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Research article

Cognitive function and brain structure in COVID-19 survivors: The role of persistent symptoms

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ABSTRACT

Persistent COVID-19 symptoms post-acute state have been shown to have a significant negative impact on brain structure and function. In this study, we conducted magnetic resonance imaging (MRI) of the whole brain in 43 working-age adults (mean age: 44.79±10.80; range: 24–65 years) with a history of COVID-19 (731.17±312.41 days post-diagnosis), and also assessed their cognitive function (processing speed, attention, working memory, executive function, and recognition memory), mental health, and sleep quality. MRI data were processed using FSL to derive regional volumes for bilateral nucleus accumbens, caudate, pallidum, putamen, thalamus, amygdala, and hippocampus, and total grey matter, white matter, and cerebral spinal fluid volume, and analysed in relation to persistent COVID-19 symptom load, mental health, and sleep quality. Higher persistent COVID-19 symptom load was significantly associated with smaller putamen volume, lower response accuracy on working memory, executive function, and recognition memory tasks, as well as a longer time to complete the executive function task, and poorer mental health and sleep quality. Smaller putamen fully mediated the relationship between persistent COVID-19 symptom load and lower executive function. Further research is required to confirm whether reduced putamen volume and its association with poor executive function persists in COVID-19 survivors in the long term.

1. Introduction

Post-acute sequelae of COVID-19 (PASC) is a highly debilitating condition, broadly defined as symptoms that develop during an infection of coronavirus disease 2019 (COVID-19), are continuously experienced ≥12 weeks post-infection, and cannot be attributed to any other plausible condition [7,73,87]. PASC is often used interchangeably with long COVID, which is a term coined by COVID-19 survivors experiencing persistent COVID-19 symptoms (PCS) [2,62]. The prevalence of PASC varies amongst the literature and has been difficult to measure given its novelty and the large array of symptoms [44]. Approximately 10–20 % of COVID-19 survivors are believed to be experiencing PCS ([25,44]; World Health Organization [99], although the Office for National Statistics estimated that only 3.3 % of the UK population (2 million people) were self-reporting PCS [76] O'Mahoney and colleagues [75], in their meta-analysis of 194 studies (from 2019 to 2022) estimated that 45 % of COVID-19 survivors experienced at least one PCS [75]. Similarly, a meta-analysis of 31 studies examining the prevalence of PCS reported a regional prevalence of 51 % in Asia, 44 % in Europe, and 31 % in the USA, with a pooled prevalence of 43 % in COVID-19 survivors [21]. Regional variations in the prevalence of PCS may be explained by differences in the severity of acute illness, population age, and other co-morbidities [25].

Many PCS have been self-reported by survivors, and recently these have been categorised into four different phenotypes [36]: (i) chronic fatigue-like syndrome (fatigue, memory loss, headaches), (ii) respiratory syndrome (dyspnoea and cough), (iii) chronic pain syndrome (myalgia and arthralgia), and (iv) neurosensorial syndrome (change in taste and smell). Females are generally more likely to report PCS [6,91,93] with fatigue being the most commonly reported symptom [20,46,88]. PCS

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post-acute infection have also been associated with substantial impairment in multiple cognitive domains, including but not limited to attention [39,81], working memory [39,55,65], recognition memory [42], and executive function [55,65,81]. Taquet and colleagues [90] in their large retrospective study (n=856,588, aged 18–64 years) reported cognitive deficits, as captured by relevant codes of the International Statistical Classification of Diseases and Related Health Problems - 10th Revision (ICD-10) [98], in survivors at six months post-diagnosis and this remained true even at the two-year mark, relative to non-COVID controls. Similarly, Zhao et al. [102] observed a cognitive slowing in long-COVID patients, particularly in the processing speed domain, compared to patients who had previously had a diagnosis of COVID-19 but not developed long COVID, a finding which has also been echoed by Vakani et al. [95].

The prominent cognitive impairment observed across multiple domains in COVID-19 survivors experiencing PCS may be indicative of abnormalities in the brain's structure [58] and/or function [55,58]. A number of studies that assessed participants both with and without PASC point towards alterations in the brain, including lower whole-brain [30], total grey matter (GM) ([10,28,31,53]; but see [32]) and white matter (WM) volumes [40], along with lower volumes of the amygdala [82], hippocampus [82,105], putamen [10,27,47,82,92], pallidum [27,47], and thalamus [10,27,47]. There is also evidence of dynamic brain changes in long-COVID patients with neuropsychiatric symptoms [11] and larger cerebral spinal fluid (CSF) volume in association with a COVID-19 history [30,40].

The neural impact of COVID-19 and its association with cognitive function is an ongoing area of research. Many studies, utilising MRI or electroencephalogram (EEG), have found a correlation between brain abnormalities and reduced cognitive performance post a COVID-19 infection [3,12,13,19,28,47], although, only a handful focus solely on PASC. Andriuta and colleagues [3] found right-sided WM hypersensitivies, especially in the superior frontal region, to be associated with cognitive slowing and executive dysfunction in patients with post-acute COVID-19 cognitive complains. More recently, Díez-Cirarda and colleagues [28] found lower GM volume in people with long-COVID symptoms (n=86, mean age: 50.71 years), compared to controls (n=36, mean age: 49.33), and that lower GM volume in patients was correlated with poorer processing speed, attention, and working memory. Heine et al. [47] observed reduced left thalamus, putamen, and pallidum volumes in adults with long-COVID symptoms who also had moderate to severe fatigue, approximately seven months post COVID-19 diagnosis (n=50, mean age: 43.40 years), compared to healthy controls (n=47, mean age: 44.5), and also found lower thalamus volume to be significantly associated with poorer short-term memory in the long-COVID group.

The present study aimed to examine the association of any persistent COVID-19 symptoms (overall load as well as specific symptoms) in COVID-19 survivors, with total GM, WM, and CSF volumes as well subcortical brain volumes and cognitive function in a working-age, non-clinical population of COVID-19 survivors (none acutely unwell at the time of investigation). Furthermore, we examined the mediating role of brain structures (that associated with PCS in this sample) in the relationship of PCS with cognitive variables. We expected multifaceted cognitive impairment [55,81,95,102] and reduced GM volumes across the brain [10,47,82,105] in association with PCS, and expected the volumes of the brain areas associated with PCS to mediate the relationship between PCS and cognitive function [28,47].

2. Materials and methods

2.1. Participants and design

The study initially involved 50 adults recruited from the general population. All recruited participants were required to (i) be able to communicate in English and be in reasonably good health, (ii) have no potential magnetic resonance imaging (MRI) contraindications (e.g., metal in the body, claustrophobia, pregnancy), and (iii) have no past or current diagnosis of a brain injury and/or psychosis. The study recruitment was open to both individuals with and without a history of COVID-19. However, only seven people without a COVID-19 history volunteered which was insufficient to provide a meaningful non-COVID comparison group (thus not reported hereafter).

The final study sample consists of 43 adults (14 male, 29 female), aged between 24 and 65 years (mean age: 44.79±10.80), with a previous diagnosis of COVID-19 (65.1 % confirmed via polymerase chain reaction test; see Supplementary Table 1 for demographic characteristics), who underwent whole-brain MRI, followed by a cognitive assessment via a mobile application tool, and a psychometric test online, via Qualtrics, on a single occasion, on average, 731.17 ± 312.41 days post a COVID-19 diagnosis (range: 183–1160).

The study was approved by the College of Health, Medicine and Life Sciences Research Ethics Committee, Brunel University London (34033-A-Sep/2022–41521–1). All participants provided informed written consent and received £25 voucher for their time.

2.2. Measures and procedure

2.2.1. Sample characterisation and self-report measures

A Qualtrics survey, taking ~30 minutes to complete, was used to acquire data relating to the participant's COVID-19 diagnosis (date, acute and chronic symptoms, hospitalisation status, subjective cognitive impairment), in addition to demographic data (age, sex, ethnicity, education, occupation, existing mental and physical illnesses), as in our previous studies [94,95].

The Qualtrics survey also included two self-report measures assessing mental health and sleep quality. Mental health was assessed using the Depression, Anxiety and Stress Scale-21 (DASS-21) [56], a 21-item scale measuring depression, anxiety, and stress. Each DASS-21 item is rated by participants on a four-point Likert scale with higher scores indicating higher levels (severity) of symptoms. Internal consistency for all DASS-21 sub-scales (Depression: Cronbach's α=0.92; Anxiety: Cronbach's α=0.75; Stress: Cronbach's α=0.88) was acceptable-to-excellent in this sample. Quality of sleep was assessed using the Pittsburgh Sleep Quality Index (PSQI) [17], which is a 19-item, four-point Likert scale assessing subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Higher PSQI scores indicate poorer sleep quality. The PSQI had an acceptable internal consistency in this sample (global score, Cronbach's α=0.75).

Data relating to acute and chronic COVID-19 symptoms were acquired through a self-report scale (Supplementary Table 2) designed specifically for this study. The scale is broadly based upon symptoms that were mentioned on the UK's National Health Service (NHS) website [72]. The scale required the participant to rate four acute symptoms (temperature, dry cough, loss of taste/smell, and other), and 26 chronic symptoms (Supplementary Table 2) on a seven-point Likert scale (Not at all/not applicable to Very Severe). Total PCS load was calculated by tallying together the sum of individual symptom ratings (with each symptom rated 0–7 as already mentioned).

2.2.2. MRI: data acquisition and processing

The imaging data were acquired using a 3 Tesla (3 T) Magnetom TIM Trio whole-body MRI scanner (Siemens Medical Solutions, Erlangen, Germany), fitted with a 32-channel head coil. For each participant, high-resolution T_1-weighted images were acquired, with the following parameters: inversion time (TI) = 1100 ms, repetition time (TR) = 1830 ms, echo time (TE) = 3.03 ms, flip angle (FA) = 11°, field of view (FOV) = 256 ×256 x 160 mm^3, voxel size = 1 ×1×1 mm^3, and a total of 160 images per participant.

All pre-processing and analysis of the T_1-weighted images were performed using FSL [Functional Magnetic Resonance Imaging of the

Brain (FMRIB) Software Library, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/, version 6.0.3] [50,86,97]. Prior to the analysis, removal of non-brain areas was performed on all T_1-weighted images utilising the Brain Extraction Tool (BET) in FSL. This tool uses a set of locally adaptive model forces which adapt to fit the brain's surface [85]. Hereafter, grey matter (GM), white matter (WM), cerebral spinal fluid (CSF), and subcortical brain structures (bilateral accumbens, caudate, pallidum, putamen, thalamus, amygdala, hippocampus) were outlined using FMRIB's Integration Registration and Segmentation Tool (FIRST) [77]. FIRST is a model-based segmentation tool that utilises both shape and appearance models constructed from an atlas of manually segmented images from the Centre for Morphometric Analysis. These manual segmentations are parameterised as surface meshes from which a point distribution is modelled. Utilising the observed intensities from each individual's T_1-weighted image, FIRST finds the most probable shape by searching through linear combinations of shape variation modes, resulting in segmentation for each tissue and subcortical structure per participant. Finally, intracranial volume (ICV) was estimated through the summation of GM, WM, and CSF volumes for each participant. During each step, processed images were carefully inspected by one of the authors (RN) to ensure accuracy of results.

2.2.3. *Cognitive function*

Participants completed a cognitive function assessment via the MyCQ mobile application tool [71]. The MyCQ mobile application tool has been validated against the Cambridge Neuropsychological Automated Test Battery [9,29]. It assesses five domains: processing speed, attention, working memory, executive function, and recognition memory, through digital versions of commonly utilised neuropsychological tests, taking ~15 min to complete [71].

Processing speed was assessed using a Simple Reaction Time (RT) task, with response accuracy (RA; % correct), average RT (ms), and RT variability examined. For this task, participants were required to tap the circle button as quickly as possible when a red circle was shown on the screen.

Attention was assessed using a Choice Reaction Time task, with RA (% correct) and average RT (ms) examined. Participants had to tap either the triangle or circle button based on the shape that was presented to them on the screen.

Working memory was assessed using the 2-Back task, with RA (% correct) used to examine task performance. In this task, participants were asked to tap 'yes' or 'no' based on whether the picture presented to them on the screen matched the picture presented to them two screens back.

Executive function was assessed using the Trail-Making B task, with RA (%, correct moves) and total task completion time (ms) examined. Participants had to produce an alternating sequence consisting of 13 numbers and 12 letters by tapping a number and a letter in ascending and alphabetical order, respectively, (e.g., 1, A, 2, B).

Recognition memory was assessed using a Visual Recognition Memory task, with RA (% correct) used to examine task performance. Participants were presented with a set of 24 images and were instructed to memorise them. They were then presented with another set of 96 images (including the 24 images presented to them earlier), and were asked to select either 'yes' or 'no' based on whether they remembered seeing the image.

2.3. *Statistical analysis*

Normality checks were performed on total PCS load, MRI data, cognitive indices, DASS-21, and PSQI (global) scores using the Shapiro-Wilk test [63,84]. All of the MRI variables, total PCS load, and sleep quality data met the assumption for normality, but some cognitive indices [processing speed RA (%), RT; attention RA (%); working memory RA (%); executive function RA (%), mean completion time; recognition memory RA (%)] and the DASS-21 variables were non-normally distributed. Given the correlational nature of this study, no data transformation was applied to the non-normally distributed data and instead, non-parametric correlations (Spearman's *rho*) were conducted for the non-normally distributed data.

Pearson's (r) correlations were used to examine whether total PCS load and age correlated with brain volumetric data (see Supplementary Table 3 for intercorrelations between subcortical structures), followed by partial correlations controlling for age and ICV. Non-parametric Spearman's (*rho*) correlations were conducted to examine the relationship of total PCS load with cognitive function and then mental health and sleep quality measures (see Supplementary Table 4 for associations between variables), followed by non-parametric partial correlations controlling for age. Spearman's (*rho*) correlations were also conducted to explore the relationship between specific subcortical structures and individual PCS.

Finally, mediation analyses (co-varying for age and ICV) were performed using 'PROCESS' toolbox to examine whether the putamen volume (the only subcortical structure that was significantly associated with total PCS load) mediated the association of total PCS load (independent variable) with executive function (RA, completion time) and recognition memory (RA) (outcome variables) (see Fig. 1); these cognitive variables had significant correlations with both PCS load and putamen volume, and a significant correlation was also present between PCS load and putamen volume (see Section 3.2). Given the non-normal distribution of some outcome variables and multiple model testing, the p values and 95 % confidence intervals were estimated using 10,000 bootstraps, equivalent to $p \leq 0.01$ [51] (the same pattern of results was obtained when using 5000 bootstraps; Supplementary Table 5). The simple PROCESS mediation model centred the mean for all variables to 0, with all p values ± 1 *SD* from the mean. Mediating effects were tested following [104]) method: (1) X and M should be correlated, (2) M and Y should be correlated, and (3) the direct effect of X on Y should be attenuated when M is accounted for, and the confidence intervals for the indirect effect should not include zero. For the sake of completion, we also examined the mediating role of putamen in PCS association with poor sleep (since sleep correlated with both PCS and putamen volume; see Section 3.4), using the same model parameters as described for the cognitive variables.

Analyses were performed using the Statistical Package for Social Sciences (SPSS) software (for Windows, version 28; IBM, New York, USA) and the 'PROCESS' toolbox (v4.1) add-on for SPSS [45]. Alpha level for testing the significance of effects was maintained at $p \leq 0.05$, unless stated otherwise.

3. Results

3.1. *Sample characteristics*

The majority of the participants were White British, held a Bachelor's degree or above and were in some form of employment, with 51.2 % being in the healthcare profession (e.g., doctor, nurse, dentist). In subjective reports, their most common health problem related to lung function (39.5 %), and the most common mental health problem was depression (44.2 %), closely followed by anxiety (32.6 %), and insomnia (25.6 %) (Supplementary Table 1). All but two participants (95.3 %) had at least one dose of the COVID-19 vaccine (Supplementary Table 1). Further characteristics of the sample, including MRI volumes, cognitive performance, mental health and sleep are provided in Table 1.

The most prevalent persistent COVID-19 symptoms reported in the entire sample, were mild cognitive problems, muscle/body ache, and exhaustion (Fig. 2). Total PCS load (total sum of individual symptom ratings) correlated significantly with increasing age [$r(43)=0.32$, $p=0.04$], but not with the number of days since diagnosis, controlling for age [$r(40)=-0.10$, $p=0.55$].

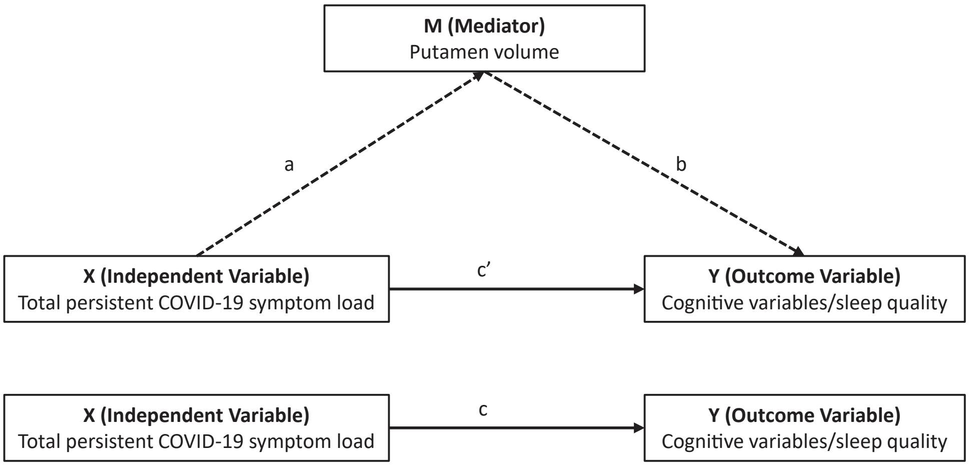
M (Mediator)
Putamen volume
a
b
X (Independent Variable)
Total persistent COVID-19 symptom load
c′
Y (Outcome Variable)
Cognitive variables/sleep quality
X (Independent Variable)
Total persistent COVID-19 symptom load
c
Y (Outcome Variable)
Cognitive variables/sleep quality

Fig. 1. The simple mediation model illustration.

Table 1
Characteristics of the sample (N = 43), classified by hospitalisation history.

		Entire Sample (N = 43)		**Hospitalised Participants (*n* = 7)**		**Non-hospitalised Participants (*n* = 36)**	
		Mean	***SD***	***Mean***	***SD***	***Mean***	***SD***
Age (years)		44.79	10.80	51.71	8.48	43.44	10.78
Brain Volumes (Total, mm^3)	Cerebral Spinal Fluid	254958.33	43424.58	261415.29	65021.50	253702.81	39091.03
	Grey Matter	607893.86	61178.09	561499.00	53461.39	616915.08	59052.03
	White Matter	587816.65	57884.76	557449.43	60563.40	593721.39	56317.77
	Intracranial Volume	1450668.84	133168.14	1380363.71	137781.56	1464339.28	129789.69
	Accumbens	943.84	192.95	888.00	262.08	954.69	179.32
	Caudate	7144.84	829.09	7072.29	613.32	7158.94	871.28
	Pallidum	3655.42	353.85	3638.86	482.89	3658.64	331.98
	Putamen	10061.23	920.91	9698.71	701.40	10131.72	949.72
	Thalamus	16652.21	1656.14	15578.86	2075.85	16860.92	1509.11
	Amygdala	3084.79	333.17	2958.00	278.64	3109.44	340.67
	Hippocampus	7880.00	860.85	7401.29	977.82	7973.08	818.91
Cognitive, Mental Health and Well-being Measures							
Processing Speed[a]	Response accuracy (%)	96.52	6.44	98.16	2.54	96.17	6.97
	RT (correct responses, ms)	405.80	112.57	431.14	140.10	400.42	107.68
	RT variability (SD of RT)	87.45	43.09	85.29	27.40	87.91	46.06
Attention[b]	Response accuracy (%)	93.21	12.41	85.12	20.40	94.97	9.50
	RT (correct responses, ms)	529.28	113.50	587.00	145.51	516.66	103.81
Working Memory[b]	Response accuracy (%)	88.83	12.15	87.43	10.50	89.13	12.61
Executive Function[a]	Response accuracy (%)	93.02	9.96	93.08	7.13	93.01	10.55
	Completion time (ms)	45878.60	48309.41	51214.86	29663.94	44746.67	51689.24
Recognition Memory[c]	Recognition accuracy (%)	90.35	8.12	93.61	3.58	89.68	8.66
Mental Health (DASS−21)	Depression	12.14	10.65	16.57	13.10	11.28	10.10
	Anxiety	6.60	7.06	8.57	6.71	6.22	7.15
	Stress	11.53	9.40	16.29	9.90	10.61	9.16
Sleep Quality (PSQI)	Global Score	9.47	4.34	10.43	4.20	9.28	4.41
Total Persistent COVID−19 Symptom Load		35.16	24.14	47.86	23.08	32.69	23.87

Note: This table is differentiated by hospitalisation status for information purposes only. Participants who required hospitalisation, relative to those who did not, generally were older, had lower subcortical brain volumes, poorer cognitive performance, poorer mental health and sleep quality, as well as higher total persistent COVID-19 symptom load.
Sample size reduced [a] by 3 (non-hospitalised), [b] by 4 (non-hospitalised), [c] by 2 (non-hospitalised).
Abbreviations: mm^3, cubic millimetre; ms, milliseconds; RT, Reaction Time; SD, Standard Deviation.
DASS-21: The Depression, Anxiety and Stress Scale-21. Higher scores indicate higher levels of depression, anxiety and stress.
PSQI: Pittsburgh Sleep Quality Index. Higher scores indicate poor sleep quality.

3.2. Associations between total persistent COVID-19 symptom load and brain volumes

Higher total PCS load was significantly associated with lower putamen volume (r=-0.44, p=0.003), and this association remained significant after controlling for age and ICV (r=-0.33, p=0.03) (Table 2). Of the 26 individual PCS that had been assessed, lack of appetite (rho=-0.50, p=0.001), muscle/body ache (rho=-0.48, p=0.001), and mild cognitive problems (rho=-0.44, p=0.003) correlated most strongly with putamen volume.

The total GM, total WM and total volumes of all subcortical structures generally had non-significant negative correlations with PCS load [r values −0.12 (for amygdala) to −0.44 (for putamen), and became negligible when controlling for age and ICV (Table 2).

3.3. Associations of persistent COVID-19 symptoms with cognitive function and the mediating role of putamen

Higher total PCS load, controlling for age, was associated with lower working memory RA (%) (rho=-0.33, p=0.05), lower executive function

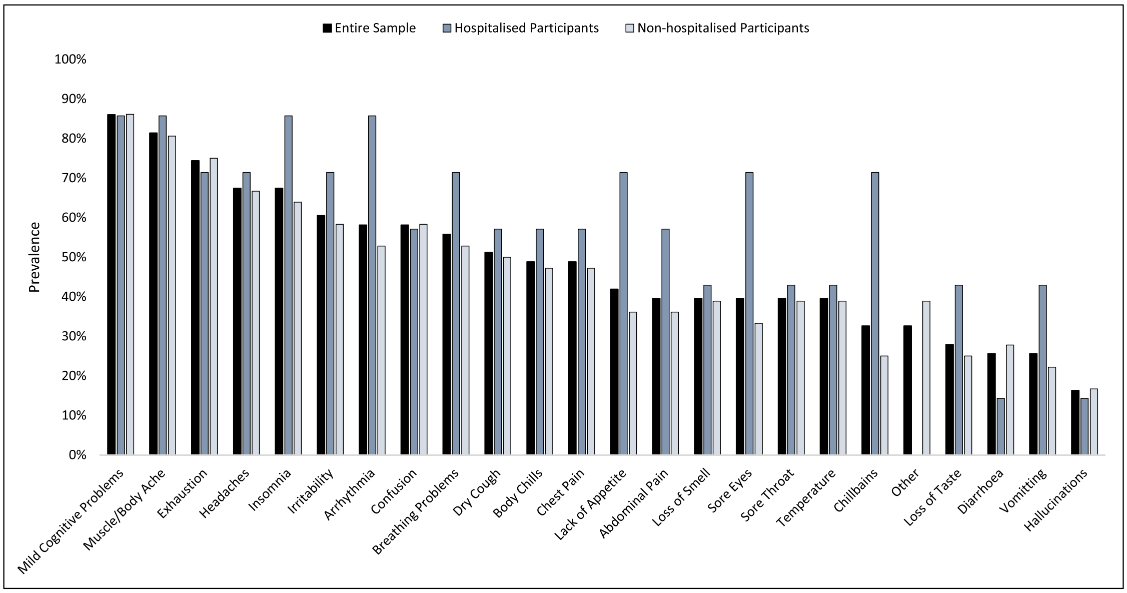

Fig. 2. Prevalence of self-reported chronic COVID-19 (persistent) symptoms, classified by hospitalisation history.

Table 2
Associations (Pearson's *r*) between brain volumes, age, and total persistent COVID-19 symptom load.

Brain Volumes (Total, mm^3)		**Age**		**Total persistent COVID-19 symptom load**		**Persistent COVID-19 symptom load controlling for age and ICV**	
		r (*df* = 43)	*p*	*r* (*df* = 43)	*p*	*r* (*df* = 39)	*p*
Cerebral Spinal Fluid		0.33	**0.03**	−0.03	0.83	−0.03	0.86
Grey Matter		−0.46	**0.002**	−0.24	0.12	0.13	0.42
White Matter		−0.21	0.18	−0.27	0.09	−0.11	0.48
Accumbens	Total	−0.36	**0.02**	−0.17	0.27	0.05	0.76
	Left	−0.43	**0.004**	−0.22	0.16	0.01	0.93
	Right	−0.20	0.19	−0.08	0.62	0.07	0.65
Caudate	Total	−0.24	0.12	−0.13	0.39	0.04	0.81
	Left	−0.21	0.19	−0.14	0.39	0.04	0.79
	Right	−0.26	0.09	−0.12	0.43	0.03	0.85
Pallidum	Total	0.18	0.25	−0.20	0.20	−0.21	0.19
	Left	0.11	0.48	−0.17	0.29	−0.11	0.50
	Right	0.23	0.15	−0.22	0.16	−0.25	0.11
Putamen	Total	−0.35	**0.02**	−0.44	**0.003**	−0.33	**0.03**
	Left	−0.26	0.10	−0.39	**0.01**	−0.28	0.08
	Right	−0.42	**0.01**	−0.47	**0.002**	−0.35	**0.02**
Thalamus	Total	−0.23	0.15	−0.24	0.12	−0.04	0.82
	Left	−0.24	0.12	−0.25	0.11	−0.05	0.76
	Right	−0.21	0.19	−0.23	0.15	−0.02	0.89
Amygdala	Total	0.15	0.33	−0.12	0.45	−0.10	0.52
	Left	0.08	0.60	−0.18	0.25	−0.16	0.32
	Right	0.17	0.29	−0.03	0.87	−0.02	0.93
Hippocampus	Total	−0.23	0.13	−0.19	0.23	0.03	0.88
	Left	−0.28	0.07	−0.13	0.39	0.09	0.59
	Right	−0.15	0.35	−0.21	0.17	−0.06	0.72

Note: Bold font indicates statistical significance ($p \leq 0.05$).
Abbreviations: ICV, Intracranial Volume; mm^3, cubic millimetre.

RA (%) (*rho*=-0.41, p=0.009), longer completion time (ms) in the executive function task (*rho*=0.39, p=0.01), and lower recognition memory RA (%) (*rho*=-0.51, p<0.001) (Table 3). Of these cognitive variables, lower RA (%) (*rho*=0.34, p=0.03) and longer completion time (ms) (*rho*=-0.44, p=0.005) in the executive function task and reduced RA (%) in the recognition memory (*rho*=0.38, p=0.01) were significantly correlated with smaller putamen volume (Table 4); and all of these remained significant when controlling for age [executive function RA (%) (*rho*=0.33, p=0.04); executive function completion time (*rho*=-0.37, p=0.02); recognition memory RA (%) (*rho*=0.42, p=0.007)].

The significant association of higher total PCS load with poorer executive function RA (%) was significantly mediated by putamen volume [Model Summary: R^2=0.22, $F_{(4,35)}$=3.78, p=0.012], with a significant indirect effect of total PCS load (i.e., mediated by the putamen volume) on executive function RA (%) (β=-0.06, SE=0.03, 95 % CI: −0.125, −0.002) and a non-significant direct effect (β=-0.07, SE=0.06, p=0.29, 95 % CI: −0.196, 0.059) (Fig. 3a). The mediation model with executive function completion time as an outcome variable yielded no significant direct or indirect effects. For recognition memory RA (%), the overall model was significant [Model Summary: R^2=0.26, $F_{(4,36)}$=5.35, p=0.002]; however, the confidence interval for the indirect effect of the total PCS load on recognition memory RA (%) contained zero, indicating that the mediating effect of putamen volume was insignificant (β=-0.02, SE=0.02, 95 % CI: −0.063, 0.020). Taken together, these findings suggest that putamen volume robustly mediated the association of total PCS load with executive function RA (%) but not recognition memory RA (%)

Table 3
Associations (Spearman's *rho*) of cognitive, mental health and sleep measures with age and total persistent COVID-19 symptom load.

		Age			**Total persistent COVID-19 symptom load**			**Persistent COVID-19 symptom load controlling for age**		
		rho	*df*	*p*	*rho*	*df*	*p*	*rho*	*df*	*p*
Cognitive Measures										
Processing Speed	Response accuracy (%)	0.06	40	0.71	−0.06	40	0.72	−0.08	37	0.64
	RT (correct responses, ms)	0.35	40	**0.03**	0.19	40	0.24	0.11	37	0.51
	RT variability (SD of RT)	−0.05	40	0.76	0.25	40	0.12	0.27	37	0.09
Attention	Response accuracy (%)	−0.37	39	**0.02**	−0.28	39	0.09	−0.19	36	0.24
	RT (correct responses, ms)	0.53	39	**<0.001**	0.33	39	**0.04**	0.22	36	0.19
Working Memory	Response accuracy (%)	−0.10	39	0.53	−0.34	39	**0.03**	−0.33	36	**0.05**
Executive Function	Response accuracy (%)	−0.07	40	0.65	−0.42	40	**0.008**	−0.41	37	**0.009**
	Completion time (ms)	0.31	40	**0.05**	0.45	40	**0.003**	0.39	37	**0.01**
Recognition Memory	Recognition accuracy (%)	0.02	41	0.92	−0.49	41	**0.001**	−0.51	38	**<0.001**
Mental Health and Sleep Quality Measures										
Mental Health (DASS−21)	Depression	0.05	43	0.75	0.38	43	**0.01**	0.38	40	**0.01**
	Anxiety	0.09	43	0.58	0.40	43	**0.009**	0.39	40	**0.01**
	Stress	0.08	43	0.59	0.32	43	**0.02**	0.34	40	**0.03**
Sleep Quality (PSQI)	Global Score	0.10	43	0.54	0.65	43	**<0.001**	0.65	40	**<0.001**

Note: Bold font indicates statistical significance ($p \leq 0.05$).
Abbreviations: DASS-21, The Depression, Anxiety and Stress Scale-21; ms, milliseconds; PSQI, Pittsburgh Sleep Quality Index; RT, Reaction Time; SD, Standard Deviation.

(Fig. 3b).

3.4. Persistent COVID-19 symptoms and mental health

Higher total PCS load was significantly associated with higher levels of depression ($rho=0.38$, $p=0.01$), anxiety ($rho=0.40$, $p=0.009$), stress ($rho=0.32$, $p=0.02$), and sleep quality ($rho=0.65$, $p<0.001$). All of these associations remained significant when co-varying for age (Table 3). Smaller putamen volume also correlated with poorer sleep quality ($rho=-0.37$, $p=0.01$) (Table 5), and this association too remained significant when co-varying for age ($rho=-0.37$, $p=0.02$). The mediation analysis revealed total PCS load to be a significant predictor of sleep quality [Model Summary: $R^2=0.45$, $F_{(4,38)}=8.20$, $p<0.001$], with a significant direct effect ($\beta=0.11$, SE=0.02, 95 % CI: 0.062, 0.160), but insignificant indirect effect with putamen volume as a mediator ($\beta=0.01$, SE=0.008, 95 % CI: −0.003, 0.030) (Fig. 4).

4. Discussion

4.1. Main findings

This study investigated the association between persistent COVID-19 symptoms and brain structural volumes, and examined how PCS load, brain volumes and their intercorrelations might relate to widely reported cognitive impairment in a working-age population. The findings revealed that higher total PCS load (especially lack of appetite, muscle/body ache, and mild cognitive problems) was associated, controlling for age, with lower putamen volume, as well as with poorer cognitive function (working memory, executive function, and recognition memory), mental health, and sleep quality. Lower putamen volume was also associated with poorer executive function and recognition memory performance, and sleep quality, and fully mediated the association of higher PCS load with poorer executive function.

Before discussing these findings in relation to previous research, it is important to consider the COVID-19-related characteristics of our sample. Approximately 88 % of the present sample reported at least one PCS, a rate that seems much higher than the predicted incidence rate for long COVID. This could be attributed to the fact that the vast majority of the present sample happened to be frontline medical workers, who in the UK have been severely impacted by long COVID [14]. For example, in a UK-based study, approximately 76 % of medical doctors were experiencing one or more long COVID complications [14]. The British Medical Association also found that 60 % of frontline medical workers were impacted in their day-to-day lives due to long COVID, and 18 % were no longer able to work [14,16]. Based upon this recent evidence and the occupation of our participants (Supplementary Table 1), the high incidence rate of PCS in this sample is not a deviation from the norm. On the other hand, it could also be argued that PCS observed in this particular sample are attributed to post-exertional malaise, in which symptoms worsen post any physically and mentally demanding activity [41], such as that experienced by healthcare workers in their highly demanding role.

The most frequently self-reported PCS in the present sample was mild cognitive problems (86 %), often referred to as 'brain fog'. With an incidence rate of >50 %, this has been one of the most prevalent long-COVID symptom in many previous studies [33,48,61,64,74]. Based on the symptom categorisation by Gentilotti et al. [36] that was explored earlier and on the observed symptom profile (Fig. 2), the current sample appears to have mainly either 'chronic fatigue-like syndrome' or 'chronic pain syndrome' [36]. The continuous experience of mild cognitive problems, or, in other words, 'chronic fatigue-like syndrome', post a COVID-19 diagnosis can have numerous psychosocial consequences [18], reflecting a relatively greater impact of the virus on the brain [25,74].

We found lower putamen volume to be associated with a higher PCS load, most strongly with muscle/body ache and mild cognitive problems. Both of these PCS have been associated with delayed clearance of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) viral particles from the upper respiratory tract in the acute stage of the infection [4]. Prolonged expression of viral particles can cause tissue damage and induce a proinflammatory response [4], which may impact the striatum, particularly the putamen [15]. Our finding of PCS and lower putamen volume association is consistent with the current literature indicating that a reduction in putamen volume occurs post a SARS-CoV-2 infection [10,27,47,82,92]. Putamen volume loss has also been associated with other viruses, such as Human Immunodeficiency Virus (HIV) [67,100]. Although HIV (*Lentivurs*) and SARS-CoV-2 (*β-coronavirus*) are not from the same viral family [49], they both can infiltrate the central nervous system (CNS) [8], [22,37,54,83,100,101], and increase proinflammatory cytokines [49]. Cytokines in general aid in controlling infections and diseases. However, an excess of cytokines can lead to tissue damage [24,68] as well as exacerbate the release of proinflammatory cytokines [68]. This overproduction of a protective measure, such as proinflammatory cytokines, towards viruses can lead to further damage, for example, cell death and tissue damage, including those of vital organs [1,24,34,68]. The response can occur directly as a

Table 4
Associations (Spearman's *rho*) between brain volumes and cognitive variables.

Brain Volumes (Total, mm^3)		**Processing Speed ($n = 40$)**						**Attention ($n = 39$)**				**Working Memory ($n = 39$)**		**Executive Function ($n = 40$)**				**Recognition Memory ($n = 41$)**	
		Response accuracy (%)		**RT (correct responses, ms)**		**RT variability (SD of RT)**		**Response accuracy (%)**		**RT (correct responses, ms)**		**Response accuracy (%)**		**Response accuracy (%)**		**Completion time (ms)**		**Recognition accuracy (%)**	
		rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Cerebral Spinal Fluid		−0.16	0.31	0.28	0.09	0.03	0.84	−0.08	0.64	−0.02	0.91	0.17	0.31	−0.13	0.42	0.05	0.75	0.23	0.16
Grey Matter		−0.06	0.73	−0.03	0.87	−0.22	0.18	0.31	**0.05**	−0.29	0.07	0.19	0.24	0.11	0.50	−0.31	0.06	0.18	0.25
White Matter		−0.02	0.93	−0.04	0.80	−0.30	0.06	0.19	0.26	−0.31	**0.05**	0.20	0.22	0.12	0.46	−0.20	0.21	0.32	**0.04**
Accumbens	Total	0.13	0.42	−0.20	0.22	−0.44	**0.005**	0.51	**0.001**	−0.50	**0.001**	0.12	0.46	0.07	0.67	−0.23	0.15	0.35	**0.02**
	Left	0.15	0.36	−0.19	0.25	−0.30	0.06	0.46	**0.003**	−0.52	**0.001**	0.17	0.30	0.11	0.49	−0.31	**0.05**	0.32	**0.04**
	Right	0.03	0.85	−0.18	0.28	−0.43	**0.005**	0.48	**0.002**	−0.32	**0.05**	0.01	0.97	−0.06	0.70	−0.03	0.88	0.29	0.07
Caudate	Total	0.14	0.40	−0.14	0.38	−0.18	0.26	0.12	0.46	−0.32	**0.05**	0.37	**0.02**	0.26	0.10	−0.39	**0.01**	0.13	0.41
	Left	0.15	0.35	−0.11	0.49	−0.19	0.24	0.12	0.49	−0.27	0.10	0.34	**0.04**	0.18	0.28	−0.33	**0.04**	0.16	0.33
	Right	0.13	0.41	−0.16	0.34	−0.11	0.49	0.09	0.57	−0.33	**0.04**	0.40	**0.01**	0.30	0.06	−0.40	**0.01**	0.07	0.67
Pallidum	Total	−0.04	0.81	−0.01	0.96	−0.31	**0.05**	−0.04	0.83	−0.35	**0.03**	0.17	0.31	0.32	**0.04**	−0.36	**0.02**	0.41	**0.009**
	Left	−0.01	0.96	−0.01	0.97	−0.26	0.10	−0.03	0.84	−0.32	**0.05**	0.24	0.13	0.26	0.10	−0.29	0.07	0.32	**0.04**
	Right	−0.09	0.60	−0.04	0.79	−0.30	0.06	−0.03	0.84	−0.33	**0.04**	0.06	0.72	0.29	0.07	−0.36	**0.03**	0.42	**0.007**
Putamen	Total	0.12	0.46	−0.23	0.16	−0.36	**0.02**	0.45	**0.004**	−0.52	**0.001**	0.003	0.98	0.34	**0.03**	−0.44	**0.005**	0.38	**0.01**
	Left	0.16	0.33	−0.25	0.12	−0.35	**0.03**	0.38	**0.02**	−0.42	**0.008**	−0.02	0.92	0.28	0.08	−0.31	**0.05**	0.37	**0.02**
	Right	0.09	0.58	−0.25	0.12	−0.35	**0.03**	0.46	**0.003**	−0.60	**<0.001**	0.02	0.92	0.30	0.06	−0.51	**0.001**	0.34	**0.03**
Thalamus	Total	−0.12	0.46	−0.05	0.75	−0.22	0.17	0.21	0.21	−0.39	**0.02**	0.20	0.23	0.02	0.90	−0.23	0.15	0.22	0.17
	Left	−0.15	0.35	−0.05	0.78	−0.23	0.15	0.25	0.13	−0.38	**0.02**	0.16	0.32	0.03	0.85	−0.23	0.15	0.22	0.17
	Right	−0.09	0.58	−0.03	0.86	−0.23	0.16	0.19	0.24	−0.38	**0.02**	0.20	0.22	0.01	0.96	−0.23	0.15	0.24	0.13
Amygdala	Total	−0.11	0.50	−0.12	0.48	−0.24	0.13	−0.08	0.63	−0.24	0.14	0.01	0.97	−0.07	0.67	−0.02	0.90	0.18	0.26
	Left	−0.18	0.28	−0.15	0.36	−0.22	0.18	−0.23	0.17	−0.19	0.26	−0.01	0.94	−0.07	0.69	−0.03	0.87	0.06	0.70
	Right	0.03	0.86	−0.02	0.91	−0.25	0.12	0.06	0.73	−0.25	0.13	0.01	0.96	0.01	0.95	−0.06	0.72	0.20	0.22
Hippocampus	Total	−0.03	0.84	−0.07	0.66	−0.21	0.20	0.37	**0.02**	−0.28	0.08	0.20	0.22	−0.16	0.33	−0.17	0.29	0.28	0.08
	Left	−0.13	0.44	−0.13	0.44	−0.17	0.29	0.33	**0.04**	−0.29	0.08	0.07	0.66	−0.25	0.11	−0.09	0.57	0.20	0.20
	Right	0.06	0.74	−0.02	0.90	−0.21	0.20	0.18	0.26	−0.22	0.19	0.26	0.11	−0.07	0.69	−0.19	0.25	0.30	**0.05**

Note: Bold font indicates statistical significance ($p \leq 0.05$).
Abbreviations: mm^3, cubic millimetre; ms, milliseconds; RT, Reaction Time; SD, Standard Deviation.

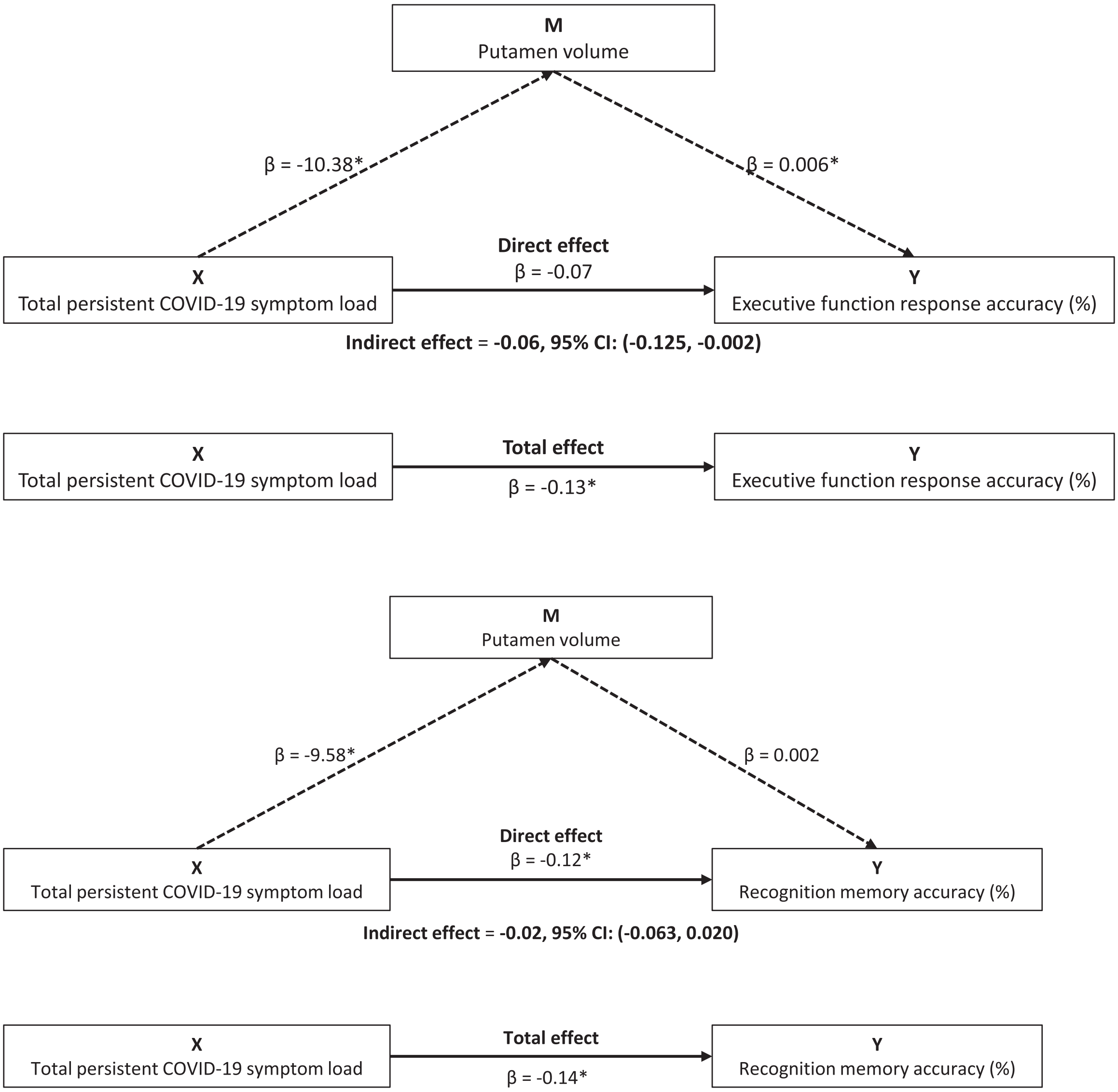
M
Putamen volume
β = -10.38*
β = 0.006*
Direct effect
β = -0.07
X
Total persistent COVID-19 symptom load
Y
Executive function response accuracy (%)
Indirect effect = -0.06, 95% CI: (-0.125, -0.002)
X
Total persistent COVID-19 symptom load
Total effect
β = -0.13*
Y
Executive function response accuracy (%)
M
Putamen volume
β = -9.58*
β = 0.002
Direct effect
β = -0.12*
X
Total persistent COVID-19 symptom load
Y
Recognition memory accuracy (%)
Indirect effect = -0.02, 95% CI: (-0.063, 0.020)
X
Total persistent COVID-19 symptom load
Total effect
β = -0.14*
Y
Recognition memory accuracy (%)

Fig. 3. a. The mediating role of putamen volume between total persistent COVID-19 symptom load and cognitive variables. b. The mediating role of putamen volume between total persistent COVID-19 symptom load and cognitive variables.

Table 5
Associations (Spearman's *rho*) of brain volumes with mental health measures.

Brain Volumes (Total, mm^3)	**Mental Health (DASS-21)**						**Sleep Quality (PSQI)**	
	Depression		**Anxiety**		**Stress**		**Global Score**	
	rho	*p*	*rho*	*p*	*rho*	*p*	*rho*	*p*
Cerebral Spinal Fluid	0.28	0.07	0.43	**0.004**	0.24	0.13	0.17	0.27
Grey Matter	0.03	0.87	0.16	0.30	−0.05	0.74	−0.15	0.34
White Matter	0.13	0.41	0.19	0.21	0.11	0.48	−0.15	0.34
Accumbens	0.02	0.91	0.02	0.88	−0.07	0.67	−0.34	**0.03**
Caudate	−0.04	0.80	−0.09	0.58	−0.10	0.55	−0.19	0.22
Pallidum	0.07	0.64	0.15	0.34	0.04	0.78	−0.18	0.25
Putamen	−0.14	0.39	0.05	0.76	−0.15	0.33	−0.37	**0.01**
Thalamus	0.18	0.26	0.18	0.26	0.06	0.72	−0.10	0.53
Amygdala	0.05	0.78	0.09	0.55	−0.10	0.51	−0.17	0.29
Hippocampus	0.13	0.40	0.15	0.34	0.05	0.75	−0.10	0.52

Note: Bold font indicates statistical significance ($p \leq 0.05$).
Abbreviations: DASS-21, The Depression, Anxiety and Stress Scale-21; mm^3, cubic millimetre; PSQI, Pittsburgh Sleep Quality Index.

result of the virus or indirectly due to the overdrive of the immune system [24]. A previous study has shown that an increase in proinflammatory cytokines can affect the striatum in COVID-19 survivors [15, 57].

As expected, higher PCS load was negatively associated with performance in the attention, working memory, executive function, and

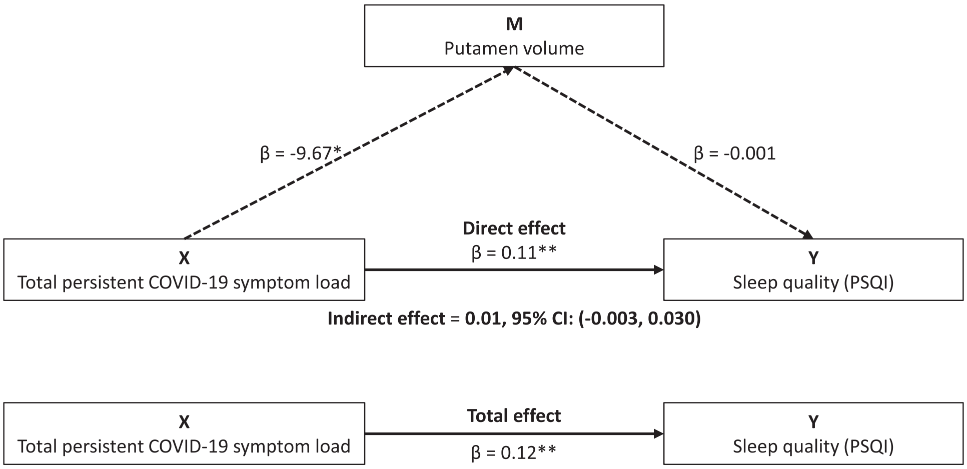

Fig. 4. The mediating role of putamen volume between total persistent COVID-19 symptom load and sleep quality.

recognition memory domains, replicating our findings in a different sample of working-age adults [94,95]. Importantly, the relationship between PCS and executive function was fully mediated by putamen volume. The putamen as part of the striatum [38], plays a vital role in learning, language, motor control, and other cognitive functions [35,38,52,59,80]. Moreover, previous functional MRI (fMRI) research supports the role of putamen in executive function [5,66,89]. In our previous studies, we observed a multi-domain cognitive impairment in individuals with PCS [94,95], and a reduction in putamen volume has been associated with disrupted global cognitive performance [26,59].

We did not find a significant association between PCS and any other brain structural volumes (except putamen), for example, hippocampus [82,105]. The majority of our sample was highly educated and, given the protective effect of education on brain health and overall cognitive function [70], may have shown a rather limited neural impact of PCS. However, it is also possible that some brain changes associated with COVID-19 or PCS may be expressed more strongly in the presence of other comorbidities or advancing age [30]; and the extent and spread of neural changes may further depend on the expressed long COVID phenotype [36]. Furthermore, some of the PCS related cognitive effects may appear in neuronal function while not being detectable in, or not associating with, volumetric changes in individual brain structures after a COVID-19 infection [81,103].

Lastly, this study replicated previously reported associations of long COVID with poor mental health and sleep [23,43,60,69,96]. Our previous work has shown that sleep quality, relative to mental health, was more impacted due to long COVID and PCS [94,95]. Similarly, in this study, PCS load was associated with both poorer mental health and sleep quality, but with a stronger impact on sleep quality. Notably, changes in sleep quality were associated with total PCS load, and not with any brain volumes. Pellitteri et al. [79] have suggested that poor sleep may be associated with underlying neuroinflammation that occurs due to COVID-19, yet this association weakens overtime. However, to gauge the trajectory and timeline of this association, a follow-up study would be required.

5. Limitations

The design of this study lacks a control (comparison) group. The original study design included a group of non-COVID participants; however, following the lifting of the pandemic-related restrictions in the UK, it became difficult to recruit a sufficient number of participants with no exposure to COVID-19 (only seven non-COVID people were assessed; thus, not included). Moreover, the findings from this study are predominantly correlational, therefore further research and replication would be required to confirm these findings. Finally, the sample was predominately female, preventing a meaningful investigation of possible sex differences in the neurobiological impacts of persistent COVID-19 symptoms [78].

6. Conclusion

The present study revealed that persistent COVID-19 symptoms may be associated with volume loss in the putamen. PCS was also associated with poor performance in attention, working memory, and executive function, as has been reported consistently in recent studies. Importantly, the relationship between higher PCS load and poorer executive function was found to be fully mediated by lower putamen volume, suggesting a reduction in putamen volume due to persistent symptoms, which then affects executive function. Further research is required to understand whether putamen volume reduction is present in follow-up assessments and continues to mediate the association of PCS with poor executive function, in particular, relative to a control (comparison) group with no history of COVID-19.

CRediT authorship contribution statement

Elena Antonova: Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis. **Veena Kumari:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Martina Vanova:** Writing – review & editing, Formal analysis. **Martina Ratto:** Resources, Methodology. **Krupa Vakani:** Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ray Norbury:** Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andrew Parton:** Writing – review & editing.

Data Availability

Data will be made available on request.

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Conflicts of interest

Martina Ratto was working for Beingwell Group, Sheffield, United Kingdom at the time of data collection for this study (now at I.S. Giancardi-Galilei-Aicardi Alassio). No conflicts of interest are reported by other authors.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2024.115283.

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