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ORIGINAL ARTICLE

Unraveling brain fog in post-COVID syndrome: Relationship between subjective cognitive complaints and cognitive function, fatigue, and neuropsychiatric symptoms

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Abstract

Background and purpose: "Brain fog" is a frequent and disabling symptom that can occur after SARS-CoV-2 infection. However, its clinical characteristics and the relationships among brain fog and objective cognitive function, fatigue, and neuropsychiatric symptoms (depression, anxiety) are still unclear. In this study, we aimed to examine the characteristics of brain fog and to understand how fatigue, cognitive performance, and neuropsychiatric symptoms and the mutual relationships among these variables influence subjective cognitive complaints.

Methods: A total of 170 patients with cognitive complaints in the context of post-COVID syndrome were evaluated using a comprehensive neuropsychological protocol. The FLEI scale was used to characterize subjective cognitive complaints. Correlation analysis, regression machine-learning algorithms, and mediation analysis were calculated.

Results: Cognitive complaints were mainly attention and episodic memory symptoms, while executive functions (planning) issues were less often reported. The FLEI scale, a mental ability questionnaire, showed high correlations with a fatigue scale and moderate correlations with the Stroop test, and anxiety and depressive symptoms. Random forest algorithms showed an R^2 value of 0.409 for the prediction of FLEI score, with several cognitive tests, fatigue and depression being the best variables used in the prediction. Mediation analysis showed that fatigue was the main mediator between objective and subjective cognition, while the effect of depression was indirect and mediated through fatigue.

Conclusions: Brain fog associated with COVID-19 is mainly characterized by attention and episodic memory, and fatigue, which is the main mediator between objective and subjective cognition. Our findings contribute to understanding the pathophysiology of brain fog and emphasize the need to unravel the main mechanisms underlying brain fog, considering several aspects.

KEYWORDS
cognitive, COVID-19, depression, fatigue, long COVID

INTRODUCTION

"Brain fog" is an umbrella term used to describe a wide variety of cognitive symptoms. This term was previously used to outline subjective mild cognitive difficulties encountered in several medical disorders, including celiac disease, rheumatological disorders (e.g., lupus, Sjögren's syndrome), endocrine disorders (e.g., hypothyroidism), chronic fatigue syndrome and fibromyalgia, among others [1–5]. Recently, the term has gained growing interest due to the frequent development of brain fog in patients who have had COVID-19 [6]. In this regard, cognitive disorders were included in the World Health Organization (WHO) definition of post-COVID syndrome (PCS) as one of the three most frequent symptoms [7]. Several studies have characterized the cognitive deficits present in PCS, emphasizing the impairment of attention and processing speed, which is the most frequent cognitive domain involved followed by episodic memory [8, 9]. Although these deficits are generally of low to moderate severity, their impact on daily-living activities and work capacity has important socioeconomic consequences [10, 11]. Recent studies have shown that cognitive disorders are associated with structural and functional brain changes in multimodal neuroimaging [12]. However, PCS is also characterized by other symptoms, including fatigue (which also has a cognitive dimension) and neuropsychiatric symptoms, such as depression and anxiety [13, 14]. The relationships among subjective cognitive complaints (known as brain fog) and objective cognitive function, fatigue and neuropsychiatric symptom severity are still unclear [15, 16]. Further knowledge about the factors associated with brain fog is necessary to further understand the mechanisms of this important and disabling symptom. In this study, we aimed to describe the characteristics of brain fog and to evaluate the relationships among brain fog and cognitive function, fatigue, depression, sleep quality, and anxiety. We evaluated the correlations between subjective cognition and several validated scales and tests for fatigue, cognitive function and neuropsychiatric symptoms. In addition, we trained several regression machine-learning models to evaluate the existence of linear and/or non-linear relationships between subjective cognitive complaints and cognitive and neuropsychiatric scales. Finally, we conducted a mediation analysis to explore the mutual influences of these variables.

METHODS

Participants and study design

We conducted a cross-sectional study including 170 patients reporting cognitive complaints in the context of PCS. The patients met the WHO criteria for PCS [7]. The following inclusion criteria were considered: (i) diagnosis of SARS-CoV-2 infection confirmed by reverse transcription polymerase chain reaction and (ii) diagnosis of PCS according to the WHO criteria (symptoms lasting 2 months and an interval of at least 3 months since the acute infection with no other potential causes). Exclusion criteria were as follows: (i) any cognitive complaint before COVID-19; (ii) history of neurological or psychiatric disorders potentially associated with PCS symptoms; (iii) history of abuse of alcohol or other drugs; (iv) uncontrolled medical conditions associated with cognitive dysfunction at the moment of the assessment; and (v) sensory disorders potentially impacting cognitive assessments. The mean age of the sample was 49.37 ± 10.96 years, and 73.10% were women. The mean time since acute COVID-19 was 14.50 ± 6.91 months. The patients' clinical and demographic characteristics are shown in Table 1.

Assessment of brain fog

We used the FLEI questionnaire to assess brain fog. FLEI is a questionnaire designed to assess subjective cognitive complaints [17]. The test is self-administered by the patient, who must respond to 35 statements using a five-point rating scale (never; rarely; sometimes; often; very often). The answer "never" receives no points, "rarely" one point, "sometimes" two points, "often" three points and "very often" four points. Questions are focused on difficulties in everyday situations in the last 6 months, examining three cognitive areas: attention (10 questions, 0–40 points), memory (10 questions, 0–40 points), and executive functioning (10 questions, 0–40 points). There are also five control questions to check the response tendency. Besides the three cognitive domains, the main score "mental ability" is calculated as the sum of the three cognitive domains (0–120 points). Higher scores indicate low subjective cognitive ability, while lower raw scores indicate high subjective ability. The questionnaire was administered using the Vienna Test System (Schuhfried) [18].

Clinical protocol

The neuropsychological protocol included the following tests: Digit Span Forward and Backward (to examine attention and verbal working memory), the Corsi block-tapping test (attention and visual working memory), the Symbol Digit Modalities Test (SDMT; divided attention, information processing speed, and memory), the Boston Naming Test (language and visual naming ability), the Judgment Line Orientation test (visuospatial abilities), Rey-Osterrieth Complex Figure (ROCF; copy and recall at 3 and 30 min, and recognition [visuospatial constructional ability, visual perception and visual memory]), the Free and Cued Selective Reminding Test (FCSRT; verbal learning and memory), verbal fluency (animals and words beginning with "p", "m", and "r" in 1 min for each one; language, semantic memory and executive function), the Stroop Color-Word Interference Test (part A: reading words; part B: naming colors;

TABLE 1 Sample description and associations of the main clinical and demographic factors with the FLEI scale.

	Sample description	Associations with FLEI scale			
	N = 170	FLEI–mental ability	FLEI–attention	FLEI–memory	FLEI–executive function
Age, years	49.37 ± 10.95 years	0.032 (0.683)	−0.095 (0.218)	0.075 (0.333)	0.104 (0.179)
Sex: women	125 (73.09%)	−1.865 (0.064)	−1.813 (0.072)	−2.948 **(0.004)**	−0.674 (0.502)
Years of education	14.87 ± 3.59	0.018 (0.818)	0.036 (0.645)	−0.010 (0.895)	0.021 (0.786)
Arterial hypertension	39 (22.94%)	−0.194 (0.846)	0.673 (0.502)	−0.543 (0.588)	−0.650 (0.517)
Diabetes mellitus	20 (11.76%)	0.021 (0.983)	0.212 (0.832)	−0.015 (0.988)	−0.125 (0.901)
Dyslipidemia	47 (27.64%)	1.014 (0.312)	1.577 (0.117)	0.255 (0.799)	0.928 (0.355)
Tobacco smoking	26 (15.29%)	−0.093 (0.926)	−0.328 (0.743)	0.716 (0.475)	−0.527 (0.599)
Months from symptom onset to assessment	14.50 ± 6.91	0.037 (0.631)	0.030 (0.698)	0.037 (0.633)	0.036 (0.642)
Olfactory or gustatory symptoms during the acute infection	113 (66.40%)	1.758 (0.081)	1.559 (0.121)	1.999 **(0.047)**	1.377 (0.170)
Headache during the acute infection	135 (78.41%)	−2.067 **(0.040)**	−2.326 **(0.021)**	−1.952 (0.058)	−1.171 (0.243)
Hospitalization	45 (26.47%)	−0.595 (0.401)	−0.680 (0.497)	−0.586 (0.559)	−1.023 (0.308)
Intensive care unit admission	12 (7.05%)	−2.024 **(0.045)**	−1.523 (0.130)	−1.469 (0.144)	−2.52 **(0.013)**
Ventilatory assistance	15 (8.82%)	−1.600 (0.112)	−1.204 (0.230)	−1.116 (0.266)	−2.039 **(0.044)**

Note: Two-sample *t*-test or Pearson's correlation coefficients (rho) are shown to evaluate the association between FLEI scores and the qualitative (e.g., arterial hypertension) or quantitative variables (e.g., age), respectively. *p* values are shown in parentheses. Statistically significance is shown by *p* values in bold.

part C: interference; selective attention, inhibition, and information processing speed), and the Visual Object and Space Perception Battery (VOSP; visuospatial and visuoperceptual abilities). Fatigue was evaluated using the Modified Fatigue Impact Scale (MFIS) and sleep with the Pittsburgh Sleep Quality Index (PSQI) [19, 20]. Depression and anxiety were assessed using the Beck Depression Inventory-II (BDI-II) and the State–Trait Anxiety Inventory (STAI), respectively [21, 22]. Patients were examined during two sessions of approximately 75 min, trying to avoid fatigue. Medication used at the time of assessment was also recorded. Further details of the assessment protocol are specified elsewhere [8].

Data analysis

Descriptive data are shown as frequency (percentage) and mean ± standard deviation. Normal distribution was checked using the Kolmogorov–Smirnov test. Chi-squared (χ^2) and two-sample *t*-tests were used to compare variables, when appropriate. Pearson's correlation coefficient was used to calculate correlations between quantitative variables. Partial correlations between the FLEI scale and cognitive and neuropsychiatric scales were also estimated, adding age and years of education as covariates. A p value <0.05 was taken to indicate statistical significance. We also used an Euler diagram to illustrate overlapping among subjective cognitive complaints, fatigue, depression, anxiety and sleep quality. We categorized patients according to the previously reported cutoffs for each scale: MFIS score ≥38 for fatigue, State Trait Anxiety Inventory (state subscale) (STAI-S) score ≥ 40 for anxiety, BDI-II score ≥19 for depression, PSQI score >5 for poor sleep quality and FLEI score >46 for subjective cognitive complaints [18–22].

Machine-learning regression algorithms

Several algorithms were used to predict the FLEI score based on the results of clinical examination (neuropsychological testing, neuropsychiatric scales, and fatigue). The following regression algorithms were applied: linear and ridge regression, Lasso, ElasticNet and random forest regressor. Three artificial neural networks with different architectures were also tested. Data were randomly split into a training set (80% of the sample) and a test set (remaining 20% of the sample). While the training set was used to derive the models, the test set provides the "gold standard" by which to validate the models. The performance metrics provided here were obtained using the test set. Results were assessed with the R^2 metric over four different iterations of the original data. We compared the results obtained from different subsets of data: the full set of features and the 15 and 10 most informative features. The most informative features were selected through a backwards sequential feature selection using a random forest regressor to optimize the R^2 metric. This metric measures the amount of variance in the predictions explained and takes a maximum value of 1 (optimal prediction). Low or negative values indicate worse models.

Mediation analysis

Based on the previous results of both correlation analyses and machine-learning regression model analyses, we examined the possible mediating role of the variables depression, anxiety, fatigue and sleep quality in the relationship between cognitive function and cognitive complaints. Six mediation models were conducted to assess the effect of the independent variable cognitive function on the dependent variable mental ability (FLEI) through the mediators. First, the effect of each mediator was evaluated separately through four simple mediation models. Second, a fifth parallel model assessed the degree to which the four mediators simultaneously mediated the relationship between cognitive function and mental ability. Finally, a more complex serial mediation model was fitted to the depression–anxiety–fatigue–sleep quality chain. Cognitive function was included in all models as a latent variable consisting of the Stroop B, Digit Span Forward, SDMT, and semantic fluency tests. These cognitive tests were chosen because they were the most significantly associated in the correlation analysis with the FLEI scale. Likewise, the goodness-of-fit of the models explored was considered acceptable considering the following statistical indices: nonsignificant χ^2 values (>0.05), a χ^2/df ratio <5, root mean square error of approximation (RMSEA) <0.080, normalized root mean square residual (SRMR) <0.080, and, finally, the comparative fit index (CFI) >0.95 [23]. In addition, the standardized coefficients and the statistical significance of the total, direct and indirect (mediated) effects were analyzed using the multilevel mediation (MLM) estimator with 5000 bootstraps samples. Bias-corrected 95% confidence intervals were also provided. All mediation models were run using the *lavaan* package based on R version 4.2.0 [24, 25].

RESULTS

Characteristics and associations of cognitive complaints

The mean FLEI score was 24.86±7.97 for attention, 25.71±7.24 for memory, 18.36±8.85 for executive function, and 68.94±22.28 for mental ability (Figure 1). Women reported higher levels of memory issues (26.65±6.54 vs. 23.04±8.41; $p=0.004$). FLEI (mental ability) and executive function were associated with intensive care unit admission (FLEI–executive function score 24.75±8.35 vs. 18.14±8.75, $p=0.013$; FLEI–mental ability score 81.75±20.09 vs. 68.36±22.19, $p=0.045$) and respiratory assistance during the acute infection. Patients with headache during the acute phase also reported more cognitive issues, especially attention disorders (FLEI–attention 25.51±7.61 vs. 22.00±8.87, $p=0.021$). Fewer symptoms were detected in patients with acute olfactory or gustatory disturbances (FLEI–memory score 24.89±7.05 vs. 27.22±7.44, $p=0.047$). There were no associations between FLEI score and other clinical or demographic factors. The associations found between FLEI score and clinical and demographic factors are shown in Table 1. Regarding the use of medications at the time point of assessment, 50 patients (29.4%) were receiving any antidepressant (20 dual-action antidepressants, 19 selective serotonin reuptake inhibitors, 9 amitriptyline, 2 vortioxetine), 33 (19.4%) were receiving benzodiazepines, 17 (10%) were receiving antiepileptic drugs for neuropathic pain (e.g., gabapentine), 8 (4.7%) were receiving weak opioids, and 5 (2.9%) were receiving corticosteroids at low doses.

Correlations between cognitive and neuropsychiatric scores and FLEI

Controlling for age and years of education, FLEI score showed high correlations with MFIS score (total; $r=0.65$, $p<0.001$) and moderate correlations with Stroop 1 ($r=-0.326$, $p<0.001$), Stroop 2 ($r=-0.310$, $p<0.001$) and Stroop 3 ($r=-0.311$, $p<0.001$), STAI (trait; $r=0.43$, $p<0.001$), STAI (state; $r=0.30$, $p<0.001$), and BDI-II scores ($r=0.45$, $p<0.001$). Correlations were low with Digit Span Forward ($r=-0.25$, $p=0.001$), Corsi Forward (−0.158, $p=0.041$), SDMT ($r=-0.24$, $p=0.001$), semantic verbal fluency ($r=-0.24$, $p=0.001$), and PSQI scores ($r=0.25$, $p<0.001$). All correlations are shown in the Supplementary Material. The Euler diagram illustrating the overlaps among patients with significant cognitive complaints, fatigue, depression, anxiety and poor sleep quality is shown in Figure 2.

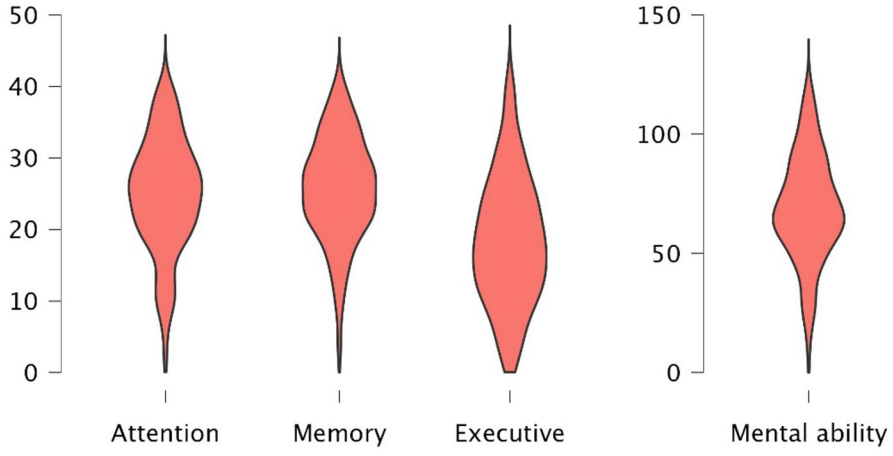

FIGURE 1 Violin plots for the FLEI domains (attention, memory and executive function) and total score (mental ability). Each violin depicts the kernel probability density of the data. The width of the area represents the proportion of patients showing each FLEI score in each domain.

Machine-learning regression model analysis

The best results were achieved by the random forest algorithm, reaching an R^2 value of 0.409 (Table 2). The best variables to predict the FLEI score were the following: Digit Span Backward, Corsi Backwards, SDMT, ROCF (copy accuracy and copy time), FCSRT total free recall, FCSRT total recall, FCSRT delayed total recall, ROCF (memory at 30 min), Stroop (part A), verbal fluency (M and R), VOSP (progressive silhouettes), MFIS (total score), and BDI-II. Regression models using age- and education-adjusted scaled-scores of neuropsychological tests are shown in the Supplementary Material.

Mediation analysis

Table 3 reports the direct, indirect (mediated) and total effects, as well as the overall statistical indices of the six mediation models tested between cognitive function and cognitive complaints through the four mediators. The statistical indices showed an acceptable goodness-of-fit with the data in the four simple models evaluated

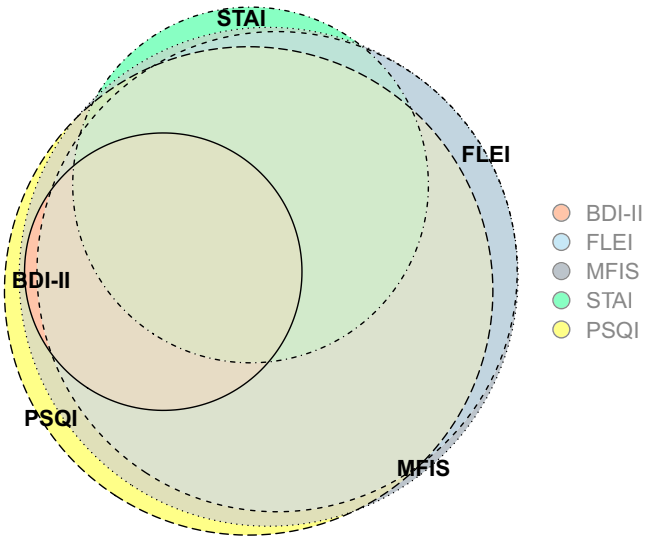

FIGURE 2 Euler diagram illustrating the relationships between cognitive complaints, fatigue, depression, anxiety and poor sleep quality. BDI-II, Beck Depression Inventory-II; MFIS, Modified Fatigue Impact Scale; PSQI, Pittsburgh Sleep Quality Index; STAI, State–Trait Anxiety Inventory.

(χ^2/df <5, $p>0.05$; RMSEA <0.08, SRMR <0.08, CFI >0.95). Thus, these simple models for each mediator showed an indirect effect of cognitive function on FLEI via depression ($\beta=-0.254$, $p<0.01$), anxiety ($\beta=-0.116$, $p<0.01$) and fatigue ($\beta=-0.340$, $p<0.001$), but not through sleep quality ($\beta=-0.059$, $p=0.133$). Age and years of education were also not statistically significant mediators ($\beta=-0.077$, $p=0.634$ and $\beta=0.581$, $p=0.227$, respectively). On the other hand, goodness-of-fit statistics indicated that the multiple parallel model fitted the data poorly ($\chi^2=257.9$, χ^2/df = 9.92, $p<0.001$; RMSEA = 0.235, SRMR = 0.169, CFI = 0.643), probably due to inclusion of a nonsignificant mediator such as sleep quality. As shown by the parameter estimates in Figure 3, there was a strong positive relationship ($\beta=1.76$, $p<0.001$) between fatigue and cognitive complaints (FLEI) perceived by the patients, and although to a lesser extent, there was also a positive relationship ($\beta=0.28$, $p<0.05$) between depression and cognitive complaints (FLEI). The results showed a significant direct effect ($\beta=-0.297$, $p<0.05$) between cognitive function and cognitive complaints (FLEI), but this relationship was partially mediated (total indirect effect, $\beta=-0.394$; $p<0.001$) through the mediators. However, only the indirect effect of the pathway via fatigue was significant ($p<0.001$) and accounted for most of the total indirect effect between cognitive functioning and FLEI (−0.317/−0.394). Finally, goodness-of-fit statistics indicated that the serial model between cognitive function and the FLEI pathway via the direction flow depression–anxiety–fatigue–sleep quality fitted the data correctly ($\chi^2=26.83$, χ^2/df = 1.58, $p=0.061$; RMSEA = 0.059, SRMR = 0.036, CFI = 0.978). All parameters, estimated as standardized regression weights, together with their level of significance, are shown in Figure 4, while the indirect effect paths are reported in Table 4. The results revealed a significant relationship identical to those described in the previous parallel model between FLEI score and both depression ($\beta=1.76$, $p<0.001$) and fatigue ($\beta=0.28$, $p<0.05$). In addition, depression had a significantly moderate relationship with anxiety ($\beta=0.584$, $p<0.001$) and fatigue ($\beta=0.37$, $p<0.001$). Consequently, the results show that the four mediators in this serial causal order fully mediate (total indirect effect, $\beta=-0.42$, $p<0.001$) the relationship between cognitive function and FLEI score, and this effect on the total was significantly greater than the direct effect ($\beta=-0.297$, $p<0.05$) alone. However, as shown in Table 4, the indirect path in which fatigue and depression are involved, both separately ($\beta=-0.069$, $p=0.099$ and $\beta=-0.142$, $p=0.070$, respectively) and especially in serial depression–fatigue

TABLE 2 R^2 scores of the regression models on predicting FLEI using the full set of features (all raw neuropsychological test scores) and the best 10 and 15 features.

Linear regression	Ridge regression	Lasso	ElasticNet	Random forest
All features ($n=37$)				
0.303	0.280	0.308	0.309	0.354
Best 15 features				
0.322	0.322	0.317	0.316	0.373
Best 10 features				
0.297	0.297	0.312	0.310	0.409

TABLE 3 Overall statistics for the six mediation models conducted between cognitive function and cognitive complaints through four mediators.

	Mediation models					
Parameters	**Depression**	**Anxiety**	**Fatigue**	**Sleep quality**	**Parallel**	**Serial**
Robust χ^2 (df)	13.53 (8)	14.89 (8)	12.9 (8)	12.88 (8)	257.9 (26)	26.83 (17)
p value	0.095	0.061	0.147	0.116	<0.001	0.061
CFI	0.978	0.970	0.988	0.977	0.643	0.978
RMSEA	0.065	0.072	0.056	0.062	0.235	0.059
SRMR	0.031	0.039	0.035	0.034	0.169	0.036
Direct effect (95% CI)	−0.412** (−0.71 to −0.12)	−0.557 ** (−0.88 to −0.23)	−0.326 * (−0.59 to −0.05)	−0.646 *** (−0.96 to −0.34)	−0.297 * (−0.58 to −0.02)	−0.297 * (−0.57 to −0.02)
Total indirect effect (95% CI)	−0.254 ** (−0.40 to −0.11)	−0.116 ** (−0.21 to −0.02)	−0.340 *** (−0.53 to −0.15)	−0.059 (−0.14 to −0.02)	−0.394 *** (−0.59 to −0.19)	−0.42 *** (−0.62 to −0.21)
Total effect (95% CI)	−0.67*** (−0.99 to −0.34)	−0.67 *** (−1.00 to −0.34)	−0.66 *** (−0.99 to −0.34)	−0.705 *** (−1.03 to −0.38)	−0.691 *** (−1.02 to −0.37)	−0.713 *** (−1.05 to −0.38)

Abbreviations: CI, confidence interval; RMSEA, root mean square error of approximation; SRMR, normalized root mean square residual.

*, **, ***: Significant at $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively.

($\beta = -0.161$, $p < 0.001$), explained most of this total indirect effect between cognitive function and FLEI score.

DISCUSSION

This study evaluated a large cohort of patients with PCS. They were assessed with a comprehensive neuropsychological battery, including a questionnaire on subjective perception and objective cognitive testing for the main cognitive domains. Our findings revealed that cognitive complaints were mainly focused on attention and episodic memory, while executive functions (planning) issues were less reported. It is well known that there may be significant discrepancies between subjective cognitive experiences and objective neuropsychological performance, as shown in other disorders [26, 27]. On the one hand, daily-life situations may be more complex and more demanding (and more likely to be influenced by external factors such as distractions or emotional factors) than neuropsychological examinations. On the other hand, cognitive complaints may be the final outcome of several processes, including cognitive functioning but also fatigue or neuropsychiatric symptoms. In addition, mood disorders could also distort subjective cognitive perception. For this reason, in our study, patients were also assessed for fatigue, depressive symptoms, anxiety, and sleep quality [28]. Interestingly, subjective cognition showed statistically significant correlations with several of these factors, especially with fatigue followed by depression and anxiety. Higher levels of fatigue, depression, and anxiety were associated with poorer subjective cognitive perception. Regarding cognitive testing, cognitive complaints were mainly correlated with the Stroop test, followed by SDMT, Digit Span Forward and semantic fluency. In this case, higher levels of cognitive complaints were correlated with lower cognitive performance. These results confirm that cognitive complaints were especially correlated with attention/processing speed, the most impaired cognitive domain in PCS [29].

Analysis of cognitive complaints according to the domains measured in the questionnaire led to interesting findings. Patients with more severe acute disease that required intensive care unit admission reported higher levels of cognitive dysfunction. This is consistent with more severe cognitive deficits in these patients and more severe neuroimaging changes [12].

We implemented several regression machine-learning algorithms to predict the severity of cognitive complaints using neuropsychological tests and other scales. Random forest, one of the most popular algorithms, obtained the best results, confirming that these variables (objective cognition, fatigue, and neuropsychiatric scales) are able to predict the presence of cognitive complaints with moderate accuracy. Furthermore, we complemented the analysis using mediation models. These models try to identify, explain, and quantify the underlying processes between an independent and dependent variable through one or more mediators. In this case, we examined the influence of several mediators (fatigue, depression, anxiety, sleep quality) in the relationship between the cause (cognitive dysfunction) and the effect (cognitive complaints). We observed that

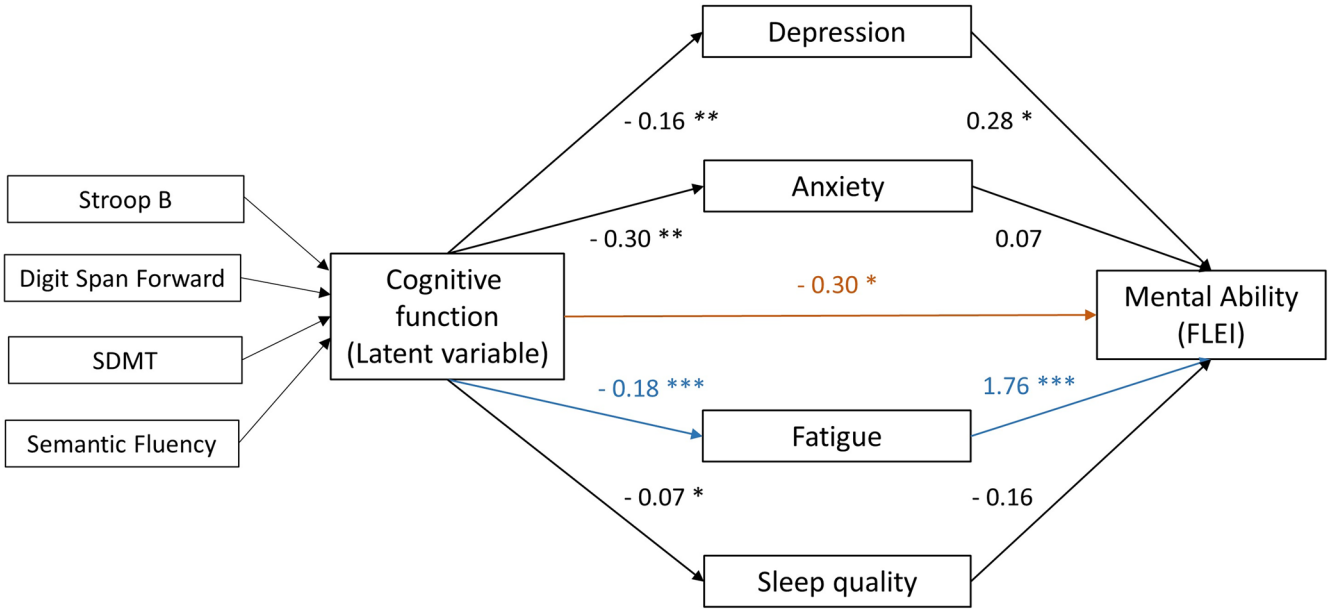

FIGURE 3 Parallel model tested. Numbers on arrows represent standardized regression weights. *, **, ***: Significant at $p < 0.05$; $p < 0.01$ and $p < 0.001$, respectively. Dotted lines indicate nonsignificant parameters. SDMT, Symbol Digit Modalities Test.

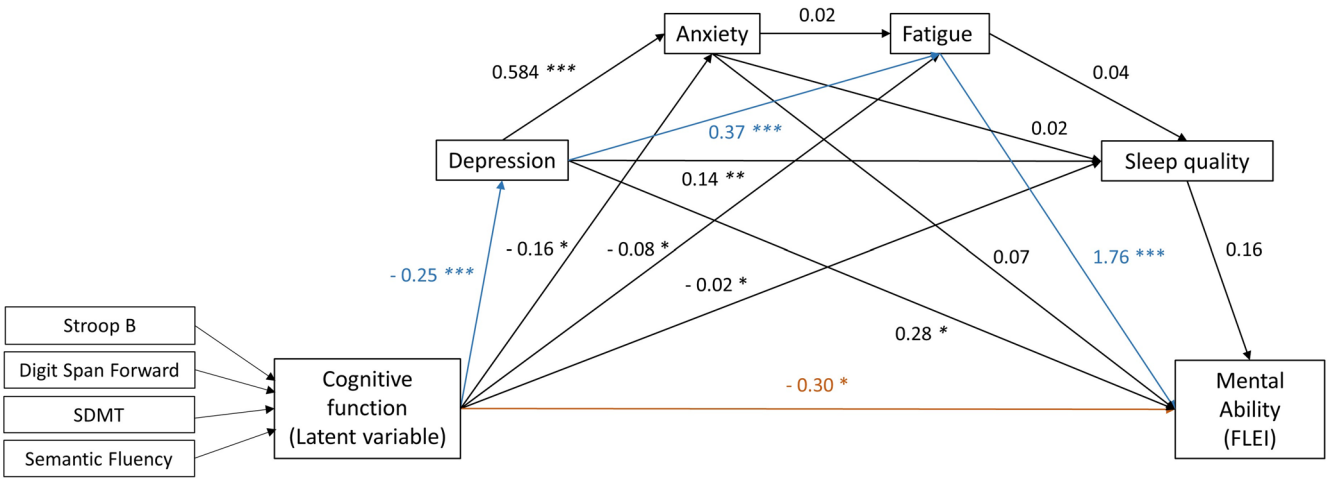

FIGURE 4 Serial model tested with depression–anxiety–fatigue–sleep direction flow. Numbers on arrows represent standardized regression weights. *, **, **: Significant at $p < 0.05$; $p < 0.01$ and $p < 0.001$, respectively. Dotted lines indicate nonsignificant parameters. SDMT, Symbol Digit Modalities Test.

fatigue mediated the effect between cognitive function and cognitive complaints. Conversely, anxiety, depression, and sleep quality did not have a statistically significant effect. However, when all the variables were included in the same model, the indirect effect was mainly explained by fatigue, while anxiety did not have a statistically significant effect, and the importance of depression was lower than fatigue. Intriguingly, in a more complex model, fatigue remained the main variable mediating the effect between objective and subjective cognition directly and throughout depression, which also had a role in mediating the effect. The magnitude of the effect was greater in the route cognition–depression–fatigue–FLEI than in cognition–fatigue–FLEI. This confirms that depression also plays a prominent role, especially due to the relationship with fatigue, but not an isolated role. This is consistent with previous reports in other disorders, in which fatigue and depression are interconnected and might share some pathophysiological mechanisms [30, 31]. In this study, we focused on central fatigue, a multidimensional concept that arises from the dissociation of inputs (e.g., motivation) and the perception of effort. Depression, which is associated with a loss of motivation, may also cause a subjective sense of fatigue [32, 33].

These findings have important practical implications. According to our findings, "brain fog" may be interpreted as the result of two main processes: objective cognitive impairment and fatigue. Regarding the other factors, only depression showed an influence mediated

TABLE 4 Indirect effects of cognitive function on FLEI for the different paths followed in the serial mediation model with depression–anxiety–fatigue–sleep direction flow.

ID	Path	Estimate	*p* value
1	Cognitive function–depression–anxiety–fatigue–sleep quality–FLEI	−0.000	0.756
2	Cognitive function–depression–anxiety–fatigue–FLEI	−0.004	0.719
3	Cognitive function–depression–anxiety–FLEI	−0.010	0.552
4	Cognitive function–depression–fatigue–sleep quality–FLEI	−0.001	0.658
5	Cognitive function–depression–fatigue–FLEI	−0.161	<0.001
6	Cognitive function–depression–sleep quality–FLEI	−0.005	0.568
7	Cognitive function–depression–FLEI	−0.069	0.099
8	Cognitive function–anxiety–fatigue–sleep quality–FLEI	−0.000	0.760
9	Cognitive function–anxiety–fatigue–FLEI	−0.004	0.721
10	Cognitive function–anxiety–sleep quality–FLEI	−0.001	0.668
11	Cognitive function–anxiety–FLEI	−0.011	0.552
12	Cognitive function–fatigue–sleep quality–FLEI	−0.001	0.666
13	Cognitive function–fatigue–FLEI	−0.142	0.070
14	Cognitive function–sleep quality–FLEI	−0.003	0.667

by fatigue. This underscores the importance of comprehensive cognitive (especially attention and processing speed and episodic memory) and fatigue assessments in patients reporting subjective cognitive complaints. Thus, a report of brain fog in the context of a neuropsychological assessment within normal limits should suggest a greater role of cognitive fatigue and vice versa. In this regard, the combination of cognitive testing, fatigue and neuropsychiatric symptoms is necessary when evaluating patients reporting cognitive complaints. Cognitive testing should be focused on attention and processing speed tests (e.g., Stroop, SDMT), but other tests should also be necessary to evaluate the state of the other cognitive domains and for differential diagnosis [34]. Furthermore, mediation analysis suggests that future studies to alleviate brain fog in these patients should focus on the improvement of cognitive functioning and fatigue. In this regard, some clinical trials on cognitive training and/or non-invasive brain stimulation have shown positive results [35, 36]. Further studies examining the pathophysiology of depressive symptoms in PCS patients and the relationship between fatigue and depression are also necessary. Due to the weak effect of depressive symptoms, antidepressant therapies could not have a direct role in brain fog but might have an indirect role by modulating fatigue. Overall, the interplay among cognitive deficits, fatigue, and neuropsychiatric symptoms should be considered in the design of future clinical trials addressing brain fog and PCS. In addition, quantitative assessment of peripheral fatigue, the consideration of previous therapies during the acute and post-acute phase (e.g., corticosteroids), and immune dysregulation and endocrine system status (e.g., the hypothalamic–pituitary–adrenal axis) may be of interest in future studies to further understand the complexities of fatigue and cognitive function.

Our study has some limitations. First, fatigue was assessed using the MFIS. Although this scale is one of the most validated and comprehensive scales for fatigue rating across different disorders, some questions may show a certain overlap with the FLEI questionnaire. This could lead us to overestimate the influence of fatigue in brain fog. Similarly, clinical symptoms of fatigue and depression partially overlap, and differential diagnosis may be challenging. Second, we used the FLEI scale as a proxy for brain fog. We preferred this scale over others because it covers the main symptoms present in PCS. However, further studies using other scales would be necessary to confirm our findings. Third, we did not measure emotional distress, another psychological dimension relevant in patients with PCS [37]. Fourth, although our neuropsychological protocol was comprehensive and covered the main cognitive domains, a more complete examination of executive functions would be of interest. In this regard, the FLEI scale examines executive function issues in daily living, focusing on planning, but a specific test of planning abilities (e.g., tower tests) was not included in the protocol.

In conclusion, brain fog is mainly characterized by attention and episodic memory complaints. Cognitive tests associated with attention/processing speed and fatigue were the most important factors underlying brain fog. Fatigue was the main mediator between objective and subjective cognition. The effect of depression in brain fog was indirect and mediated through fatigue. Our findings emphasize the role of fatigue and cognitive functioning in the pathophysiology of brain fog and support the need to consider several factors in the diagnosis and treatment of patients with PCS reporting brain fog.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Ethics and Research Committee from HCSC (code 20/633-E).

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SUPPORTING INFORMATION

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

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