Journal of Psychiatric Research 176 (2024) 377–383

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Cognitive performance in adults with post-COVID syndrome: Results from a German case-control study

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ARTICLE INFO

Keywords:
Post-acute COVID-19 syndrome
Neuropsychological tests
Cognitive dysfunction
Mental fatigue
Case-control studies

ABSTRACT

Numerous studies on post-COVID syndrome (PCS) describe persisting symptoms of cognitive impairment. Previous studies, however, often investigated small samples or did not assess covariates possibly linked to cognitive performance. We aimed to describe 1) global and domain-specific cognitive performance in adults with PCS, controls with previous SARS-CoV-2 infection and healthy controls, 2) associations of sociodemographics, depressive symptoms, anxiety, fatigue, somatic symptoms and stress with cognitive performance and subjective cognitive decline (SCD), using data of the LIFE-Long-COVID-Study from Leipzig, Germany. Group differences in cognitive performance and associations with sociodemographic and neuropsychiatric covariates were assessed using multivariable regression analyses. Our study included n = 561 adults (M_{age}: 48.8, SD: 12.7; % female: 70.6). Adults with PCS (n = 410) performed worse in tests on episodic memory (b = −1.07, 95 % CI: −1.66, −0.48) and visuospatial abilities (b = −3.92, 95 % CI: −6.01, −1.83) compared to healthy controls (n = 64). No impairments were detected for executive function, verbal fluency, and global cognitive performance. Odds of SCD were not higher in PCS. A previous SARS-CoV-2 infection without PCS (n = 87) was not linked to cognitive impairment. Higher age and higher levels of stress and fatigue were linked to worse performance in several cognitive domains. Routine administration of tests for episodic memory and visuospatial abilities might aid in the identification of individuals at risk for cognitive impairment when reporting symptoms of PCS. Low numbers of participants with severe COVID-19 infections possibly limit generalizability of our findings.

1. Background

Until January 2024, approximately 775 million cases of COVID-19 infections have been reported worldwide, including more than 7 million deaths (World Health Organization 2024b). COVID-19 is considered a disease affecting multiple organs, including the nervous system. Effects of COVID-19 pose great challenges for healthcare systems at large, with estimates from the Institute of Health Metrics and Evaluation suggesting that up to 3.7 million people with a previous SARS-CoV-2 infection develop post COVID-19 condition (World Health

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https://doi.org/10.1016/j.jpsychires.2024.06.036
Received 25 March 2024; Received in revised form 18 June 2024; Accepted 24 June 2024
Available online 25 June 2024

Organization 2024a). The World Health Organization (WHO) has therefore defined post-COVID-syndrome (PCS) as the prolonged effects of a probable or confirmed history of SARS-CoV-2 infection, with symptoms usually occurring three months after the initial infection, these symptoms lasting for at least two months, and no alternative explanation available (World Health Organization, 2021). Common symptoms of PCS involve fatigue, shortness of breath, and cognitive impairments, e.g., memory impairments or difficulty concentrating. Underlying mechanisms explaining cognitive impairment in PCS are not fully understood yet, but are suggested to be multifactorial (Rogers et al., 2020). Explanations include direct infection of the nervous system, chronically elevated inflammatory markers in PCS, or cerebrovascular ischemia due to endothelial dysfunction (Maamar et al., 2022; Heneka et al., 2020). In severe cases of COVID-19 infection, hypoxia can cause damage to the central nervous system (Thakur et al., 2021).

Studies on cognitive complaints in PCS describe brain fog and self-reported cognitive impairments in 70–80% of patients (Guo et al., 2022; Ziauddeen et al., 2022; Davis et al., 2021). Where domain-specific cognitive function was assessed, studies most often reported impairments in memory, attention and executive function (Rizzi et al., 2024; Crivelli et al., 2022; Sobrino-Relaño et al., 2023; Richter and Theodoridou 2023), but also in global cognitive performance (Sobrino-Relaño et al., 2023; Daroische et al., 2021). A meta-analyses reported the pooled proportion of individuals with PCS exhibiting cognitive impairment to amount to 22%, with greater proportions in studies applying objective measures of cognitive impairment than in studies using subjective ascertainments (36 and 18%, respectively; (Ceban et al., 2022);).

However, many earlier studies relied on self-reported impairments, without comprehensive cognitive assessments conducted, did not include a control group or tested very small samples. Further, only few studies investigated the impact of factors such as depression, anxiety, somatic symptoms or fatigue on cognitive performance in large samples of adults with PCS. We therefore aimed to describe 1) group differences in global and domain-specific cognitive performance in a sample of adults with PCS, compared to controls with either a previous COVID-19 infection or healthy controls, 2) associations of anxiety, depression, fatigue, stress and somatic symptoms with cognitive performance in PCS, using data from the LIFE Long-COVID study from Leipzig, Germany.

2. Material and methods

2.1. Recruitment and participants

Participants of the LIFE-Long-COVID-Study were recruited in two waves (July to December 2021, July 2022 to February 2023). Wave 1 included adults with a confirmed previous SARS-CoV-2-infection, recruited, e.g., via the university outpatient post-COVID clinic at Leipzig University Hospital, many of whom reported persisting symptoms. In addition, participants of the LIFE-Adult cohort, comprising 10,000 inhabitants of Leipzig, with previous SARS-CoV-2-infection were recruited, regardless of reported PCS-symptoms. Further, previous participants of the LIFE-Adult-Study without a prior SARS-CoV-2-infection were included as a control group. The LIFE-Adult-Study is described in detail elsewhere (Loeffler et al., 2015; Engel et al., 2023). In wave 2, participants completed an online screening tool, assessing previous infections and neuropsychiatric symptoms. Participants of wave 2 were recruited via the university outpatient post-COVID clinic, general practitioner and neurologist practices, advertisements in pharmacies, self-help groups and social media channels of the University of Leipzig. Participants with a current COVID-19-diagnosis or aged under 18 years were excluded from participation. The online screening tool assessed history of previous SARS-CoV-2-infections and neuropsychiatric symptoms typical of PCS. Assessments covered:

- depressive symptoms, assessed using the Centre for Epidemiological Studies Depression Scale (CES-D; (Radloff 1977);)
- anxiety, assessed using the Generalized Anxiety Disorder Scale (GAD-7; (Spitzer et al., 2006);)
- physical symptoms, assessed using the Patient Health Questionnaire (PHQ-15; (Kroenke et al., 2002);)
- fatigue, assessed using the Multidimensional Fatigue Inventory (MFI-20; (Smets et al., 1995);).

A cut-off value of $\geq$23 points on the CES-D (range: 0–60), $\geq$10 for the GAD-7, $\geq$10 for the PHQ-15 indicated presence of depression, anxiety and moderate levels of somatization, respectively, following established criteria. Regarding fatigue, we considered the MFI-20-subscales "mental fatigue" and "reduced motivation". A score $\geq$ the 75th percentile of respective reference values was chosen to indicate presence of fatigue. Participants who scored above the respective cut-off value of $\geq$1 of these assessments were considered PCS cases.

2.2. Outcomes and covariates

All participants underwent structured interviews at the LIFE study centre, including cognitive testing, interviews and questionnaires. We assessed global and domain-specific cognitive performance as well as subjective cognitive decline as outcomes, using the following tests:

- Montreal Cognitive Assessment (MoCA; (Nasreddine et al., 2005);) for global cognition
- Verbal Fluency Test "animals" for verbal fluency (Heyman et al., 1989)
- Trail Making Test A and B (TMT-B/TMT-A-ratio) for executive function (Reitan 1992)
- Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning-Test for episodic memory (Heyman et al., 1989)
- CERAD Word List Memory Test for delayed recall/memory (Heyman et al., 1989)
- CERAD Constructional Praxis Test for visuospatial abilities (Heyman et al., 1989).

Subjective cognitive decline (SCD) was assessed using the question "Do you feel that your memory has become worse since your SARS-CoV-2 infection?", answering options: yes/no.

As covariates, we included information on age, sex, and education (assessed in years of formal education). Further, all participants completed questionnaires including the assessments of the online screener (see above; depressive symptoms, anxiety, somatic symptoms, fatigue), which was used for participant selection. We further controlled for symptoms of stress, assessed using the Perceived Stress Scale (PSS-10; (Schneider et al., 2020)).

2.3. Statistical analyses

Descriptive statistics are provided using means and standard deviations or percentages, respectively. Group differences were evaluated using chi-square-tests and one-way ANOVA, as appropriate. Associations of PCS or a previous COVID-19 infection with cognitive outcomes were assessed using multivariable regression analyses. Of the considered cognitive outcomes, four had distributions which satisfied the normality assumption (MoCA, CERAD Word List Learning, Verbal Fluency Test, Trail Making Test), and were therefore analyzed using ordinary least squares regression models. Scores for the Constructional Praxis Test and Word List Memory Test indicated ceiling effects and were analyzed using Tobit regression, with right-censoring at the upper limit (maximum score). Odds of SCD were assessed using logistic regression models. Due to systematic differences between groups with a previous SARS-CoV-2 infection (who filled out the online screener) and those without (no online screener), observations were matched on age, sex, and criteria included in the online screener (depressive and anxiety symptoms, somatic symptoms, fatigue-subscales "mental fatigue" and "reduced

motivation") using entropy balancing (Hainmueller 2012). Entropy balancing is a non-parametric approach to match covariate moments of observations from one sample (participants who filled out the online screener) to observations of a control sample (healthy controls) comparable in pre-specified observable characteristics. Descriptive statistics are provided using unmatched observations, while regression analyses were conducted using entropy balancing weights, accounting for systematic between-group differences. To account for multiple testing, analyses were corrected applying the Benjamini-Hochberg-procedure to reduce the false discovery rate to 5% (Benjamini and Hochberg 1995).

2.4. Ethics approval and consent to participate

The LIFE-Long-COVID-Study is conducted in accordance with the Declaration of Helsinki and was approved by the responsible ethics board at the Medical Faculty of the University of Leipzig (reference: 345/21-ek). All participants provided written informed consent to participate prior to participation.

3. Results

3.1. Descriptive analyses

A total of n = 580 individuals participated in the LIFE-Long-COVID-Study. After excluding participants with missing information on the PCS criteria (n = 19), n = 561 participants contributed to analyses. Characteristics of participants by group are summarized in Table 1.

Participants with a previous SARS-CoV-2 infection were on average older than PCS and non-COVID observations ($p < 0.001$). The proportion of women was higher in the PCS group than in the COVID-19 and healthy control group ($p < 0.001$). Average scores for CES-D, GAD-7, PHQ-15, MFI-subscales "mental fatigue" and "reduced motivation", as well as PSS-10 scores were higher in the PCS group than in the other two groups ($p < 0.001$). Regarding cognitive performance, the healthy control group showed slightly better performance in the Verbal Fluency Test ($p = 0.016$) and in the Word List Learning Test ($p = 0.013$). Prevalence of SCD was higher in PCS participants than in the COVID-19 and healthy control group ($p < 0.001$). Overall, 9.9% of participants with a previous SARS-CoV-2 infection reported inpatient treatment due to the infection, with no differences between PCS and participants with previous SARS-CoV-2 infection ($p = 0.873$).

3.2. Factors associated with cognitive performance in cases and controls

Table 2 describes results of multivariable regression analyses assessing factors linked to cognitive performance in PCS participants and those with a previous SARS-CoV-2 infection (ref.: healthy controls).

PCS participants (b = −0.49, 95% CI: −1.29, 0.29) and individuals with a previous SARS-CoV-2 infection (b = 0.15, 95% CI: −0.84, 1.14) did not differ from healthy controls regarding global cognition (MoCA). Higher age (b = −0.09, 95% CI: −0.11, −0.06) was linked to lower MoCA-scores.

PCS or a previous SARS-CoV-2 infection were not associated with performance in the Verbal Fluency Test ($b_{PCS} = -1.19$, 95% CI: −3.95, 1.56; $b_{COVID} = -2.13$, 95% CI: −4.57, 9.32). Higher levels of depressive symptoms were linked to better performance (b = 0.26, 95% CI: 0.08, 0.44), while higher levels of stress were associated with worse performance (b = −0.34, 95% CI: −0.57, −0.11). Mental fatigue was linked to worse performance in the Verbal Fluency Test (b = −0.42, 95% CI: −0.71, −0.14).

PCS and COVID-19 observations did not differ from healthy controls in the Trail Making Test ($b_{PCS} = -0.22$, 95% CI: −0.53, 0.09; $b_{COVID} = -0.24$, 95% CI: −0.60, 0.13). Higher age (b = 0.02, 95% CI: 0.01, 0.03) and higher levels of stress (b = 0.04, 95% CI: 0.02, 0.07) were associated with worse performance.

PCS participants performed worse than healthy controls in the Word List Learning Test (b = −1.07, 95% CI: −1.66, −0.48). A previous SARS-CoV-2 infection was not associated with performance in the Word List Learning Test (b = −1.01, 95% CI: −2.07, 0.06). Higher age (b = −0.11, 95% CI: −0.14, −0.08) and higher levels of mental fatigue (b = −0.25, 95% CI: −0.40, −0.11) were associated with worse performance.

Regarding the Word List Memory Test, PCS and COVID-19 observations did not differ from healthy controls ($b_{PCS} = -0.85$, 95% CI: −1.78, 0.08; $b_{COVID} = 0.00$, 95% CI: −0.64, 0.65). Higher age (b = −0.07, 95% CI: −0.11, −0.04) and higher levels of mental fatigue (b = −0.11, 95% CI: −0.19, −0.03) were linked to worse performance, whereas female sex was associated with better performance (b = 0.80, 95% CI: 0.28, 1.32).

PCS participants performed worse in the Constructional Praxis Test ($b_{PCS} = -3.92$, 95% CI: −6.01, −1.83; $b_{COVID} = -3.11$, 95% CI: −5.41, −0.81; p_{COVID} n. s. After adjusting for multiple testing). No further covariates were associated with performance in the Constructional Praxis Test.

Observations with PCS or a previous SARS-CoV-2 infection did not differ from healthy controls regarding the odds of reporting SCD. Higher

Table 1
Participant characteristics in the PCS, COVID and non-COVID-group (n = 561).

	Total (n = 561)	PCS (n = 410)	Previous SARS-CoV-2 infection (n = 87)	Healthy controls (n = 64)	p†
Age, M (SD)	48.8 (12.7)	47.1 (12.2)	55.7 (13.0)	50.1 (12.4)	**<0.001**
Female, %	70.6	77.1	55.2	50.0	**<0.001**
Education (years), M (SD)	10.9 (1.2)	10.9 (1.3)	10.8 (1.1)	10.9 (1.4)	0.922
CES-D sum score, M (SD)	17.1 (7.0)	19.2 (6.6)	10.9 (4.3)	12.3 (4.6)	**<0.001**
GAD-7 sum score, M (SD)	6.2 (4.6)	7.5 (4.5)	2.2 (2.2)	2.8 (2.8)	**<0.001**
PHQ-15 sum score, M (SD)	11.0 (6.3)	13.5 (5.2)	4.3 (3.4)	3.9 (3.1)	**<0.001**
Mental fatigue MFI-subscale, M (SD)	12.3 (4.6)	14.1 (3.8)	7.0 (2.2)	7.9 (3.5)	**<0.001**
Reduced motivation MFI-subscale, M (SD)	9.8 (3.7)	10.9 (3.5)	6.5 (2.1)	7.5 (2.7)	**<0.001**
PSS-10 sum score, M (SD)	27.7 (7.4)	30.3 (6.2)	19.9 (4.9)	21.6 (5.6)	**<0.001**
In-patient stay due to COVID-19	9.9 (49)	9.8 (40)	10.3 (9)	n.a.	0.873
MoCA, M (SD)	26.2 (2.5)	26.1 (2.5)	26.6 (2.5)	26.7 (2.7)	0.097
Verbal Fluency Test, M (SD)	24.7 (6.4)	24.4 (6.4)	24.5 (6.0)	26.8 (6.5)	**0.016**
CERAD Word List Learning, M (SD)	23.1 (3.7)	22.9 (3.6)	22.9 (3.5)	24.4 (4.3)	**0.013**
CERAD Word List Memory, M (SD)	8.1 (1.8)	8.0 (1.9)	8.2 (1.7)	8.6 (1.8)	0.074
TMT-B/TMT-A, M (SD)	2.3 (0.9)	2.2 (0.9)	2.3 (0.9)	2.4 (0.9)	0.281
Constructional Praxis Test, M (SD)	10.6 (1.1)	10.6 (1.2)	10.7 (0.6)	10.7 (0.7)	0.035
Subjective cognitive decline, %	74.7	86.5	45.4	39.1	**<0.001**

CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CES-D: Centre for Epidemiological Studies Depression Scale; GAD: Generalized Anxiety Disorder Scale; M: Mean; MFI: Multidimensional Fatigue Inventory; MoCA: Montreal Cognitive Assessment; PHQ: Patient Health Questionnaire; PSS: Perceived Stress Scale; SD: standard deviation; TMT: Trail Making Test. †: reported *p*-values are unadjusted, while the threshold for statistical significance is set using the Benjamini–Hochberg adjustment (false discovery rate = 0.05); significant group differences highlighted in bold type.

Table 2
Associated factors of cognitive performance per group (n = 561), multivariable regression analyses.

	Outcomes											
Independent variables	MoCA				Verbal Fluency Test				Trail Making Test (TMT-B/TMT-A)			
	Coeff.	95% CI	p†	% R^2	Coeff.	95% CI	p†	% R^2	Coeff.	95% CI	p†	% R^2
Long-COVID	−0.50	−1.29; 0.29	0.215	0.94	−1.19	−3.95; 1.56	0.394	1.09	−0.22	−0.53; 0.09	0.157	0.63
COVID (ref.: non-COVID)	0.15	−0.84; 1.14	0.770	0.37	−2.13	−4.57; 0.32	0.088	3.52	−0.24	−0.60; 0.13	0.202	0.44
Age	−0.09	−0.11; −0.6	**<0.001**	22.14	−0.06	−0.15; 0.03	0.194	5.65	0.02	0.01; 0.03	**<0.001**	1.20
Female	−0.13	−1.21; 0.96	0.818	2.47	0.57	−1.49; 2.63	0.587	0.85	0.06	−0.22; 0.33	0.689	0.51
Education	0.29	−0.05; 0.63	0.100	16.60	0.58	−0.19; 1.35	0.138	20.85	−0.06	−0.14; 0.02	0.154	1.91
Depression (CES-D)	0.08	0.00; 0.17	0.044	1.01	0.26	0.08; 0.44	**0.006**	1.00	0.01	−0.03; 0.04	0.715	0.31
Stress (PSS-10)	−0.03	−0.12; 0.06	0.524	0.45	−0.34	−0.57; −0.11	**0.004**	2.00	0.04	0.02; 0.07	**0.002**	0.17
MFI-scale "Reduced motivation"	−0.16	−0.36; 0.03	0.105	1.75	0.03	−0.31; 0.36	0.876	5.80	−0.04	−0.08; 0.00	0.046	1.07
MFI-scale "Mental fatigue"	0.03	−0.08; 0.14	0.0612	1.70	−0.42	−0.71; −0.14	**0.003**	5.41	−0.02	−0.06; 0.01	0.170	2.47
Anxiety (GAD-7)	0.03	−0.08; 0.13	0.646	0.30	0.25	−0.05; 0.54	0.105	1.38	0.00	−0.05; 0.05	0.960	0.07
Somatic symptoms (PHQ-15)	−0.06	−0.13; 0.01	0.084	3.17	0.12	−0.06; 0.31	0.198	6.12	−0.01	−0.03; 0.02	0.631	0.77
R^2	0.386				0.200				0.247			
	Outcomes											
Independent variables	Word List Learning Test				Word List Memory Test				Constructional Praxis Test			
	Coeff.	95% CI	p†	% R^2	Coeff.	95% CI	p†	% R^2	Coeff.	95% CI	p†	% R^2
Long-COVID	−1.07	−1.66; −0.48	**<0.001**	1.17	−0.85	−1.78; 0.08	0.074	1.25	−3.92	−6.01; −1.83	**<0.001**	1.17
COVID (ref.: non-COVID)	−1.01	−2.07; 0.06	0.063	1.95	0.00	−0.64; 0.65	0.994	0.59	−3.11	−5.41; −0.81	0.008	0.76
Age	−0.11	−0.14; −0.08	**<0.001**	17.42	−0.07	−0.11; −0.04	**<0.001**	17.17	−0.04	−0.09; 0.00	0.066	1.80
Female	0.59	−0.22; 1.40	0.154	4.23	0.80	0.28; 1.32	**0.002**	6.32	−0.85	−2.14; 0.43	0.192	11.17
Education	0.58	0.04; 1.13	0.036	15.34	0.14	−0.16; 0.44	0.357	9.05	0.48	−0.01; 0.96	0.054	8.07
Depression (CES-D)	0.08	−0.05; 0.21	0.238	0.41	0.07	0.00; 0.14	0.50	0.38	0.10	−0.03; 0.23	0.118	4.10
Stress (PSS-10)	−0.11	−0.22; 0.01	0.069	1.04	−0.05	−0.12; 0.02	0.156	0.78	0.04	−0.08; 0.15	0.547	1.01
MFI-scale "Reduced motivation"	0.13	0.01; 0.25	0.038	1.26	0.00	−0.07; 0.07	0.955	1.43	−0.10	−0.28; 0.09	0.299	9.00
MFI-scale "Mental fatigue"	−0.25	−0.40; −0.11	**<0.001**	6.54	−0.11	−0.19; −0.03	**0.006**	6.07	−0.11	−0.29; 0.07	0.219	1.38
Anxiety (GAD-7)	0.00	−0.12; 0.12	0.968	1.09	0.02	−0.07; 0.12	0.614	0.96	−0.01	−0.21; 0.20	0.961	1.78
Somatic symptoms (PHQ-15)	0.08	−0.02; 0.17	0.121	0.88	0.04	−0.02; 0.10	0.175	0.69	0.02	−0.09; 0.14	0.685	6.35
R^2	0.326				0.111				0.100			

CES-D: Centre for Epidemiological Studies Depression Scale; CI: confidence interval; coeff: coefficient; GAD: Generalized Anxiety Disorder Scale; MFI: Multidimensional Fatigue Inventory; MoCA: Montreal Cognitive Assessment; PHQ: Patient Health Questionnaire; PSS: perceived Stress Scale. †: reported *p*-values are unadjusted, while the threshold for statistical significance is set using the Benjamini–Hochberg adjustment (false discovery rate = 0.05); significant associations highlighted in bold type.

age (OR = 1.12, 95% CI: 1.05, 1.18), higher levels of stress (OR = 1.21, 95% CI: 1.07, 1.37) and mental fatigue (OR = 1.46, 95% CI: 1.23, 1.72) predicted higher odds of reporting SCD. Higher levels of "reduced motivation" (OR = 0.82, 95% CI = 0.69, 0.96) were linked to lower odds of SCD (results for SCD not tabulated).

Supplementing the main analyses, we compared observations with PCS and a previous SARS-CoV-2 infection, using the same models as described above, plus an assessment of inpatient treatment (yes/no) as covariate to assess potential associations of cognitive performance with disease severity. In-patient treatment due to COVID-19 was not associated with any of the cognitive outcomes assessed (Appendix, Table 1):

4. Discussion

Our study aimed to describe differences in cognitive performance between adults with PCS, participants with a previous SARS-CoV-2 infection and healthy controls. Analyses revealed that PCS was linked to impaired performance in episodic memory and visuospatial abilities. A previous SARS-CoV-2 infection without PCS symptomatology was not associated with deficits in global or domain-specific cognitive performance. These findings suggest a link between PCS and cognitive impairment, which was, however, detected only in certain cognitive domains.

Previous reviews and meta-analyses reported that memory, executive function and attention are the cognitive domains most frequently impaired in PCS (Crivelli et al., 2022; Bertuccelli et al., 2022; Zeng et al., 2023; Nicotra et al., 2023). The findings from our study regarding deficits in episodic memory corroborate these findings for the memory domain, however, we did not observe impairments in executive function in either PCS subjects or participants with a previous SARS-CoV-2 infection. We observed deficits in visuospatial abilities, which have been less extensively studied than, e.g., memory or executive functions (Bertuccelli et al., 2022). Similar findings were, however, reported in several previous studies (Delgado-Alonso et al., 2022; Abdelghani et al., 2022; Raman et al., 2021). We observed no association between a previous SARS-CoV-2-infection and deficits in cognitive performance, corroborating recent findings from a neuroimaging study reporting brain changes and impaired cognitive function in adults with PCS, but not in controls recovered from SARS-CoV-2-infection (Del Serrano Pueblo et al., 2024).

We detected no associations of several cognitive domains with PCS. This might, in part, be due to the case-control design applied and the large number of covariates we were able to assess (including depressive and anxiety symptoms, fatigue, somatic symptoms and stress), which may explain differences in cognitive performance between PCS and control groups to some degree. Further, our study might differ from previous investigations as our sample included only a small amount of severe courses of COVID-19, as indicated by the low number of hospitalized cases. On another note, non-significant group differences might partially be explained by the cognitive assessments applied in our study, which were originally designed to detect age-related cognitive decline. Notably, other studies also did not detect cognitive impairment in PCS, e.g. (Whiteside et al., 2022; Dressing et al., 2022), or reported impaired cognitive performance solely for memory but no other cognitive domains (Guo et al., 2022).

Regarding factors associated with cognitive performance, higher levels of fatigue, particularly the domain "mental fatigue", were linked to impaired performance in the Verbal Fluency Test, Word List Learning Test and Memory Test, corroborating findings from Mexico reporting lower cognitive performance in PCS subjects reporting fatigue (González-Hermosillo et al., 2021). Higher age was linked to worse performance in several cognitive domains (executive function, learning, memory), as well as global cognition and SCD. This is in line with previous findings, reporting associations between higher age and greater

risk of impaired cognitive performance in PCS (Ferrucci et al., 2021; Walle-Hansen et al., 2021; Damiano et al., 2023). Sex differences were detected solely in the Word List Recall Test, with women performing better than men. While PCS tends to affect women more frequently (Quan et al., 2023), evidence on sex differences in cognitive performance in PCS is currently scarce, complicating comparison of these findings with other studies. It has to be pointed out that the respective proportion of variance explained by the neuropsychiatric factors (anxiety, depression, stress, fatigue etc.) assessed in our study was, on average, rather small and explained less group differences in cognitive performance than, e.g., sociodemographic factors like age or education (see Table 2). These findings point towards the need for identifying further relevant factors which might explain cognitive impairment in PCS.

We detected no association of anxiety with cognitive performance in our sample, which differs from results reported by Miskowiak and colleagues, reporting a link between increased levels of anxiety and poorer cognitive performance in PCS (Miskowiak et al., 2021). However, the respective study solely included participants discharged from inpatient treatment due to COVID-19, suggesting that cases might only partially be comparable to our study. Surprisingly, depressive symptoms were linked to slightly better performance in the Verbal Fluency Test in our study. However, this association was not detected for any other cognitive outcome assessed, arguing against a general association of depressive symptoms and cognitive performance in our sample. Findings on depressive symptoms and PCS are currently inconclusive: While some studies found depression to be linked to impaired cognitive function (Miskowiak et al., 2021), others reported no association between anxiety or depression and cognitive performance (Woo et al., 2020). One possible explanation refers to our study's inclusion criteria, which entailed symptoms of depression and/or anxiety as necessary for a case definition of PCS: Participants with a previous SARS-CoV-2 infection with $\geq$23 points on the CES-D were deemed PCS cases, therefore, depressive symptomatology was, on average, lower in participants with a previous SARS-CoV-2 infection than in healthy controls. Healthy controls had better performance in the Verbal Fluency Test, as shown in descriptive analyses (Table 1). Therefore, the observed association of depressive symptoms with better performance in the Verbal Fluency Test might in part be due to our case definition of PCS, leading to an overall higher level of depressive symptoms in healthy controls than in participants with a previous SARS-CoV-2 infection.

While subjective reports of cognitive decline were highly common among participants, especially among PCS cases, adults with PCS were not more likely to report SCD when controlled for covariates. Higher levels of fatigue, stress and older age were associated with higher odds of SCD, aligning with previous findings linking fatigue and older age to increased odds of SCD (Zhang et al., 2023). It should be noted that assessments of (mental) fatigue, but also anxiety or depression include cognitive complaints, e.g., trouble concentrating, which are similar to problems assessed when measuring symptoms of SCD. This may have partially contributed to the observed association between fatigue and higher odds of SCD observed in our study. Analyses of follow-up assessments from the LIFE-Long-COVID-Study, which are currently ongoing, will be able to reveal whether reports of SCD prevail in the long run, and whether SCD in PCS is linked to greater risks of cognitive decline longitudinally. However, symptoms of subjective cognitive decline can be very burdensome for those affected, raising e.g. fear of dementia (Jessen et al., 2020; Comijs et al., 2002). This finding points towards the challenge of selecting appropriate tools to capture cognitive performance and health-related outcomes in PCS, as many instruments applied in our study were originally designed to capture age-related cognitive decline.

In supplementary analyses, comparing PCS and previously SARS-CoV-2-infected participants, no association between inpatient treatment for COVID-19 and cognitive performance was detected. This is in line with a review by Ceban and colleagues, reporting no effect of hospitalization on cognitive outcomes in PCS (Ceban et al., 2022), suggesting that cognitive impairment due to PCS is likely independent of initial disease severity. However, due to the rather low number of hospitalized cases in our study, this line of thought should be interpreted with caution.

4.1. Strengths and limitations

Our study comprised a large sample of participants and tested cognitive performance in PCS applying two control groups (previous SARS-CoV-2 infection, healthy controls). Further, we applied a wide range of cognitive tests, thereby allowing for statements on domain-specific cognitive performance in PCS. The large set of covariates included in our study, e.g., depression, anxiety, stress, and fatigue, allowed to gain a better understanding of the factors associated with cognitive function in PCS. Possible heterogeneity between cases and controls was addressed using covariate balancing, i.e., entropy balancing, which might increase robustness against selection bias. Therefore, we were able to address several shortcomings of earlier studies on PCS and cognition identified in earlier studies (Di Pietro et al., 2021; Søraas et al., 2021; Nicotra et al., 2023).

Several limitations need mentioning when interpreting our findings. Since information on date of the last SARS-CoV-2 infection was not available for a large number of participants, we were not able to assess potential impact of time since the last SARS-CoV-2 infection on cognitive performance. Certain studies suggest that cognitive impairment in PCS tend to improve over time (Del Brutto et al., 2022), therefore, we cannot rule out that controlling for time passed since (last) infection may have slightly altered our findings. Our sample included only small numbers of participants hospitalized due to COVID-19, suggesting that the majority of participants had endured rather mild courses of infection. However, analyses controlling for a potential impact of hospitalization due to COVID-19 did not reveal any association of inpatient treatment with cognitive performance, therefore, we are confident that possible selection effects should not have impacted our findings in any meaningful way. We were able to assess a variety of cognitive domains, however, the neuropsychological assessments applied may have lacked sufficient sensitivity to identify subtle impairments in cognitive performance in PCS as they were derived from a test battery designed to detect age-related cognitive decline and dementia. Application of more sensitive measures, e.g., Symbol Digit Modalities Test or Stroop Test for attention and executive function might provide appropriate measures to detect PCS-related impairments. What is more, recent studies recommend administration of a minimum of two cognitive tests to assess cognitive performance in PCS (Matias-Guiu et al., 2023). Lastly, our case definition of PCS included symptoms of depression and anxiety, which is in line with the WHO's clinical case definition of PCS (World Health Organization, 2021). However, this may have led to lower levels of depressive symptoms in participants with a previous SARS-CoV-2 infection than in healthy controls and respective associations of depressive symptoms with cognitive performance in our study, which might also be due to sampling criteria. This raises the question of appropriate strategies to identify cases of PCS, without running the risk of reducing PCS solely on psychosomatic attributions (Thoma et al., 2023).

5. Conclusion

In sum, our findings only partially support the pattern of impairment in memory, executive function and attention in PCS, which has been reported in several studies on cognitive function in PCS so far. Still, we detected impaired cognitive performance in episodic memory and visuospatial skills in adults with PCS. Administration of cognitive screenings in adults with PCS assessing the respective domains in routine care might aid the identification of adults at increased risk of cognitive impairment when experiencing long-term symptoms after a

SARS-CoV-2 infection. Our results underline the need to establish the optimal cognitive assessments suitable to detect cognitive impairment in PCS, which may enhance quality of future studies and enhance comparability of findings. While subjective complaints about impaired memory were highly common in PCS individuals, objective cognitive deficits were rather small or even non-significant in certain cognitive domains. Subjective cognitive decline can cause serious concerns in those affected, therefore, caution is advised to recognize these symptoms and provide appropriate care and consultation for persons reporting SCD and seeking help. Studies with repeated follow-up assessments will increase knowledge on trajectories of cognitive performance in PCS. Further, a greater effort is needed in developing a shared framework for the definition of PCS cases in order to increase comparability between studies.

Availability of data and materials

Due to privacy protection, restrictions apply to the availability of the data. Data from the LIFE-Long-COVID-Study are available to researchers who submit a detailed written proposal, including objectives, measures, names of all researchers involved, and how results and newly generated data will be returned for further use. Data are provided upon approval by the data use- and access-committee. Inquiries are to be submitted to info-life@lists.uni-leipzig.de.

Role of the funding source

The project described in this manuscript is funded by means of the Free State of Saxony (State Ministry of Science and Cultural Affairs of Saxony, SMWK). The SMWK had no role in the design and conduct of the LIFE-Long-COVID-Study, analyses of data, interpretation of findings or decision to submit results.

CRediT authorship contribution statement

Andrea E. Zülke: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Melanie Luppa:** Writing – review & editing. **Kerstin Wirkner:** Writing – review & editing, Supervision, Resources, Project administration. **Matthias Reusche:** Writing – review & editing, Software. **Christian Sander:** Writing – review & editing, Project administration. **Ronja Büchner:** Writing – review & editing. **Georg Schomerus:** Writing – review & editing. **Florian Then Bergh:** Writing – review & editing, Project administration. **Jörg Lehmann:** Writing – review & editing, Project administration. **A. Veronica Witte:** Writing – review & editing. **Arno Villringer:** Writing – review & editing. **Samira Zeynalova:** Writing – review & editing, Project administration. **Markus Löffler:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Christoph Engel:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Steffi G. Riedel-Heller:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

None.

Acknowledgements

The authors wish to thank all participants of the LIFE-Long-COVID-Study for their cooperation, as well as all general practitioners, neurologists, self-help groups and the post-COVID outpatient clinic at Leipzig University Hospital for their support in recruitment of participants.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.06.036.

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