Original Article

Subjective and Objective Cognitive Deficits in Patients with Post-COVID Syndrome

A Challenge for Neuropsychologists

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Abstract: Cognitive impairment is a prominent symptom of the post-COVID syndrome (PCS). However, the correspondence between subjective cognitive complaints (SCC) and objective results is inconsistent. Here, we investigated this discrepancy. This longitudinal study included *N* = 42 individuals who reported SCC as PCS after mild infection at inclusion. Data collection comprised questionnaires and neuropsychological assessment at baseline and follow-up (FU). At FU – on average 15 months after acute COVID-19 – 88 % of patients reported persisting SCC. There was an approx. 40 % discrepancy between subjective report and test results at both visits. Patients with SCC and objective impairment indicated elevated fatigue and reduced quality of life compared to patients without SCC at FU. A growing number of patients is anticipated to request neuropsychological assessments even after mild infections.

Keywords: longitudinal study, subjective cognitive decline, objective cognitive impairment, fatigue, long-COVID

Subjektive und objektive kognitive Beeinträchtigungen bei Patient_innen mit Post-COVID-Syndrom: Eine Herausforderung für Neuropsycholog_innen

Zusammenfassung: Kognitive Beeinträchtigungen zählen zu den Hauptsymptomen des Post-COVID-Syndroms (PCS). Allerdings stimmen Angaben zu subjektiven kognitiven Beschwerden (SCC) und objektive Testergebnisse nicht immer überein. Ziel war die Untersuchung dieser Diskrepanz. Diese Langzeitstudie umfasst 42 Proband_innen, die SCC als PCS-Symptome zu Studieneinschluss nach leichter Infektion berichteten. Die Datenerhebung beinhaltet Fragebögen und neuropsychologische Testung zu Baseline und Follow-up (FU). Zum Zeitpunkt des FU – im Mittel 15 Monate nach akuter COVID-19-Erkrankung – berichteten noch 88 % der Patient_innen anhaltende SCC. Die Diskrepanz zwischen subjektiver Einschätzung und Testergebnis betrug etwa 40 % zu beiden Testzeitpunkten. Patient_innen mit SCC und objektiven Beeinträchtigungen berichteten im FU im Vergleich zu Patient_innen ohne SCC signifikant erhöhte Fatigue und schlechtere Lebensqualität. Zukünftig werden steigende Patientenzahlen auch nach leichter Infektion neuropsychologische Hilfe aufsuchen.

Schlüsselwörter: Langzeitstudie, subjektive kognitive Beschwerden, objektivierbare kognitive Beeinträchtigung, Fatigue, Long-COVID

Introduction

Symptoms of COVID-19 after SARS-CoV-2 infection do not remit in all cases immediately after the acute infection but may persist or even newly appear, leading to functional impairment and reduced quality of life (Ceban et al., 2022; Rass et al., 2021). These symptoms are described by different terminologies depending on their chronological development. The National Institute for Health and Care Excellence (NICE) published a guide-

line for the definition of the long-term effects of COVID-19, differentiating between the terms *acute COVID-19*, *ongoing symptomatic COVID-19,* and *post-COVID-19 syndrome (PCS)* (Shah et al., 2021). PCS is defined as symptoms that develop during or after infection, continue for more than 12 weeks after infection, and cannot be explained by an alternative diagnosis. This definition is also implemented in the German S1 Guideline for Long-/Post-COVID (Koczulla et al., 2022).

The World Health Organization (WHO) consensus describes cognitive impairment as one of the most frequent symptoms of PCS (Davis et al., 2021; WHO, 2021). A meta-analysis based on 43 studies found that 20 % are affected by cognitive impairment 12 or more weeks following COVID-19 diagnosis (Ceban et al., 2022). Another systematic review reported incidence rates ranging up to 78 % (Schou et al., 2021). Varying ranges of incidence may arise because of differences in the time lapse between infection and assessment, distinct definitions of cognitive impairment, use of subjective reports vs. objective measurements, cognitive screening vs. extensive neuropsychological assessment to describe cognition, and variations in disease severities and comorbidities.

Importantly, PCS affects not only patients who suffered from severe COVID-19 courses but also those with mild disease severity (van Kessel et al., 2022). Patients with mild COVID-19 have rarely been studied, even though they represent the majority of COVID-19 survivors (Hampshire et al., 2021; Kaswa & Govender, 2020; Kirchberger et al., 2023). A systematic review verified that these patients might suffer from cognitive impairment in terms of PCS and prospectively consult their general practitioners in large numbers (van Kessel et al., 2022).

Cognitive impairment as part of PCS is observed in clinical routine when evaluating patients' reduced earning capacity, inability to work, or occupational disability (Koczulla et al., 2022; Peper & Schott, 2021). Cognitive impairment, even after asymptomatic to moderate acute COVID-19, may significantly impact the ability to work and carry out daily activities (Widmann et al., 2023), thus reducing the overall quality of life. Patients rate the influence of their impairment on working ability as moderate to severe (Davis et al., 2021).

Successful management of PCS requires correctly identifying symptoms (van Kessel et al., 2022). Extensive neuropsychological assessments that cover multiple cognitive domains are preferable to screening or single psychometric tests, as the latter detect cognitive impairment less frequently (Biagianti et al., 2022; Premraj et al., 2022; Schild et al., 2022; Vanderlind et al., 2021). So far, studies have reported deficits in the domains of attention, executive functions, learning and memory, language, and visuoconstruction (Becker et al., 2021; Delgado-Alonso et al., 2022; García-Sánchez et al., 2022). Deficits can often affect multiple domains (García-Sánchez et al., 2022).

Concerning the chronological development, meta-analyses did not show significant differences regarding proportions of cognitive deficits 3–6 versus 6 months after infection (Ceban et al., 2022; Premraj et al., 2022). Another systematic review reported 1-year follow-up data from N = 8,591 COVID-19 survivors documenting memory impairment (19 %) and concentration deficits (18 %) as the most prevalent symptoms (Han et al., 2022).

It is important to highlight that these meta-analyses and reviews did not distinguish between cognitive impairments that were subjectively perceived and those that were objectively measured. The incidence rates reported in meta-analyses seem to be higher among studies using objective cognitive tests than those based on subjective reports (Ceban et al., 2022).

A study of N = 102 nonhospitalized patients reported improved objective cognition via a cognitive screening test 6 to 7 months compared to 3 months post-COVID-19 (impaired score declined from 55.9 % to 41.2 %) (del Corral et al., 2022). Another study in hospitalized patients (N = 299) showed subjective cognitive complaints (SCC) in 23 % of patients at 3 months and 28 % at 12 months post-COVID-19 (Lorent et al., 2022). Interestingly, SCC was reported at comparable rates of around 30 % for ICU-treated, ward-treated, and home-isolated patients 6 months after COVID-19 (Pihlaja et al., 2023). Objective cognitive impairment was verified in 36 %, 34 %, and 9 % of patients in these groups, respectively. In particular, a considerable discrepancy of around 24 % between SCC and objective results was observed in home-isolated patients (n = 49) with mild acute COVID-19. Similarly, Blackmon et al. (2022) reported comparable rates of SCC in outpatient (n = 76) and hospitalized patients (n = 26) (27–40 %) on average 24 days after confirmed SARS-CoV-2 infection with significantly less objective impairment in outpatients. Almeria et al. (2020) reported SCC in 34 % (n = 12) of their sample of hospitalized patients 10 to 35 days after discharge. Gomzykova et al. (2022) described a cohort of COVID-19 patients with different degrees of disease severity receiving primary health care that included 28.5 % of patients with SCC. A cognitive screening test indicated cognitive impairment in 40 % of these SCC cases. Miskowiak et al. (2021) analyzed a group of patients (N = 29) 3 to 4 months after hospital discharge: 80 % of them reported SCC contrasting with objective cognitive impairment (≤1 *SD* below demographically adjusted norms) in 59 % of these patients. Another cross-sectional study included only patients reporting SCC (N = 52) (Schild et al., 2022): Cognitive screening

tests confirmed objective impairment in 25% and extensive neuropsychological assessment impairment in almost 60% of these patients. Here, we report follow-up data of this cohort.

Only a few studies have reported lower rates of SCC compared to objective test results. One study observed this pattern in $N = 72$ noncritical, mild-to-moderate COVID-19 cases 3.8 months postdiagnosis (15% vs. 40%) (Henneghan et al., 2022). Another study that included individuals following asymptomatic to moderate COVID-19 courses showed that, even when subjects do not report any SCC, objective impairment in selective tasks may be present up to 9 months after infection (Zhao et al., 2022).

These studies generally confirm discrepancies between patients' self-reports and objective neuropsychological test results. To ensure clarity, it is thus important to conduct well-designed studies that clearly define patient groups. This may involve taking into account factors such as the severity of COVID-19, time frames between infection and assessment, and using appropriate methods such as self-reporting versus objective testing, and screening versus more extensive assessment. Solid data for SCC and objective impairment are essential for planning therapeutic interventions and providing reliable patient prognoses (see other contributions to this issue: Hasting et al., 2023; Maurer-Karattup & Rost, 2023; Widmann et al., 2023).

Patients with cognitive impairment within PCS often experience other psychiatric and health-related symptoms. However, results on associations with anxiety, depression, sleep, and fatigue are inconsistent (Almeria et al., 2020; Delgado-Alonso et al., 2022). In one study, only outpatients showed associations of anxiety, depression, fatigue, and pain with objective cognitive test results (Blackmon et al., 2022). When focusing on patients with SCC, Almeria et al. (2021) found higher scores for anxiety and depression in patients reporting SCC than in those who did not. In another study (Miskowiak et al., 2021), objective cognitive impairment correlated with SCC, lower work function, and reduced quality of life in a group of $N = 29$ patients 3–4 months after hospital discharge. Gomzykova et al. (2022) reported that patients with SCC were significantly older, had lower levels of education, and higher scores on depression and anxiety scales than patients without SCC. These findings agree with the results found in a correlation analysis between psychological symptoms (anxiety, depressive symptoms, fatigue, and sleep disturbance) and SCC, but not with objective impairment (Henneghan et al., 2022).

This study analyzed the congruence of subjective and objective cognitive performance in a cohort of patients initially presenting with SCC or fatigue as part of PCS. To our knowledge, this is the first study to report domain-specific findings. Other factors that might influence subjective perception of cognition, such as depression, anxiety, sleep, quality of life, demographic variables, and personality factors, were taken into account.

Methods

Sample and Procedure

This study was granted ethical approval by the Institutional Review Board of the University of Cologne (20–1501) and was registered at the German Clinical Trials Register (DRKS00024434). Patients self-referred to our specialized neurological or psychiatric post-COVID-19 outpatient clinics between 3/2021 and 9/2021 (latest infection date of a patient in 3/2021). They were assigned to one of the clinics based on available time slots. Patients were invited for a follow-up (FU) assessment at least 6 months after baseline. None of the patients had had vaccinations before their COVID-19 disease.

Inclusion criteria for enrollment were having a history of asymptomatic or mild to moderate acute COVID-19 (i.e., indicated by official proof of infection certificate and no hospitalization during the acute infection), persistent SCC or fatigue at least 3 months after infection, and a minimum age of 18 years. PCS symptoms other than SCC and fatigue were not exclusion criteria and are reported in Table S2 (Schild et al., 2022). Exclusion criteria were a known premorbid mild cognitive impairment, dementia, or a history of severe psychiatric (e.g., depressive episodes, suicidality) or neurological condition within the previous 2 years. Written informed consent was obtained from all patients before their study inclusion.

The baseline visit (minimum 3 months after a COVID-19 infection) and FU included collecting demographic information, obtaining a medical history, blood draw, and psychiatric and neuropsychological assessment. If necessary, further examinations were conducted.

We defined SCC as part of the PCS as a self-perceived cognitive impairment that developed during or after a COVID-19 infection, continued for more than 12 weeks after infection, and could not be explained by other reasons (e.g., comorbidities or medication). We defined fatigue as a somatic, cognitive, or psychiatric state of exhaustion that continued for more than 12 weeks after infection and could not be explained by other reasons. Note that our study does not allow for a clear demarcation between fatigue and SCC or determining which condition is secondary to the other.

SCC and fatigue were part of the inclusion checklist and collected within the initial clinical interview before the neuropsychological assessment. For FU, we implemented

a questionnaire on PCS symptoms. If not stated otherwise, we report here information retrieved from this questionnaire. Patients indicated symptoms experienced at the moment of assessment, e.g., cognitive symptoms or fatigue, among others. We assessed domain-specific subjective cognitive complaints for learning and memory, attention and concentration, executive functions, and language. Where necessary, we explained domains further to the patients, e.g., having problems in organization and planning behavior (executive functions). The cognitive domain of visuoconstruction was not listed. There was a "further comments" section for adding unevaluated symptoms, for elaborated explanations, or any other comments. We generated the values for the variable "global cognition" by counting the number of patients indicating SCC in at least one cognitive domain or showing objective impairment in at least one cognitive domain, respectively.

We administered the cognitive screening test Mini-Mental State Examination (MMSE) at the beginning and the Montreal Cognitive Assessment (MoCA) at the end of each visit (Folstein et al., 1975; Nasreddine et al., 2005). In addition, neuropsychologists with specialized training conducted comprehensive cognitive evaluations based on the DSM-5 framework (except for social cognition). For further information on test selection, see Schild et al. (2022).

Patients were categorized either as having or not having neurocognitive disorder (NCD) based on the normative data on age, sex, and education for these tests. Following the classification of the DSM-5 Manual (American Psychiatric Association, 2013), we assigned NCD if at least two test scores lay below one standard deviation from the mean of the norms. Hence, this study's definition of objective cognitive impairment is based on extended neuropsychological results, not on cognitive screening tests.

Based on subjective and objective impairment, we defined three groups: SCC+NCD– (patients who reported SCC but did not show NCD in neuropsychological assessment), SCC+NCD+ (patients who reported SCC and showed NCD), and SCC– (patients who did not report SCC; including patients with and without NCD). Because of the small sample size for the SCC– group, we did not further differentiate between NCD+ and NCD–. At baseline, two patients reported fatigue and no SCC, $n = 1$ patient (2.38%) having SCC–NCD+ and $n = 1$ SCC–NCD– (2.38%); at FU, $n = 1$ patient (2.38%) had SCC–NCD+ and $n = 4$ patients had SCC–NCD– (9.52%). We assessed detailed data on SCC only at FU, hence conducting no longitudinal comparisons between groups.

We used additional questionnaires to assess symptoms of depression and anxiety (Hospital Anxiety and Depression Scale, HADS; Herrmann-Lingen et al., 2018), fatigue (Fatigue Severity Scale, FSS; Krupp, 1989), sleep quality (Pittsburgh Sleep Quality Index, PSQI; Buysse et al., 1989), and daytime sleepiness (Epworth Sleepiness Scale, ESS; Johns, 1991). We determined the quality of life using the Short-Form-36 Health Survey (SF-36; Bullinger et al., 1995). We then created a total general health score by computing the unweighted mean of the domain-specific values of the SF-36 (range 0–100, with lower values indicating worse health ratings). For FU visits, we implemented a questionnaire assessing the Big Five personality traits in the test battery (BFI-10; Rammstedt et al., 2012). Again, we report no longitudinal comparisons for these variables here as we plan to analyze group differences at FU using these scales.

Statistical Analyses

We carried out statistical data processing using the software R (Version 2022.07.0; R Core Team, 2022). We used an alpha level of $p < .05$ for all statistical tests. We performed variance analyses to test for differences between SCC/NCD groups in relevant variables at FU; namely, we performed ANOVA to analyze possible group differences concerning age, years of education, MoCA score, BFI-10 subscales, HADS depression and anxiety, ESS score, and SF-36 total score. If the ANOVA yielded significant results, we performed Tukey's posthoc tests for adjusting *p*-values to examine pairwise group comparisons.

However, if assumptions for ANOVA analyses were not met, we applied Kruskal-Wallis tests for multiple comparisons; this concerned the scores for premorbid IQ, MMSE, BFI-10 subscales (Extraversion, Agreeableness, Neuroticism, Openness), PSQI, and days between infection and baseline assessment and between infection and FU assessment. If Kruskal-Wallis tests yielded significant results, we performed Dunn's posthoc tests with Bonferroni correction to examine pairwise group comparisons.

Furthermore, we performed Fisher's exact test for associations between groups and gender distribution.

Results

Sample Demographics

This analysis included $N = 42$ patients (FU M_{Age} = 46.21 years, SD_{Age} = 10.29 years, 18 male) who completed the baseline and FU assessments. Ten patients who initially completed the baseline assessment were excluded because of incomplete data at FU. We administered FU assessments on average 448.14 days after infection (SD = 126.17). The level of education was high, with a mean of 15.79 years of education (SD = 2.28).

Reports of SCC and Objective Impairment at Baseline and FU

At baseline, only two patients (4.76 %) did not report SCC (SCC–). Of those reporting SCC, 25 patients showed objective cognitive impairment (59.52 %, SCC+NCD+), while 15 did not (35.71 %, SCC+NCD–). The rate of SCC in the sample decreased from baseline to FU by 11.90 % (5 patients did not report SCC anymore). Of the 37 patients who reported SCC at FU, 17 showed objective cognitive impairment (40.48 %, SCC+NCD+), while 20 did not (47.62 %, SCC+NCD–; Table 1). However, Fisher's exact test for nominal data did not show significant associations between group distributions and time points, $p = .204$.

Table 1. Demographic, personality, and psychiatric information for the three groups depending on the presence of SCC and NCD at FU ($N = 42$)

	Sample	Group					
Demographics	$N = 42$	SCC+NCD– $N = 20$; 47.62 %	SCC+NCD+ $N = 17$; 40.48 %	SCC– $N = 5$; 11.90 %			
					F/χ^2	p	Direction
Male, N (%)	18 (42.86)	9 (45.00)	6 (35.29)	3 (60.00)		.682[a]	
	M (SD)	M (SD)	M (SD)	M (SD)			
Age, years	46.21 (10.29)	45.15 (9.31)	47.59 (11.57)	45.80 (11.12)	0.26[b]	.770	
Premorbid IQ	107.44 (10.94)[c]	110.05 (8.57)	102.71 (12.60)	114.50 (6.61)[d]	7.99[e]	.018	Posthoc test *n. s.*[f]
Education, years	15.79 (2.28)	16.40 (2.30)	14.76 (1.99)	16.80 (2.17)	3.25[b]	<.050	Posthoc test *n. s.*[g]
Time infection – Baseline, days	243.88 (121.74)	246.80 (133.64)	252.24 (126.55)	203.80 (25.88)	0.13[e]	.939	
Time infection – FU, days	448.14 (126.17)	450.40 (138.83)	459.53 (129.51)	400.40 (33.26)	0.42[e]	.661	
Cognitive screenings							
MMSE (< 27)		29.50 (0.76)	29.41 (1.23)	30.00 (0.00)	2.42[e]	.298	
MoCA (≤ 25)		27.85 (1.63)	25.94 (2.79)	28.00 (2.55)	3.69[b]	.034	SCC+NCD+ < SCC+NCD–[g]
Personality facets BFI-10							
Extraversion		3.47 (0.81)[h]	3.29 (1.22)[i]	3.50 (1.08)[d]	0.13[e]	.936	
Agreeableness		3.30 (0.70)[h]	3.46 (0.82)[i]	3.12 (1.49)[d]	0.37[e]	.831	
Conscientiousness		3.73 (0.94)[h]	3.82 (0.91)[i]	3.88 (0.75)[d]	0.06[b]	.947	
Neuroticism		2.87 (0.88)[h]	3.04 (1.17)[i]	2.62 (1.11)[d]	0.47[e]	.791	
Openness		3.73 (1.15)[h]	2.79 (0.99)[i]	2.25 (0.87)[d]	7.74[e]	.021	Posthoc test n. s.[f]
Psychiatric and health-related scales (cut-offs)							
HADS Depression (>10)		6.60 (4.60)	6.82 (5.26)	4.40 (3.44)	0.52[b]	.598	
HADS Anxiety (>10)		7.10 (3.88)	6.81 (5.00)[j]	5.40 (3.51)	0.31[b]	.735	
FSS (>36)		38.05 (15.91)	44.35 (15.41)	23.80 (12.76)	3.50[b]	.040	SCC+NCD+>SCC–[g]
PSQI (>10)		7.70 (3.28)	9.24 (5.07)	8.80 (3.96)	0.46[e]	.795	
ESS (>10)		9.40 (4.47)	10.71 (5.61)	5.60 (3.36)	2.12[b]	.133	
SF-36 Total		52.84 (18.38)	50.38 (24.40)	77.69 (12.49)	3.57[b]	.038	SCC+ NCD+ < SCC–[g]

Notes. SCC+ NCD– = presence of SCC, but no NCD; SCC+ NCD+ = presence of SCC and NCD; SCC– = no presence of SCC. [a]Fisher's exact test; [b]F value (ANOVA); [c]$N = 41$; [d]$N = 4$; [e]χ^2 (Kruskal-Wallis Test); [f]Dunn Test with Bonferroni corrected p-values; [g]Tukey Test; [h]$N = 15$; [i]$N = 14$; [j]$N = 16$.

Congruence Between SCC and Objective Results at FU

Concerning FU data, we observed discrepancies between reports of SCC in a semistructured interview and objective impairment based on neuropsychological assessment (Table 2). Regarding global cognition, the congruence rate, defined as the percentage of SCC confirmed by objective impairment in extensive neuropsychological assessment, was only 48.65%. The discrepancy remained for specific cognitive domains. Reports of SCC in specific domains were confirmed by objective test results in 46.67% for learning and memory, 50.00% for executive functions, 34.78% for language, and only 24.24% for attention and concentration. Deficits in the domain of visuoconstruction were not subjectively perceived. Domain-specific impairment rates for objective cognition will be reported elsewhere (Schild et al., 2023; in prep.).

Differences Between Groups SCC+NCD–, SCC+NCD+, and SCC– at FU

Demographic Variables

While there were no significant differences between SCC+NCD–, SCC+NCD+, and SCC– groups regarding age at FU, $F(2, 39) = 0.26$, $p = .770$, $\eta^2 = .013$, gender, $p = .682$, or time between infection and baseline, $\chi^2(2, N = 42) = 0.13$, $p = .939$, and time between infection and FU, $\chi^2(2, N = 42) = 0.42$, $p = .661$, a Kruskal-Wallis test found significant group differences in premorbid IQ, $\chi^2(2, N = 41) = 7.99$, $p = .018$. However, subsequent Dunn's posthoc group comparisons yielded no significant results. Descriptively, the mean premorbid IQ was lowest in the SCC+NCD+ group and highest in the SCC– group (Table 1). ANOVA also found significant group differences in years of education, $F(2, 39) = 3.25$, $p = .050$, $\eta^2 = .143$, although Tukey's posthoc group comparisons yielded no significant results. Descriptively, however, it showed the same pattern as premorbid IQ, with the SCC+NCD+ having the lowest and SCC– group having the highest mean in years of education (Table 1).

Personality

The Kruskal-Wallis test found significant group differences only in the personality factor openness, $\chi^2(2, N = 32) = 9.51$, $p = .009$. Again, subsequent Dunn's posthoc group comparisons found no significant results.

Psychiatric and Health-Related Scales

For FSS, mean group sum scores of SCC+NCD– and SCC+NCD+, but not SCC– group, were above the cut-off (>36) at FU, indicating clinically relevant severity of fatigue symptoms. An ANOVA comparing FSS sum scores across groups showed significant results, $F(2, 39) = 3.50$, $p = .040$, $\eta^2 = .152$. Subsequently, Tukey's posthoc pairwise comparisons indicated higher values, meaning greater fatigue symptoms, for the SCC+NCD+ group compared to the SCC– group, $t(39) = -2.62$, $p = .033$, $d = -1.33$. There were 11 patients from the SCC+NCD– group with a score above the cut-off for FSS, 13 patients of the SCC+NCD+, and 1 of the SCC– group who scored for clinically relevant severity of fatigue symptoms.

Regarding the HADS subscales of depression and anxiety as well as PSQI scores, no group-level mean scores lay above the cut-off (>10) or showed significant differences in sum scores across groups.

Table 2. Frequencies of subjective cognitive decline compared with objective cognitive impairment at FU in general and grouped for different cognitive domains ($N = 42$)

	Subjective impairment; semistructured interview *N* (%)	Congruence between subjective and objective impairment %
Global cognition		
Cognitive impairment	37 (88.10)	48.65
Cognitive domain		
Learning and memory	30 (71.43)	46.67
Attention and concentration	33 (78.57)	24.24
Executive functions	22 (52.38)	50.00
Language	23 (54.76)	34.78
Visuoconstruction	0 (0.00)	/

Notes. Objective impairment is defined when patients fulfill NCD criteria showing below-threshold test performance in this domain. Congruence of subjective and objective impairment is defined as a percentage of subjective impairment confirmed by objective impairment in extensive neuropsychological assessment.

While the mean score for the SCC+NCD+ group was above the clinically-relevant cut-off (>10) for the ESS, there were no significant differences in sum scores across groups.

Finally, we found significant differences in the SF-36 total score across groups, $F(2, 39) = 3.57$, $p = .038$, $\eta^2 = .155$. Subsequently, Tukey's posthoc pairwise comparisons indicated lower values, meaning a worse health-related quality of life, for the SCC+NCD+ group compared to the SCC– group, $t(39) = 2.61$, $p = .034$, $d = 1.33$. Group means for the SF-36 subscales at FU may be found in Figure 1. The SCC– group had the highest quality of life across all domains. The SCC+NCD+ and SCC+NCD– groups were most affected by role limitations because of physical health and energy/fatigue. While SCC+NCD– patients also were severely impaired in their role functions because of emotional problems, this was much less pronounced in SCC+NCD+ patients. Additionally, the impact of pain on health-related quality of life was descriptively most pronounced in SCC+NCD+ patients.

Cognitive Screening Tests

MMSE scores did not differ between groups and showed little variance, indicating ceiling effects. Additionally, the screening test detected cognitive impairment (<27) in only one patient from the SCC+NCD+ group.

MoCA scores differed significantly between groups, $F(2, 39) = 3.69$, $p = .034$, $\eta^2 = .159$. Tukey's posthoc comparisons indicated significant differences between SCC+NCD+ and SCC+NCD– groups, $t(39) = 2.55$, $p = .039$, $d = 0.84$. The MoCA indicated cognitive impairment (<26) in a total of 10 patients (SCC+NCD– = 2 patients, SCC+NCD+ = 7, and SCC– = 1).

Discussion

This study analyzed the congruence between SCC and objective neuropsychological test results in patients at FU who reported SCC or fatigue at study inclusion. Moreover, we considered the potential influence of associated variables. We collected data on demographics, SCC, neuropsychological functions, personality factors, and psychiatric and health-related variables in patients who self-referred to the post-COVID outpatient clinic.

The results suggest a reduction in SCC and objective impairment from study inclusion over 15 months. The congruence between SCC and objective impairment was approximately 40 % for both visits, indicating a higher rate of patients reporting SCC than presenting objective impairment. There was a significant group difference at FU for premorbid IQ and years of education, although posthoc comparisons were not significant. SCC+NCD– patients showed higher openness trait scores than SCC+NCD+ patients. Psychiatric profiles were comparable in these

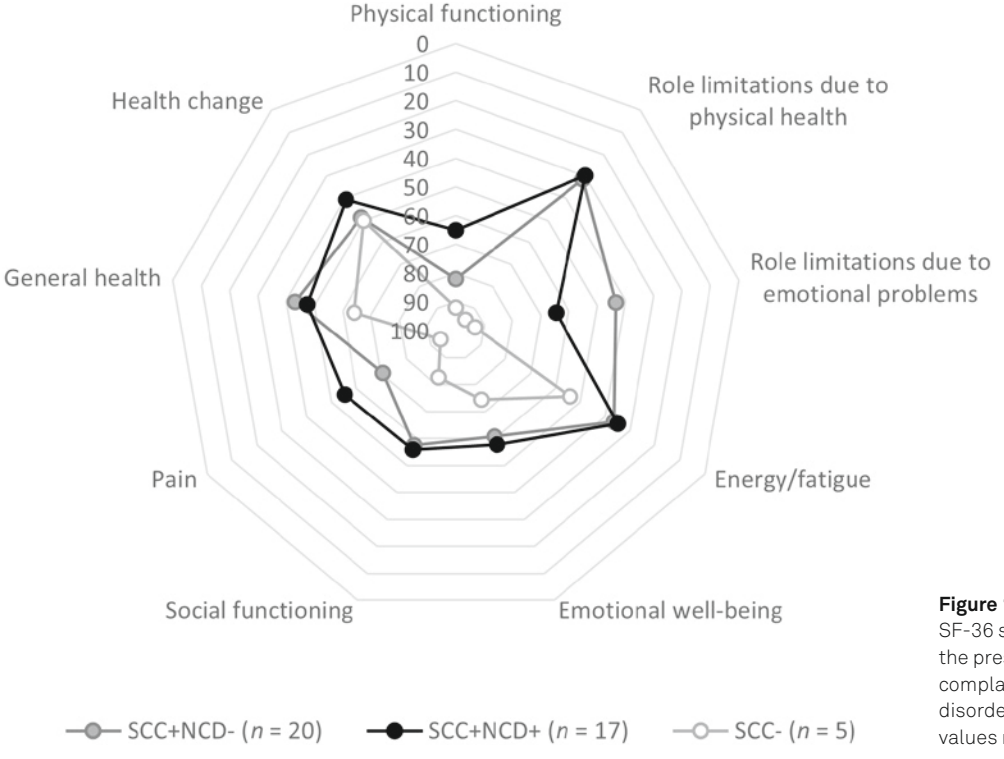

Figure 1. Network diagram of means for SF-36 subscales grouped depending on the presence of subjective cognitive complaints (SCC) and neurocognitive disorder (NCD) at FU ($N = 42$). Higher values reflect a higher quality of life.

groups. SCC+NCD+ patients, on the other hand, showed significantly higher fatigue scores and lower quality of life than SCC– patients. The detection rate of cognitive deficits was much higher when applying extensive neuropsychological tests as compared to cognitive screening tests.

Reports of SCC and Objective Impairment at Baseline and FU

Throughout the study, fewer patients reported SCC. Additionally, fewer patients were diagnosed with objective cognitive impairment, irrespective of SCC. Nevertheless, about 88 % of patients reported SCC 15 months after COVID-19. In comparison, the observation time frame in our study was longer than in other studies reporting data only up to 1 year after infection (Ceban et al., 2022; Han et al., 2022; Heesakkers et al., 2022; Kim et al., 2022). These studies focused on different disease severities of acute infection and different methods to assess cognitive impairment and do not report longitudinal results of extensive neuropsychological assessment. This limits the generalizability and comparability of these results to our study. Data from a cohort of nonhospitalized patients using cognitive screening tools showed a slight reduction in SCC rate over time (3 months compared to 6–7 months; del Corral et al., 2022). Another study of hospitalized patients showed a slight increase in SCC from 3 months to 1 year FU (Lorent et al., 2022). Our data, based on detailed neuropsychological testing, are congruent with the trend of cognitive improvement over time, showing overall high rates of affected patients with higher proportions of SCC than for objective impairment.

Congruence Between SCC and Objective Results at FU

SCC rates were high, even 15 months after COVID-19. We found a considerable discrepancy of about 50 % between SCC and objective impairment at FU for global cognition and specific cognitive domains. Interestingly, no patient reported impairment in visuoconstructional abilities. It is important to point out that visuoconstruction was not explicitly mentioned on the PCS symptom checklist. However, no patient mentioned this deficit in the "further comments" section. To the best of our knowledge, this is the first study to indicate SCC in all cognitive domains (except for visuoconstruction).

Clinicians frequently encounter a discrepancy between the deficits reported by patients and their neuropsychological test results. This might reflect the difficulty of evaluating one's own cognitive functioning in both ways: neglecting objective impairment versus subjective overestimation of cognitive impairment (Adewusi et al., 2021; Shulman et al., 2006; Voruz et al., 2022). Alternative explanations might be the following: (1) The cognitive performance level of patients showing a discrepancy between SCC and objective, measurable impairment might be above average even though deficits have developed or have elevated cognitive reserve capacities enabling results within the normative range. (2) Objective cognitive impairment might result from a longer period of increased cognitive effort, i.e., a secondary effect of fatigue. (3) Other factors such as personality traits, psychiatric, or health-related problems. Further research is necessary to acquire additional insights into these potential explanations.

Differences Between Groups SCC+NCD–, SCC+NCD+, and SCC– at FU

Our sample is characterized by an average age of 49 years and a relatively high level of education, comparable to samples from other studies on cognition and PCS (Becker et al., 2021; Ceban et al., 2022; Hampshire et al., 2021; Han et al., 2022). Significant group differences resulted for years of education and premorbid IQ, although subsequent posthoc tests detected no significant differences. Descriptively, SCC+NCD– and SCC– patients had higher IQ scores and more years of education than SCC+NCD+ patients. These findings might indicate a generally higher performance level of these patients: A large meta-analysis (N = 615,812) found positive correlations between IQ and education years (Ritchie & Tucker-Drob, 2018). The DSM-5 also acknowledges the problem of measuring cognitive impairment in patients with a high level of education (Falkai et al., 2018).

When we considered personality factors according to the 5-factor theory of personality (Costa & McCrae, 1992), we found significant group differences only for Openness, whereas posthoc tests failed to confirm significance. Descriptively, SCC+NCD– patients scored higher than the other two groups. Openness to new experiences is associated with characteristics such as unconventional thinking, curiosity, imagination, and intellect (McCrae & Costa, 1997). Additionally, Openness is a personality trait that correlates highly with intelligence (Anglim et al., 2022). Whether personality factors play a significant role in the context of PCS needs to be investigated in future studies.

A significant group effect resulted in higher fatigue scores in SCC+NCD+ than in SCC– patients. Nevertheless, the fatigue scores for both SCC+ groups, either NCD+ or NCD–, lay above the cut-off value for clinically relevant fatigue, and absolute numbers were also comparable between these groups. Hence, our data do not provide clear evidence that fatigue was directly or exclusively associated with NCD+. In most studies, fatigue or other psychiatric and health-related variables are treated as independent outcome variables and not as covariates of cognitive functions (Ceban et al., 2022; Premraj et al.,

2022). Future studies should address this relationship. We cannot exclude that fatigue may have been triggered in some of our patients by the strain of sustained effort required to pass the neuropsychological assessment. The patients expressed that the assessment did not accurately represent their everyday or professional lives, which requires prompt and sustained responsiveness. This would contrast with the time-limited and highly focussed test situation of the neuropsychological evaluation. Self-report questionnaires might be more reliable because they assess everyday functioning, compared to objective neuropsychological tests that refer only to one specific situation (Henneghan et al., 2022). Qualitative and quantitative approaches that extensively "translate" subjective impairment into objective results are needed to gain more insights. Additionally, SCC should be evaluated in more detail, e.g., the degree of impairment (subtle vs. severe) or its presentation (consistent vs. fluctuating) should be considered in future studies.

Other psychiatric characteristics, such as depression, anxiety, or sleep quality, did not differ between groups and exceeded clinical cut-off scores. The fatigue score was elevated for all three groups, whereas daytime sleepiness was above the cut-off only for SCC+NCD+ patients. On the contrary, both SCC groups showed comparable reductions in health-related quality of life, in particular in domains of physical health and energy/fatigue and, for SCC+NCD+ patients, also emotional problems. This corresponds to other findings on quality of life, even though these studies did not focus on subjective and objective cognitive impairment (Huang et al., 2022; Lorent et al., 2022). To conclude, the relationship between neuropsychiatric and health-related variables, such as depression, anxiety, fatigue symptoms, sleep quality, and subjective and objective impairments in patients with PCS remains unclear. Therefore, we need to consider alternative explanations that better reflect the complex relationship between cognition and neuropsychiatric symptoms of PCS rather than assuming direct associations between them (Scharfenberg et al., 2022).

The cognitive screening test MMSE did not reveal significant group differences; only one patient scored below the threshold of cognitive impairment. In contrast, the MoCA detected significant group differences between SCC+NCD+ and SCC+NCD− patients. In the group of SCC+NCD+ patients ($n = 17$), only 7 patients scored below the threshold in this screening test, suggesting that this cognitive screening test did not detect cognitive impairment in more than half of the patients presenting with objective cognitive impairment as measured by extensive neuropsychological assessment. This clearly indicates that an in-depth neuropsychological assessment may more reliably detect cognitive impairment than less sensitive cognitive screening tests, particularly in patients with mild symptom severity (Bertuccelli et al., 2022; Ceban et al., 2022; Koczulla et al., 2022; Peper & Schott, 2021). Therefore, studies employing cognitive screening tests may underestimate the prevalence of objective cognitive impairment rates. These findings are consistent with the baseline data of our study (Schild et al., 2022); nevertheless, additional research is needed to further investigate this highly pertinent topic.

Limitations

The following limitations should be considered: First, the sample size was relatively small, and we included only patients with mild acute COVID-19 courses who had been infected before the availability of vaccination in Germany. Second, the study sample may have been subject to selection bias because of self-referral. Third, although we focused explicitly on patients with SCC following COVID-19, a control group consisting of patients without SCC or patients without COVID-19 could have potentially yielded further insights: A healthy control group would have allowed us to evaluate comparable environmental circumstances during the global pandemic; however, in our study, we compared test scores to prepandemic normative data, which could not guarantee such comparability. Fourth, our sample did not assess cognitive performance in neurocognitive domains before the global pandemic; some patients might already have had high levels of cognitive performance before the pandemic that declined because of COVID-19 and PCS but were still within the normative range, therefore not warranting classification of NCD. Finally, the group of patients not reporting SCC is very small, so the reduced statistical power may have masked group differences.

Relevance for Practice

A major strength of this study is its focus on a rarely investigated issue that considerably influences further diagnostic and therapeutic approaches. This is the first longitudinal study to describe both subjective and objective cognitive impairment over 15 months. It demonstrates the relevance of distinguishing between subjective and objective cognitive impairment. In addition, monitoring other pertinent factors, such as fatigue, quality of life, sleep, etc., may be useful for gaining a more comprehensive understanding of the patient's overall well-being (Blackmon et al., 2022). This study found that fatigue scores exceeded

the clinical threshold among patients reporting SCC. Therefore, we highly recommend that patients who report SCC and fatigue undergo a thorough neuropsychological assessment.

Further data are required, particularly on individuals with asymptomatic to mild COVID-19 disease courses, to establish initial decision-making flow charts for neuropsychologists (Blackmon et al., 2022). This also applies to treatment options aimed at enhancing cognition, such as cognitive training, as their effectiveness in patients with PCS has not yet proved to be as high as in other patient populations. In particular, it is crucial to consider this in light of other symptoms, such as fatigue, which may impede treatment compliance.

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History
Received: February 15, 2023
Accepted: March 10, 2023

Acknowledgement
We want to thank all patients who participated in our study. Moreover, we thank all reviewers and the editorial team of this issue for their helpful comments and language corrections.

Conflict of Interest
The authors AKS, DS, LK, KK, AR, YG, DM, LS, FS, CF, SJ, and FM have no relevant financial or nonfinancial interests to disclose. GRF serves on the editorial board of *Cortex, Neurological Research and Practice, NeuroImage: Clinical, Zeitschrift für Neuropsychologie,* and *DGNeurologie*; receives royalties from the publication of the books *Funktionelle MRT in Psychiatrie und Neurologie, Neurologische Differentialdiagnose, and SOP Neurologie*; receives royalties from the publication of the neuropsychological tests *KAS and Köpps*; received honoraria for speaking engagements from Bayer, Desitin, DGN, Ergo DKV, Forum für medizinische Fortbildung (Forum for Medical Education) FomF GmbH, GSK, Medica Academy Messe Düsseldorf, Medicbrain Healthcare, Novartis, Pfizer, and Sportärztebund NRW. FJ receives fees for advice and presentations (2020–2022) for Abbvie, AC immune, Biogen, Eisai, GE Healthcare, Grifols, Janssen, Lilly, MSD, and Novo Nordisk Roche. OAO received honoraria from Biogen and Boston Scientific, which does not relate to the contents of this publication. CW has received institutional support from Novartis, Alexion, Sanofi Genzyme, Biogen, and Roche, unrelated to the submitted work, and received personal compensation from BioNTech for participating in an educational discussion.

Funding
The research leading to these results received funding from the German Research Foundation under grant nos. PR 1274/8–1; FR 4479/1–1; WA4101/2–1, supporting CF (FR 4479/1–1) and CW (WA 410/2–1). Open access publication enabled by the University of Cologne.

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