Original Article

The Leipzig Treatment Program for Interdisciplinary Diagnosis and Therapy of Neurocognitive Post-COVID Symptoms

Experiences and Preliminary Results

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Abstract: This study introduces a 3-week group program designed for patients with neurocognitive post-COVID-19 syndrome (PCS). The program represents a combination of evidence-based components of neurorehabilitation and cognitive behavioral therapy (CBT). Following a detailed assessment, we develop a personalized bio-psycho-social model that integrates perceived complaints and identifies modifiable and influencing factors. We employed physiotherapeutic, cognitive, and communicative training methods to improve patients' awareness of energy limits and implement compensatory strategies, including pacing and mindfulness techniques. *N* = 33 patients completed the program between June 2021 and November 2022. A pre-post comparison of questionnaire-based self-assessments revealed significant positive effects on mood, self-efficacy, and participation but not on fatigue symptoms. The study provides recommendations for the neuropsychological treatment of patients with PCS.

Keywords: neuropsychological therapy, post-COVID, fatigue, pacing, neurocognitive PCS

Das Leipziger Behandlungsprogramm zur interdisziplinären Diagnostik und Therapie neurokognitiver Post-COVID-Symptome: Erfahrungen und erste Ergebnisse

Zusammenfassung: Wir stellen ein 3-wöchiges Gruppenprogramm für Betroffene mit neurokognitivem Post-COVID-Syndrom (PCS) vor. Es kombiniert evidenzbasierte Komponenten der Neurorehabilitation mit Elementen der kognitiven Verhaltenstherapie. Nach einem ausführlichen Assessment wird ein bio-psycho-soziales Modell erarbeitet, anhand dessen individuelle Beschwerden berücksichtigt und beeinflussende und modifizierbare Faktoren identifiziert werden. Physiotherapeutisches, sprachtherapeutisches und kognitives Funktionstraining dienen u. a. der verbesserten Wahrnehmung eigener Energiegrenzen und der Umsetzung kompensatorischer Strategien, einschließlich Pacing- und Achtsamkeitstechniken. 33 Betroffene absolvierten das Programm zwischen Juni 2021 und November 2022. Prä-Post-Vergleiche fragebogenbasierter Selbsteinschätzungen zeigten signifikant positive Effekte auf Stimmung, Selbstwirksamkeit und Partizipation, während sich für die Fatigue kein signifikanter Effekt zeigte. Wir leiten Empfehlungen für die neuropsychologische Behandlung von Menschen mit PCS ab.

Schlüsselwörter: Neuropsychologische Therapie, Post-COVID, Fatigue, Pacing, neurokognitives PCS

Introduction

The post-COVID-19 syndrome (PCS) is characterized by the presence of symptoms that persist beyond 12 weeks after the resolution of an acute COVID-19 infection (Koczulla et al., 2022). PCS is commonly regarded as a debilitating illness that affects approximately 10 % of individuals following SARS-CoV-2 infection (Davis et al., 2023). The symptomatology of PCS is heterogeneous but frequently comprises neurocognitive impairment, fatigue, and mental disorders. PCS may occur irrespective of age or severity of the acute illness, with the highest number of diagnoses found among individuals aged 36 to 50 years (Hartung et al., 2022). In the latter study, fatigue was the most prominent symptom among PCS patients and was common among females, younger individuals, and those

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with a history of depression or a higher number of acute COVID symptoms. While certain symptoms, such as mental health conditions, may ameliorate within the first year following infection, a noteworthy proportion of patients continue to experience persistent symptoms that may interfere with their ability to resume work.

Cognitive deficits are frequent and can affect all domains, including attention, memory, executive function, and language (Hampshire et al., 2021; Koczulla et al., 2022). Hartung et al. (2022) found that factors associated with cognitive impairment include older age, male gender, shorter education, and history of neuropsychiatric disease. There is evidence that cognitive impairment may worsen over time (Holdsworth et al., 2022; Taquet et al., 2022). Furthermore, cognitive impairment is independent of mental health conditions and can occur in hospitalized and nonhospitalized patients following COVID-19 (Woo et al., 2020). Moreover, elderly patients with mild cognitive impairment may have an increased risk of converting to dementia status (Liu et al., 2021; Perrottelli et al., 2022).

Several biological hypotheses about the pathological mechanisms underlying PCS have been proposed, opening perspectives for medical treatment (Davis et al., 2023). Because mental disorders (particularly depression, anxiety, or somatic stress disorders) often co-occur with PCS, it is being debated whether these are indicators of the effect of the virus on the brain, a reaction to the experienced impairment, or an exacerbation of premorbid mental disorders (e.g., Mazza et al., 2022). That a pre-existing psychiatric disorder comprises a risk factor for post-COVID depression might be explained by negative thinking styles (Palladini et al., 2021), reducing the capacity to cope with restrictions because of the illness. An alternative explanation is that altered neuroimmunological conditions observed in depression (Gorlova et al., 2023) may increase vulnerability for PCS. Either way, post-COVID depression seems to exacerbate both fatigue and neurocognitive symptoms (Gouraud et al., 2021; Poletti et al., 2021). Although pharmacological trials are underway, no causal medical treatment is currently considered evidence-based or applicable to the general population. Therefore, symptomatic treatment is warranted, and an integrative, interdisciplinary approach appears most promising. Because clinical neuropsychology traditionally lies at the intersection of physical and mental illness, it may play a crucial role in diagnosing and treating PCS.

Neurocognitive symptoms and fatigue are commonly seen in other postinfection syndromes (Choutka et al., 2022) and neuroimmunological conditions such as multiple sclerosis (MS; Hansen et al., 2021). Thus, neuropsychologists have substantial experience treating most functional impairments commonly reported for PCS. Cognitive rehabilitation is widely accepted for treating cognitive impairment in other neurological diseases. Measures may include specific and repetitive training of circumscribed cognitive functions and the establishment of compensatory strategies. Of special relevance is the adaptation of memory aids, checklists, or digital reminders as well as modifying the person's environment (Thöne-Otto et al., 2020). Compensation for attention deficits may include allowing more time for tasks, taking more frequent breaks, or scheduling appointments according to individual attentional resources. In addition, neuropsychological therapy may involve assisting the patient in reassessing their strengths and weaknesses, increasing awareness of energy limits, adapting their personal goals, and strengthening their self-confidence (cf. German Guidelines for Neuropsychological Treatment, https://www.gnp.de/fachinformationen/leitlinien). To complement well-established neuropsychological therapy for cognitive impairment with treatment options for fatigue, we reviewed the literature to identify the most promising approaches and compiled these into the 10-day treatment program outlined below.

Heine et al. (2015) analyzed 45 studies involving 2,250 people with MS, assessing the effects of exercise therapy. The authors conclude that exercise therapy may reduce fatigue. Potential negative side effects (e.g., increase in MS relapses) did not differ between the treated and control groups. Despite promising results, the authors suggest conducting additional research to ascertain the suitability of exercise as a treatment option for patients with severe manifestations of fatigue.

After conducting a narrative review of 14 studies, including ten randomized controlled trials, Garis et al. (2021) recommend yoga as an add-on treatment for people with MS. The authors propose that practicing yoga, particularly through breathing exercises, may improve the interaction between the sympathetic and parasympathetic nervous systems, which may alleviate fatigue. Lovette et al. (2022) reviewed the effects of mindfulness-based interventions for patients with mild TBI. They reviewed 29 studies and rated the impact on eight outcome domains. Qualitative results described benefits across all domains. Therefore, the authors concluded that mindfulness-based interventions exert an impact on diverse clinical domains, including cognition, with a specific emphasis on attention.

Another group of patients prone to cognitive impairment and fatigue are those with cancer. According to the European Society for Medical Oncology (ESMO) guidelines (Fabi et al., 2020), based on systematic reviews and meta-analyses, exercise during active treatment may reduce systemic inflammation and improve cancer-related fatigue. However, there is no specific exercise regimen but rather a focus on overall well-being. Psychosocial interventions reviewed in the guidelines included psychosocial counseling, psychotherapy, psychoeducation, and mind-body interventions.

Besides secondary fatigue in neurological and other diseases, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) was studied well before the SARS-CoV-2-pandemic. The fact that a subset of PCS patients suffers from CFS highlights the importance of respective treatment guidelines for our endeavor. The effect of exercise training has been debated for these patients. For some patients, especially those with postexertional malaise (PEM), some reports indicated the risk of symptoms worsening after training (The National Institute for Health and Care Excellence (NICE), 2021). Similarly, the effect of CBT was questioned, given that CFS is acknowledged as a systemic disease that may not be treatable with psychological means. In this context, Bested and Marshall (2015) described the benefits of CBT as follows: "What CBT can do is to help patients cope with being chronically ill and manage their emotional reactions better so that they do not waste valuable energy on worrying or feeling guilty about things that they cannot control" (p. 242).

The German Long/Post-COVID Guideline (Koczulla et al., 2022) recommends treatment strategies like those described above, the primary goal being symptom relief and preventing chronicity. Treatment should include improvement of sleep and pain, stress reduction and relaxation, strengthening of individual resources, and support for appropriate coping strategies (neither excessive demands nor inappropriate avoidance of activities). Individuals may receive instruction to metered exercise training, cognitive performance training, and/or psychotherapeutic or psychopharmacological treatment depending on the individual symptoms, which may be physical, cognitive, or emotional. PEM should be prevented by carefully dosing and, if necessary, supervising physical activity and individualized energy management (pacing).

At the outset of our treatment program development, there existed little research on neuropsychological rehabilitation modalities tailored to patients diagnosed with PCS. In the meantime, a few interdisciplinary approaches have become available: Garcia-Molina et al. (2021, 2022) applied an 8-week outpatient neurorehabilitation program for patients with PCS, including neuropsychological rehabilitation (cognitive training, compensatory strategies, and mood intervention). Patients received cognitive training at home with individualized tasks based on pretreatment assessment. The implementation of the program yielded significant enhancements in memory and verbal fluency.

Palladini et al. (2021) reported the results of a case-control study with a 2-month cognitive remediation program. They found a significant effect on global cognitive functioning, verbal fluency, and executive functions, with no effect in a control group. A 6-week program evaluated by Daynes et al. (2021) focused on aerobic exercise and reported positive effects on global cognitive function and depression. Finally, Albu et al. (2021) reported an 8-week multidisciplinary program and found improvements in several functions, including fatigue and cognitive performance. Two other study protocols described interdisciplinary rehabilitation programs that address breathing, cognitive deficits, and fatigue (Besnier et al., 2022; Kupferschmitt et al., 2022).

Because there is a strong link between cognition, mental state, and fatigue, we evaluated all three aspects of neurocognitive PCS in our patients. Additionally, we offered psychoeducation on coping with the resulting difficulties in everyday life. In line with CBT, we employ a personalized bio-psycho-social model of the disease to identify modifiable variables that may influence symptoms. The program's main goals were to change how patients perceive their impairment and to help them adjust their daily demands to their current condition. This included changing their coping strategies and improving self-help and self-care strategies. We expected improvements in self-assessment of self-efficacy, participation, psychological distress, and severity of depressive symptoms. We also expected secondary improvements in self-reported fatigue upon improving coping and mood.

Methods

Patient Assignment, Inclusion Criteria, and Description of Sample

Patients with PCS were referred to the interdisciplinary post-COVID outpatient consultation at Leipzig University Hospital by a general practitioner or specialist. We then performed basic diagnostics and an internal examination (cardiological or pneumatological). In case of abnormalities in a neuropsychological screening (MoCA test; Nasreddine et al., 2005), self-assessment questionnaires, and/or neuropsychiatric complaints, we added a neurological post-COVID consultation, in which we administered the Post-COVID Functional Status (PCFS) scale as a broad indicator of functional limitations, complemented by a more detailed anamnesis of difficulties in daily living. The PCFS scale was originally developed to guide post-COVID-19 care after hospital discharge and to assess functional sequelae after 6 months (Klok et al., 2020). Because of a prolonged latency period following the infection, some patients in the present sample exhibited low scores on the PCFS; clinical decisions concerning admission to the program were based on the combination of information from the above procedures. If patients were seeking treatment and had sufficient resilience for a day-clinic setting, we admitted them to the treatment program. Content-based inclusion criteria were age between 18 and 65 years, mild to moderate cognitive impairment (MoCA > 20), and/or fatigue as the main complaints. Exclusion criteria comprised other neurological or mental illnesses to be treated with priority. Lier et al. (2022) describe the procedures and the results of a sample of 105 patients examined in the neurological consultation in detail.

35 patients (24 female, 11 male) were admitted to the treatment program between June 2021 and November 2022. One male patient dropped out during treatment after having tested positive for SARS-CoV-2 again and had to be quarantined. Another male patient was unable to meet the program requirements. Thus, this report refers to N = 33 patients who completed the program during this period. Their mean age was 49.2 years (SD ± 9.8). The mean time since their initial SARS-CoV-2 infection was 11.6 months (SD ± 4.3). The mean PCFS at admission was 1.98 (SD ± 0.9). Medical records or clinical interviews indicated a history of mental illness prior to the SARS-CoV-2 infection in 13 patients (39 %). 19 patients (58 %) fulfilled the criteria for a comorbid mental illness (mostly adjustment disorder or depressive episodes) at admission. Table 1 describes the main patient characteristics at baseline.

We obtained written informed consent from each patient and performed all assessment and treatment procedures in accordance with the Declaration of Helsinki (World Medical Association, 2013) as well as local legislation and institutional requirements.

Neuropsychological Assessment

After a brief semistructured clinical interview, patients were subjected to a standardized compilation of neuropsychological tests covering the cognitive domains of *attention* (intensity, selective attention, processing speed and flexibility: Testbatterie zur Aufmerksamkeitsprüfung TAP, Subtests Alertness and Vigilance; Zimmermann & Fimm, 2012; Trail-Making-Test TMT A and B, Rodewald et al., 2012), *memory* (short term and working memory: Wechsler Memory Scale-Revised, Subtests Digit Span forward and backward, Block Span forward and backward, Härting et al., 2000; verbal learning and retention: California Verbal Learning Test CVLT, Niemann et al., 2018) and *executive functions* (logical reasoning: Leistungsprüfsystem, Subtest LPS-3, Horn, 1983; interference processing: Farb-Wort-Interferenz-Test FWIT, Wolfram et al., 1986; action planning and monitoring: Standardisierte Link'sche Probe SLP, Metzler, 2000; verbal fluency: Regensburger Wortflüssigkeitstest, Subtests lexical and semantic word fluency, Aschenbrenner et al., 2000). We implemented the neuropsychological assessment on the first 2 days of the program. Furthermore, patients completed a set of questionnaires on the first and the last day of the program to assess the perceived self-efficacy in symptom coping and level of activity and participation (HEALTH-49 subscale D and E, Rabung et al., 2007), psychological distress because of physical and mental symptoms (Symptom Check List SCL-90-R, Franke, 1995), severity of depressive symptoms (Beck-Depressions-Inventar BDI-II, German version by Hautzinger et al., 2009), fatigue (Fatigue Symptom Severity FSS, Krupp et al., 1989, German version of the Fatigue Impact Scale FIS-D, Häuser et al., 2003), and daytime sleepiness as an indicator for sleep disorders (Epworth Sleepiness Scale ESS, Johns, 1991). To quantify *fatigue* beyond subjective questionnaire data, we applied TAP Alertness testing once in the morning and once at lunchtime after 3 hours of cognitive load. We adapted the procedure of repetitive testing from Neumann et al. (2014), who showed that reaction time performance is sensitive to the effects of fatigue in MS patients. In addition, we administered the TAP Vigilance subtest after 1 pm to assess the impact of fatigue on sustained attention capacity after exposure to mental and physical load (Herzig & Grundl, in press). To assess their satisfaction with the program, patients rated their impression of improvement on the BESS-Scale (Schmidt et al., 2018) at the end of treatment.

Treatment

The outpatient program comprised 10 treatment days within 3 weeks, carried out in a fixed group of 3–4 patients. The therapy modules (cf. Figure 1 for an overview and below for a detailed description) were distributed over 3–4 units per day. Days without therapy and weekends were used for home assignments to try out the group's suggestions in everyday life and to adapt them if necessary.

Two qualified neuropsychologists (certified by the German Neuropsychological Society [Gesellschaft für Neuropsychologie, GNP]) with additional training in CBT conducted the *neuropsychological treatment*. In the first group session, we developed an individually customized bio-psycho-social model of illness and recovery, where patients were guided to focus on modifiable factors and resources. We implemented a symptom-tracking technique, which led patients to assess physical and cognitive capacity as well as mood throughout the day. They learned to evaluate their observations regarding energy highs and lows and possible delayed effects as in PEM. This promoted a more differentiated self-perception and served as an important prerequisite for pacing (Bested & Marshall, 2015), which

Table 1. Demographic, medical, and physiological information, cognitive screening, depression, and fatigue self-assessment at baseline (*N* = 33)

Demographics		*N*	%
Male/female		9/24	27/73
Education 12/10 school years		16/17	48/52
Sociomedical status	Sick leave Working Retired	13 19 1	39 58 3
Medical/physiological information		**N**	**%**
Current diagnoses (ICD-10)	F06.7/F06.8 R53 F43.2/F32.x/F33.x/F45.0	26 27 19	79 82 58
History of mental illness		13	39
Severity of acute disease	Hospitalization/ICU	3/2	15.2
Schellong Test	pathological result		15
	M	*SD*	Range
Months since infection	11.6	4.3	5-24
PCFS	1.98	.9	0-3
Vital capacity ratio	1.3	.24	.84-1.7
6-minute walking test	1.0	.14	.68-1.3
IPN-Test	3.15	1.0	1-5
Cognitive screening			
MoCA score	26.2	2.2	21-30
LPS-3 (percentile)	71.8	5.0	12-98
Depression and fatigue self-assessment			
Depression – BDI-II	16.2	8.6	2-37
Fatigue severity FSS	5.4	1.1	2.1-6.9
Fatigue impact FIS-D	80.4	24.6	31-129

Notes. ICD-10 Diagnoses: F06.7 – mild cognitive impairment; F06.8 – other specified mental disorders due to brain damage and to physical disease; R53 – Fatigue; F43.2 – adjustment disorder, F32.x/F33.x depressive episode or recurrent depressive disorder; F45.0 – somatisation disorder. ICU – Intensive Care Unit. Schellong Test = lying-to-standing orthostatic test; PCFS *Post-COVID-Functional Status* ranges from Score 0 (no limitations) to Score 4 (severe limitations). *Vital capacity ratio* ("Spirotest" Riester GmbH, Jungingen, Germany), ratio from 1 = normal, < 1 = below average, > 1 above average. 6 Minute Walking Test: ratio actual/target (Butland et al., 1982), ratio from 1 = normal, < 1 = below average, > 1 above average; IPN-Test: performance quotient (Institute for Prevention and Aftercare IPN, Trunz, 1997). MoCA *Montreal Cognitive Assessment* Score < 26 indicates cognitive impairment. LPS-3 *Leistungsprüfsystem subtest 3* – test of logical reasoning, percentile according to the age-specific norm; BDI-II *Beck Depression Scale* score 9-13 minimally depressed; 14-19 mildly depressed; 20-28 moderately depressed; FSS *Fatigue Severity Scale* Score 1-7. Fatigue Impact Scale FIS-D sum score (max 120, scores > 50 indicate clinically relevant impairment).

we introduced as a coping strategy. Patients were instructed to actively set priorities and assess their current energy capacity before they started with any given task, set a timer for the estimated capacity, re-evaluate after the set time, and then either to continue for an adapted duration, switch task, or rest. To tackle complex or lengthy tasks, they were broken down into manageable sub-goals, increasing the attentional focus on the task by employing elements of goal management training (Stamenova & Levine, 2019). The patients were encouraged to employ pacing to mental and physical demands throughout the subsequent program and to practice with everyday tasks at home. Information concerning relaxation and mindfulness techniques were provided and practiced, including a 7-minute body scan (modified based on Löhmer et al., 2014). Further sessions focused on compensation strategies for cognitive deficits, psychoeducation on sleep hygiene (adapted from Bested & Marshall, 2015, and Müller & Paterok, 2010), and nutritional counseling. We implemented resource activation in the final group session using the ZRM® images (Storch & Krause, 2018). Neuropsychological treatment also comprised 2–3 sessions of computer-assisted *cognitive training* per week: Tapping into the frequently compromised domains of attention and memory, patients trained selective attention and reaction speed as well as working memory (REVE and WOME by HASOMED/RehaCom®). Once pacing had been introduced, patients chose the duration of training according to their current energy capacity.

Speech and language therapists provided group sessions on communication and text processing, addressing word-finding difficulties and cognitive deficits in communication situations as well as providing another opportunity to apply pacing in a social situation.

Physiotherapy consisted of daily sessions with light to moderate strength and fitness training, mobilization, stretching, and breathing exercises. Exercises from Qi Gong sensitized patients to appreciative body perception and economy of movement. When indicated, patients received advice on self-help to deal with pain or orthostatic disbalance. As in the other therapy modules, the patients were encouraged to implement pacing during physical sessions to adopt optimal activity rhythms.

Social therapists provided information on sociolegal issues in accordance with social security law (SGB IX), including legal support concerning vocational rehabilitation.

Once a week, *medical specialists* held one-to-one consultations with patients to tailor the information given in the group sessions, adapt medication, and make recommendations about further treatment options.

Statistical Analyses of Treatment Effects

A pre-post comparison of the questionnaire scores was submitted to statistical analyses using SPSS v29. Patients were considered completers if they attended 8 out of 10 scheduled treatment days and concluded posttreatment assessment. Parameters were tested for normal distribution using the Kolmogorov-Smirnov test. Given that most variables did not fulfill the criteria for parametric testing, we used the Wilcoxon-Test for dependent samples as a nonparametric test to compare changes before and after rehabilitation. Because we expected improvement, we applied one-tailed tests. Effects were evaluated at original alpha level of $p < .05$. Further, we examined intercorrelations between depression, fatigue, self-efficacy, and participation at pretest and correlated pretest results with pre-post differences of these variables using Spearman correlations.

Results

Neuropsychological Assessment

Figure 2 shows the percentile ranks in the neurocognitive subtests for all patients, ranging from low PCFS on the left to high PCFS on the right. Performance deficits varied across patients and cognitive domains, leading to an overall performance within the age norm (respective medians, except for a general tendency to respond slowly to targets

Modules of Intervention in a 3-Week-Group-Treatment Programme (10 Days of Treatment)

Assessment	Psychoeducation and Information	Exercise and Behavioural Activation	Compensation
Neurological-psychiatric: incl. Schellongtest, blood parameters	Medical consultation	Day clinic schedule to regulate daytime structure	Fatigue management
Neuropsychological: attention, memory, executive functioning, mood, fatigue	Bio-psycho-social model of illness and recovery	Cognitive training	Compensatory strategies for cognitive deficits (e.g., external memory aids)
Physiotherapeutic: strength and endurance, vital capacity, oximetry, 6-minute walking-test	Pacing and energy management sleep hygiene	Communication and text processing	Mindfulness and acceptance Qigong
	Nutritional counseling	Training of fitness and strength	
	Social security counseling, incl. planning of occupational reintegration	“Homework” on individual projects	Resource activation

Key Aspects implemented Across Modules:

- **Recognition** of PCS as a physical illness while keeping the therapeutic focus on modifiable factors
- **Exchange** of experience in a closed group of 3-4 participants
- **Practice pacing** by allowing for individualized breaks and alternating physical and mental demands between sessions
- **Transfer** to the home and work environment facilitated by a day-clinic setting and therapy-free days

Figure 1. Overview of the interdisciplinary treatment modules.

in a vigilance task in favor of high accuracy of responses). However, partial performance deficits were observed in all patients, across cognitive domains and PCFS scores. We identified symptom clusters with more than 30 % of affected patients in phasic alertness (TAP) and verbal learning (CVLT 1st trial and learning total). Processing speed under visual exploration requirements (TMT-A) and reading speed (FWIT) as well as logical reasoning (LPS-3) appeared relatively well preserved.

Statistical Analysis of Treatment Effects

In their qualitative evaluations, patients rated the program as helpful. The BESS-Scale (score range 5–25; scores > 15 indicate an improvement) indicated a slight improvement in well-being at the end of the program (M = 18.23; SD = 3.54).

Table 2 provides an overview of the descriptive statistics and Wilcoxon-test comparisons between pre- and post-treatment measures. These revealed a significant reduction of depressive symptoms (BDI, p = .001), higher self-efficacy (HEALTH-49 Scale D, p = < .001), and participation (HEALTH-49 Scale E, p < .001,) with medium effect sizes (r = .4) as well as marginally significant reductions in general psychological or physical distress (SCL-90-S – GSI, p =.05,) and intensity of complaints (SCL-90-S – PSDI, p= .05), with small effect sizes (r = .2). Differences in the number of complaints (SCL-90-S – PST, p = .07), fatigue measures (FIS-D, p = .17, FSS, p = .18), and daytime sleepiness (ESS, p = .19, all with small effect sizes r = .1) did not reach significance.

The questionnaires for depression (BDI-II), general distress (SCL-GSI), and fatigue (FIS-D, FSS) were highly intercorrelated at pretest (cf Table 3). In addition, we analyzed how far depression and fatigue at baseline affected the difference between pre- and posttesting for depression or fatigue self-assessments as well as self-efficacy and participation. Interestingly, pretest depression (BDI-II) was significantly correlated with changes in BDI-II scores pre-post (BDI-II pre, r = –.40) but not with changes in fatigue (pre-post difference FIS D, r = .23; pre-post difference FSS, r = –.11), self-efficacy (pre-post difference HEALTH-49 D, r = –.31) or participation (pre-post difference HEALTH-49 E, r = .06). On the other hand, pretest fatigue (FIS-D) was significantly correlated with changes in fatigue (pre-post difference FIS-D, r = .53) but did not vary with changes in depression (pre-post difference BDI-II r = .26), self-efficacy (pre-post difference HEALTH-49 D, r = –.28), or participation (pre-post difference HEALTH-49 E, r = .14). Further correlations are reported in Table 3.

		Percentile Ranks per Subtest per Patient																																				
	PCFS	0	0,5		1					1,5		2											2,5			3									MD	IQR	<16	%
Attention	TMT-A	40	84	30	85	23	30	70	45	20	90	75	80	86	60	65	40	43	82	40	50	93	80	98	47	40	13	16	18	60	90	30	80	25	50	50	**1**	3
	TMT-B	22	2	70	35	33	84	84	35	35	90	90	65	80	80	38	70	84	90	30	30	75	60	65	7	10	30	65	2	30	96	60	95	32	60	50	**4**	12
	TAP tonic alertness 9:15 am	24	88	84	3	1	16	10	16	24	16	42	8	5	42	4	14	16	69	12	42	38	62	54	90	69	58	27	1	69	10	27	38	1	24	44	**11**	33
	TAP phasic alertness 9:15 am	18	76	76	4	2	12	7	10	10	7	31	4	14	34	2	16	14	76	7	24	27	69	73	76	58	54	8	1	14	2	34	10	1	14	27	**18**	55
	TAP phasic value 9:15 am	21	31	27	14	99	42	18	18	12	12	38	14	95	38	12	69	34	54	12	18	31	69	69	12	31	58	4	4	2	3	69	4	58	27	42	**12**	36
	TAP tonic alertness 12:15 pm	54	84	18	18	1	62	27	18	42	79	69	14	3	14	4	7	31	58	42	21	18	76	62	1	31	58	16	2	31	10	50	66	1	27	44	**10**	30
	TAP phasic alertness 12:15 pm	50	54	21	18	3	46	24	21	21	14	42	5	24	14	5	5	14	42	31	16	16	62	58	1	50	24	34	1	4	5	21	34	1	21	29	**12**	36
	TAP phasic value 12:15 pm	38	16	62	38	99	38	34	58	14	1	16	8	100	34	66	54	7	27	21	38	50	34	42	5	82	8	84	2	1	27	10	10	34	34	40	**10**	30
	TAP Viligance 0-15 min; msec	16	46	7	12	7	12	18	7	8	14	8	7	7	10	7	5	4	8	54	14	8	12	14	24	8	7	10	4	7	10	5	10	5	8	5	**28**	85
	TAP Vigilance 16-30 min; msec	18	42	3	24	10	18	24	16	16	18	18	8	12	14	12	8	5	12	66	16	16	16	12	18	18	12	18	1	16	16	16	18	7	16	6	**13**	39
	TAP Vigilance 0-15 min; misses	73	73	73	73	73	73	73	73	73	73	73	69	73	73	73	73	42	73	73	73	73	73	73	73	73	73	73	73	73	73	73	73	73	73	0	**0**	0
	TAP Vigilance 16-30 min; misses	86	86	31	86	31	86	86	86	84	86	86	86	86	86	86	86	31	86	86	86	42	86	86	62	86	84	86	42	86	86	86	84	7	86	2	**1**	3
	TAP Vigilance 0-15 min; errors	66	66	66	66	66	62	66	66	66	38	2	27	66	66	66	66	66	18	66	62	66	66	66	27	66	24	62	18	66	66	66	66	66	66	4	**1**	3
	TAP Vigilance 16-30 msec; errors	54	54	18	54	10	54	54	54	54	54	54	50	54	54	54	54	31	10	54	54	54	54	54	54	54	54	54	18	54	54	54	54	54	54	0	**2**	6
Memory	WMS-R digit span forward	77	35	69	35	34	57	97	77	48	77	25	8	75	53	8	77	69	95	87	2	2	88	67	77	48	85	48	2	57	67	15	67	67	67	42	**6**	18
	WMS-R digit span backward	80	5	2	58	34	58	80	38	8	80	80	5	12	87	5	80	71	78	98	2	30	93	38	88	38	52	38	34	86	80	27	80	67	58	50	**7**	21
	WMS-R blockspan forward	77	32	71	32	50	32	5	58	58	58	65	13	57	98	78	85	90	8	65	5	3	2	58	85	5	25	95	5	57	7	28	58	27	57	52	**9**	27
	WMS-R blockspan backward	70	13	55	23	55	13	55	22	85	22	32	13	73	97	40	85	92	27	32	55	13	23	22	70	5	2	85	31	40	45	27	70	45	40	48	**6**	18
	CVLT supraspan	4	43	93	57	25	25	10	4	7	13	34	53	30	25	10	29	10	25	34	4	17	74	57	4	43	23	1	79	17	13	4	74	13	25	33	**13**	39
	CVLT learning sum	33	43	91	50	7	32	13	33	22	9	44	51	37	27	29	86	1	68	37	1	55	94	74	22	13	4	7	13	29	7	1	58	13	29	37	**12**	36
	CVLT delayed recall I	83	26	36	23	16	39	15	83	19	53	70	28	74	53	23	94	2	83	70	16	36	70	36	15	53	8	19	2	36	53	11	36	39	36	34	**6**	18
	CVLT delayed recall II	93	62	17	3	22	33	3	62	10	76	85	20	34	62	34	76	1	92	62	2	62	62	34	8	62	1	29	0	49	74	4	49	76	34	52	**9**	27
Executive Function	LPS3	82	69	84	55	43	64	95	87	67	76	85	84	80	98	83	96	96	50	81	50	70	82	76	87	43	50	76	75	60	87	12	91	28	76	25	**1**	3
	SLP	41	8	71	99	83	47	61	90	25	53	99	53	78	96	25	1,1	98	6	98	1	5,5	16	90	98	6	3	20	25	90	78	1	20	16	47	74	**8**	24
	RWT lexical fluency	25	75	63	5	10	33	38	63	25	38	40	90	90	10	10	90	90	22	77	21	13	38	50	10	15	80	16	10	13	38	50	63	10	38	50	**10**	30
	RWT semantic fluency	90	84	38	80	10	50	38	10	38	25	90	37	90	16	90	82	42	13	78	38	38	90	90	42	10	62	80	21	13	90	44	38	12	42	57	**6**	18
	FWIT reading speed	84	99	98	n.a.	31	92	98	99	50	99	84	50	31	31	70	99	99	98	92	31	99	99	99	50	99	50	70	50	33	98	99	92	16	92	49	**0**	0
	FWIT interference	16	50	93	n.a.	7	31	93	69	70	70	70	70	50	50	70	31	99	98	50	7	50	70	84	16	16	16	16	1	33	84	84	99	50	50	46	**3**	9

Figure 2. Results of the neuropsychological assessment. Percentile ranks per cognitive domain and subtest per patient, clustered according to PFCS score. Age and education-specific norms were applied where available. Values below clinically relevant thresholds are shaded in light (PR <16) and dark grey (PR <3). MD = median. IQR = inter quartile range. <16/%: number and ratio of patients who score below PR = 16 in the respective subtest. PCFS post COVID functional status. TMT: Trail Making Test; TAP: Test of Attentional Processing; WMS-R: Wechsler Memory Scale-Revised; CVLT: California Verbal Learning Test; LPS 3: test of logical reasoning; SLP: Standardized Link'sche Probe test of action planning and control; RWT: test of verbal fluency; FWIT: STROOP-Test paradigm.

Table 2. Comparisons of pretest/posttest self-assessment

	N	Pre-Test Percentile			Post-Test Percentile					
		25.	50. (Median)	75.	25	50 (Median)	0.75	*Z*[1]	*p* (*1-tailed*)	*r*
Beck Depression Inventory (BDI-II)	32	9.00	15.00	21.50	9.00	11.00	18.00	-3.47	**<.001**	**0.4**
SCL-90-S General distress (GSI)	33	.46	.60	.85	.32	.51	.93	-1.68	**.05**	0.2
SCL-90-S Intensity of Complaints (PSDI)	33	1.25	1.46	1.92	1.21	1.50	1.75	-1.62	**.05**	0.2
SCL-90-S Number of Complaints (PST)	33	26.50	35.00	49.00	23.50	33.00	50.50	-1.50	.07	0.1
HEALTH-49 Self-efficacy (Scale D)	33	7.00	9.00	12.50	9.50	12.00	13.00	-3.35	**<.001**	**0.4**
HEALTH-49 Participation (Scale E)	33	9.00	12.00	15.00	8.00	9.00	14.00	-3.22	**<.001**	**0.4**
Fatigue Impact Scale (FIS-D)	33	67.50	86.00	101.00	64.00	80.00	97.00	-.94	.17	0.1
Fatigue Severity Scale (FSS)	33	4.79	5.67	6.10	4.05	5.40	6.16	-.89	.18	0.1
Epworth Sleepiness Scale (ESS)	33	8.00	10.00	12.00	6.50	10.00	11.50	-.89	.19	0.1

Notes. [1] Wilcoxon-Test *Z*-Score; Level of significance *p* < .05 (1-tailed). Effect size: 0.1 < *r* ≤ 0.3 weak effect; 0.3 < *r* ≤ 0.5 medium effect; *r* > 0.5 large effect. Beck Depression Inventory II: Sum score (14-19 mild, 20-28 moderate, >29 severe), SCL-90-S Symptom-Check-List Questionnaire. GSI sum of all scores divided by the number of items completed (usually 90), PSDI mean intensity of complaints on a Likert-scale 0-4. PST: Number of items with a score >0 (out of 90 items), HEALTH-49 Scale D (score 0-20): An increase indicates improvement of self-efficacy, HEALTH-49 Scale E (Score 0-24): A decrease indicates an improvement of participation, FIS-D sum score (max 120, scores > 50 indicate clinically relevant impairment), FSS mean of a Likert-scale 1-7, ESS sum score (max 24; scores > 10 indicate enhanced daytime sleepiness). Signficant results (p ≤ .05) and medium effect sizes are printed bold).

Table 3. Spearman correlations for study variables

		Pretest results						Pre-post differences				
	Variable	BDI-II	SCL-GSI	FIS-D	FSS	Scale D	Scale E	BDI-II	FIS-D	FSS	Scale D	Scale E
Pretest results	BDI-II	1.00										
	SCL-GSI	.84**	1.00									
	FIS-D	.72**	.71**	1.00								
	FSS	.50**	.52**	.72**	1.00							
	Scale D	-.55**	-.45**	-.57**	-.40*	1.00						
	Scale E	.54**	.47**	.80**	.65**	-.57**	1.00					
Pre-post differences	BDI-II	.40*	.40*	.26	.29	-.04	.15	1.00				
	FIS-D	.23	.25	.53**	.31	-.14	.56**	.34	1.00			
	FSS	-0.11	-.08	.14	.39*	.12	.25	.22	.53**	1.00		
	Scale D	-0.31	-.17	-.28	-.06	.61**	-.38*	-.17	-.25	.00	1.00	
	Scale E	.06	.02	.14	.06	-.05	.44*	.09	.60**	.48**	-.30	1.00

Notes. **p* < .05, ** *p* < .01. BDI-II – Beck Depression Inventory. SCL-GSI – Symptom-Check-List Questionnaire 90-S, general psychological and physiological distress. FIS-D – Fatigue Impact Scale – German version. FSS – Fatigue Severity Scale. Scale D HEALTH-49 – Self-efficacy (higher scores indicate higher self-efficacy). Scale E HEALTH-49 – Participation (higher scores indicate higher impairment of participation). Note that in the "Pretest results" section of the table, we report intercorrelations at baseline, while in the section "Pre-post differences," we correlate the *changes* between pre- and posttesting.

Discussion

This article established a 10-day interdisciplinary treatment program designed for individuals diagnosed with PCS. Neuropsychological assessment revealed partial performance deficits in all patients across cognitive domains, confirming previous findings that cognitive deficits in patients with PCS are diverse and affect different cognitive functions (Hampshire et al., 2021; Koczulla et al., 2022). In our sample, phasic alertness and verbal learning were most frequently impaired (see Figure 2). Cognitive screening using the MoCA failed to reliably detect the presence of cognitive deficits, as it mostly yielded results within the normal range. Furthermore, cognitive deficits occurred across the severity of impairments in everyday life, as indicated by PCFS scores. Our findings thus support evidence that extensive neuropsychological assessment is necessary to detect neurocognitive deficits in PCS patients and to validate subjective complaints (cf Schild et al., 2022, 2023; Widmann et al., 2023, this issue).

Regarding the causal classification of neurocognitive deficits, the personalized bio-psycho-social model developed at the beginning of the program allowed a transparent consideration of pathophysiological causes such as neuroinflammation and secondary impairment because of mental illness or fatigue. Invariably, we treated cognitive impairment as a disorder of brain function, taking complaints seriously and providing patients with appropriate training and coping strategies.

Severe cognitive impairment was rare in our study sample, so our treatment program focused mostly on compensatory strategies to deal with deficits in everyday life, particularly in occupational settings. The computer-based cognitive training served as a practice field for the application of pacing and a place to experience improved cognitive performance, thus supporting self-esteem. This was also the case in the speech and language therapists' sessions, where patients worked on texts or presented information, e.g., from their field of work. They appreciated feeling competent and were able to emphasize their strengths.

Patients reported general improvements in well-being (BESS) at the end of treatment. In accordance with our hypotheses, there was a significant increase in self-efficacy (HEALTH-49 Scale D) and activities and participation (HEALTH-49 Scale E) as well as improvements in measures of mental health, including severity of depressive symptoms (BDI-II) and general psychological distress (SCL-90-S-GSI).

Nevertheless, we did not observe improvements in self-reported fatigue. While this casts doubt on the effectiveness of the program in treating fatigue, methodological and contextual factors might explain this weak effect. First, for patients who had been on sick leave before treatment, participation was a challenge per se, so they experienced more rather than less fatigue during the program. In contrast, patients who tolerated an 8-hour workday before treatment may have found the program relaxing in comparison, though they knew they would have to return to the challenges of everyday life. Second, the FIS-D questionnaire asks for an assessment of the patient's condition during the previous 4 weeks, which is longer than the treatment program, whereas the BDI-ll covers only the previous 2 weeks and may therefore be more sensitive to change (Meesters et al., 2021). The treatment programs that reported improvements in fatigue at the end of treatment (e.g., Albu et al., 2022, Daynes et al., 2021, Palladini et al., 2022) all used 6–8 weeks of therapy. Here, we showed that 10 days might be sufficient, particularly for patients with mild PCS, to increase self-efficacy in managing symptoms, which may lead to better adjustment to their condition in the longer term. A follow-up evaluation is underway.

Improving depression appears to be a linchpin for neuropsychological therapy in patients with PCS. As previously noted, several studies consistently demonstrated bidirectional relationships between depression and fatigue, on the one hand, and depression and cognitive function, on the other hand (Mazza et al., 2022). Our results showed that self-assessments of depression and fatigue were highly correlated at baseline, whereas changes in fatigue correlated neither with baseline depression nor with changes in depression. Similarly, changes in depression correlated neither with baseline fatigue nor with changes in fatigue. Our results align with considerations regarding the application of CBT in patients with ME/CFS: The treatment may not improve fatigue per se, but it may help patients to change a dysfunctional appraisal of their condition (de Gier et al., 2023) and thus increase their feeling of self-efficacy. PCS has been interpreted as a form of somatic stress disorder (e.g., Bodenburg, 2021), and there are strong correlations between higher scores on fatigue, somatization, and depression questionnaires and poorer functional outcome as measured by PCFS (Lier et al., 2022). Considering the role of neuroinflammation and the immune system in developing neurocognitive PCS, it is important to note that psychological factors significantly influence the immune response (Rustenhoven & Kipnis, 2022). Therefore, they are a central target in symptomatic treatment.

Many of our patients benefited from the structured program, and the daily exercise improved their physical condition. This contrasts with the debate about whether graded exercise might harm patients with ME/CFS. We argue that there is a need for better differentiation of concepts, as not all patients with fatigue after COVID-19 also have chronic fatigue syndrome (ME/CFS) according to the Canadian criteria (Carruthers et al., 2011), including PEM. In our group, we interviewed patients regarding this disturbance pattern, but for most of them, the reports did not correspond to PEM. In addition, our patients were encouraged to use pacing in both physically and mentally challenging group sessions. Given these circumstances, the patients appreciated the combination of neuropsychological and physiotherapeutic interventions.

Limitations

We collected the data under clinical conditions, focusing on the design and implementation of the treatment, while carrying out the evaluation concurrently. The study, therefore, lacks a randomized control group and blinding of the investigators. A follow-up study on the sustainability of the effects is pending. In addition, we assessed all outcome measures by self-report with a high risk of bias. However, in the absence of biomarkers that could be used in clinical practice to evaluate subjective complaints, our procedure represents the current state of the art.

The program described is an outpatient program, i.e., it is suitable for patients who can tolerate 3–4 hours of treatment 3–4 days a week. Therefore, we included only patients with mild fatigue and cognitive impairment. If we detected severe cognitive impairment, our clinic offered patients a more extensive neurorehabilitation program. The exclusion of more severely impaired patients may have led to a variance reduction in the outcome measures and limited the generalizability to other patient subgroups of PCS (e.g., patients with post intensive care syndrome).

Relevance for Practice

In any multimodal therapy program, it is difficult to identify effective individual factors for general recommendations. Nonetheless, we posit that the following observations are relevant when considering implementation in alternative treatment settings.

Our results show that even after 5 to 24 months of suffering from PCS, patients still profited from detailed information to better understand their symptoms and how to manage them. At the start of the program, we conducted a comprehensive assessment that included neurological, neuropsychological, and physiotherapeutic evaluations, which served to validate subjective complaints and informed diagnoses and recommendations for further treatment. It also reassured patients by identifying preserved domains of functioning that could be used as resources for compensation and fatigue management.

According to patient feedback, effective management of fatigue was frequently cited as the most beneficial advice received. We found that very few patients were aware of pacing before treatment; rather, they had adopted a strategy of symptom neglect ("I have to ..."; "Things have to be done ...") or an exercise-oriented "all-or-nothing" model of recovery. Hence, re-evaluating dysfunctional cognitions was a crucial factor.

The temporal structure of the day clinic program ensured sufficient alternation between activation and rest, allowed for the reassessment of current energy limits in a safe environment, and provided opportunities for transfer to everyday life.

The setting of a small, fixed group of 3–4 patients facilitated a trusting exchange of experiences and mutual validation. In addition, the overall therapeutic stance of recognizing the reported symptoms as part of a physical illness while focusing on modifiable aspects within a broader bio-psycho-social model promoted acceptance. It paved the way for more proactive self-management strategies.

Patients often find it difficult to have their needs taken seriously. The invisibility of the disease makes it difficult to acknowledge, even by the patients themselves. Patient needs were often at odds with high work or home demands and with their meritocratic self-esteem. Patients are motivated to adjust their daily activities by encouraging resting when needed, using mindfulness-based techniques, and experiencing the effects of pacing. On the other hand, social and legal restrictions as well as financial responsibilities led patients to carry on as before and meet their professional demands as best as they could. The inclusion and counseling of relatives and employers were not feasible in the current setting because of the conciseness of the program. Still, we highly recommend this for outpatient care of patients with PCS.

Much of the information given in the psychoeducation modules of the program can now be found on websites of post-COVID support groups, specialized centers, or health insurance. Nevertheless, we are convinced that the combination of psychoeducation, practical application of pacing, and interactions with proficient specialists and other group members constituted pivotal elements in the efficacy of this treatment program. We, therefore, advocate the widespread implementation of these components in alternative treatment environments for individuals with PCS.

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