rome – Italy (September 2021 and June 2022), due to COVID-19 respiratory symptoms about one year before the enrollment for the present study. At that time, the diagnosis of SARS-CoV-2 infection was performed by Nasopharyngeal swabs (NPS) taken for SARS-CoV-2 detection using RealStar® SARS-CoV-2 RT-PCR Kit 1.0 (Altona Diagnostics, Germany), targeting E and S viral genes; (2) the lack of pre-existing significant chronic medical conditions before the COVID-19 infection at that time; (3) the subsequent recovery at the hospital discharge (mean duration of the hospitalization: 13.3 days ± 1.3 SE); (4) fluency in the Italian language; and (5) a negative SARS-CoV-2 test during the Day visit of the present study. The exclusion criteria included: (1) major medical illness at the enrollment of the present study; (2) any major psychiatric or neurological illnesses; (3) any substance addiction or significant chronic alcohol consumption or smoking and relative medications.

The control (Control) group was constituted of 15 adults enrolled based on the following inclusion criteria: (1) matched age (59.1 years ± 1.7 SE), sex, and education; (2) lack of pre-existing significant medical conditions before the enrollment in the present study; (3) no COVID-19 infection based on the participants' declaration and a standard molecular test for COVID-19 antibodies in the blood plasma (Younes et al., 2020; Xiao et al., 2020); (4) fluency in the Italian language; and (5) a negative SARS-CoV-2 test during the Day visit of the present study. The exclusion criteria were those of the experimental group, plus no COVID-19 infection, according to the declaration of the participants and a standard molecular test for COVID-19 antibodies in blood plasma (Younes et al., 2020; Xiao at al., 2020).

The long COVID symptoms were investigated by an inventory including questions on clinically relevant information on the period from the hospital discharge at the time of the COVID-19 infection to the current enrollment for the present study. The investigated symptoms included myalgia, chronic fatigue syndrome (CFS, see the following), dyspnea, sleep disorder, migraine-like headaches, ageusia, anosmia, affective/mood and cognitive deficits, difficulty in concentrating, the subjective complaint of being mentally slow, fuzzy, or spaced out, and others less common according to previous seminal studies (Jennings et al., 2021; Del Brutto et al., 2021; Mazza et al., 2021; Raveendran et al., 2021). In the experimental group of post-COVID-19 patients, these symptoms were attributed to long COVID syndrome only if (1) appeared after the original COVID-19 infection, (2) lasted for at least two months after the ascertained negativization of the Covid-19 assay, and (3) could not be explained by an alternative diagnosis (Soriano et al., 2022).

The local Ethics Committee approved the study in compliance with the Declaration of Helsinki, the Good Clinical Practice guidelines, and local regulatory requirements (Ref. 109/2020). Informed consent was obtained from all participants.

2.2. Clinical and neuropsychological assessment

In all participants, the general clinical condition was assessed as follows: (1) 30-item Geriatric Depression Scale (Yesavage et al., 1982–1983) and Neuropsychiatric Inventory (NPI; Cummings et al., 1994) to probe mood and affective status and behavioral condition; (2) Edinburgh Handedness Inventory (EHI; Oldfield, 1971); and Epworth Sleepiness Scale to probe sleep (ESS; Johns, 1991).

In all participants, the cognitive functions were assessed as follows: (1) the mini-mental state exam (MMSE) tested the global cognitive status (Folstein et al. 1983), where a score less than 26 would indicate poor overall cognitive functioning; (2) the forward and backward digit span test probed focused attention and short-term memory (Monaco et al., 2013); (3) the Prose Memory test evaluated the episodic memory (Novelli et al., 1986); (3) the Trail making test part B and B-A probed the executive function and attention (Reitan, 1958); (4) the Verbal fluency test for letters and category (fruits, animals, or car trades) assessed language, executive functions, and semantic memory (Novelli et al., 1986); and (5) the Trail making test part A revealed the information processing speed (Reitan, 1958).

2.3. The DePaul symptom questionnaire

The DePaul Symptom Questionnaire (DSQ) was developed and successfully tested to measure myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS) symptomatology and to determine whether individuals meet existing case definitions (Jason et al., 2010). It can accurately differentiate individuals with ME and CFS from healthy controls and participants with other chronic illnesses (Jason et al., 2010). With 54 questions, the DSQ assesses critical symptoms of ME and CFS, such as fatigue, post-exertional malaise, sleep, pain, neurological/cognitive impairments, and autonomic, neuroendocrine, and immune symptoms.

Each DSQ item requires participants to rate the frequency and severity of the symptoms experienced over the past six months based on a 5-point Likert scale. Symptom frequency is rated from 0 to 4. Concerning the score, 0 stands for "not always," 1 for "rarely," 2 for "about half the time," 3 for "most of the time," and 4 for "all of the time." Symptom severity is also rated from 0 to 4, with 0 for "no symptoms present," 1 for "mild symptoms," 2 for "moderate symptoms," 3 for "severe symptoms," and 4 for "very severe symptoms." A binary "2/2 threshold" variable was created by examining the frequency and severity scores of each symptom; participants who rated two or higher for both frequency (about half the time, most of the time, or all of the time) and severity (moderate, severe, or very severe) were considered to have the symptom.

2.4. rsEEG recordings and preliminary data analysis

High-density rsEEG recordings were performed at the Laboratory of Neuroscience of Human Higher Functions of the Department of Physiology and Pharmacology "V. Erspamer," the Sapienza University of Rome (Italy). The rsEEG activity was made in a room that was electrically protected, had low lighting, and minimal sound. During the rsEEG recording, the subject was placed in a cozy armchair and told to be awake, psychophysically calm (no movement), and to allow their thoughts to roam freely (no mental planning or specific cognitive functions). All participants were able to follow these instructions without difficulty.

For the recording it we used Ag/AgCl exploring sensors from an electrode cap. The skin impedances of the electrodes were kept below 10 kΩ. With AFz acting as the ground electrode, the continuous EEG activity was recorded at 1,000 Hz using an antialiasing bandpass between 0.01 Hz and 100 Hz, referenced to FCz. The A bipolar vertical electrooculogram (EOG, bandpass between 0.3 Hz and 100 Hz) was also acquired from paired electrodes positioned around the dominant eye using a standard montage.

The participant's behavior and continuous rsEEG activity were observed by the experimenters. They kindly asked participants to keep a level of vigilance at the time they recognized the appearance of signs of drowsiness or light sleep such as loss of muscular neck tone and dominant theta rhythms or K complexes and sleep spindles. In each case, the experimenter noted all abnormalities found during the recording so that they could be taken into

account during subsequent analysis of the electroencephalographic signal.

Co-authors belonging to the Sapienza University of Rome Unit analyzed all rsEEG data without being aware of participants' diagnoses. The recorded rsEEG data were processed offline using the EEGLAB toolbox (Delorme A and Makeig S, 2004; version eeglab14_1_2b), running in the MATLAB software (Mathworks, Natick, MA, USA; version: R2014b).

The preprocessing procedure has been described in detail in previous work published in international journals (Babiloni et al., 2022). In summary, the rsEEG data were divided into 2-seconds epochs (i.e., 5 minutes = 150 rsEEG epochs of 2 seconds) and analyzed offline. A three-step procedure was carried out on the EEG data with the aim of identifying and eliminating (1) electrodes with prolonged artifactual activity that could be caused by poor electrical contacts or other factors, (2) only a few rsEEG epochs that have artifacts in the recording channels with good signals, and (3) the intrinsic components of the rsEEG epochs with artifacts. The third step was performed by using an independent component analysis (ICA) from the EEGLAB toolbox, in order to be sure that unexpected blinks or eye movements, head muscle artifacts, and line noise were not included in the recording (Crespo-Garcia et al., 2008; Jung el al., 2000). For each rsEEG dataset, less than 6 ICA components were removed from the original ICA solutions based on 61 ICA components.

As a result of the above procedures, the artifact-free epochs showed the same proportion between the post-COVID and Control groups (>80%). In particular, the mean of artifact-free rsEEG epochs (each of 2 seconds) was 125 (±4.4 SE; 81.5%; 125 epochs of 2 seconds = 250 seconds) in the Control group and 118 (±4.7 SE; 80.7%; 118 epochs of 2 seconds = 236 seconds) in the post-COVID group. A statistical procedure (T-test) showed no statistically significant difference ($p > 0.05$) in the amount of artifact-free rsEEG epochs between the two groups (Control vs. post-COVID: $p = 0.3$).

2.5. Spectral analysis of the rsEEG epochs

Only artifact-free epochs were used to analyze the FFT power spectrum with the Welch technique, Hanning windowing function and no phase shift. The frequency resolution for the spectral power density was 0.5 Hz. For the purposes of the study, the following individual frequency bands were considered: delta, theta, alpha 1, alpha 2, and alpha 3. The ranges of those individual frequency bands were defined by transition frequency (TF) and individual alpha frequency (IAF; for a detailed definition, see Babiloni et al., 2018) as follows: delta from TF −4 Hz to TF −2 Hz, theta from TF −2 Hz to TF, low alpha (alpha 1 and alpha 2) from TF to IAF peak, and high-frequency alpha (or alpha 3) from IAF to IAF + 2 Hz. Specifically, the individual alpha 1 and alpha 2 bands were computed as follows: alpha 1 from TF to the frequency midpoint of the TF-IAF range and alpha 2 from that midpoint to the IAF peak. Because the individual rsEEG power density peaks at the beta and gamma frequency bands were evident only in a few subjects (<10%), the beta 1, beta 2, and gamma bands were defined based on the standard fixed frequency ranges used in the reference rsEEG studies of our Consortium (Babiloni et al., 2017a,b, 2018a,b,c, 2019, 2020b; Pascarelli et al., 2020): beta 1 from 14 to 20 Hz, beta 2 from 20 to 30 Hz, and gamma from 30 to 40 Hz. Furthermore, we selected the beginning of the beta frequency range at 14 Hz to avoid the overlapping between individual rsEEG alpha and fixed beta frequency ranges (i.e., individual alpha frequency band ranged from TF to 14 Hz with an IAF equal to 12 Hz).

2.6. Cortical sources of rsEEG epochs as computed by eLORETA

The exact low-resolution brain electromagnetic tomography (eLORETA, LORETA-KEY software v20151222, http://www.uzh.ch/keyinst/loreta.htm) method was used to linearly estimate the cortical source activity generating scalp-recorded rsEEG rhythms (Pascual-Marqui, 2007). It uses a realistic mathematical model of an MRI-based head volume conductor (i.e., MNI-152) for this aim. For each person and frequency band from delta to gamma, the estimated rsEEG source activities were the eLORETA current density solutions computed in the frontal, central, parietal, occipital, temporal, and limbic macroregions of interest (ROIs) of the cortical generation model (see *Supplementary Materials*, *Cortical sources of rsEEG epochs as computed by eLORETA,* for more details).

2.7. Statistical analysis of the eLORETA rsEEG source activity

To assess the two working hypotheses, two statistical sessions were performed using the commercial tool STATISTICA 10 (StatSoft Inc., https://www.statsoft.com). In both statistical sessions, MANOVA was computed using the rsEEG source activities (i.e., regional normalized eLORETA solutions) as a dependent variable ($p < 0.05$).

It is a widely accepted principle that utilizing ANOVA models assumes that dependent variables should approximate Gaussian distributions. Therefore, we evaluated this characteristic in the eLORETA current density solutions of interest using the Kolmogorov-Smirnov test. The assessment for Gaussian distributions was conducted with a significance level of $p > 0.05$ (i.e., $p > 0.05$ = Gaussian, $p \leq 0.05$ = non-Gaussian). Since the distributions of the eLORETA current density solutions were non-Gaussian in certain instances, all variables underwent a log10 transformation and were re-assessed ($p > 0.05$ = Gaussian). The result of this process approximated the distributions of all eLORETA current density solutions to be Gaussian ($p > 0.05$ = Gaussian), thereby permitting the utilization of the ANOVA model.

Mauchly's test assessed the sphericity assumption, and the degrees of freedom were adjusted by the Greenhouse-Geisser procedure where necessary ($p < 0.05$). Duncan test was used for post-hoc comparisons ($p < 0.05$, Bonferroni corrected). The Grubbs test was utilized to control for outliers ($p < 0.01$).

The first ANOVA aimed to test whether the rsEEG source activities (i.e., regional normalized eLORETA solutions) exhibited abnormalities in post-COVID patients compared to individuals in the Control group. The ANOVA involved factors such as Group (Control and post-COVID), band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). To confirm this first hypothesis, two conditions needed to be met: (i) a statistically significant ANOVA effect involving the Group and Band factors ($p < 0.05$); (ii) post-hoc Duncan tests revealing statistically significant differences ($p < 0.05$, Bonferroni corrected) in the eLORETA current density solutions between the Control and post-COVID groups (i.e., Control ≠ post-COVID).

In the second statistical analysis, the objective was to examine whether the rsEEG source activities (i.e., regional normalized eLORETA solutions) were associated with the occurrence of "brain fog" symptoms in post-COVID participants. To address this, four separate ANOVAs were conducted using the eLORETA regional normalized solutions as dependent variables, focusing on varying thresholds of "brain fog" symptoms: (i) greater than or equal to 2 symptoms; (ii) greater than or equal to 3 symptoms; (iii) greater than or equal to 4 symptoms; (iv) greater than or equal to 5 symptoms. The ANOVAs used the following factors: Group (Control, post-COVID with numbers of symptoms below the threshold, post-COVID_BF-, post-COVID with numbers of symptoms above the threshold, post-COVID_BF +), Band (alpha1, alpha2, alpha3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The confirmation of the hypothesis may require (i) a statistically significant ANOVA effect including the factor Group ($p < 0.05$) and (ii) a post-hoc Duncan test indicating statistically significant

($p < 0.05$, Bonferroni corrected) differences in the eLORETA solutions between post-COVID_BF- and post-COVID_BF + subgroups (i.e., post-COVID_BF- ≠ post-COVID_BF +).

3. Results

3.1. Demographic, clinical data in control and post-COVID groups

Table 1 summarizes the most relevant demographic (i.e., age, sex, and education attainment) and clinical (i.e., MMSE, Geriatric Depression Scale, Neuropsychiatric Inventory, and Epworth Sleepiness Scale) in the Control and post-COVID groups. A statistically significant difference was found for the GDS score ($p = 0.001$), showing a higher score in the post-COVID group than in the Control group. No statistically significant differences were found between the groups ($p > 0.05$) in the other variables. Of note, both groups had normal scores on clinical scales. Furthermore, there were high MMSE scores in both groups, indicating a normal cognitive status.

Table 2 reports the mean values of the following neuropsychological tests in the Control and post-COVID individuals: Prose memory test, Digit span (forward and backward), TMT (A, B, and B-A), Verbal fluency for letters, Verbal fluency for the category. No statistically significant differences were found between the groups ($p > 0.05$). Notably, both groups have normal scores on these tests, confirming a global normal cognitive status.

3.2. DePaul symptoms in post-COVID group

Fig. 1 shows, for each post-COVID participant, the number of symptoms in the DePaul Questionnaire with a rating of frequency and severity of 2 or more. Note that 3 out of 36 participants reported having no symptoms at all, while 6 out of 36 reported having only one symptom in the last six months.

3.3. Demographic and clinical data in the control, post-COVID_BF-, and post-COVID_BF + groups

Tables 3–6 report the most relevant demographic (i.e., age, sex, and education) and clinical (i.e., MMSE, score) features of the Control and post-COVID subgroups (i.e., post-COVID_BF- and post-COVID_BF +), stratified for several symptoms. Specifically, Table 3 refers to several symptoms greater than or equal to 2 symptoms, Table 4 refers to the number of symptoms greater than or equal to 3 symptoms, and Table 5 refers to the number of symptoms greater than or equal to 4. Lastly, Table 6 refers to several symptoms greater than or equal to 5. For each stratification, no statistically significant differences were found among the three groups ($p > 0.05$) for age, sex, and MMSE score. On the contrary, a statistically significant difference ($p > 0.05$) was found for education, so this variable was used as a covariate in the contrasts between post-COVID groups. Each table shows the relative point values of significance.

3.4. Statistical comparison of the eLORETA rsEEG source activities in the control and post-COVID groups

The mean TF was 6.3 Hz (±0.2 SE) in the Control group and 6.6 Hz (±0.2 SE) in the post-COVID group. Furthermore, the mean IAF was 9.5 Hz (±0.2 SE) in the Control group and 9.7 Hz (±0.1 SE) in the post-COVID group. No statistically significant differences were found ($p > 0.05$).

Fig. 2 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions, $\log_{10}$ transformed) relative to a statistically significant ANOVA interaction effect ($F(35, 1715) = 2.03$; $p = 0.0004$) among the factors Group (Control and post-COVID), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). In the Control group, dominant eLORETA parietal, occipital, and temporal alpha 2 and alpha 3 source activities were observed as a physiological reference. Low eLORETA widespread delta, theta, and alpha 1 source activities were also observed, while beta and gamma source activities were shallow. Compared to the Control group, the post-COVID group showed lower eLORETA parietal, occipital, and temporal alpha 2 and alpha 3 source activities. The Duncan planned post-hoc test ($p < 0.05$ Bonferroni correction for 8 frequency bands X 6 ROIs = 48, $p < 0.05/48 = 0.001$) showed that the discriminant pattern Control > post-COVID was fitted by the occipital alpha 2 ($p = 0.00001$) and alpha 3 ($p = 0.00001$) source activities. These findings were not due to outliers from those individual eLORETA solutions ($\log_{10}$ transformed), as shown by Grubbs' test with an arbitrary threshold of $p < 0.001$.

In the Supplementary Materials, we described two control analyses. The first control analysis estimated the rsEEG power density spectra at the scalp electrode level and compared them between the whole COVID-19 (N = 36) and Healthy control (N = 15) groups. The results showed no statistically significant effect ($p > 0.05$), possibly due to the burring of rsEEG electric fields over the scalp (see Table SM1 and Figure SM1; *Supplementary Materials, Comparisons in the regional normalized rsEEG scalp power density between the Control and post-COVID groups*).

The second control analysis compared the rsEEG source activity between the Control (N = 15) and post-COVID (N = 25) subgroups perfectly matched for age, sex, and education attainment (see Table SM2). The results of the control analysis confirmed the main one (see Figure SM2). They did not depend on outliers, as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$ (see Figure SM3; *Supplementary Materials, Control analysis in the regional normalized rsEEG source activity between the Control and post-COVID groups.*).

3.5. Statistical comparison of rsEEG source activities in the control, post-COVID_BF-, and post-COVID_BF+

Concerning the stratification of post-COVID participants for the number of "brain fog" symptoms greater than or equal to 2, Fig. 3

Table 1
Mean values (±standard error of the mean, SE) of the demographic and clinical data as well as the results of their statistical comparisons ($p < 0.05$) in the groups of healthy Control (HC, N = 15) and post-COVID (N = 36) participants. All subjects in both groups had values of clinical variables in the normal range. Legend: M/F = males/females; MMSE = Mini-Mental State Evaluation; GDS = Geriatric Depression Scale; NPI = Neuropsychiatric Inventory; ESS = Epworth Sleepiness Scale; n.s. = not significant ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL DATA IN HEALTHY CONTROL (HC) AND POST-COVID PARTICIPANTS	HC	Post-COVID	Statistical analysis
N	15	36	
Age (mean years ± SE)	59.1 ± 1.7	59.8 ± 1.0	n.s. (T-Test)
Sex (M/F)	8/7	21/15	n.s. (Fisher's exact test)
Education (mean years ± SE)	14.0 ± 1.0	12.1 ± 0.6	n.s. (T-Test)
MMSE score (mean score ± SE)	29.9 ± 0.1	29.1 ± 0.2	n.s. (Mann Whitney U test)
GDS score (mean score ± SE)	1.7 ± 0.3	4.4 ± 0.4	0.001 (T-Test)
NPI score (mean score ± SE)	0.0 ± 0.0	0.0 ± 0.0	n.s. (T-Test)
ESS score (mean score ± SE)	0.5 ± 0.3	0.9 ± 0.4	n.s. (T-Test)

Table 2
Mean values (±SE) of the neuropsychological scores (i.e., Prose memory test, Digit span forward and backward, Trail Making Test part A, B, and B-A, Verbal fluency for letters, Verbal fluency for the category) as well as the results of their statistical comparisons (T-test; $p < 0.05$) in the healthy Control (HC, N = 15) and post-COVID (N = 36) participants. The cut-point for normality and the percentage of the participants with the pathological score are also reported. Legend: n.s. = not significant ($p > 0.05$).

NEUROPSYCHOLOGICAL MARKERS IN HEALTHY CONTROL (HC) AND POST-COVID PARTICIPANTS				
	Cut–off of abnormality.	**HC (mean ± SE; *%subjects with abnormal score*)**	**Post-COVID (mean ± SE; *%subjects with abnormal score*)**	**Statistical analysis**
Prose Memory	< 8	13.0 ± 1.3; 14%	13.9 ± 0.6; 9%	n.s. (T-Test)
Trail-making test A	> 93	49.3 ± 3.3; 0%	42.7 ± 4.5; 7%	n.s. (T-Test)
Trail-making test B	> 282	68.4 ± 10.7; 0%	56.1 ± 7.9; 0%	n.s. (T-Test)
Trail-making test B-A	> 187	10.3 ± 12.5; 0%	13.9 ± 6.3; 0%	n.s. (T-Test)
Digit span Forward	< 4.26	7.1 ± 0.3; 0%	6.7 ± 0.2; 3%	n.s. (T-Test)
Digit span Backward	< 2.65	4.7 ± 0.5; 8%	4.9 ± 0.2; 3%	n.s. (T-Test)
Letter fluency	< 17	35.9 ± 2.8; 0%	39.5 ± 1.6; 0%	n.s. (T-Test)
Letter category	< 25	44.4 ± 2.3; 0%	46.4 ± 1.4; 0%	n.s. (T-Test)

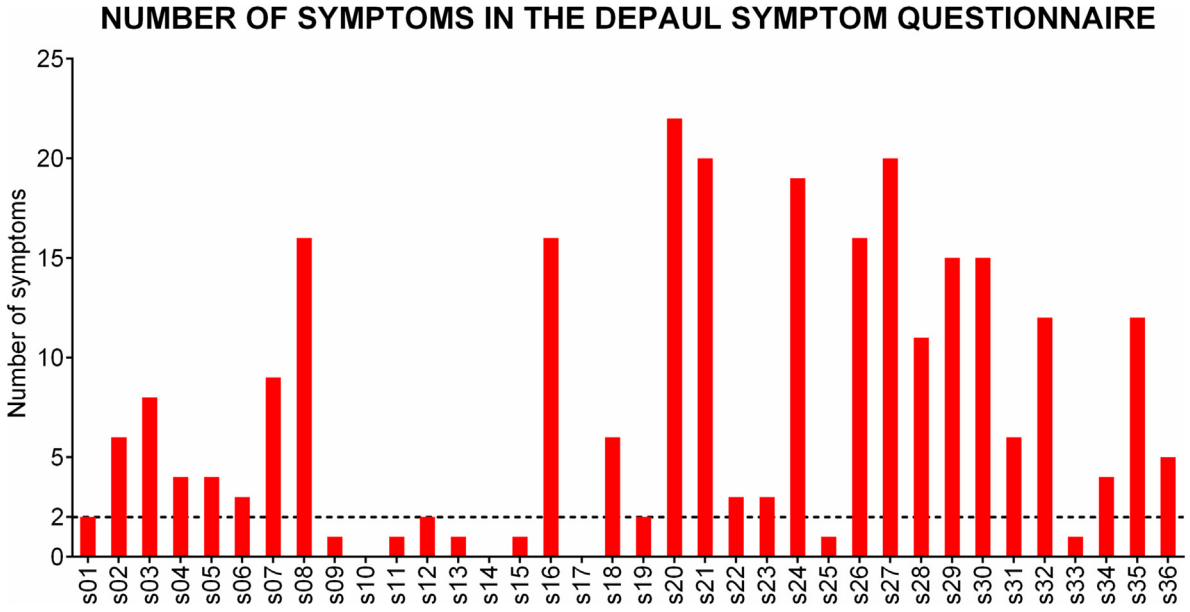

Fig. 1. Number of symptoms in the DePaul Questionnaire (DSQ) with a rating of frequency and severity of 2 or more in the last six months. The DSQ assesses key symptoms of myalgic encephalomyelitis (ME) and chronic fatigue syndrome (CFS), such as fatigue, post-exertional malaise, sleep, pain, neurological/cognitive impairments, and autonomic, neuroendocrine and immune symptoms.

Table 3
Mean values (±SE) of the demographic and clinical data (i.e., MMSE score) as well as the results of their statistical comparisons ($p < 0.05$) in the healthy Control and post-COVID participants, stratified in post-COVID_BF- and post-COVID_BF + based on the number of the DePaul symptoms (i.e., greater than or equal to 2 symptoms). Legend: HC = healthy Control; post-COVID_BF- = post-COVID participants without "brain fog" (i.e., number of DePaul symptoms lower than 2); post-COVID_BF+ = post-COVID participants with "brain fog" (i.e., number of DePaul symptoms greater than or equal to 2 symptoms); M/F = males/females; MMSE = Mini-Mental State Evaluation; n.s. = not significant ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL DATA IN HEALTHY CONTROL (HC) AND POST-COVID SUB-GROUPS (Greater than or equal to 2 symptoms)				
	HC	**post-COVID_BF-**	**post-COVID_BF+**	**Statistical analysis**
N	15	9	27	
Age (mean years ± SE)	59.1 ± 1.7	61.4 ± 2.3	59.3 ± 1.2	n.s. (ANOVA)
Sex (M/F)	8/7	6/3	15/12	n.s. (Freeman-Halton)
Education (mean years ± SE)	14.0 ± 1.0	14.6 ± 1.2	11.3 ± 0.6	p = 0.01 (ANOVA; HC, BF- > BF +)
MMSE score (mean score ± SE)	29.9 ± 0.1	28.7 ± 0.6	29.3 ± 0.2	n.s. (Kruskal-Wallis)

Table 4
Mean values (±SE) of the demographic and clinical data (i.e., MMSE score) as well as the results of their statistical comparisons ($p < 0.05$) in the healthy Control and post-COVID participants, stratified in post-COVID_BF- and post-COVID_BF + based on the number of the DePaul symptoms (i.e., greater than or equal to 3 symptoms). Legend: HC = healthy Control; post-COVID_BF- = post-COVID participants without "brain fog" (i.e., number of DePaul symptoms lower than 3); post-COVID_BF+ = post-COVID participants with "brain fog" (i.e., number of DePaul symptoms greater than or equal to 3 symptoms); M/F = males/females; MMSE = Mini-Mental State Evaluation; n.s. = not significant ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL DATA IN HEALTHY CONTROL (HC) AND POST-COVID SUB-GROUPS (Greater than or equal to 3 symptoms)	HC	post-COVID_BF-	post-COVID_BF+	Statistical analysis
N	15	12	24	
Age (mean years ± SE)	59.1 ± 1.7	62.0 ± 1.9	58.7 ± 1.2	n.s. (ANOVA)
Sex (M/F)	8/7	7/5	14/10	n.s. (Freeman-Halton)
Education (mean years ± SE)	14.0 ± 1.0	14.2 ± 1.1	11.1 ± 0.6	p = 0.01 (ANOVA; HC, BF- > BF +)
MMSE score (mean score ± SE)	29.9 ± 0.1	28.9 ± 0.5	29.3 ± 0.2	n.s. (Kruskal-Wallis)

Table 5
Mean values (±SE) of the demographic and clinical data (i.e., MMSE score) as well as the results of their statistical comparisons ($p < 0.05$) in the healthy Control and post-COVID participants, stratified in post-COVID_BF- and post-COVID_BF + based on the number of the DePaul symptoms (i.e., greater than or equal to 4 symptoms). Legend: HC = healthy Control; BF- = post-COVID participants without "brain fog" (i.ie., number of DePaul symptoms lower than 4); BF- = post-COVID participants with "brain fog" (i.ie., number of DePaul symptoms greater than or equal to 4 symptoms); M/F = males/females; MMSE = Mini-Mental State Evaluation; n.s. = not significant ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL DATA IN HEALTHY CONTROL (HC) AND POST-COVID SUB-GROUPS (Greater than or equal to 4 symptoms)	HC	post-COVID_BF-	post-COVID_BF+	Statistical analysis
N	15	15	21	
Age (mean years ± SE)	59.1 ± 1.7	60.0 ± 2.1	59.6 ± 1.0	n.s. (ANOVA)
Sex (M/F)	8/7	9/6	12/9	n.s. (Freeman-Halton)
Education (mean years ± SE)	14.0 ± 1.0	14.3 ± 0.9	10.6 ± 0.5	p = 0.002 (ANOVA; HC, BF- > BF +)
MMSE score (mean score ± SE)	29.9 ± 0.1	28.8 ± 0.4	29.4 ± 0.2	n.s. (Kruskal-Wallis)

Table 6
Mean values (±SE) of the demographic and clinical data (i.e., MMSE score) as well as the results of their statistical comparisons ($p < 0.05$) in the healthy Control and post-COVID participants, stratified in post-COVID_BF- and post-COVID_BF + based on the number of the DePaul symptoms (i.e., greater than or equal to 5 symptoms). Legend: HC = healthy Control; post-COVID_BF- = post-COVID participants without "brain fog" (i.e., number of DePaul symptoms lower than 5); post-COVID_BF+ = post-COVID participants with "brain fog" (i.ie., number of DePaul symptoms greater than or equal to 5 symptoms M/F = males/females; MMSE = Mini-Mental State Evaluation; n.s. = not significant ($p > 0.05$).

DEMOGRAPHIC AND CLINICAL DATA IN HEALTHY CONTROL (HC) AND POST-COVID SUB-GROUPS (Greater than or equal to 5 symptoms)	HC	post-COVID_BF-	post-COVID_BF+	Statistical analysis
N	15	18	18	
Age (mean years ± SE)	59.1 ± 1.7	60.4 ± 1.8	59.2 ± 1.1	n.s. (ANOVA)
Sex (M/F)	8/7	10/8	11/7	n.s. (Freeman-Halton)
Education (mean years ± SE)	14.0 ± 1.0	13.4 ± 0.9	10.9 ± 0.6	p = 0.02 (ANOVA; HC, BF- > BF +)
MMSE score (mean score ± SE)	29.9 ± 0.1	28.9 ± 0.4	29.4 ± 0.2	n.s. (Kruskal-Wallis)

shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions, $\log_{10}$ transformed) relative to a statistically significant ANOVA interaction effect ($F(20, 470) = 2.38$; $p = 0.0007$) among the factors Group (Control, post-COVID_BF-, and post-COVID_BF +), Band (alpha 1, alpha 2, alpha 3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The years of education were used as a covariate. The post-COVID_BF- group showed lower occipital alpha source activities than the Control group. Furthermore, compared to the post-COVID_BF group, the post-COVID_BF + group showed lower diffuse alpha source activities. The Duncan planned post-hoc testing ($p < 0.05$ uncorrected) showed that the discriminant pattern post-COVID_BF- > post-COVID_BF + was fitted by the occipital alpha 2 ($p = 0.03$) and alpha 3 ($p = 0.03$) source activities. These findings were not due to outliers from those individual eLORETA solutions ($\log_{10}$ transformed), as shown by Grubbs' test with an arbitrary threshold of $p < 0.01$. In the Supplementary Materials, we repeated the analysis, matching the three groups for education (see Table SM3). The results of the control analysis confirmed the main one (see Figure SM4). The results were not due to outliers, as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$ (see Figure SM5; *Supplementary Materials, Regional normalized cortical rsEEG power density in the Control and the post-COVID groups with numbers of symptoms below (post-COVID_BF) and above (post-COVID_BF +) the threshold*).

Concerning the stratification of post-COVID participants for a number of the "brain fog" symptoms greater than or equal to 3, Fig. 4 shows the grand average of regional rsEEG source activities

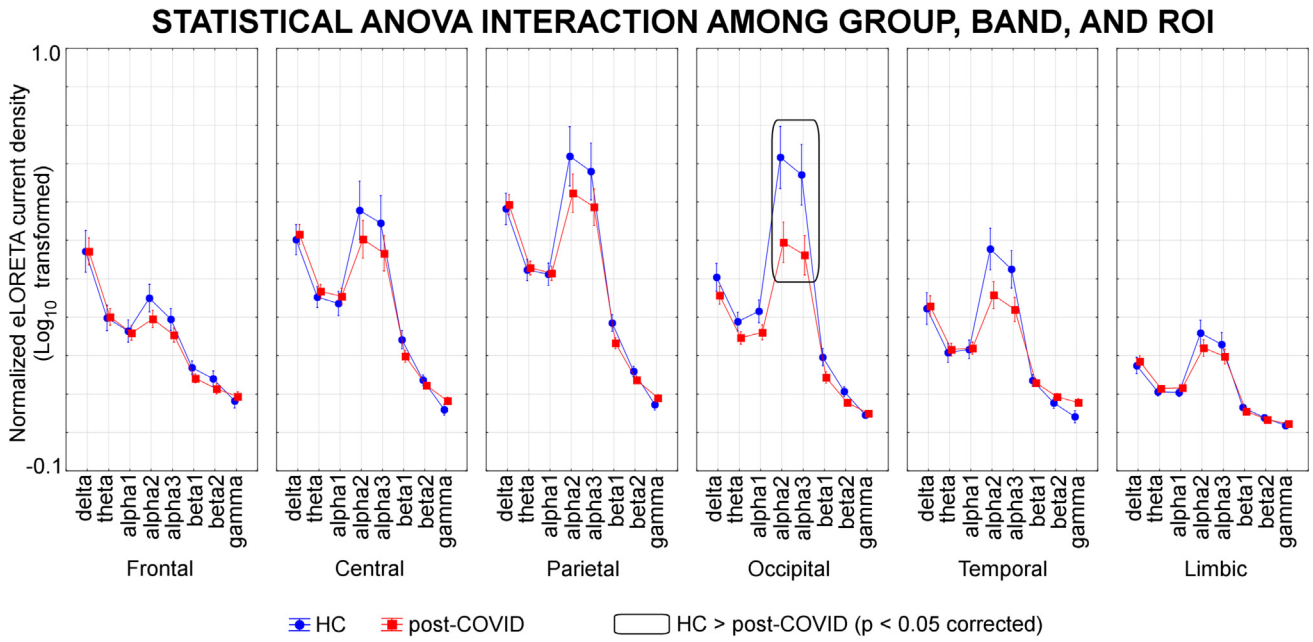

Fig. 2. Regional normalized eLORETA solutions (mean across subjects, log_{10} transformed) of cortical sources of eyes-closed resting-state EEG (rsEEG) rhythms relative to a statistical ANOVA interaction among the factors Group (Control, N = 15; post-COVID, N = 36), Band (delta, theta, alpha 1, alpha 2, alpha 3, beta 1, beta 2, and gamma), and ROI (frontal, central, parietal, occipital, temporal, and limbic). This ANOVA design used the eyes-closed regional normalized eLORETA solutions as a dependent variable. The rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA pattern of Control ≠ post-COVID ($p < 0.05$, Bonferroni corrected).

(i.e., regional normalized eLORETA solutions, log_{10} transformed) relative to a statistically significant ANOVA interaction effect ($F(20, 470) = 3.67$; $p = 0.00001$) among the factors Group (Control, post-COVID_BF-, and post-COVID_BF +), Band (alpha 1, alpha 2, alpha 3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The years of education were used as a covariate. The Duncan planned post-hoc testing ($p < 0.05$ Bonferroni correction for 3 frequency bands X 6 ROIs = 18, $p < 0.05/18 = 0.003$) showed that the discriminant pattern post-COVID_BF- > post-COVID_BF + was fitted by the occipital alpha 2 ($p = 0.001$) and alpha 3 ($p = 0.001$) source activities. Furthermore, the Duncan planned post-hoc testing ($p < 0.05$ uncorrected) showed that the discriminant pattern post-COVID_BF- > post-COVID_BF + was fitted by the parietal alpha 2 ($p = 0.01$) and alpha 3 ($p = 0.01$) source activities. These findings were not due to outliers from those individual eLORETA solutions (log_{10} transformed), as shown by Grubbs' test with an arbitrary threshold of $p < 0.01$. In the Supplementary Materials, we repeated the analysis, matching the three groups for education (see Table SM4). The results of the control analysis confirmed the main one (see Figure SM6). The results were not due to outliers, as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$ (see Figure SM7; *Supplementary Materials, Regional normalized cortical rsEEG power density in the Control and the post-COVID groups with numbers of symptoms below (post-COVID_BF) and above (post-COVID_BF +) the threshold*).

Concerning the stratification of post-COVID participants for a number of the "brain fog" symptoms greater than or equal to 4, Fig. 5 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions, log_{10} transformed) relative to a statistically significant ANOVA interaction effect ($F(20, 470) = 2.31$; $p = 0.001$) among the factors Group (Control, post-COVID_BF-, and post-COVID_BF +), Band (alpha 1, alpha 2, alpha 3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The years of education were used as a covariate. The Duncan planned post-hoc testing ($p < 0.05$ uncorrected) showed that the discriminant pattern post-COVID_BF- > post-COVID_BF + was fitted by the occipital alpha 2 ($p = 0.01$) and alpha 3 ($p = 0.02$) source activities. These findings were not due to outliers from those individual eLORETA solutions (log_{10} transformed), as shown by Grubbs' test with an arbitrary threshold of $p < 0.01$. In the Supplementary Materials, we repeated the analysis, matching the three groups for education (see Table SM5). The results of the control analysis confirmed the main one (see Figure SM8). The results were not due to outliers, as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$ (see Figure SM9; *Supplementary Materials, Regional normalized cortical rsEEG power density in the Control and the post-COVID groups with numbers of symptoms below (post-COVID_BF) and above (post-COVID_BF +) the threshold*).

Concerning the stratification of post-COVID participants for a number of the "brain fog" symptoms greater than or equal to 5, Fig. 6 shows the grand average of regional rsEEG source activities (i.e., regional normalized eLORETA solutions, log_{10} transformed) relative to a statistically significant ANOVA interaction effect ($F(20, 470) = 1.94$; $p = 0.009$) among the factors Group (Control, post-COVID_BF-, and post-COVID_BF +), Band (alpha 1, alpha 2, alpha 3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). The years of education were as covariate. The Duncan planned post-hoc testing ($p < 0.05$ uncorrected) showed that the discriminant pattern post-COVID_BF- > post-COVID_BF + was fitted by the occipital alpha 2 ($p = 0.01$) source activity. These findings were not due to outliers from those individual eLORETA solutions (log_{10} transformed), as shown by Grubbs' test with an arbitrary threshold of $p < 0.01$. In the Supplementary Materials, we repeated the analysis, matching the three groups for education (see Table SM6). The results of the control analysis confirmed the main one (see Figure SM10). The results were not due to outliers, as shown by Grubbs' test with an arbitrary threshold of $p > 0.001$ (see Figure SM11; *Supplementary Materials, Regional normalized cortical rsEEG power density in the Control and the post-COVID groups with numbers of symptoms below (post-COVID_BF) and above (post-COVID_BF +) the threshold*).

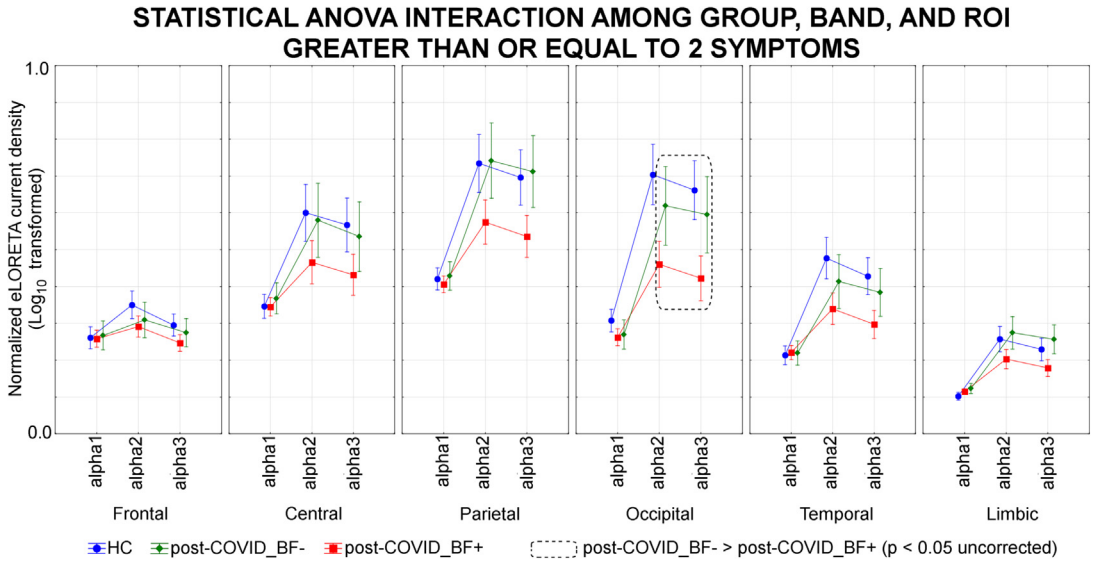

Fig. 3. Regional normalized eLORETA solutions (mean across subjects, $\log_{10}$ transformed) of cortical sources of eyes-closed resting-state EEG (rsEEG) rhythms relative to a statistical ANOVA interaction among the factors Group (Control, post-COVID_BF-, and post-COVID_BF +), Band (alpha 1, alpha 2, alpha 3), and Region of Interest, ROI (frontal, central, parietal, occipital, temporal, and limbic). This ANOVA design used the eyes-closed regional normalized eLORETA solutions as a dependent variable and the years of education as a covariate. Post-COVID participants were stratified using the number of "brain fog" symptoms greater than or equal to 2. The dashed rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA pattern of post-COVID_BF- ≠ post-COVID_BF+ ($p < 0.05$ uncorrected). Legend: post-COVID_BF- = post-COVID participants without "brain fog" (i.e., number of DePaul symptoms lower than 2); post-COVID_BF+ = post-COVID participants with "brain fog" (i.e., number of DePaul symptoms greater than or equal to 2 symptoms).

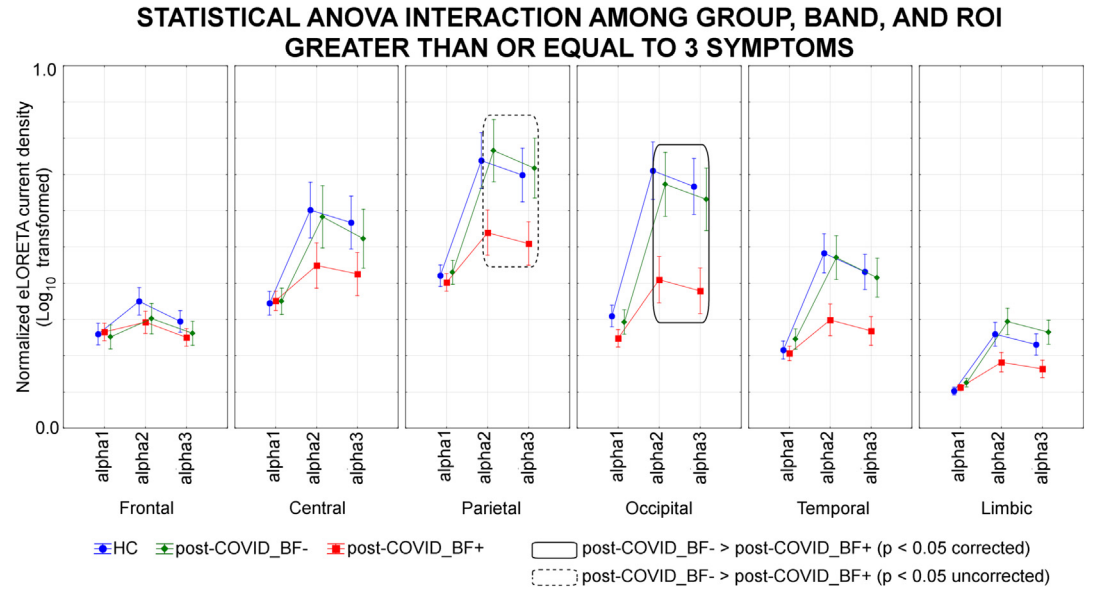

Fig. 4. Regional normalized eLORETA solutions (mean across subjects, $\log_{10}$ transformed) of cortical sources of rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Control, post-COVID_BF-, and post-COVID_BF +), Band (alpha 1, alpha 2, alpha 3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). This ANOVA design used the eyes-closed regional normalized eLORETA solutions as a dependent variable and the years of education as a covariate. Post-COVID participants were stratified using the number of "brain fog" symptoms greater than or equal to 3. The rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA pattern of post-COVID_BF- ≠ post-COVID_BF+ ($p < 0.05$ Bonferroni corrected, continuous line; $p < 0.05$ uncorrected, dashed line;). Legend: post-COVID_BF- = post-COVID participants without "brain fog" (i.e., number of DePaul symptoms lower than 3); post-COVID_BF+ = post-COVID participants with "brain fog" (i.e., number of DePaul symptoms greater than or equal to 3 symptoms).

4. Discussion

Previous studies reported that many long COVID persons with heterogeneous "brain fog" symptoms showed abnormal rsEEG rhythms (Kopańska et al., 2022; Cecchetti et al., 2022; Furlanis et al., 2023). Here, we enrolled post-COVID seniors experiencing "brain fog," examined after about one year from the hospitalization for SARS-CoV-2 and tested the hypothesis that abnormal rsEEG rhythms reflecting vigilance/consciousness level dysfunctions may occur regardless of cognitive and psychiatric disorders. The main results showed that ≥ 90% of the post-COVID seniors manifested ***no cognitive or psychiatric*** disorders. In contrast, 75% of them were characterized by ≥ 2 persistent and substantial chronic ***fatigue*** symptoms, according to the DePaul questionnaire. Compared to the control persons (no COVID), the whole post-COVID group globally showed lower posterior rsEEG ***alpha*** source activi-

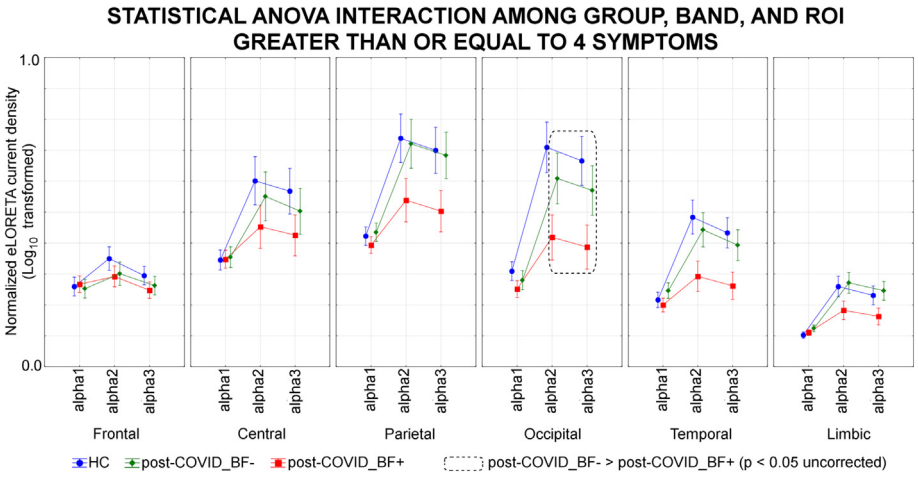

Fig. 5. Regional normalized eLORETA solutions (mean across subjects, $\log_{10}$ transformed) of cortical sources of rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Control, post-COVID_BF-, and post-COVID_BF +), Band (alpha 1, alpha 2, alpha 3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). This ANOVA design used the eyes-closed regional normalized eLORETA solutions as a dependent variable and the years of education as a covariate. Post-COVID participants were stratified using the number of "brain fog" symptoms greater than or equal to 4. The dashed rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA pattern of post-COVID_BF- ≠ post-COVID_BF+ ($p < 0.05$ uncorrected). Legend: post-COVID_BF- = post-COVID participants without "brain fog" (i.e., number of DePaul symptoms lower than 4); post-COVID_BF+ = post-COVID participants with "brain fog" (i.e., number of DePaul symptoms greater than or equal to 4 symptoms).

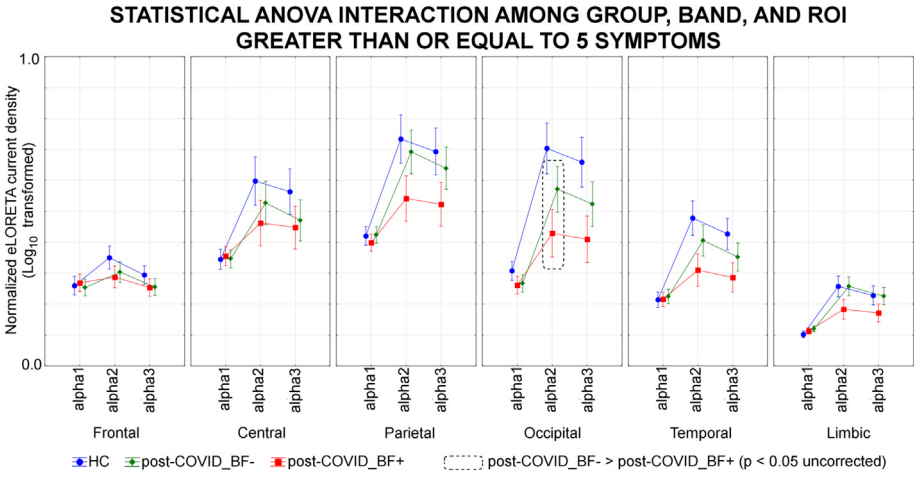

Fig. 6. Regional normalized eLORETA solutions (mean across subjects, $\log_{10}$ transformed) of cortical sources of rsEEG rhythms relative to a statistical ANOVA interaction among the factors Group (Control, post-COVID_BF-, and post-COVID_BF +), Band (alpha 1, alpha 2, alpha 3), and ROI (frontal, central, parietal, occipital, temporal, and limbic). This ANOVA design used the eyes-closed regional normalized eLORETA solutions as a dependent variable and the years of education as a covariate. Post-COVID participants were stratified using the number of "brain fog" symptoms greater than or equal to 5. The dashed rectangles indicate the cortical regions and frequency bands in which the eLORETA solutions statistically presented a significant eLORETA pattern of post-COVID_BF- ≠ post-COVID_BF+ ($p < 0.05$ uncorrected). Legend: post-COVID_BF- = post-COVID participants without "brain fog" (i.e., number of DePaul symptoms lower than 5); post-COVID_BF+ = post-COVID participants with "brain fog" (i.e., number of DePaul symptoms greater than or equal to 5 symptoms).

ties. Notably, this effect was more significant in the subgroup of post-COVID-19 seniors experiencing ≥ 2 fatigue symptoms of the "brain fog" syndrome, and the same was true for the subgroups of those experiencing ≥ 3, 4, or 5 fatigue symptoms. Therefore, in post-COVID seniors with no chronic diseases, "brain fog" was associated with abnormal posterior rsEEG alpha rhythms and subjective chronic fatigue but not cognitive or psychiatric disorders. These results suggest a relationship between altered brain neurophysiological oscillatory mechanisms at alpha frequencies underpinning vigilance/consciousness level dysfunction and the subjective experience of chronic fatigue in post-COVID-19 seniors with "brain fog."

The present results extend previous evidence showing that chronic fatigue symptoms are common in post-COVID persons experiencing "brain fog". They may contribute to explaining the significant variability of the "brain fog" syndrome, including chronic fatigue, difficulties concentrating or calculating, the subjective complaint of being mentally slow, concerns in problem-solving, fuzzy and confused, forgetful, spaced out, reduced visual-spatial skills, problems in naming, and objective cognitive and psychiatric disorders (Asadi-Pooya et al., 2022; Jennings et al., 2021; Del Brutto et al., 2021; Mazza et al., 2021; Raveendran et al., 2021; Ceban et al., 2022). Our post-COVID seniors were 60 years old, on average, hospitalized due to the severity of the acute COVID-19 symptoms about one year before the enrollment, and had not had pre-infection and actual chronic diseases at the time of the present experiments. These characteristics of our cohort may explain the presence of post-COVID "brain fog" with ≥ 2 fatigue symptoms in 75% of the cases but only ≤ 10% with cognitive or psychiatric disorders. Previous reference studies enrolled cases

from the general COVID-19 population, with a broad age range and young participants, and showed that 30–45% of cases with post-COVID experienced fatigue symptoms ≥ 4 months after that infection (Ceban et al., 2022; Salari et al., 2022) and 20%-30% of cases ≥ 6 months after (Mantovani et al., 2021; Simani et al., 2021). Indeed, a previous study enrolling post-COVID seniors about 60 years old, on average, observed chronic fatigue in a similar proportion of the present cohort (Furlanis et al., 2023).

The present results also extend previous literature showing that post-COVID seniors with "brain fog," after about one year from the SARS-CoV-2 acute infection, were not associated with rsEEG rhythms characterized by widespread background delta-theta rhythms (<7 Hz) or frontal-temporal intermittent delta (<4 Hz) rhythmic activity or non-convulsive epileptiform EEG waves, which are typically observed in ≥ 60% of the patients during the hospitalization for acute COVID-19 symptoms (Antony and Haneef, 2020; Cecchetti et al., 2020; Vespignani et al., 2020; Koutroumanidis et al., 2021; Pellinen et al., 2020; Petrescu et al., 2020). Notably, abnormal increases of rsEEG delta and theta rhythms were also reported in previous studies enrolling post-COVID persons with a substantial number of cases with cognitive and psychiatric symptoms and risk factors related to chronic diseases (Pati et al., 2020; Kopańska et al., 2022; Cecchetti et al., 2022; Furlanis et al., 2023). Considering these present data, significant background rsEEG delta and theta rhythms may be associated with more severe post-COVID "brain fog" syndrome with heterogeneous symptoms. Furthermore, the diffuse abnormalities of those delta and theta rhythms were reported by several studies developed in critically ill COVID-19 patients with an indication of neurological symptoms, including encephalopathy (e.g., confusion, fluctuating alertness, or delayed awakening after stopping sedation in the intensive care unit); they showed that most (60–90%) were characterized by abnormal resting-state EEG (rsEEG) activity, such as dominant background delta-theta rhythms (<7 Hz) or intermittent delta (<4 Hz) rhythmic activity, and non-convulsive epileptiform activity or alpha (8–12 Hz) coma in a minority of cases (Antony and Haneef, 2020; Cecchetti et al., 2020; Vespignani et al., 2020; Koutroumanidis et al., 2021; Pellinen et al., 2020; Petrescu et al., 2020).

At the present early stage of the research, the poor widespread rsEEG alpha rhythms observed in the current post-COVID seniors with chronic fatigue symptoms may be tentatively explained by a neurobiological model with several interacting factors. Previous studies reported that long COVID persons were affected by vascular complications (e.g., micro-thrombosis, capillary congestion and pericytes dysfunction, etc.) and endothelial dysfunction; these complications may cause hypoxia triggering a vicious cycle with hypoxia-related inflammation that induces the deterioration of vascular function, hypoxia-related high cytokine levels and neuroinflammation, T-cell exhaustion, subcortical white-matter lesions, and widespread abnormal neurotransmission underpinning body sensations, mood, and cognitive processes (Østergaard, 2021; Ceban et al., 2022; Leng et al., 2023). Notably, these neurobiological effects may be due not only to the primary effect of COVID-19 but also to its secondary consequences. For instance, patients hospitalized during the acute COVID-19 infection may be socially isolated for several days. After their discharge from hospitals, some of them may show a tendency to remain socially isolated and inactive to avoid contracting the virus again or because of the perception of the environment around them as dangerous (Hwang et al., 2020). Such social isolation, reduced physical activity, and later re-starting of job activities may be associated with chronic stress, anxiety, and social/mood disorders and contribute to the abnormality in brain activity (Jacubowski et al., 2015). Future studies will have to collect this kind of psychosocial-physiological information and disentangle the primary and secondary effects of COVID-19 on the post-COVID manifestations and brain activity.

Along the same line, we cannot provide a conclusive neurophysiological model explaining the relationships between the reduction in the posterior rsEEG alpha rhythms, possibly reflecting vigilance dysregulations, and fatigue symptoms without cognitive and psychiatric disorders in the present post-COVID seniors. Instead, we can speculate based on the neurophysiological basis of rsEEG alpha rhythms (Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999; Hughes and Crunelli, 2005; Liu et al., 2012) and a recent theory explaining functional somatic symptoms (e.g., abnormal motor control, convulsions, speech output difficulties, dizziness, cognitive and affective symptoms, pain, chronic fatigue, etc.) apparently "*sine materia*," namely not due to the organic diseases that typically induce them (Jungilligens et al., 2022).

Concerning the dominant posterior rsEEG alpha rhythms, there is consensus that they would be produced by an 8–12 Hz oscillatory synchronization of the activity in diffuse neural populations within sensory thalamocortical and sensory and associative corticothalamic circuits that (1) would dampen the global arousal in posterior visual-spatial cortical areas and (2) would filter out irrelevant external sensory information in the regulation of quiet vigilance/consciousness levels (Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999; Babiloni et al., 2020). Within the dynamics between the neural bases underpinning competing psychophysiological needs and attentional resources, the efficient processing of external sensory information and its integration with endogenous and interoceptive sensory information would be associated with coordinated region- and task-specific decrease of posterior rsEEG alpha rhythms while task-irrelevant cortical areas would be inhibited by an enhancement of local EEG alpha rhythms (Klimesch, 1999; Pfurtscheller and Lopes da Silva, 1999; Babiloni et al., 2020). At the cellular level, rsEEG alpha rhythms in the visual (somatosensory) cortex would derive from a circuit functionally linking cortical pyramidal and thalamic neurons (Hughes and Crunelli, 2005). In the geniculate thalamic nuclei, glutamatergic high-threshold relay neurons would induce rhythmic action potentials at the alpha frequency in GABAergic interneurons (Hughes and Crunelli, 2005). In their turn, those interneurons would cause rhythmic action potentials at that frequency in standard thalamocortical relay neurons projecting to corticothalamic pyramidal neurons located in the visual (somatosensory) cortex (Hughes and Crunelli, 2005). Notably, this circuit would be modulated from cholinergic basal forebrain projections (Hughes and Crunelli, 2005) and neurons of the thalamic Pulvinar nucleus in relation to the general cortical arousal depending on vigilance/consciousness levels and attention processes (Liu et al., 2012).

A recent theory explains functional somatic symptoms based on abnormalities in the brain network activities constructing the body sensations of general wellness/energy and related affective-emotional experiences within the physiological model of allostasis (Jungilligens et al., 2022). Specifically, these activities would underpin allostatic representations predicting the optimal endocrine, neurovegetative, and brain neurophysiological activities determining mental (affective-emotional and cognitive) and behavioral outcomes controlling vital physiological variables, such as body temperature, hydration, acid-basic equilibrium and blood volume, flow, oxygenation, glycemia, etc. (Jungilligens et al., 2022). These processes would counteract the actual and forecasted environmental and endogenous stressors based on autobiographic procedural and semantic memories (Jungilligens et al., 2022). The neural basis of these predictive allostatic representations may emerge from the activity of the default mode network to that of the limbic neural system and brainstem (Jungilligens et al., 2022). These representations would be compared with prediction errors computed from sensory and associative posterior neocorti-

cal areas (Jungilligens et al., 2022). In case of significant errors, the salience brain network would trigger refining the allostatic representations and related subjective experiences (Jungilligens et al., 2022). Abnormalities in these brain networks may induce many "brain fog" symptoms, including subjective sensations of energy exhaustion (i.e., ***chronic fatigue***) or hypervigilance/hyperarousal with anxiety and negative mood, muscle tension, and related chronic pain (Jungilligens et al., 2022).

Considering the above neurophysiological models and the present findings, it can be speculated that in post-COVID seniors with chronic fatigue symptoms, the reduction of the posterior rsEEG alpha rhythms may reflect poor background cholinergic and glutamatergic neuromodulation of the thalamocortical signals unbalancing the arousal in the sensory and associative parietal, temporal, and occipital cortical regions. As a result, the allostatic predictive errors from posterior cortical areas would be inaccurate, possibly associated with background sensations of fatigue and feelings of psychophysical malaise at different degrees, with poor general vigilance, energy, and wellness. Future studies should test this speculative explanation at various spatial scales of the brain networks and neuromodulation in relation to the emergence of body sensations, feelings, emotions, and behavior.

As a final remark, we observed differences in the mean education attainment between the post-COVID and Control groups. There was a lower mean education attainment in the post-COVID group than in the Control group. This difference did not confound the core rsEEG results of the present study, as they were confirmed when education attainment was taken into account as a covariate in the statistical models or the post-COVID and Control groups were subsampled to be perfectly matched for that variable. However, such a mean difference in education attainment may be insightful. Namely, it reflects a protective factor. Based on previous evidence on the beneficial effects of education attainment in patients experiencing COVID-19 or other diseases requiring invasive mechanical ventilation in intensive care units (Fernández-Gonzalo et al., 2020; Godoy-González et al., 2023), we speculate that the education attainment may at least partially protect from the most severe clinical manifestations of COVID-19 and reduce the probability for hospitalization in persons with an acute COVID-19 syndrome. As a consequence, the random sampling of persons with an experience of hospitalization due to acute COVID-19 syndrome would form groups with lower mean education attainment compared to groups of persons enrolled from the population of people unaffected by COVID-19. This tentative explanation should be tested by future studies to be performed in larger samples of post-COVID and control participants.

5. Limitations

The following methodological limitations should be considered in interpreting the present results. The present observational and cross-sectional study did not include follow-ups and was based on rsEEG recordings carried out in relatively small groups of post-COVID and control participants. Therefore, it did not allow the stratification of the post-COVID and control participants for age, sex, socio-affective, socioeconomic, and education attainment and the description of the symptoms over time. Notably, the monocentric nature of the present study and the large spread of the SARS-CoV-2 virus in Italy amplified the difficulty of enrolling control participants who did not suffer from COVID-19 and were matched to the post-COVID participants for the mentioned variables, etc. For the same reason, we were unable to enroll patients never experiencing COVID-19 with other pathologies inducing "brain fog" (e.g., patients with multiple sclerosis). These limitations did not allow us to investigate (1) the causal relationships between post-COVID and various combinations of age, sex, socio-affective, socioeconomic, and education attainment and (2) the specificity between the post-COVID "brain fog" and the present rsEEG findings. Therefore, the results of this monocentric study motivate future multi-centric and longitudinal studies aimed at enrolling a large number of post-COVID and Control persons for serial clinical and rsEEG recordings to cross-validate and extend the present findings.

6. Conclusions

In the present study, we tested the hypothesis that in post-COVID seniors claiming "brain fog," rsEEG rhythms may be abnormal and substantiate the clinical syndrome even when cognitive and psychiatric disorders are absent. To this aim, we selected post-COVID seniors with no pre-infection and actual organic chronic disease about one year after hospitalization for SARS-CoV-2 infection. The results showed that over 90% of all post-COVID seniors did not suffer from cognitive or psychiatric disorders. On the contrary, 75% of them showed ≥ 2 fatigue symptoms. The post-COVID group globally showed lower posterior rsEEG alpha source activities than the Control group. This effect was more significant in the long COVID-19 patients experiencing ≥ 2 fatigue symptoms. These results suggest that in post-COVID seniors with no chronic diseases and cognitive/psychiatric disorders, "brain fog" can be associated with abnormal posterior rsEEG alpha rhythms and subjective chronic fatigue, possibly related to vigilance and allostatic dysfunctions.

Disclosure statement

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Consent to participate and publication

Informed consent was obtained from all participants.

Authors' contribution

CB and GDE designed the project. CB, GDE, GN, and PV conceived the experiment; EGC recruited the participants; GN and DJ recorded the data; FT and AMM ran neuropsychological assessments and scoring; GN, LV, and AMM analyzed EEG data; CB supervised data analysis; GN ran the statistics; GN, FT, EGC, LV, and CB drafted the manuscript and reply letter to the Editorial staff. All authors contributed to manuscript editing and critically discussed the results.

Conflict of interest statement

None of the Authors have potential conflicts of interest to be disclosed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2024.02.034.

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