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Neural basis of fatigue in post-COVID syndrome and relationships with cognitive complaints and cognition

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ABSTRACT

The main objective was to evaluate structural and functional connectivity correlates of fatigue in post-COVID syndrome, and to investigate the relationships with an objective measure of mental fatigue and with subjective cognitive complaints. One-hundred and twenty-nine patients were recruited after 14.79 ± 7.17 months. Patients were evaluated with fatigue, neuropsychological, and subjective cognitive complaints assessments. Structural and functional magnetic resonance imaging were acquired, and functional connectivity, white matter diffusivity and grey matter volume were evaluated. Fatigue was present in 86 % of patients, and was highly correlated to subjective cognitive complaints. Fatigue was associated with structural and functional connectivity mostly in frontal areas but also temporal, and cerebellar areas, showing mental fatigue different pattern of functional connectivity correlates compared to physical fatigue. White matter diffusivity correlates were similar in fatigue and subjective cognitive complaints, located in the forceps minor, anterior corona radiata and anterior cingulum. Findings confirm that fatigue in post-COVID syndrome is related to cerebral connectivity patterns, evidencing its brain substrates. Moreover, results highlight the relationship between fatigue and subjective cognitive complaints. These findings point out the relevance of the multidisciplinary assessment of post-COVID syndrome patients with subjective cognitive complaints, in order to unravel the symptomatology beneath the patient's complaints.

1. Introduction

Post-COVID syndrome (PCS) occurs in individuals with history of SARS-CoV-2 infection, in which several symptoms persist over more than three months after infection (Soriano et al., 2022). Among symptoms of PCS, fatigue is one of the most frequent and most disabling, along with cognition, and is usually persistent (Premraj et al., 2022). Fatigue symptomatology may affect between 35 and 60 % of patients after infection (Fernández-de-Las-Peñas et al., 2021), and both physical and cognitive fatigue have been described in PCS patients (Delgado-Alonso et al., 2022; Heine et al., 2023). These fatigue symptoms adversely affect patients' working status and quality of life (Delgado-Alonso et al., 2022).

Fatigue can be defined as a devastating experience of weakness, tiredness, and reduced capacity of physical and cognitive function not commensurate to the activity performed (Chaudhuri and Behan, 2004). Fatigue has been deeply analyzed in other medical conditions, such as multiple sclerosis and chronic fatigue syndrome. Although similarities have been described (Azcue et al., 2022; Heine et al., 2023), the unique characteristics of PCS warrant a specific investigation within this context.

The neural correlates of fatigue have been scarcely investigated in PCS. One previous study evaluated the structural correlates of fatigue in PCS and revealed altered volume and shape of the thalamus and basal ganglia structures, together with microstructural white matter (WM) changes, specifically, fractional anisotropy (FA) of the left thalamus,

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which was associated with physical fatigue (Heine et al., 2023). Another study revealed inverse relationships between fatigue symptoms and the volume from several frontal areas in post-COVID patients (Deters et al., 2023). However, given that PCS patients also present functional connectivity (FC) changes (Díez-Cirarda et al., 2022; Voruz et al., 2023), we hypothesized that functional brain connectivity may also be involved in fatigue symptomatology in PCS. Unraveling the neurobiological basis of fatigue in PCS is crucial for improving patient outcomes and developing effective interventions.

The relationships between fatigue and results from objective neuropsychological assessments are still controversial. Few studies have addressed the relationship between fatigue and cognition in PCS, suggesting low correlations with attention and executive functions deficits (Calabria et al., 2022; Heine et al., 2023). A previous study from our group revealed a mediational effect of fatigue between objective cognitive symptoms and subjective cognitive complaints (Delgado-Alonso et al., 2023), suggesting that subjective cognitive complaints result from both fatigue and cognitive impairment. This may suggest distinct neural mechanisms underlying fatigue and objective cognition in PCS.

The main objective of the present study was to evaluate structural and functional connectivity correlates of fatigue in PCS after 14 months from infection. Furthermore, given the relationship between fatigue, objective cognition, and subjective cognitive complaints, we also aimed to investigate the relationship between them.

2. Methods

2.1. Participants

We performed a cross-sectional evaluation of 129 participants after SARS-CoV-2 infection (with mean evolution since first symptoms of 14.79 ± 7.17 months). Patients were consecutively recruited through the Department of Neurology at Hospital Clinico San Carlos between November 2020 and July 2022.

Inclusion criteria for the PCS group were: 1) Diagnosis of COVID-19 confirmed by RT-PCR at least three months before the inclusion in the study; 2) Fatigue and/or cognitive complaints temporally related to the SARS-CoV-2 infection. Patients were excluded if they presented with other neurological or psychiatric disorders that could affect the study outcomes. Specifically, exclusion criteria included: 1) Any fatigue and/or cognitive complaints before COVID-19; 2) History of stroke, traumatic brain injury, or any neurological disorder; 3) Active psychiatric disorder or previous psychiatric disorder (e.g. schizophrenia or psychosis); 4) History of abuse of alcohol or other toxics; 5) Drugs or uncontrolled medical conditions associated with symptoms at the moment of the assessment; 6) Sensory disorder potentially biasing assessments; 7) Deep WM cerebral small vessel disease (Fazekas grade 2 or higher). PCS patients underwent a clinical and neuropsychological assessment. All neuroimaging analyses were performed on 129 patients with PCS, except for WM analyses, in which two patients were excluded due to differences in diffusion-weighted imaging parameter acquisition.

2.2. Fatigue assessment

Clinical assessment included the Modified Fatigue Impact Scale (MFIS) questionnaire for fatigue assessment (Kos et al., 2005). MFIS questionnaire is a subjective questionnaire regarding fatigue symptomatology and includes 21 items, scored from 0 “never” to 4 “almost always”. The scale provides a global score, MFIS total score (global fatigue), and three subscales: 1) MFIS Cognitive subscale, which ranges from 0 to 40 (mental fatigue); 2) MFIS Physical subscale ranging from 0 to 36 (physical fatigue); and 3) MFIS Psychosocial subscale, ranging from 0 to 8. Higher scores indicate greater fatigue. Fatigue diagnosis is established with the cut-off of MFIS total score $\geq$ 38 (Strober et al., 2020).

Moreover, the Stroop test, which measures selective attention and cognitive control (Word, Color, and Word-Color trials) (Golden, 2001), was included as an objective measure of mental fatigue. The Stroop test consists of three trials: 1) Stroop Words: patients named the color of words in congruent font color; for example, the word "yellow" is shown in color yellow; 2) Stroop Colors: patients named the color of 4-character string of “X”; and 3) Stroop Word-Color: patients named the color of words in incongruent font color, for example, the word "red" is shown in color yellow. The Word-Color trial is a measure of cognitive control and inhibition task; naming the color of words in an incongruent font color involves inhibition of the automatized response to reading the word. The Stroop test Word-Color trial (Stroop W-C) has been used in diverse fatigue studies as an objective measure of mental fatigue (Baran et al., 2020; Feng et al., 2019; Wolfgang and Schmitt, 2009).

2.3. Subjective cognitive complaints

Subjective cognitive complaints were evaluated with the questionnaire for complaints of cognitive disturbances “*Fragebogen zur geistigen LEIstungsfähigkeit*” (FLEI) (Beblo et al., 2010). This test is a self-administered questionnaire that includes 35 items with a Likert scale with 5 options, ranging from “never” (0 points) to “very often” (4 points). Questions are focused on difficulties in everyday situations in the last six months, examining three cognitive areas: attention (10 items), memory (10 items), and executive functions (10 items). The questionnaire includes 5 control items to control response tendency. The main score (FLEI Total) is calculated as the sum of the three cognitive areas (0–120 points). Higher raw scores (or low percentile ranks) indicate lower subjective cognitive performance. Scores can be divided into three subgroups: "below-average level" when the percentile is lower than 16, "average level" when the percentile ranks between 16 and 84, and "above-average level" when the percentile is higher than 84 (Beblo et al., 2011). The questionnaire was administered using the Vienna Test System® (Schuhfried) (Beblo et al., 2012).

2.4. Neuropsychological and clinical assessment

PCS patients underwent a comprehensive neuropsychological evaluation. A trained neuropsychologist administered the cognitive protocol evaluating attention, working memory, processing speed, executive functions, memory, language, and visuoperceptive and visuospatial abilities. Specifically, the tests included were: Forward and Backward Digit Span, Corsi Block-Tapping Test (forward and backward), Symbol Digit Modalities Test (SDMT), Free and Cued Selective Reminding Test (FCSRT), Rey-Osterrieth Complex Figure (ROCF) (copy and recall at 3, 30 min, and recognition), verbal fluency (animals and words beginning with “p”, “r”, and “m” in one minute each one), Stroop Word-Color Interference Test, Boston Naming Test (BNT), Judgment Line Orientation (JLO), and the Visual Object and Space Perception Battery (VOSP). These tests were validated, and normative data are available in our country, adjusted by age and education level (Peña-Casanova et al., 2009, 2012). Impairment was set at two cut-off scores: first, at the scaled score of five or less, which is equivalent to a percentile of $\leq$ 5 or z-score $\leq$ 1.65, and at the scaled score of seven or less, which is equivalent to a percentile of $\leq$ 16 or z-score $\leq$ 1.

Clinical assessment also included the evaluation of anxiety with the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 2017), depression with the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996), olfactory function with the Brief Smell Identification Test (BSIT) (Doty et al., 1996) and sleep quality with the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). According to previous literature, the following cut-offs were used: BSIT $\leq$ 8 was categorized as having abnormal olfaction; STAI-S $\geq$ 40 was considered clinically significant anxiety; BDI-II $\geq$ 19 was regarded as moderate or severe depression (Beck et al., 1988); PSQI $>$ 5 defined poor sleep quality and MFIS $\geq$ 38 was considered as having fatigue (Strober et al., 2020).

2.5. Neuroimaging acquisition and analysis

Patients were scanned using a 3.0T Magnet (GE Signa Architect) and a 48-channel head coil. 3D T1-weighted images were acquired in a Sagittal MPRAGE sequence with the following parameters: number of slices = 200, slice thickness = 1 mm, field of view 256 mm, matrix = 256×256, flip angle = 8, preparation time = 974 ms, recovery time = 700 ms, TR = 7.7 ms, TE = 3.1 ms, NEX= 1, acquisition time = 9:27.

The resting-state fMRI data were obtained in an axial orientation using a sequence sensitive to blood oxygen level-dependent (BOLD) contrast, and multi-slice gradient echo EPI sequence (TR = 3000 ms, TE = 30 ms, matrix size = 64×64, flip angle = 90°, FOV = 220×220 mm, slice thickness = 3.4 mm, no gap, 205 vol, 48 slices, voxel size = 3.4 × 3.4 × 3.4 mm, acquisition time = 10′15″).

Diffusion-weighted images were acquired in axial multishell diffusion 1 shot echo-planar sequence, with 3 b values (500,1000, 2000), and 125 diffusion directions, and the following parameters: number of slices = 64, slice thickness = 2.2 mm, field of view 256 mm, matrix = 116×166, TR = 6780 ms, TE = 3.1 ms, NEX = 1, acquisition time = 14:35. An additional opposing gradients sequence was acquired, for geometrical distortions correction purpose.

2.5.1. Resting-state fMRI

FC analysis was performed using Conn Functional Connectivity Toolbox 18.b. (Whitfield-Gabrieli and Nieto-Castanon, 2012). After removing the first 5 scans, each subject' 200 functional images were realigned and unwarped, non-linear coregistered with structural data, slice timing corrected (interleaved bottom-up), and spatially normalized into the standard MNI space (Montreal Neurological Institute). Outliers were detected (ART-based scrubbing), and finally, images were smoothed using a Gaussian kernel of 8 mm FWMH. As recommended, band-pass filtering was performed with a frequency window of 0.008 to 0.09 Hz (Weissenbacher et al., 2009).

Because SARS-CoV-2 infection is a novel disease, we have no prior hypothesis on brain functional correlates related to fatigue symptoms. Therefore, we performed a whole-brain Region of interest (ROI) ROI-to-ROI approach analysis according to Conn toolbox options to test the association between fatigue and FC in PCS. The Atlas used was the Automated Anatomical Labeling atlas (AAL) parcellation included in the CONN toolbox, including cortical, subcortical and cerebellar areas.

We carried out regression analyses with: 1) MFIS Total; 2) MFIS Cognitive subscale; 3) MFIS Physical subscale; 4) Stroop W-C (trial 3, inhibition task); 4) FLEI Total score. Statistical analyses were carried out with age, sex, and education as covariates, and significance was set at $p < 0.05$ FDR-corrected (two-sided).

2.5.2. Diffusion-weighted images

Diffusion data were preprocessed and analyzed in FMRIB Software Library (FSL) (v.6.0.5) (Smith et al., 2006). First, each subject's images were concatenated and radiologically oriented. Then, topup was applied to estimate and correct susceptibility-induced distortions (fieldmap estimation) (Andersson et al., 2003). Then, BET brain extraction was applied (Smith, 2002). Eddy command was used to correct for distortion (eddy currents, susceptibility-induced distortions, and subject's motion) (Andersson and Sotiropoulos, 2016) with a fieldmap estimated by topup. After, dtifit command was applied to fit diffusion tensors into the eddy-corrected data. For voxelwise statistical analyses, data were processed by applying the standard FSL pipeline for Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006). Finally, FA, mean diffusivity, radial diffusivity (RD), and axial diffusivity (AD) whole-brain maps were calculated. Randomise was performed with 5000 permutations. We carried out regression analyses with: 1) MFIS Total; 2) MFIS Cognitive subscale; 3) MFIS Physical subscale; 4) Stroop W-C (trial 3, inhibition task); 4) FLEI Total score. Statistical analyses included age, sex, education, and TIV as covariates.

WM indexes were also calculated for the main WM tracts that showed significant associations. WM results used the JHU ICBM-DTI-81 white-matter labels, White-Matter Tractography Atlas and Julich Histological Atlas. WM cluster significance was set at $p < 0.05$ FWE-corrected (two-sided), Threshold (T value) > 2 and $k > 300$ voxels.

2.5.3. T1-weighted images

T1-weighted images were preprocessed and analyzed with the DARTEL tool (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) in SPM12 (Ashburner et al., 2014). After orientation and segmentation, the mean template was created, and spatial normalization was performed into the Montreal Neurological Institute (MNI) template space. Then, images were modulated, and smoothing with an isotropic Gaussian kernel of 8 mm full-width at half maximum (FWHM) was applied. Total Intracranial Volume (TIV) was calculated. The AAL atlas parcellation was used for GM results localization. In addition, WFU Pickatlas was used to create ROI masks based on FC results with AAL atlas. We carried out regression analyses with: 1) MFIS Total; 2) MFIS Cognitive subscale; 3) MFIS Physical subscale; 4) Stroop W-C (trial 3, inhibition task); 4) FLEI Total score. Whole-brain regression analyses with and without masks were performed with age, sex, education, and TIV as covariates in the analysis. Significance was set at $p < 0.05$ FWE-corrected (two-sided).

2.6. Statistical analyses

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 26.0 (IBM corp., Armonk, NY: IBM Corp). Sociodemographic, clinical, and cognitive characteristics of the sample were calculated using T-test and or Chi-squared tests for quantitative or categorical data, respectively.

All neuroimaging analyses included age, sex, and education as nuisance covariates. Moreover, GM and WM analyses were also controlled for TIV. Covariates were demeaned before including in neuroimaging analyses. All neuroimaging analyses were corrected for multiple comparisons, using FWE for grey matter and diffusion analyses, and FDR for functional connectivity analyses, which has been found more suitable in this type of analysis, balancing the type I and type II errors (Chumbley et al., 2010; Genovese et al., 2002; Noble et al., 2022). Correlation analyses were performed with partial correlation coefficient estimation, using age, sex, and education as covariates, and set at $p < 0.05$. Bonferroni correction was also indicated in correlation analyses, corrected by the number of cognitive tests at $p < 0.0017$. Correlations were interpreted as small, moderate, and large when scores were 0.10, 0.30 and 0.50, respectively (Hojat and Xu, 2004).

Post-hoc analyses were performed to evaluate associations between cognition, clinical aspects, and brain correlates of fatigue with the number of reinfections, days of evolution, age and sex. Age differences were calculated by dividing the sample by the median split on age. Moreover, brain correlates of fatigue were also analyzed separately in hospitalized and non-hospitalized patients. Analyses were performed controlling for age, sex, education and TIV when needed, and results were corrected by Bonferroni correction.

2.7. Ethics and patient consent

The present study was approved by the ethics committee from Hospital Clínico San Carlos (reference: 21/062-E), and participants provided written informed consent prior to research participation.

3. Results

3.1. Characteristics of PCS patients

PCS patients were recruited after 14.79 ± 7.17 months of evolution since the acute infection. These patients had a mean age of 49.35 ± 10.29, 14.97 ± 3.62 years of education, and 73.64 % were female.

During the acute phase, 28.1 % were hospitalized. Neurological symptoms in the acute phase included headache in 82.17 % of the patients, and 55.03 % presented hyposmia and ageusia. Most of the patients were infected only once (86 %). The main demographic and clinical characteristics of the sample are depicted in Table 1.

3.2. Fatigue and clinical symptoms in PCS patients

After 14 months from SARS-CoV-2 infection, 86.8 % (112/129) of PCS patients presented with a global fatigue diagnosis. Regarding subscales, patients showed an MFIS Cognitive mean subscale (mental fatigue) of 26.16 ± 7.13, an MFIS Physical mean subscale (physical fatigue) of 24.64 ± 7.89, and an MFIS Psychosocial mean subscale of 5.19 ± 2.33 (Table 2).

Global fatigue was accompanied by 44.2 % (57/129) of anxiety (mean 40.50 ± 11.70), 26.4 % (34/129) of depression (14.60 ± 8.68), 84.3 % (109/129) of sleep disturbance (10.15 ± 4.60) and 27.2 % (35/129) of olfactory dysfunction (9.41 ± 2.20).

3.3. Neuropsychological profile of PCS patients: objective and subjective cognition

Regarding objective cognition, patients revealed greater cognitive deficits in attention, executive functions, and processing speed, accompanied by deficits in memory and visuospatial abilities (Supplementary Table S1). Impaired performance in the Stroop W-C inhibition subtest was found in 45.3 % of patients.

Regarding subjective cognitive complaints, 85.9 % of patients reported reduced subjective cognitive performance in FLEI total score, showing 89.1 % reduced subjective cognitive performance in FLEI attention subscale, 86.7 % in FLEI memory subscale, and 64.8 % in FLEI executive functions (Table 2).

3.4. Relationships between fatigue and cognition

Regarding associations between global fatigue and objective cognition, MFIS Total score showed low correlations with Stroop W ($r = -0.210$; $p = 0.020$), fluency (animals) ($r = -0.192$; $p = 0.034$) and VOSP object discrimination ($r = -0.178$; $p = 0.050$) and almost significant for Stroop W-C ($r = -0.177$; $p = 0.051$). In fact, MFIS Cognitive subscale was the only MFIS subscale to show significant correlations with Stroop W-C ($r = -0.194$; $p = 0.033$). MFIS Physical subscale showed low correlations with Stroop W ($r = -0.204$; $p = 0.025$), and VOSP object decision ($r = -0187$; $p = 0.039$). None of these correlations survived Bonferroni correction $p < 0.0017$.

Regarding associations between global, cognitive and physical fatigue with subjective cognitive complaints, MFIS Total score and subscales showed significant and large correlations with FLEI Total score and subscales ($p < 0.05$). Similarly, the relationships between an objective measure of mental fatigue (Stroop W-C) and FLEI Total and subscales showed significant and moderate correlations ($p < 0.05$) (see Fig. 1).

Table 1
Sociodemographics and clinical characteristics of PCS patients.

	Mean (SD)
Age (years)	49.35 ± 10.29
Sex	73.64 % (95/129)
Education (years)	14.97 ± 3.62
Evolution (months)	14.79 ± 7.17
Number of Infections	
One	86 % (111/129)
Two	13.2 % (17/129)
Three	0.8 % (1/129)
Neurological symptoms in the acute stage	
Headache	82.17 % (106/129)
Hyposmia & Ageusia	55.03 % (71/129)
Premorbid Risk Factors	
Hypertension	25.58 % (33/129)
Diabetes	10.07 % (13/129)
Dyslipidemia	24.03 % (31/129)
Smoking habit	14.96 % (19/129)

Table 2
Fatigue and cognitive scores in PCS.

Fatigue Score	Mean (SD)	Min – Max	Altered (%)
MFIS Total score	55.96 ± 15.26	16 - 84	86.8 %
MFIS Cognitive score	26.16 ± 7.13	1 - 40	–
MFIS Physical score	24.64 ± 7.89	1 - 40	–
MFIS Psychosocial score	5.19 ± 2.33	0 - 10	–
Stroop Test			
STROOP W	89.84 ± 23.40	37 - 131	Scaled-score ≤ 5: 31 % Scaled-score ≤7: 50.4 %
STROOP C	61.59 ± 15.67	23 - 102	Scaled-score ≤5: 34.1 % Scaled-score ≤7: 45.7 %
STROOP W-C	36.14 ± 12.41	12 - 82	Scaled-score ≤5: 25.8 % Scaled-score ≤7: 45.3 %
Subjective Cognitive Complaints			
FLEI Total	75.27 ± 32.39 (percentile 9.10 ±13.83)	0 - 120	85.9 %
FLEI Attention subscale	26.65 ± 10.46 (percentile 8.39 ±13.80)	0 - 40	89.1 %
FLEI Memory subscale	27.75 ± 10.11 (percentile 7.92 ±12.39)	0 - 40	86.7 %
FLEI Executive Functions subscale	20.58 ± 12.25 (percentile 17.84 ±21.84)	0 - 40	64.8 %

SD = Standard Deviation; Scalar = Scalar Score for cut-off. MFIS = Modified Fatigue Impact Scale; Stroop W-C = Stroop Word-Color subtest, inhibition task. FLEI = Questionnaire for complaints of cognitive disturbances.

3.5. Functional connectivity associations with fatigue in PCS

MFIS Total score showed negative correlations with FC between the frontal middle orbital cortex and the right cuneus, and positive associations with FC between the left cerebellum and the bilateral temporal pole ($p < 0.05$ FDR-corrected) (Fig. 2).

MFIS Cognitive subscale revealed significant negative associations with FC between left frontal orbital areas and posterior areas, including cerebellum, lingual, and right cuneus. Moreover, MFIS Cognitive subscale showed negative correlations with FC between the anterior cingulum and the left insula with the right Heschl gyrus ($p < 0.05$ FDR-corrected) (Fig. 2).

MFIS Physical subscale showed significant correlations with FC between the left cerebellum and the bilateral temporal pole ($p < 0.05$ FDR-corrected) (Fig. 2).

3.6. White matter integrity associated with fatigue in PCS

MFIS Total score was inversely associated with FA in frontal WM tracts, including the forceps minor, the anterior thalamic radiation, the superior longitudinal fasciculus or the callosal body ($p < 0.05$ FWE-corrected) (Fig. 3, Supplementary Table S2). In addition, MFIS Total score also showed positive relationships with RD and MD in similar tracts, including the forceps minor, the superior longitudinal fasciculus and the callosal body ($p < 0.05$ FWE-corrected) (Fig. 3). That is, the

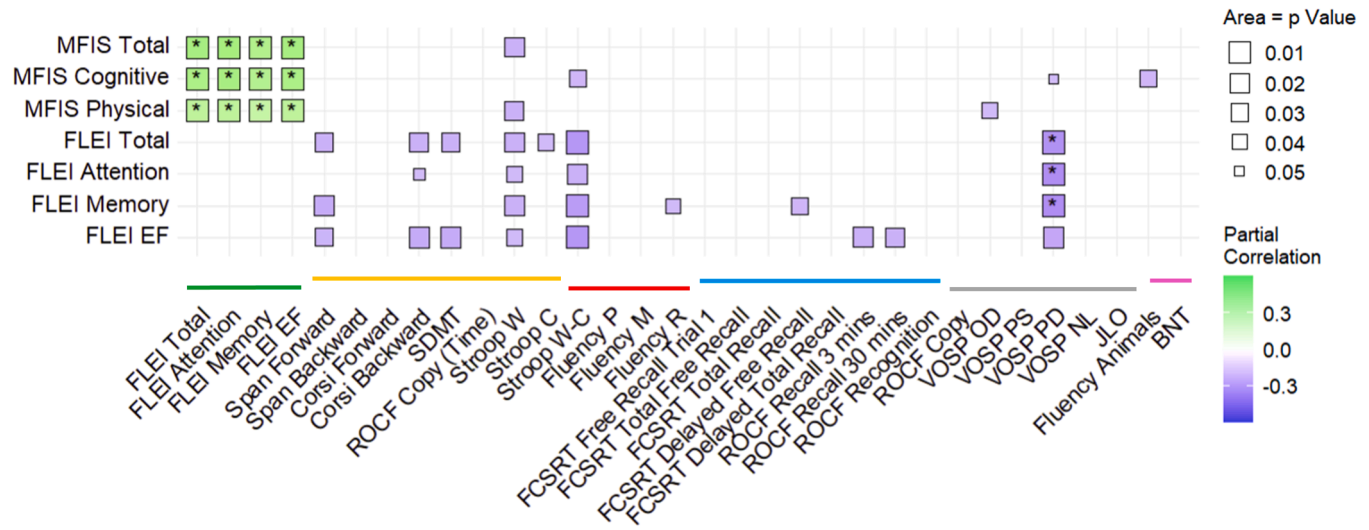

Fig. 1. Correlations between fatigue and subjective and objective cognition. Fig. 1 Legend: * $p < 0.0017$ (Bonferroni correction); MFIS = Modified Fatigue Impact Scale; FLEI = Questionnaire for complaints of cognitive disturbances (total score). Stroop *W*= Stroop Word subtest; Stroop C = Stroop Color subtest; Stroop W-C = Stroop Word-Color Interference subtest; ROCF = Rey-Osterrieth Complex Figure; SDMT = Symbol Digit Modalities Test; FCSRT = Free and Cued Selective Reminding Test; VOSP = Visual Object and Space Perception Battery; JLO = Judgment Line Orientation; BNT = Boston Naming Test. Green line = FLEI questionnaire; Yellow: Attention and Working Memory; Red line = Executive Functions; Blue line = Learning and Memory; Grey line = Visuospatial and visuoconstructive ability; Pink line = Language.

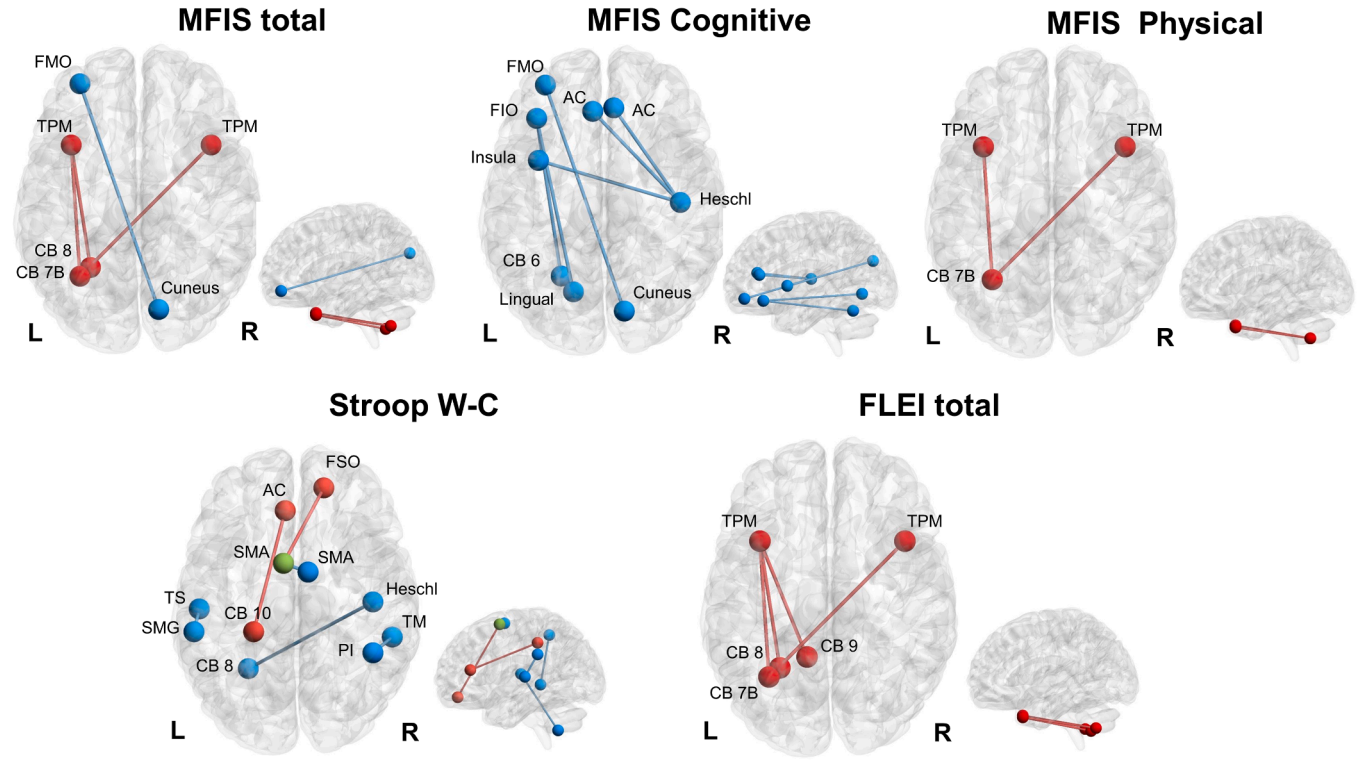

Fig. 2. FC correlates of fatigue, Stroop W-C and FLEI in PCS. Fig. 2 Legend: Blue= Negative correlations; Red= Positive correlations. MFIS = Modified Fatigue Impact Scale; Stroop W-C = Stroop Word-Color subtest, inhibition task. FLEI = Questionnaire for complaints of cognitive disturbances (total score). FMO =Frontal Mid Orbital; TPM = Mid Temporal Pole; CB = Cerebellar; AC = Anterior Cingulate; SMA = Supplementary Motor Area; TM = Mid Temporal; TS = Superior Temporal; SMG = Supramarginal Gyrus; PI = Parietal Inferior.

more global fatigue, the more reduced FA and increased RD and MD in these WM tracts. Peak coordinates are specified in Table S2.

Similarly, MFIS Cognitive subscale showed inverse correlations with FA in frontal WM tracts, including the left forceps minor and the cingulum ($p < 0.05$ FWE-corrected), and positive correlations with RD and MD in the bilateral cingulum, the forceps minor and the anterior thalamic radiation (Fig. 3, Table S2).

Similarly, MFIS Physical subscale showed inverse correlations with FA in frontal WM tracts, including the right forceps minor and the superior longitudinal fasciculus ($p < 0.05$ FWE-corrected). Also, positive associations were found with RD and MD, mainly in the right cingulum, the superior longitudinal fasciculus, and the inferior fronto-occipital

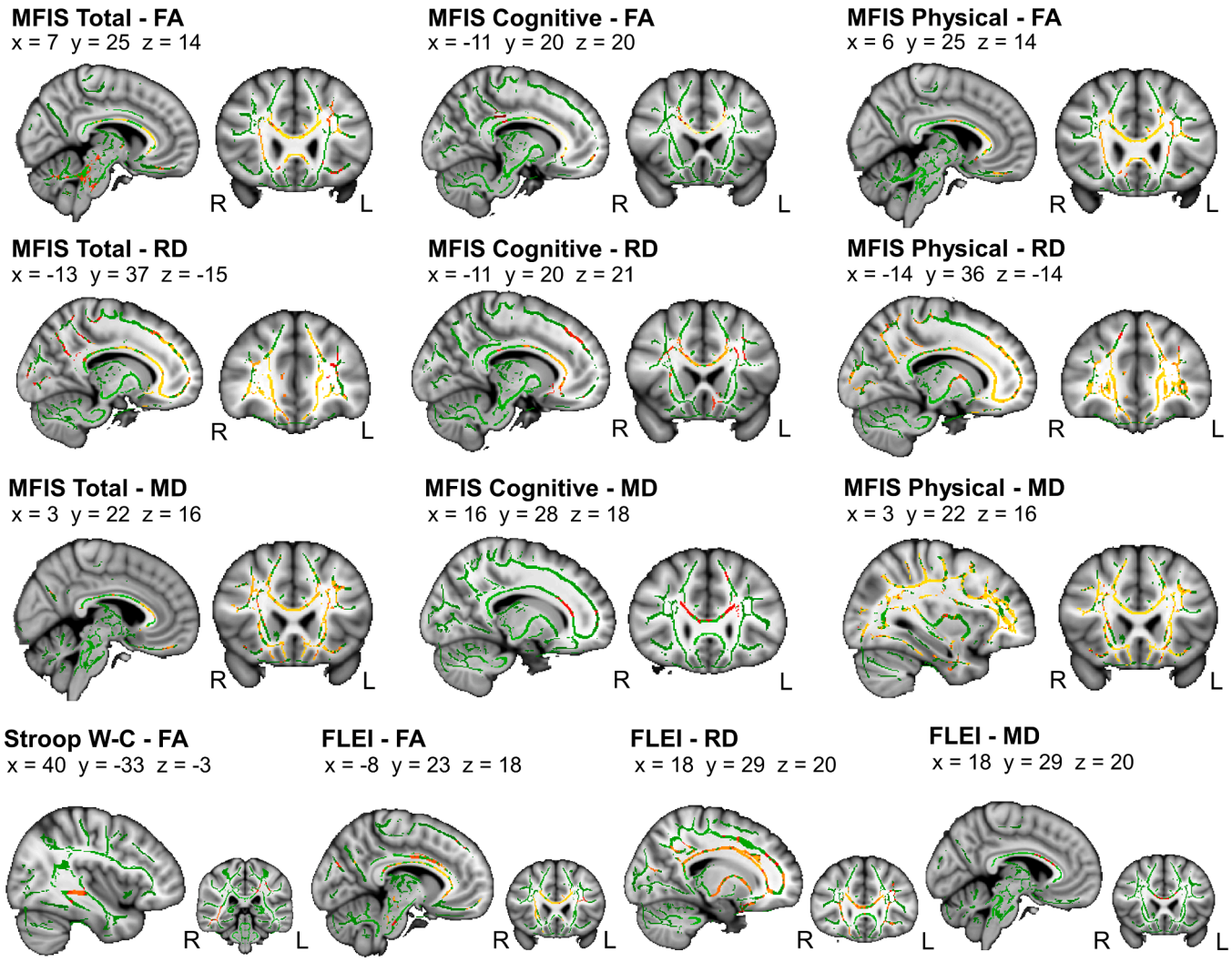

Fig. 3. White matter diffusivity associations with fatigue, FLEI and Stroop W-C in PCS. Fig. 3 Legend: FA = Fractional anisotropy; RD = Radial Diffusivity. Coordinates are MNI. *R* = Right; *L* = Left. MFIS = Modified Fatigue Impact Scale; FLEI = Questionnaire for complaints of cognitive disturbances (total score).

fasciculus ($p < 0.05$ FWE-corrected) (Fig. 3, Table S2).

3.7. Grey matter volume associated with fatigue in PCS

We found no significant associations between global, mental or physical fatigue symptoms and grey matter volume in PCS analyzing whole-brain, and neither applying a grey matter mask in those areas that showed FC related to fatigue.

3.8. Brain correlates of Stroop W-C

Stroop W-C showed significant associations with FC and WM. In detail, Stroop W-C showed positive associations with FC between the frontal orbital cortex and left superior motor area, and between the left cingulate and cerebellum ($p < 0.05$ FDR-corrected). At the same time, it showed inverse correlations with FC between the bilateral temporo-parietal areas and the left cerebellum with the right Heschl gyrus ($p < 0.05$ FDR-corrected) (Fig. 2). Moreover, Stroop W-C was positively associated with FA in the inferior fronto-occipital fasciculus and the optic radiation (Fig. 3, Table S2).

3.9. Brain correlates of FLEI Total score

FLEI Total score significantly correlated with FC and WM diffusivity. Regarding FC correlations, FLEI Total score showed significant correlations with FC between the left cerebellum and the bilateral temporal pole ($p < 0.05$ FDR-corrected) (Fig. 2). Moreover, at $p < 0.001$ uncorrected level, negative associations were found with FC between the right frontal superior orbital and the left insula and positive associations with FC between the right frontal inferior orbital and the right cerebellum.

Regarding WM diffusivity, FLEI Total score showed significant and negative correlations with FA and positive correlations with RD and MD mostly in frontal tracts, including the forceps minor, the anterior corona radiata, inferior fronto-occipital fasciculus ($p < 0.05$ FWE-corrected) (see Fig. 3 and Table S2).

3.10. Associations with sociodemographic and clinical data

Post-hoc associations were evaluated between cognitive, clinical, and brain changes related to fatigue with number of reinfections, days of evolution since the infection, age, and sex. Results revealed significant associations between the number of times the patients were infected with COVID-19 and mental fatigue and its brain FC correlates. Specifically, the number of infections showed trends to significance with increased MFIS Cognitive subscore ($r = 0.172$; $p = 0.062$) and was significantly associated with the FC related to MFIS Cognitive subscore, specifically with FC between the left inferior frontal orbital and the left lingual gyrus ($r = -0.297$; $p = 0.001$), and between the FC between the

cingulum and the right Heschl gyrus ($r = 0.232$; $p = 0.009$). On the contrary, no significant correlations were found between days of evolution and cognitive, clinical and brain changes related to fatigue.

Regarding age, older patients had lower cognitive dysfunction in Stroop W-C, SDMT, and verbal fluency compared to younger patients but showed greater alterations in FA, MD and RD of the WM tracts associated with fatigue ($p < 0.0017$ - Bonferroni corrected) (Supplementary Table S3). Furthermore, comparisons between sex did not reveal significant differences in cognitive, clinical, or FC results, but men compared to women showed greater alterations in FA, MD and RD of the WM tracts associated with fatigue ($p < 0.0017$ - Bonferroni corrected) (Supplementary Table S4).

3.11. Hospitalized and non-hospitalized patients

The brain structural and functional correlates of fatigue in hospitalized and non-hospitalized patients were also analyzed independently. One patient had missing data regarding hospitalization; therefore, analyses were performed with 92 non-hospitalized and 36 hospitalized patients. Non-hospitalized patients were younger and had increased years of education compared to hospitalized patients (Supplementary Table S5).

Non-hospitalized patients presented with similar FC correlates to those found in the whole group regarding global fatigue, cognitive fatigue or physical fatigue ($p < 0.05$ FDR corrected) (Figure S1). Hospitalized patients also revealed similar FC correlates but showed greater negative associations, mostly between frontal, cerebellar, and occipital regions (Figure S1).

Focusing on WM correlates, non-hospitalized patients revealed correlations between MFIS total score and reduced FA and increased RD and MD mostly in forceps minor, callosal body, cingulum and inferior fronto-occipital fasciculus ($p < 0.05$ FWE-corrected) (Figure S2, Supplementary Table S6). Similarly, MFIS cognitive subscale was associated with reduced FA and increased RD in the forceps minor and cingulum tracts. MFIS physical subscale also revealed associations with reduced FA and increased RD and MD in forceps minor, cingulum, anterior thalamic radiation and inferior fronto-occipital tracts (Figure S2, Supplementary Table S6). However, correlations between fatigue and WM integrity or diffusivity indexes in the hospitalized group did not survive FWE correction.

4. Discussion

The present study aimed to investigate the brain correlates of fatigue in post-COVID syndrome. Main findings revealed that global fatigue in PCS was associated with FC mostly in frontal areas but also temporal, and cerebellar areas, showing mental fatigue different pattern of FC compared to physical fatigue. Subjective cognitive complaints shared similar FC correlates compared to physical fatigue but not compared to mental fatigue. Moreover, global fatigue was also associated with WM FA MD and RD, mostly in WM tracts of frontal areas, including the forceps minor, anterior corona radiata and anterior cingulum. Overall, these findings suggest a role of central nervous system involvement in the pathophysiology of fatigue in PCS.

Patients from the present study presented with global fatigue in 86.8 % of the sample after 14 months follow-up. Fatigue has been found to be one of the most prevalent and disabling symptoms in PCS (Premraj et al., 2022). Therefore, it was expected a high prevalence of fatigue symptomatology among participants of the study. Regarding cognitive deficits in PCS, results reinforce previous findings that showed greater impairment in attention, processing speed and executive functions, followed by memory, visuospatial and language deficits (Ferrucci et al., 2022; García-Sánchez et al., 2022; Silva et al., 2021).

Moreover, 85.9 % of the patients referred subjective cognitive complaints. Fatigue symptoms showed large correlations with subjective cognitive complaints and low correlations with objective cognitive deficits. Previous studies also revealed large relationships between fatigue and subjective cognitive complaints (Kinsinger et al., 2010), and identified fatigue as a mediator between objective and subjective cognitive complaints, suggesting that subjective cognitive complaints were increased when the patient presented high levels of global fatigue (Delgado-Alonso et al., 2023; Matias-Guiu et al., 2022). Moreover, mental fatigue was also found to be more strongly related to neuropsychiatric symptoms than to objective cognitive deficits (Calabria et al., 2022). Among cognitive domains, fatigue correlated with attention and executive functions tests in PCS patients, similar to previous studies (Calabria et al., 2022; Holtzer et al., 2010).

Fatigue showed both functional connectivity and white matter correlates in PCS. On the one hand, global fatigue was related to reduced FC between frontal and occipital areas and increased FC between cerebellar and temporal areas. Physical fatigue showed a similar pattern of connectivity, with increased physical fatigue associated with increased connectivity between the cerebellum and bilateral temporal areas. Cerebellum has been widely related to behavioral alterations, including global fatigue (Arm et al., 2019; Damasceno et al., 2016) and specifically related to physical fatigue perception (Casamento-Moran et al., 2023). Moreover, middle temporal pole has also been related to global fatigue in other disorders (Fuchs et al., 2019; Hanken et al., 2016). On the other hand, mental fatigue revealed a different pattern of FC correlates compared to global or physical fatigue in PCS. Brain areas showing FC associations with mental fatigue were located in the left prefrontal areas, anterior cingulate, left insula, and temporal, occipital and cerebellum. Interestingly, left prefrontal, anterior cingulate and the left insula are central hubs of the so-called “fatigue network” related to mental fatigue (Wylie et al., 2020). These results revealed that mental fatigue in PCS patients is also related to poorer FC between these brain areas and other areas of the brain such as cerebellar and temporal areas. Indeed, FC alterations between prefrontal and lobule 6 of the cerebellum related to mental fatigue were previously reported (Wylie et al., 2020). Other disorders such as chronic fatigue syndrome and multiple sclerosis shared similar substrates of FC alterations related to mental fatigue. A previous study in chronic fatigue syndrome showed connectivity changes between inferior frontal gyrus and lingual gyrus and cerebellar areas, and between the insula and middle temporal during a mental fatigue task inside the scanner (Boissoneault et al., 2018). Multiple sclerosis patients also presented with lower connectivity related to mental fatigue in cerebellar areas (Hidalgo de la Cruz et al., 2017), and in frontal areas (Cercignani et al., 2021). Furthermore, hospitalized patients revealed a more complex FC correlates of fatigue, showing FC correlates in similar areas compared to non-hospitalized patients, but also associations with reduced FC mostly between frontal and posterior areas, including cerebellar and occipital areas. This could suggest a greater participation of the central nervous system in the pathophysiology of fatigue in the subgroup of hospitalized patients with PCS compared with non-hospitalized patients.

Worth to highlight, subjective cognitive complaints measured through FLEI Total score showed a similar pattern of FC correlates than physical, or global fatigue, but not mental fatigue. This could be linked to the fact that global fatigue has a direct effect on subjective cognitive complaints (Delgado-Alonso et al., 2023) and that physical fatigue has been associated with subjective cognitive complaints (Davenport et al., 2022; Marrie et al., 2005; Middleton et al., 2006) and identified as predictor of subjective cognitive complaints (Marrie et al., 2005; Middleton et al., 2006).

Fatigue was evaluated with the MFIS questionnaire, which is a subjective questionnaire that measures the patient’s perceived fatigue. Therefore, we decided to evaluate objective mental fatigue through the Stroop W-C interference task (Baran et al., 2020; Feng et al., 2019; Wolfgang and Schmitt, 2009). FC correlates related to Stroop W-C overlapped with FC correlates of mental fatigue in several areas, including anterior cingulate, prefrontal, cerebellar and Heschl gyrus. Similarities in the FC substrates between objective and subjective mental

fatigue align with the significant association between MFIS cognitive subscale and Stroop W-C. Results also revealed connectivity differences between subjective and objective mental fatigue. Previous studies reported increased activation in superior frontal areas, temporal areas, anterior cingulate and cerebellum during the Stroop interference task (Harrison et al., 2005).

Furthermore, MFIS Cognitive subscale showed FC correlates in the anterior cingulate, insula and prefrontal cortex, which are also part of the executive control network part of the attention system (Petersen and Posner, 2012). Interestingly, the cognitive processes involved in the Stroop W-C task include the sustained and focused attention, that have also been related to the executive control network part of the attention system (Petersen and Posner, 2012). Indeed, a relationship between mental fatigue and attention network has been previously suggested (Hanken et al., 2014), which is consistent with results from the present study. This is reinforced by the FC correlates of Stroop W-C task. The Stroop W-C task involves several cognitive processes, including the sustained and focused attention, suggesting shared neural basis between subjective mental fatigue measured through the MFIS Cognitive subscale, objective mental fatigue measured through Stroop W-C task, and the executive control network part of the attention network.

WM correlates of fatigue are consistent with FC correlates. WM tracts in PCS showed associations with fatigue in frontal areas, showing reduced FA and increased MD and RD related to fatigue in PCS. WM tracts mainly involved in global, physical and mental fatigue in PCS were the forceps minor, cingulum, anterior thalamic radiation, corpus callosum, superior longitudinal fasciculus and inferior fronto-occipital fasciculus. That is, WM correlates were similar in both physical and mental fatigue in PCS. A recent review in multiple sclerosis revealed similar results, consistently showing reduced FA and increased MD and RD in similar tracts linked to physical and mental fatigue symptoms (Arm et al., 2019). Similarly, these WM tracts also presented alterations in multiple sclerosis patients with fatigue (Gobbi et al., 2014; Novo et al., 2018; Pardini et al., 2010, 2014; Rocca et al., 2014). Interpretation of WM integrity and diffusivity measures is complex and should always be taken with caution. FA has been related to microstructural integrity, an increment in RD has shown associations with demyelination in diverse diseases and increased MD has been inversely related to membrane density (Alexander et al., 2011). Therefore, these results suggest that the presence of both physical and mental fatigue in PCS is partly related to several microstructural changes, including demyelination.

Furthermore, PCS patients showed no grey matter volume associations with global, physical or mental fatigue. Contrary to these findings, a previous study which focused on subcortical structures, identified reduced grey matter volume and structural surface deformation in PCS with global fatigue (Heine et al., 2023). Our study focused on whole-brain and cortical specific structures related to FC correlates. Furthermore, patients from the previous study had 7 months of mean evolution since the infection, and patients from the present study were recruited at 14 months follow-up. Therefore, results differences may be due to different neuroimaging analyses approach and patients' characteristics.

Overall, these results suggest that fatigue in PCS has structural and functional brain correlates, presenting white matter integrity and diffusivity associations in frontal areas and FC correlates in frontal, cerebellar, temporal and occipital areas. Previous studies in chronic fatigue syndrome or multiple sclerosis revealed similar areas associated with fatigue, which could suggest partially shared pathophysiological substrates of fatigue symptoms (Boissoneault et al., 2018; Cercignani et al., 2021; Hidalgo de la Cruz et al., 2017). Interestingly, mental fatigue and its brain FC correlates may be more susceptible to the number of reinfections. Moreover, subjective cognitive complaints were strongly related to fatigue, but showed a weaker association with objective cognitive performance, and shared FC substrates with physical fatigue. These findings point out the relevance of the multidisciplinary assessment of PCS patients with subjective cognitive complaints, including a comprehensive neuropsychological battery and fatigue evaluation, to disentangle the symptomatology beneath the patient's complaints.

The study of the neural basis of global, physical, and mental fatigue in PCS patients is relevant because there is a need for specific interventions to improve these symptoms. Few studies demonstrated the efficacy of neuromodulation treatments to improve physical fatigue (Oliver-Mas et al., 2023) and global and mental fatigue (Santana et al., 2023). In this sense, the present findings revealed the involvement of the central nervous system in the pathophysiology of fatigue in PCS, and identified specific brain areas related to global, physical, and mental fatigue, which could help in the design of specific interventions, and pave the way to the use of non-invasive brain stimulation techniques to alleviate both physical and mental fatigue in these patients. Personalized treatments based on specific neuroimaging results has been previously performed in other disorders, such as depression (Cash et al., 2021; Fox et al., 2012, 2013).

Some limitations should be considered. First, the present study presents a cross-sectional design, and longitudinal studies are needed to study whether these brain correlates are permanent or dynamic and to identify if they are part of compensatory mechanisms or part of a recovery process. Second, we used the MFIS scale, one of the most validated scales to evaluate the impact of fatigue. Other studies using other scales and assessments (e.g. objective assessments of physical fatigue, informant's observation of family and relatives) are needed to confirm these findings. The study did not include a secondary group of patients with mental fatigue due to other biological conditions. Future studies should be performed to compare whether the brain substrates of fatigue in PCS share a similar pattern compared to other disorders such as multiple sclerosis or chronic fatigue syndrome. Moreover, the present study included an unbalanced number of women and men due to the increased percentage of women affected by PCS and thus, it reflects the reality of the condition. However, it would be of interest for future studies to include a balanced number of men and women to evaluate sex differences in PCS.

In conclusion, patients with post-COVID syndrome at 14 months from the infection presented functional connectivity and white matter associations with fatigue symptoms, mostly in frontal but also temporal and cerebellar areas. These findings suggest a role of central nervous system involvement in the pathophysiology of fatigue in PCS. Cognitive and physical fatigue differed in the functional connectivity patterns. Functional connectivity correlates of subjective cognitive complaints were similar to physical fatigue, while connectivity related to mental fatigue partially overlapped with Stroop W-C connectivity correlates. The existence of several brain characteristics associated with fatigue severity detected by MRI could constitute a neuroimaging biomarker to objectively evaluate this symptom in clinical trials. In addition, the involvement of the central nervous system in the pathophysiology of fatigue in PCS paves the way for the use of non-invasive brain stimulation techniques to alleviate fatigue in these patients.

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Author statement

This statement is to certify that all Authors have seen and approved

the manuscript being submitted. We warrant that the article is the Authors' original work. We warrant that the article has not received prior publication and is not under consideration for publication elsewhere.

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. This research has not been submitted for publication nor has it been published in whole or in part elsewhere. We attest to the fact that all Authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission

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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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Supplementary materials

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