*Psychological Medicine*

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# Altered corticostriatal connectivity in long-COVID patients is associated with cognitive impairment

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## Original Article

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## Abstract

**Background.** The COVID-19 pandemic has had a significant impact on the health of millions of people worldwide, and many manifest new or persistent symptoms long after the initial onset of the infection. One of the leading symptoms of long-COVID is cognitive impairment, which includes memory loss, lack of concentration, and brain fog. Understanding the nature and underlying mechanisms of cognitive impairment in long-COVID is important for developing preventive and therapeutic interventions.

**Methods.** Our present study investigated functional connectivity (FC) changes in patients with long-COVID and their associations with cognitive impairment. Resting-state functional MRI data from 60 long-COVID patients and 52 age- and sex-matched healthy controls were analyzed using seed-based functional connectivity analysis.

**Results.** We found increased FC between the right caudate nucleus and both the left and right precentral gyri in long-COVID patients compared with healthy controls. In addition, elevated FC was observed between the right anterior globus pallidus and posterior cingulate cortex as well as the right temporal pole in long-COVID patients. Importantly, the magnitude of FC between the caudate and the left precentral gyrus showed a significant negative correlation with Montreal Cognitive Assessment (MoCA) scores and a negative correlation with Trail Making Test B performance in the patient group.

**Conclusion.** Patients with long-COVID present enhanced FC between the caudate and the left precentral gyrus. Furthermore, those FC alterations are related to the severity of cognitive impairment, particularly in the domain of executive functions.

## Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected more than 775 million people worldwide since its onset in December 2019. The virus causes coronavirus disease 2019 (COVID-19), which is characterized by fever, cough, dyspnea, diarrhea, and myalgia (da Rosa Mesquita et al., 2021). Although most individuals fully recover from the acute phase of SARS-CoV-2 infection, estimations assume that more than 400 million people are affected by lingering symptoms for months or even years (Al-Aly et al., 2024). Both severe COVID-19 survivors, who were hospitalized for treatment, and mild courses reported long-term effects, including fatigue, cognitive impairment, depression, dyspnea, pain, vegetative symptoms, and olfactory disturbances (Al-Aly et al., 2024; Ariza et al., 2022; Kubota, Kuroda, & Sone, 2023). These persistent symptoms are commonly referred to as long-COVID or post-COVID-19 conditions. Many of the symptoms associated with long-COVID are characteristic of post-acute infection syndromes, which are known to potentially affect nearly every organ system (Al-Aly et al., 2024). Long-COVID and post-COVID-19 conditions are defined by the German AWMF S1 guideline as the development of new symptoms after acute infection with COVID-19 with no other medical explanation (Koczulla et al., 2022). While long-COVID covers the range of symptoms occurring four weeks beyond the acute phase of COVID-19, in post-COVID-19 conditions, the symptoms must persist longer than three months after the initial onset of the infection (Koczulla et al., 2022).



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In contrast, the WHO defines long-COVID and post-COVID-19 conditions equally as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, lasting for at least two months. Individuals impacted by long-COVID or post-COVID-19 conditions have symptoms or complaints that significantly impair their daily functions and reduce their quality of life by negatively influencing their social and occupational lives. This study merely refers to the long-COVID condition, if the references cited give no explicit differentiation between long-COVID and post-COVID-19 conditions.

Cognitive impairment is one of the most frequently reported manifestations of long-COVID and can significantly impact an individual's occupational and functional abilities. A meta-analysis of 48 studies revealed that more than 20% of patients with post-COVID-19 conditions present cognitive dysfunction (Ceban et al., 2022). Consistent with these findings, a cross-sectional study revealed that of all COVID-19 survivors, 40% displayed cognitive impairment, with the majority of those individuals experiencing deficits within the executive function domain (Kubota et al., 2023).

Cognitive functions rely on several brain regions and their structural and functional connections. The potential neurobiological mechanism underlying cognitive impairments in individuals with long-COVID needs further investigation, as the specific brain regions affected by COVID-19 remain unclear. This study focused on alterations within the basal ganglia (BG), a group of subcortical nuclei, due to their crucial role in the development of various neurological disorders, particularly those involving cognitive deficits, and their extensive connections with other brain regions (Lanciego, Luquin, & Obeso, 2012; Peters, Dunlop, & Downar, 2016). The BG is relevant for controlling voluntary movements, decision-making, and executive functions (Lanciego et al., 2012; L. Liu et al., 2023). BG changes are associated with cognitive decline, especially executive deficits, in Alzheimer's disease and Huntington's disease (Finke, Bublak, Dose, Müller, & Schneider, 2006; L. Liu et al., 2023). Due to their positioning at the intersection of cognitive, limbic, and motor loops, the BG might also be related to cognitive impairments in patients with long-COVID, as there is evidence for structural (Besteher et al., 2022; Douaud et al., 2022; Hafiz et al., 2022; Heine et al., 2023), metabolic (Rudroff, 2024) and functional changes (Mohammadi & Ghaderi, 2024; Rudroff, 2024; Voruz et al., 2023).

Our study builds upon a foundation of consistent findings across multiple imaging modalities, including structural MRI, magnetic resonance spectroscopy, perfusion-weighted imaging, and functional MRI. Structural abnormalities such as volume reductions, enlargements, and hyperintensities within the BG have been documented in long-COVID patients (Mohammadi & Ghaderi, 2024). In a previous article, we reported structural changes within the BG in the form of increased gray matter volume, in neuropsychiatric long-COVID patients compared with healthy controls (Besteher et al., 2022). Consistent with these findings, there are volume expansions in the caudate region among long-COVID patients (Douaud et al., 2022) and greater gray matter volumes in the putamen and the globus pallidus (Hafiz et al., 2022). The structural and metabolic changes within the BG reported by Deuter et al. were linked to cognitive impairment, with the severity of these alterations correlating with the intensity of symptoms (Deuter et al., 2024). Helms et al. reported that 56% of long-COVID patients exhibit hyperintensities in the BG, indicating brain tissue damage and inflammation (Helms et al., 2020). A recent study revealed concentrated inflammation within the BG in patients suffering from cognitive deficits (Rudroff, 2024). Additionally, long-COVID patients present reduced cerebral blood flow in both the left and right caudate nuclei (Qin et al., 2021).

Furthermore, FC alterations in resting-state fMRI in the BG have been identified (Voruz et al., 2023). More precisely, the extent of synchronization of activity between different brain regions was enhanced, indicating hyperconnectivity between the left prefrontal cortex and bilateral caudate nucleus in severe patients following 6–9 months of SARS-CoV-2 infection (Voruz et al., 2023). As synchronization can reflect the integration of information across regions, these results may imply that communication between these regions is disrupted in patients with long-COVID.

Consistent with that, a systematic review presented increased connectivity between the temporal subregion of the left default mode network B and the bilateral caudate nucleus (Mohammadi & Ghaderi, 2024). Additionally, another study revealed reduced connectivity within the nigrostriatal and corticostriatal networks, which corresponds with cognitive deficits (Rudroff, 2024). We therefore hypothesize that patients with long-COVID present alterations in the resting-state FC of the BG with other subcortical or cortical regions. Furthermore, we assume that these FC changes are associated with the severity of cognitive impairment.

## Methods and materials

### *Participants*

We conducted a cross-sectional study, including a total of 112 participants. The groups included 60 long-COVID patients (LC) and 52 healthy control (HC) participants. To maintain a naturalistic approach in our study design, we included both men and women aged from 20 to 80, who were 8 weeks to 16 months post-acute COVID-19. Both groups were matched regarding age and sex, with no significant differences in the mean values. The mean age was 45.38 years (±13.33) in the LC group and 41.19 years (±11.17) in the HC group. The LC group consisted of 23 men and 37 women, and the HC group consisted of 24 men and 30 women. An overview of the demographic characteristics is shown in Table 1.

The LC patients were recruited from the post-COVID outpatient clinic, hosted by the Department of Internal Medicine IV (Infectiology) and from the Department of Neurology of University Hospital Jena. At both clinics, a positive polymerase chain reaction (PCR) test was applied to verify infection with SARS-CoV-2. The participants reported one or more of the leading neuropsychiatric symptoms of long-COVID, including fatigue, concentration issues, and memory difficulties. The timepoint and severity of COVID-19 infection were assessed according to the WHO, including mild disease (ambulatory cases, WHO scores of 1 to 3), moderate disease (hospitalized cases, score of 4, no oxygen therapy, and score of 5, oxygen by mask or nasal cannula), and critical disease (hospitalized cases with scores of 6 to 9, requiring intensive care and ventilation) (World Health, 2020). Seven of our patients were hospitalized, while three received oxygen therapy. All other patients were treated ambulatory.

Healthy control participants were recruited through press releases and social media. The healthy control group consisted of 26 COVID-19 survivors without long-COVID symptoms and 26 control participants without prior SARS-CoV-2 infection. In healthy COVID-19 survivors, prior infection was confirmed by a documented positive PCR result in their history and SARS-CoV-2 serology. In healthy controls without SARS-CoV-2 infection, the absence of antibodies against SARS-CoV-2 was confirmed by SARS-CoV-2 serology. The serological test was complemented by

**Table 1.** Demographic data of the LC and HC groups

| Measures | p-Value | Statistical test | LC, mean (SD) n = 60 | HC, mean (SD) n = 52 |
|---|---|---|---|---|
| Age (years) | 0.092 | t-test | 45.38 (13.33) | 41.19 (11.17) |
| Sex | 0.334 | Chi-squared | 23 M, 37F | 24 M, 30F |
| IQ (MWT-B) | 0.044 | t-test | 109.1 (16.74) | 115.5 (15.79) |
| Education in years | 0.189 | t-test | 11.18 (1.02) | 11.42 (0.92) |
| BMI (kg/m$^2$) | 0.104 | t-test | 26.07 (4.39) | 24.4 (4.01) |
| Severity of COVID–19 (WHO) | – | – | 2.3 (0.9) | n/a |
| Time since COVID–19 in months | – | – | 9.14 (4.43) | n/a |
| Handedness (right/left) | – | – | 58/2 | 50/2 |

LC, long-COVID group; HC, healthy control group; SD, standard deviation; F, female; M, male; IQ (MWT-B), premorbid IQ (measured by the German version of the multiple-choice vocabulary, called in the German Mehrfachwahl-Wortschatz-Intelligenz test); WHO, World Health Organization (provides guidelines for severity of symptoms and duration of COVID-19); and BMI, body mass index.

a Western blot to differentiate antibodies from vaccination and infection.

The cutoff criteria for inclusion in the long-COVID group were the presentation of at least one of three neuropsychiatric complaints (fatigue, lack of concentration, and depressed mood), an IQ higher than 80, and duration of symptomatology for at least four weeks beyond the acute phase of COVID-19.

The criteria used to exclude participants from the study were ineligibility for an MRI scan; previous diagnosis of significant neurological, psychiatric, or unmedicated internal medical conditions; and a current or past substance abuse disorder.

All the participants provided written informed consent to participate in the study. The study was approved by the local Ethics Committee of University Hospital Jena.

### Neuropsychological assessment

On the day of scanning, all participants received a psychiatric screening according to the MINI-Interview for DSM-5 (Sheehan et al., 1998) because of the absence of previous psychiatric disorders and current substance abuse. The diagnoses were confirmed by a board-certified psychiatrist (B.B.). All participants were screened for cognitive impairment with the Montreal Cognitive Assessment (MoCA) (Malek-Ahmadi et al., 2015) and Parts A and B of the Trail Making Test (TMT) (Partington & Leiter, 1949) to measure mental flexibility, attention, and motor performance (Ariza et al., 2022).

The MoCA is efficient in detecting mild cognitive impairment and is already well-established for detecting Alzheimer's disease (Nasreddine et al., 2005). A meta-analysis from 2022 revealed that the MoCA is also efficient in detecting cognitive impairment associated with COVID-19 (Crivelli et al., 2022). The MoCA relies on various cognitive functions, such as attention, concentration, executive function, memory, visuospatial skills, conceptual thinking, and orientation (Julayanont, Phillips, Chertkow, & Nasreddine, 2013; Nasreddine et al., 2005). The score ranges from 0 to 30, with a higher score indicating better cognitive performance and a score below 26 indicating cognitive impairment. The executive function domain contains a simplified TMT B version and cube drawing test, which measures the flexibility and ability to plan, organize, and execute tasks (Julayanont et al., 2013).

In TMT A, individuals are instructed to connect numbers in ascending order as quickly as possible. It assesses visual scanning and processing speed (Müller et al., 2014). The TMT B assesses executive functions, particularly cognitive flexibility, working memory, and set-shifting abilities. The test requires the individual to connect both numbers (1–13) and letters (A–L) in alternating order. The performance on TMT A and B is measured by the time it takes for the individual to complete the test correctly. A shorter completion time indicates better cognitive flexibility and executive functioning, whereas a longer completion time suggests potential deficits in these areas (Müller et al., 2014).

Additionally, symptoms of depression and fatigue were assessed with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery, Smeyatsky, de Ruiter, & Montgomery, 1985) and the Fatigue Assessment Scale (FAS) (Drent, Lower, & De Vries, 2012), respectively.

All participants completed the multiple-choice vocabulary intelligence test (MWT-B), a German language inventory similar to the National Adult Reading Test (Antretter, Dunkel, & Haring, 2013), to estimate the crystallized intelligence quotient (IQ) and confirm the inclusion criterion of an IQ higher than 80. The tests were administered by clinical psychologists (mean duration: approximately 60 minutes).

### MRI data acquisition

Magnetic resonance imaging was performed at the Werner Kaiser MRI Research Centre in Jena via a 3 Tesla Siemens MAGNETOM *Prisma fit* scanner with a 64-channel head coil. We acquired an axial structural image with a 3-dimensional magnetization prepared rapid gradient echo (MPRAGE) sequence (TR 2400 ms, TE 2.22 ms, α 9°, 208 contiguous sagittal slices, FoV 256 mm, voxel resolution 0.8 × 0.8 × 0.8 mm; acquisition time 6:38 minutes). For the resting-state fMRI (rsfMRI) data, we acquired an echo-planar imaging (EPI) sequence, 450 time points, a TE of 30 ms, a TR of 1580 ms, a flip angle of 90 degrees, a FOV of 21 cm × 21 cm, an in-plane isometric voxel size of 2 mm, 84 axial slices, and an acquisition time of 12 minutes.

### Anatomical and functional data preprocessing

Anatomical and functional data processing was performed using fMRIPrep 20.1.1 (Esteban et al., 2019) (RRID:SCR_016216), together with FMRIB's ICA-based Xnoisifier (FIX) (Griffanti et al., 2014; Salimi-Khorshidi et al., 2014) for noise removal in the functional MR data. The structural images were corrected for intensity nonuniformity and then skull-stripped and spatially normalized to MNI space (ICBM 152 Nonlinear Asymmetrical

template version 2009c) (Fonov, Evans, McKinstry, Almli, & Collins, 2009). Brain tissue segmentation of cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM) was also performed on the extracted T1W images.

For each resting-state fMRI scan per subject, the following preprocessing steps were performed. First, a reference volume and its skull-stripped version were generated. Head motion parameters for the blood oxygenation level-dependent (BOLD) reference (transformation matrices and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering was performed via mcflirt (FSL 5.0.9) (Jenkinson, Bannister, Brady, & Smith, 2002). With the realigned BOLD images, the noise-related signal was removed using FIX, a noise classifier pretrained on the baseline scan of 20 participants, and then applied to all participants. The denoised BOLD data were resampled into standard MNI152NLin2009cAsym space. Moreover, confounding time series of average global WM and CSF signals were obtained. The final preprocessed data were generated after bandpass filtering between 0.01 and 0.08 Hz to capture spontaneous neural fluctuations at rest after regressing the global WM and CSF signals.

The seed-based rsFC maps were calculated as Pearson correlation coefficients between the regions of interest defined in the basal ganglia atlas (Melbourne subcortex atlas, scale II) and each voxel at the whole-brain level (Tian, Margulies, Breakspear, & Zalesky, 2020). The following regions of interest (ROIs) were included for further analysis: aGP (anterior globus pallidus), pGP (posterior globus pallidus), aPUT (anterior putamen), pPUT (posterior putamen), aCAU (anterior caudate nucleus), and pCAU (posterior caudate nucleus) in each hemisphere (Figure 1). The resting-state functional connectivity (rsFC) maps were calculated and Fisher Z was transformed for the statistical analysis.

### *Statistical analysis*

Our analyses of behavioral and demographic data were performed via IBM SPSS Statistics (version 29), with $p \leq 0.05$ as the threshold for significance.

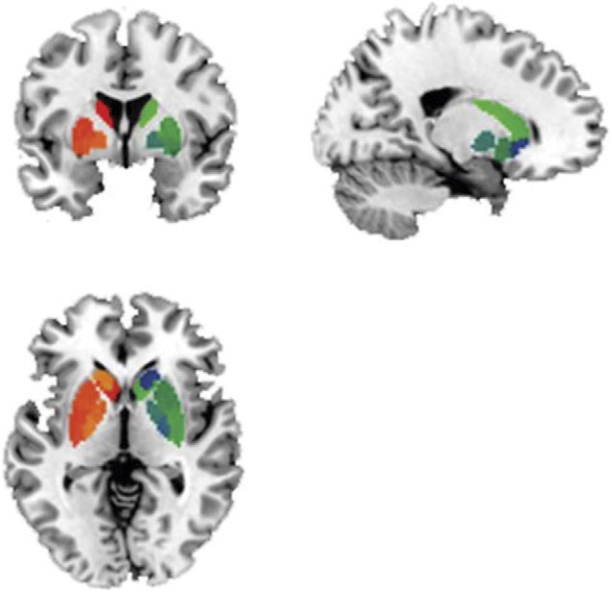

**Figure 1.** Obtained significant clusters of the basal ganglia.
*Note*: pCAU, neon green; aCAU, light green; pGB, light blue; and aGB, dark green (right hemisphere).

The distribution of sex was compared between the HC and LC groups by use of a chi-square test, whereas two-sample t-tests were used to compare other demographic characteristics and the clinical symptoms reported on the scanning day.

To investigate the factors associated with long-COVID related cognitive impairment, we performed an ANCOVA on the MoCA and TMT A and B scores to determine which variables contributed most to the variance in cognitive impairment in long-COVID patients: age, sex, years of education, initial severity of COVID-19, duration of the long-COVID period and severity of depression and fatigue. Variance inflation factor analysis was conducted to assess the risk of multicollinearity among the predictors in the ANCOVA model.

To investigate the FC changes between healthy controls and patients with long-COVID, we performed a two-sample t-test on each ROI in SPM12 (statistical parametric mapping software, SPM; Welcome Department of Imaging Neuroscience, United Kingdom), with age and sex used as control covariates. Correction for multiple comparisons was applied with the familywise error approach (FWE, cluster level correction at $p < 0.05$, with an initial threshold of $p < 0.005$ for each voxel). Consequently, the mean FC values were extracted from the derived significant clusters connected to the seeds of aGB and pCAU for each participant. Pearson correlation analysis was used to investigate the associations between the extracted FC values and the behavioral measurements. We added IQ as a control variable in this partial correlation analysis, as our LC and HC groups differed significantly with respect to IQ. These correlations were visually presented via R (version 3.6.3).

## Results

### *Clinical characteristics*

Healthy control and LC patients significantly differed with respect to cognitive status measured by MoCA ($p < 0.001$, $d = -0.77$), TMT A ($p < 0.001$, $d = 0.974$) and B ($p < 0.001$, $d = 0.635$), as well as depressive symptoms measured by MADRS ($p < 0.001$, $d = 1.021$) and fatigue symptoms measured with FAS ($p < 0.001$, $d = 1.462$). Descriptive statistics of the psychometric data are given in Table 2.

### *Factors associated with long-COVID cognitive impairment*

An ANCOVA was conducted to assess the influence of age, sex, education, the severity of acute COVID-19 infection, duration of long-COVID symptoms, depression, and fatigue severity on the MoCA and TMT A and B scores among patients. Age was found to have a significant negative effect on MoCA scores (estimate = −0.05, t = −2.39, p = 0.021, $\eta^2 = 0.13$), with older age being associated with lower MoCA scores. Sex also had a significant effect on the MoCA score (estimate = −1.70, t = −3.02, p = 0.004, $\eta^2 = 0.06$), with males having lower MoCA scores than females. Depression severity also significantly affected MoCA scores, with greater depression severity linked to lower MoCA scores (estimate = −0.09, t = −2.06, p = 0.045, $\eta^2 = 0.32$). Education, severity of acute COVID-19 infection, duration of long-COVID symptoms, and fatigue severity did not significantly affect MoCA scores (Table 3). The Variance Inflation Factor values for all the predictors were below the threshold of 10, indicating no significant multicollinearity.

For Trail Making Test A, none of the predictors were statistically significant. For TMT B, age showed a significant positive association with TMT-B performance (estimate = 0.64, p = 0.0079, $\eta^2 = 0.16$),

**Table 2.** Descriptive statistics of the psychometric data

| Psychometric tests | Statistical test | p-Value | Degrees of freedom (df) | Cohen's d | LC, mean (SD) n = 60 | HC, mean (SD) n = 52 |
|---|---|---|---|---|---|---|
| MoCA | t-test | <0.001 | 109 | −0.775, 95% CI [−1.160, −0.386] | 25.97 (2.32) | 27.70 (2.03) |
| TMT A | t-test | <0.001 | 106 | 0.974, 95% CI [0.572, 1.372] | 32.63 (11.5) | 23.67 (5.7) |
| TMT B | t-test | <0.001 | 107 | 0.635, 95% CI [0.248, 1.019] | 67.45 (23.6) | 54.05 (174) |
| MADRS | t-test | <0.001 | 84 | 1.021, 95% CI [0.533, 1.504] | 12.52 (8.3) | 4.69 (5.9) |
| FAS | t-test | <0.001 | 75 | 1.462, 95% CI [0.881, 2.035] | 33 (9.38) | 20 (6.76) |

*Note*: MoCA, Montreal cognitive assessment; TMT, trail making test; MADRS, Montgomery-Asberg depression rating scale; and FAS, fatigue assessment score.

**Table 3.** Predictors of MoCA scores among long-COVID patients

| Predictor | p-Value | Effect size ($\eta^2$) | Beta coefficient (β) | Standard error (SE) | t-Value |
|---|---|---|---|---|---|
| Age | 0.021 | 0.13 | −0.05 | 0.02 | −2.39 |
| Sex | 0.004 | 0.06 | −1.70 | 0.56 | −3.02 |
| Depression severity | 0.044 | 0.32 | −0.09 | 0.04 | −2.06 |
| Education in years | 0.200 | 0.04 | −0.36 | 0.28 | −1.30 |
| Severity of acute COVID–19 infection | 0.932 | 0 | 0.02 | 0.29 | −0.09 |
| Duration of long-COVID symptoms | 0.783 | 0 | −0.02 | 0.06 | −0.28 |
| Fatigue severity | 0.061 | 0.09 | −0.08 | 0.39 | −1.9 |

**Table 6.** MNI coordinates (mm) of the significant brain regions

| Seed region | | MNI coordinates (mm) x | y | z | k | p (FWE-corr) |
|---|---|---|---|---|---|---|
| Anterior globus pallidus (right hemisphere) | Posterior cingulate cortex | −4 | −60 | 22 | 3812 | <0.001 |
| | Temporal pole | 40 | 12 | −28 | 427 | 0.011 |
| Posterior caudate (right hemisphere) | Right precentral gyrus | 48 | −4 | 38 | 828 | <0.001 |
| | Left precentral gyrus | −60 | 2 | 22 | 923 | <0.001 |

**Table 7.** Pearson correlation of FC and the results of the psychometric tests

| Test | Seed | Connected region | p-Value | Pearson Corr. |
|---|---|---|---|---|
| MoCA | pCAU (right hemisphere) | Left precentral gyrus | 0.032 | −0.282 |
| TMT B | pCAU (right hemisphere) | Left precentral gyrus | 0.037 | 0.279 |

*Note*: MoCA, Montreal cognitive assessment; TMT, trail making test; and pCAU, posterior caudate.

indicating that older age is associated with longer completion times. However, TMT B completion time was not influenced by sex, the severity of acute COVID-19 infection, duration of long-COVID symptoms, years of education, depression, or fatigue severity (see more details in the Supplementary Material in Tables 4 and 5).

### *Basal ganglia connectivity changes and relationships with behaviorals data*

Functional connectivity analyses revealed increased connectivity between the right pCAU and both the left and right precentral gyri in the LC group compared with the HC group (*familywise error [fwe]* corrected, $p_{fwe} < 0.05$) (Figure 2). The MNI coordinates of the significant clusters are presented in Table 6. Furthermore, we detected increased FC between the right aGB with the posterior cingulate cortex and the temporal pole (Figure 3) in the LC group. No other significant differences in FC of the putamen were found in the LC group compared with the HC group.

Higher mean FC between the right pCAU and the left precentral gyrus was correlated with greater cognitive impairment, as measured by the MoCA score (r = −0.30, p = 0.03) and the time taken to complete TMT B (r = 0.29, p = 0.04) (Table 7). The findings were presented via a scatter plot, with a line of best fit and a 95% confidence interval (Figure 4, Figure 5).

There was no significant correlation between the TMT A score and the FC data for the pCAU. Moreover, there was no significant correlation between FC changes in aGB and MoCA or TMT A or B scores.

## Discussion

Our study investigated FC alterations seeded from the BG in patients with long-COVID and their associations with cognitive

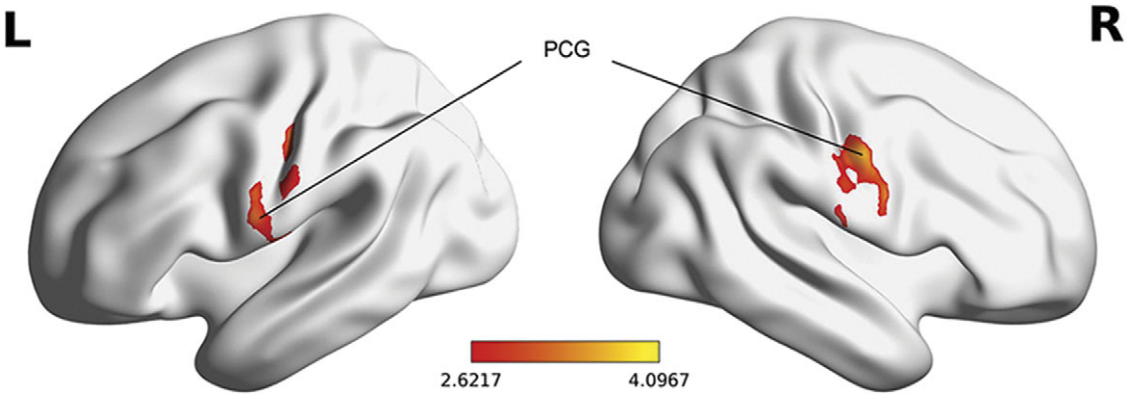


**Figure 2.** Increased FC between the posterior caudate and both the left and right precentral gyri in patients with long-COVID compared with controls. Right precentral gyrus (x = 48, y = −4, z = 38, k = 828, pFWEc < 0.001), left precentral gyrus (x = −60, y = 2, z = 22, k = 923, pFWEc < 0.001). The results of two-sample t-tests (p < 0.05, FWE-corrected) between long-COVID patients and healthy controls are presented as overlays.
*Note*: PCG, precentral gyrus.

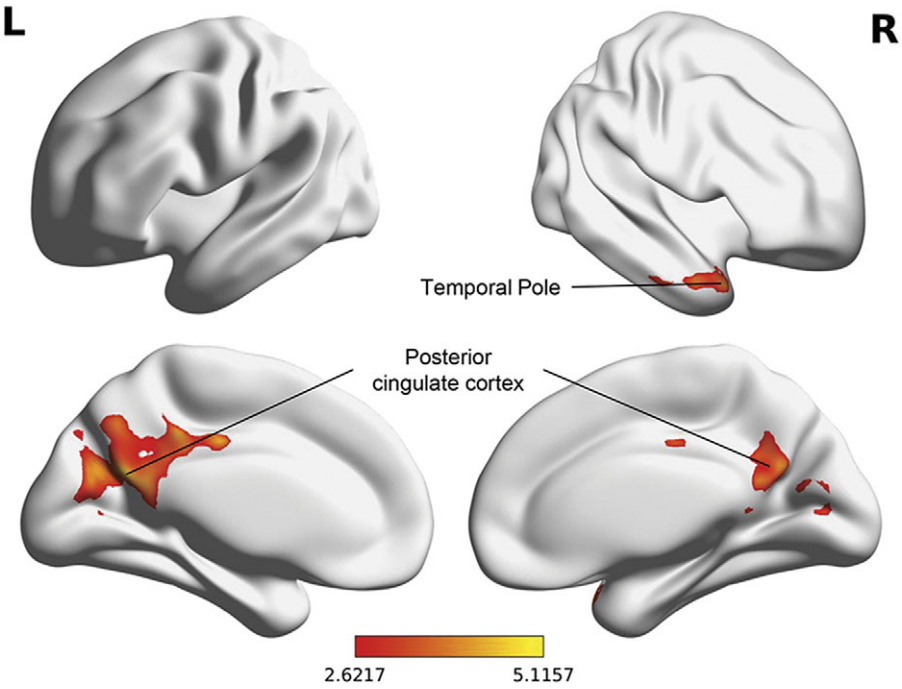


**Figure 3.** Increased FC between the posterior globus pallidus and temporal pole and posterior cingulate cortex in patients with long-COVID compared with controls. Posterior cingulate cortex (x = −4, y = −60, z = 22, k = 3812, pFWEc < 0.001), temporal cortex (x = 40, y = 12, z = −28, k = 427, pFWEc = 0.011). The results of two-sample t-tests (p < 0.05, FWE-corrected) between long-COVID patients and healthy controls are presented as overlays.

impairment. The LC group significantly differed from the healthy control group with respect to cognitive status measured by the MoCA and executive functions measured by TMT A and B. Furthermore, the severity of the cognitive impairment tested by the MoCA was correlated with age, sex, and severity of depressive symptoms, but it was not correlated with the severity of the initial infection or the duration of long-COVID symptoms. Moreover, we showed that patients have increased FC within the corticostriatal loop, specifically between the right dorsal caudate and the left and right precentral gyri (PCGs). As those higher FC values of the right dorsal caudate to the left precentral gyrus were related to lower general cognitive status (MoCA score) and worse executive functions (longer time taken for TMT B) in the LC group, functional changes within the corticostriatal loop seem to be associated with cognitive impairment in long-COVID.

Given that the correlation between the MoCA score and FC was found only in the left PCG, we hypothesize that this effect might be related to the hemispheric dominance of the LC group, as only two out of sixty individuals in the LC group were left-handed. Each PCG within a hemisphere is part of the primary motor cortex and is responsible for contralateral movement planning and execution. Well-characterized neurodegenerative disorders, such as Alzheimer's disease, also present pronounced clinical and brain physiological alterations linked to the dominant hemisphere in early stages (Lubben, Ensink, Coetzee, & Labrie, 2021). Moreover, patients with Huntington's disease also demonstrate increased attentional weighting to the left hemifield (Finke et al., 2006). In long-COVID patients, recent findings suggest that reductions in gray matter volume, particularly in the left hemisphere, are associated with deficits

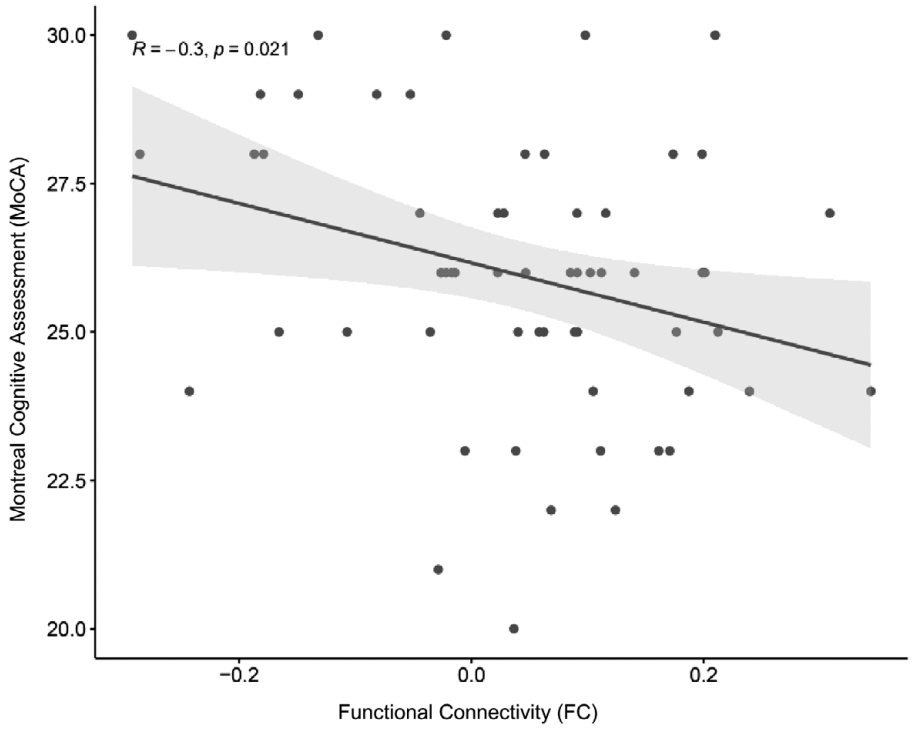


**Figure 4.** Scatter plot for MoCA scores and FC of the posterior caudate to the left precentral gyrus in long-COVID patients.

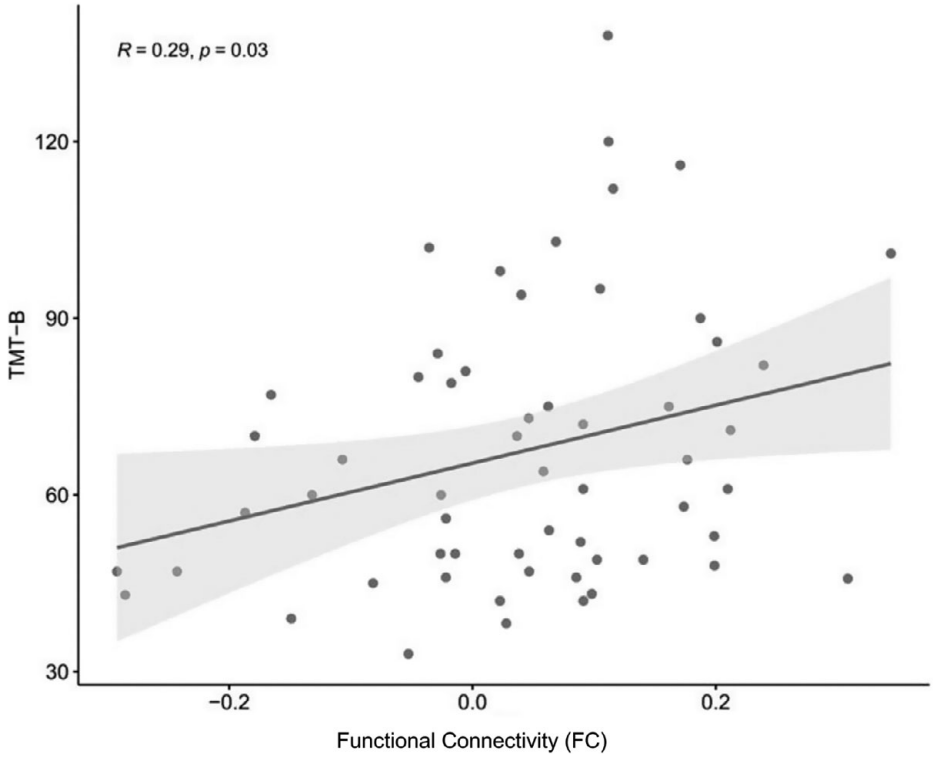


**Figure 5.** Scatter plot for TMT B scores and FC of the posterior caudate to the left precentral gyrus in long-COVID patients.

in neuropsychological assessments. This finding is supported by a study that demonstrated that left hemispheric reduction in gray matter volume aligns with the observed cognitive deficits (Deuter et al., 2024). Similarly, Díez-Cirarda et al. reported a reduction in gray matter volume in the precentral gyrus, which was correlated with cognitive decline (Díez-Cirarda et al., 2022).

We also observed increased FC between the right globus pallidus and posterior cingulate cortex, along with the right temporal lobe.

Both the posterior cingulate cortex and temporal pole are part of the default mode network. However, since we did not find any correlation of FC between the anterior globus pallidus and the default mode network structures with cognitive functions, our discussion focuses on the mechanism underlying altered FC within the corticostriatal loop.

The corticostriatal loop is a neural circuit that connects cortical regions such as the precentral gyrus and striatal structures within the BG (Peters et al., 2016). Among other functions, the loop is relevant for decision-making and executive functions. The caudate nucleus is part of the striatum along with the putamen and the nucleus accumbens (Lanciego et al., 2012; L. Liu et al., 2023). The caudate is responsible for working memory and executive functioning (Haber, 2016). The BG is involved in the pathophysiology of diseases leading to cognitive decline, which presents executive dysfunctions such as Alzheimer's disease or Huntington's disease (Finke et al., 2006; L. Liu et al., 2023). MRI studies in Alzheimer's disease already prove changes in metabolic activity within the striatum, and those changes are correlated with the severity of executive dysfunction, as measured by the TMT B (L. Liu et al., 2023; X. Liu et al., 2021).

The mechanisms behind cognitive impairment in long-COVID seem to be multifactorial. Evidence suggests that cellular damage resulting from viral invasion is linked to a dysregulated immune response and mitochondrial dysfunction, both of which contribute to increased oxidative stress (Parry, Wani, & Yaseen, 2020; Pierce, Shen, Cintron, & Hiebert, 2022). The integrity of neural circuits and cognitive function is disturbed by this oxidative stress, and the invasion of cytokines, chemokines, and reactive microglia causes imbalances in myelin maintenance (Quan et al., 2023). Additionally, COVID-19 can compromise the blood–brain barrier, permitting the infiltration of fibrinogen and other proinflammatory agents, which causes neural inflammation (Quan et al., 2023). This inflammation has already been found to be concentrated within the BG (Rudroff, 2024). The ACE-2 receptor serves as an entry point for SARS-CoV-2, as the spike protein on the surface of the virus binds to those receptors, allowing the virus to enter and infect the cell (Montani et al., 2022; Pierce et al., 2022). SARS-CoV-2 has the potential to directly infect neurons, glial cells, and the capillary endothelium by binding its spike protein to ACE-2 receptors, leading to neural tissue invasion and subsequently triggering neuroinflammation and the activation of microglia (Montani et al., 2022; Quan et al., 2023; Xu & Lazartigues, 2022).

Histological samples of the caudate show expression of ACE2, which puts the caudate at risk for neuronal damage (Chen et al., 2020). Moreover, the overexpression of ACE-2 receptors is associated with the development of cognitive deficits in long-COVID patients (Quan et al., 2023). Patients with Alzheimer's disease show downregulation of ACE2 in the BG (Cui, Su, Cao, Ma, & Qiu, 2021), and researchers have further proposed that this downregulation could be a shared pathogenesis for the executive dysfunctions in both Alzheimer's disease and COVID-19. This finding might indicate that patients with long-COVID could be at increased risk for developing further cognitive decline. Moreover, an autopsy study revealed SARS-CoV-2 RNA and protein in the BG (Stein et al., 2022), and our own group consistently reported structural changes within the BG in patients with long-COVID (Besteher et al., 2022). Furthermore, another systematic review reported that cerebrovascular damage in the acute phase of COVID-19 causes hyperintensities and microhemorrhages of white matter, especially within the BG (Manca, De Marco, Ince, & Venneri, 2021). In summary, the BG shows overlapping structural and functional abnormalities, emphasizing its vulnerability to COVID-19-related damage. The communication between the BG and cortical structures, specifically the caudate and the left PCG, which is relevant for executing cognitive psychomotor tasks, seems to be disrupted in patients with long-COVID. These FC alterations indicate widespread network disruptions and are likely associated with the presence of ACE2 receptors within the BG. Due to cerebrovascular damage caused by the invasion and transmission of SARS-CoV-2, along with inflammation and disrupted neuronal integrity within the central nervous system, the resulting functional alterations are likely to impair cognitive efficiency (Swain et al., 2021).

There are several limitations to the interpretation of our findings. Compared with the cross-sectional design of this study, a follow-up longitudinal study would be better for identifying the specificity of symptoms and FC alterations within a longer period. The heterogeneity of the individual time span between the initial onset of COVID-19 and the screening as a part of the study also limits our study. Individuals infected with COVID-19 may exhibit varying rates of disease progression, leading to various symptoms. With respect to selection bias, there is an overrepresentation of nonhospitalized cases in this study, as only 7 out of 60 patients were treated in a hospital. Another limitation of this study is the use of a screening tool for cognitive impairment. The MoCA has limited sensitivity for detecting cognitive impairment in younger adults and might lead to underestimation of cognitive impairments in those patients (McIntyre et al., 2019). A methodological limitation is that FC analysis measures statistical correlations representing synchronization between brain regions. Nevertheless, it does not provide direct evidence of the causality of these alterations. It is also possible that other confounding variables also influence the observed FC patterns that we were not analyzing.

In conclusion, this study highlights the key role of the BG in cognitive processes, highlighting how they are critically affected by long-COVID. Inflammation processes within the BG, particularly those affecting neuronal pathways such as the corticostriatal loop, are significant consequences of long-COVID. While neuroinflammation is a known consequence of viral and systemic diseases, our study offers new insights into the specific impact of long-COVID on the BG. The pattern of neuroinflammation, metabolic disruption, and structural and functional changes observed in the BG differentiates long-COVID from other postviral syndromes (Al-Aly et al., 2024; Mohammadi & Ghaderi, 2024). To advance our understanding of these mechanisms, future research should prioritize longitudinal studies, which can help differentiate between transient changes and those indicative of long-term sequelae, providing more evidence on the causality and permanence of observed alterations.

**Supplementary material.** The supplementary material for this article can be found at http://doi.org/10.1017/S0033291725000054.

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**Ethical standard.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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