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Attention deficits and depressive symptoms improve differentially after rehabilitation of post-COVID condition – A prospective cohort study

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ABSTRACT

Background: Depressive and cognitive symptoms like fatigue, loss of energy or sleep disorders characterise the post-COVID condition. Post-COVID psychosomatic rehabilitation should focus on both symptom groups. The current prospective cohort study addresses the change in these symptoms in the context of a psychosomatic rehabilitation.

Method: ***N*** = 80 patients with post-COVID symptoms underwent psychological testing on admission and discharge: PHQ-9 questionnaire for depression, TAP - test battery for the attention test with the sub-tests working memory, sustained attention, divided attention and alertness. Sample characteristics, including health-related and work-related parameters, the general symptom load and the course of symptoms during the five weeks of rehabilitation were evaluated.

Results: On admission, the PHQ-9 indicated the presence of depressive symptoms in post-COVID patients (PHQ-9 15.15 ± 5.11). Over the course of rehabilitation, the depressive symptoms decreased to a sub-clinical level (PHQ-9 8.80 ± 4.61), suggesting a strong effect of post-COVID inpatient rehabilitation (Cohen's d 1.57). At the same time, post-COVID patients showed clinically relevant impairments in attention and working memory that persisted throughout the rehabilitation period despite multimodal post-COVID treatment.

Conclusion: Over the course of post-COVID rehabilitation, depressive symptoms appear to be significantly reduced. With regard to cognitive impairment, a comparable effect within the short period of 5 weeks is not evident. Our results suggest the need for specific treatment of persistent neuropsychological deficits following post-COVID rehabilitation.

1. Introduction

Many of those who have recovered from an acute COVID-19 infection report the persistence and/or new onset of symptoms which are collectively referred to as post-COVID condition. Common symptoms of post-COVID condition include fatigue, dyspnoea, palpitations, cognitive deficits, pain, olfactory and gustatory disturbances, sleep disturbances, or psychological complaints such as anxiety or depressed mood [1]. These persistent symptoms impair the ability to perform and function in daily life. This is often followed by psychological stress, such as anxiety or depressive symptoms [2–4].

In Germany, >1,000,000 people receive rehabilitative treatment annually due to a health condition, of which almost 150,000 are treated in psychosomatic rehabilitation (cf. German Pension Insurance Statistics

Abbreviations: CBT, cognitive behavioural therapy; M, mean; MoCa, Montreal cognitive assessment; PHQ-9, Brief patient health questionnaire mood scale, German version; PoCoRe, Post-COVID rehabilitation; PR, percentile; SD, standard deviation; TAP, Test Battery for Attention.

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Volume 2021). Psychosomatic rehabilitation also plays an important role in the care of post-COVID patients and is in line with the research agenda of post-COVID fatigue [5]. Psychosomatic rehabilitation is an established care model with a capacity of about 150,000 treatment places annually [6]. Given the pressing demand for post-COVID treatment, there is a significant effort to utilize these existing structures and adapt already well-evaluated treatment programs to cater to the specific needs of post-COVID patients [7,8]. One adapted concept is the multimodal treatment concept [9], which combines a detailed medical examination and care, clinical psychological assessment and treatment and a carefully designed, comprehensive exercise program. This approach aims to address both the physical and psychological distress experienced by individuals recovering from post-COVID conditions. The multimodal treatment concept for patients with post-COVID-syndrome aligns with the research agenda of post-COVID fatigue [10] and is consistent with the Stanford Hall consensus statement for post-COVID-19 rehabilitation [11]. It appears to hold promise as a viable therapeutic option [12].

Psychosomatics is chiefly familiar with cognitive impairment in the context of depressive disorders, PTSD or anxiety disorders. Cognitive disorders, such as deficient executive functions, attention and memory, are very common and frequently mentioned symptoms in the context of post-COVID condition [13,14]. Cognitive deficits are mostly those impairments that seriously jeopardise the ability to work and lead to long-term work absences or early retirement [15].

Depressive symptoms can occur without an obvious trigger (endogenous) or reactively as a consequence of serious life events, such as heart disease or a SARS-CoV-2 infection [16]. Depressive symptoms can occur in response to the changes related to illness and lifestyle (e.g. due to quarantine measures, job loss). There are also lines of research which indicate a link between immune activation and depression [17,18]. Cognitive deficits can also be a part of a neurological or mental illness such as multiple sclerosis or depression. In the ICD-11, difficulty concentrating is a diagnostic secondary symptom of depression, in addition to the core symptoms of depressed mood and loss of interest. Since post-COVID condition is both a neurological illness and accompanied by psychological challenges, depressive and cognitive symptoms might be highly interlinked in post-COVID condition [19,20]. Consequently, patients with post-COVID condition may also benefit from psychotherapeutic treatment [21]. The aim of the study was to show the therapeutic effects of post-COVID psychosomatic rehabilitation on depressive symptoms and cognitive deficits. Cognition is a broad term and encompasses diverse domains, such as executive functions, attentional functions, memory functions, praxis, language, etc. This study focuses on the following domains: attention (including measures of alertness) and working memory. In the following, “cognitive impairment” refers to the domains studied here. Since fatigue and fatiguability may be symptoms of post-COVID condition, cognitive fatiguability was recorded as a conditional parameter with regard to cognitive performance.

To contribute to the knowledge of cognitive impairment in post-COVID condition, this study addresses the following research questions:

1. Are psychological complaints and cognitive impairments present to a clinically relevant extent in post-COVID patients at the beginning of post-COVID rehabilitation?
2. Do psychological complaints (in particular depressive symptoms) improve with adequate psychosomatic rehabilitation treatment (including cognitive training and antidepressant strategies)?
3. Do cognitive impairments caused by SARS-CoV-2 improve under adequate psychosomatic rehabilitation treatment (including cognitive training and antidepressant strategies)?

2. Materials and methods

2.1. Sample and procedure

The prospective cohort study is based on clinical, standardised examination, including psychological (PHQ-9 [22]) and neuropsychological testing (TAP [23]) at two measurement points: admission and discharge. This study is based on a sub-sample of the patient data collected in the multicentre PoCoRe study [24]. The data collection for this sub-sample took place between March 2022 and end of September 2022, in the post-COVID treatment concept [9,24] in a German rehabilitation clinic. The multi-modal rehabilitation concept included individual and group psychotherapy (CBT), a comprehensive neuropsychological assessment (TAP), followed by cognitive training in a group setting (2 × 50 min per week) and in an individual setting (as needed), individualised aerobic exercise training, body awareness training, breathing therapy, relaxation techniques and social counselling. The duration of rehabilitation was five weeks. All consecutively admitted post-COVID patients were included. In case of post-COVID condition, the previous course of infection was irrelevant for inclusion in the study (e.g. mild symptoms to severe course with hospitalisation). Data were generated as part of the PoCoRe study and were not part of routine diagnostics. The research was approved by the ethics committee of the Centre for Clinical Research, University Hospital Regensburg (identification 22–2814-101) in February 2022. Prior to study participation, patients were informed about the study objectives and the study procedure in a personal information consultation and received standardised participant information sheets. After this, voluntary written informed consent for study participation and storage, evaluation and transfer of study-related data were obtained from each study participant by research associates. Withdrawal of written consent was possible at any time, without giving reasons or involving disadvantages to their treatment.

Eligibility criteria for the post-COVID sub-sample at the beginning of the rehabilitation included a SARS-CoV-2-infection and, following post-COVID syndrome, complaints that are present >12 weeks after the onset of SARS-CoV-2 infection and cannot be explained otherwise, as well as the presence of functional limitations that may threaten the ability to work.

Exclusion criteria were being younger than 18 years, demonstrating insufficient knowledge of the German language to fill in the questionnaires and displaying current psychotic symptoms, substance dependence or abuse or other organic brain disorders.

We define fatiguability as the degree of exhaustion reflected in objective measures of performance (e.g. TAP alertness) that show significantly slowed responses or deterioration in reaction time associated with activities (e.g. solving cognitive tasks).

2.2. Measures

Depression: PHQ-9, German version. The PHQ-9 [22] is a screening instrument that is routinely used in somato-medical settings with nine questions on depressiveness. Each question tests one of the nine DSM criteria for diagnosing major depression. The interpretation of the PHQ-9 sum score makes it possible to determine the severity of depressive symptoms (1–4 minimal depressive symptoms, 5–9 mild depressive symptoms, 10–14 moderate depressive symptoms, 15–27 severe depressive symptoms) and can be used as a measure for assessing the effect of therapy or for diagnosing progression. The PHQ-9 has a good sensitivity to change and can therefore be seen as a reliable progression measure for depressive symptoms [25].

Screening for cognitive impairment: Montreal cognitive assessment (MoCa). The MoCa is a well validated and highly sensitive tool for detecting mild cognitive impairment and distinguishing from “normal” senile forgetfulness. The test lasts about 10 min, contains 30 questions and is performed by healthcare professionals. Cognitive

abilities like memory, contextual thinking, attention and concentration, arithmetic, temporal and spatial orientation, behaviour, language, and the ability to recognise complex shapes and patterns are tested. The interpretation of the sum score gives an initial estimation of the severity of possible cognitive impairment: scores of 26–30 are considered unremarkable / no limitations, scores of 19–25 are considered to indicate mild cognitive impairment, scores below this are considered to indicate dementia [26]. The recommended cut-off score [26] from the original study was based on a sample of participants with relatively high education. A re-examination of the MoCa cut-off scores suggest 23 as cut-off for dementia, rather than the initially recommended score of 26 [27].

Cognitive performance assessment: Test Battery for Attention (TAP). The TAP is computer-based and offers various sub-tests with which the diverse sub-aspects of attention and related aspects of visual perception can be recorded in a differentiated manner. In this study, the sub-tests alertness (cognitive domain: intensity of attention), working memory (cognitive domain: executive functions, control of the focus of attention), sustained attention (cognitive domain: intensity of attention), divided attention (cognitive domain: attentional selectivity, focused attention, visuo-spatial attention) were used. The alertness indicator provides information about the basal reactivity, general processing speed, reaction stability and the tonic and phasic alertness. For working memory, sustained and divided attention. The mistakes made and omissions were taken into account. Standardisation for adults and children is available [28]. The test takes about 45 min to complete. In addition to objectifying cognitive performance decline, the TAP was also used in this study as an objective measure of cognitive fatiguability (alertness subtest).

2.3. Statistical analysis

Statistical analysis was conducted using SPSS 28 [29] for Windows. The sample characteristics and the description of the pre-existing diseases and the work-related parameters were determined using descriptive statistics (frequency analysis). Statistical analyses of the Likert-scaled items and scores included descriptive measures in terms of means (M) and measures of dispersion (standard deviation (SD)). *t*-tests for connected samples (with repeated measurements) were used for calculating differential outcomes of symptoms within the sub-groups from admission to discharge. Effect sizes (Cohen's d) were calculated based on estimated means and the pooled standard deviation from the observed means. The significance level was set to $\alpha = 0.05$ on both sides and corrected according to Bonferroni to avoid α-error accumulation. Effect sizes of Cohen's $d = 0.2$ were considered small, 0.5 medium and 0.8 strong.

Correlation and regression analyses were calculated; the latter to examine the variance contribution of the depressive symptoms to the cognitive deficits.

3. Results

3.1. Sample characteristics

During the period from March 2022 to end of September 2022, 80 post-COVID patients were included. The gender distribution was consistent with the female preponderance reported in previous studies [30] or the greater psychological burden of post-COVID on women [31]. In this study, 68% were female, and the average age was 50.89 years (SD = 8.78), which is a typical age for a rehabilitation population. In our sample 22% of patients had been hospitalised during their acute SARS-COV-2 infection, 5% required intensive care. The remaining patients remained in quarantine at home during their acute infection. Pre-existing diseases prior to SARS-COV-2 infection were 28% cardiac diseases (Congenital Heart Defect CHD, myocardial infarction, hypertension, arteriosclerosis), 32% pneumological diseases (chronic obstructive pulmonary disease COPD, asthma), 14% blood diseases (haemophilia, thrombophilia), 6% cancers (colon cancer, breast cancer, prostate cancer), 6.3% chronic intestinal diseases (Crohn's disease, ulcerative colitis), 21% thyroid or adrenal disorders, 11.3% diabetes mellitus or hyperlipidaemia and 32% anxiety or depressive disorders. The frequency of pre-existing mental disorders seems to indicate that mental stress is a risk factor or at least a moderating factor for post-COVID symptoms.

Regarding the occupational situation, 50% stated that they were mainly mentally active in their job, 48% that they were equally mentally and physically active. More than half of the patients (52%) had a higher education (>12 school years, plus vocational training or studies). Sick leave within the last 12 months was 100–365 days for 47%, 25–99 days for 21%, 10–24 days for 14% and 9 days for only 9%, 5% percent were not on sick leave.

The sample characteristics can also be found in Table 1.

3.2. Psychological symptom load on admission

The PHQ-9 showed a clinically relevant symptom load on admission. In 1% of the cases the post-COVID patients scored in the normal range (1–4 points), 41% in the mild symptom burden range (5–9 points), 26% in the moderate symptom burden range and 31% in the severe symptom burden range. The overall symptom load was severe (M = 15.15, SD = 5.11).

3.3. Course of symptoms

3.3.1. Symptomatology form t1 to t2 - differences within the groups

The depressive symptomatology was significantly reduced from PHQ-9 admission (M = 15.15, SD = 5.11) to discharge (M = 8.80, SD = 4.61, Cohen's d = 1.57). On item-level, there was an overall improvement (effect sizes ranging from medium to large), with the exception of concentration problems, hopelessness (reason when asked: persistently experienced cognitive impairments and uncertainty about the further

Table 1
Sample characteristics.

Variables	Post-COVID inpatients $n = 80$
Demographic characteristics	
Mean age (SD)	50.89 (8.78)
Gender (% female)	68%
Disease characteristics SARS-CoV-2 infection	
Hospitalisation during acute SARS-COV-2 infection	22%
Intensive care necessary	5%
Quarantine at home during acute infection	73%
Pre-existing diseases prior to SARS-COV-2 infection	
Cardiac diseases (CHD, myocardial infarction, hypertension, arteriosclerosis)	28%
Pneumological diseases (COPD, asthma)	32%
Blood diseases (haemophilia, thrombophilia)	14%
Cancers (colon CA, breast CA, prostate CA)	6%
Chronic intestinal diseases (Crohn's disease, ulcerative colitis)	6%
Thyroid or adrenal disorders	21%
Diabetes mellitus or hyperlipidaemia	11%
Anxiety or depressive disorders	32%
Type of work / employment	
Mainly mentally active	50%
Equally mentally and physically active	48%
Mainly physically active	2%
Education level	
Higher education (>12 school years, plus vocational training or studies)	52%
Sick leave within the last 12 months	
100–365 days	47.%
25–99 days	215%
10–24 days	14%
9 days	9%
No sick leave	5%

course of the impairments.) and sleep disorder (see Table 2). The effect sizes were moderate to high (see Table 2). On discharge, the overall symptom load was: 26% scored in the normal range (1–4 points), 46% in the mild symptom burden range (5–9 points), 17% in the moderate symptom burden range and 11% in the severe symptom burden range. Despite the specific cognitive treatment and the improvement in depressive symptoms, the cognitive impairments persisted in the form of impairments in working memory, sustained attention and divided attention, as well as in a reduced alertness (see Figs. 1 to 3). (See Fig. 4.)

On admission, the test result in the MoCa was marginally within the normal cognitive performance level (M = 26.18, SD = 2.31). Scores of 19–25 are considered mild cognitive impairment, scores below this are considered to indicate dementia. In the MoCa 37% of the patients scored below 26, which is indicative of mild cognitive impairment in patients with a relatively high education, as is predominantly the case in our sample (52% higher education). There were no post-COVID patients which scored below 23, which would indicate cognitive impairment independent of the level of education. The other patients were within the normal range in this test.

In the TAP testing, post-COVID patients scored largely below average to low average in the TAP test (percentile ranges from 0 to 21). Only the divided attention test (mistakes made) was average (percentile rank 42–50) on admission. On discharge, the not processed tasks (omissions) in working memory were also average; the patients did not omit more stimuli than the average. On discharge, percentile rank in sustained attention was 16–21 (mistakes made) and 0 (not processed/omissions), in divided attention 42–50 (mistakes made) and 10–12 (not processed/omissions). In the TAP sub-tests working memory, sustained attention and divided attention, there was no statistically significant change in performance from admission to discharge.

Alertness was tested twice each test time (twice on admission and twice on discharge). On both admission and discharge, cognitive strain occurred between the first and second alertness tests in the form of the TAP sub-tests working memory, sustained attention, and divided attention. Although the alertness scores on admission were within the average range (PR 66 to 69), this level could not be increased but largely maintained. On discharge, alertness 1 had worsened, but the patients were still in the average range (PR = 38); the effect was small (d = 0.32). As a measure of cognitive fatiguability, the difference between the first alertness test and the second alertness test was taken at the respective measurement time point. At T1, the patients in Alertness 2 (without warning tone) reacted MDN = 3.33 faster than in Alertness 1. At T2, this difference was MDN = 19.63. In the Alertness condition with warning tone, patients responded MDN = 2.54 faster at T1 in Alertness 2, and 19.63 slower at T2. There was no strong fatiguablity, which can also be explained by the training effect of the task.

The results of the TAP test analyses can be found in Tables 3 and 4.

Table 2
PHQ-9: Depressive symptoms - differences within the groups from admission to discharge.

	T1	T2		
	M(SD)	M(SD)	p	d
PHQ-9 total	15.15 (5.11)	8.80 (4.61)	<0.001	1.57
loss of joy or interest	1.85 (1.00)	0.96 (0.63)	<0.001	0.99
loss of energy / fatigue	2.58 (0.72)	1.69 (0.97)	<0.001	1.03
loss of appetite	1.16 (1.05)	0.61 (0.81)	0.004	0.53
self-deprecation and self-doubt	1.20 (1.20)	0.67 (0.92)	<0.001	0.57
psychomotor changes: agitation or deceleration	1.27 (1.08)	0.61 (0.68)	<0.001	0.63
suicide ideations	0.20 (0.50)	0.04 (0.20)	<0.001	0.42

Note. T1 admission, T2 discharge, M median, SD standard deviation, p significance level, d Cohen's d, Cohen's d effect sizes: 0.2 small, 0.5 medium, 0.8 large; Bonferroni correction has been used.

3.3.2. *Correlation: Depression and cognitive impairments*

In the correlation analysis of the depressive symptoms on admission and the TAP results on admission, no significant correlations were found for the most part. Significant correlations were found for three items of the PHQ-9 and sub-tests of the TAP: loss of interest/pleasure and sustained attention (not processed/omissions) $r = 0.32$; hopelessness and working memory (mistakes made) $r = 0.39$; sleep disturbances and working memory (mistakes made) $r = 0.38$. The PHQ-9 depression total score was also not significantly related to cognitive impairment on admission. Astonishingly, there was a medium correlation between the PHQ-9 depression total score and alertness on discharge ($r = 0.30$). Lower scores in the depression scale (= less symptom burden) are thus associated with higher scores (= worse outcome) in alertness.

3.3.3. *Variance explanation of cognitive impairment due to depressive symptoms on discharge*

Although there was little correlation between depressive symptoms and TAP scores on admission, we considered it important to examine the contribution of depression to the variance in cognitive impairment on discharge. Regression analyses were calculated for the individual depression symptoms, as well as for the PHQ-9 total depression score and the respective cognitive impairments (TAP-Scores).

The model specifications for the individual symptoms and the respective TAP domains were all non-significant. The separate depressive symptoms do not therefore contribute to explaining the cognitive impairments in the TAP that persist unchanged on discharge.

The model specification with the PHQ-9 depression sum score and the TAP domains was significant only for depression and alertness ($p = .04$), which is in line with the results of the previous correlation analyses. The variance explanation by the PHQ-9 depression score was a regression coefficient B = 0.013. Thus, depression as measured by the PHQ-9 explains 1.3% of the total variance of alertness, which can be regarded as negligible.

4. Discussion

The current study investigates the clinically relevant extent to which depressive symptoms and cognitive impairments (here in the domains of alertness, attention and working memory) are present in post-COVID patients undergoing psychosomatic post-COVID rehabilitation. In addition, it was tested whether depressive symptoms and cognitive impairments improve over the course of rehabilitation (five weeks). Our study reveals that patients with post-COVID syndrome report depressive symptoms to a clinically relevant extent on admission. Furthermore, mental health problems seem to be a risk factor for post-COVID also in our sample, especially since the prevalence in our sample was 32%. The 12-month prevalence of depressive disorders is 10.7% in Germany and 12.7% in the United States. The 12-month prevalence rates for anxiety disorders in Germany are 14.5%, in the USA 17.2%. The lifetime prevalence rate in the general population has been stable for years, at around 30% (USA 29.5%, Germany 31.1%) [32]. During the COVID-19 pandemic, this also remained largely stable: 31.9% anxiety disorders, 33.7% depressive disorders [33]. The participating post-COVID patients demonstrated cognitive impairment at rehabilitation onset. While for short tests evaluating simple reaction times (alertness) the overall patient group seemed to be within a healthy performance range, deficits became obvious for more complex tests (Divided Attention, Working Memory) or tests of longer duration (Sustained Attention). In contrast to the significantly improved levels of depression, these attention-related parameters did not demonstrate any advancements from T1 to T2. For alertness, it was observed that the patients even tended to deteriorate in individual cognitive sub-components during rehabilitation. Our data

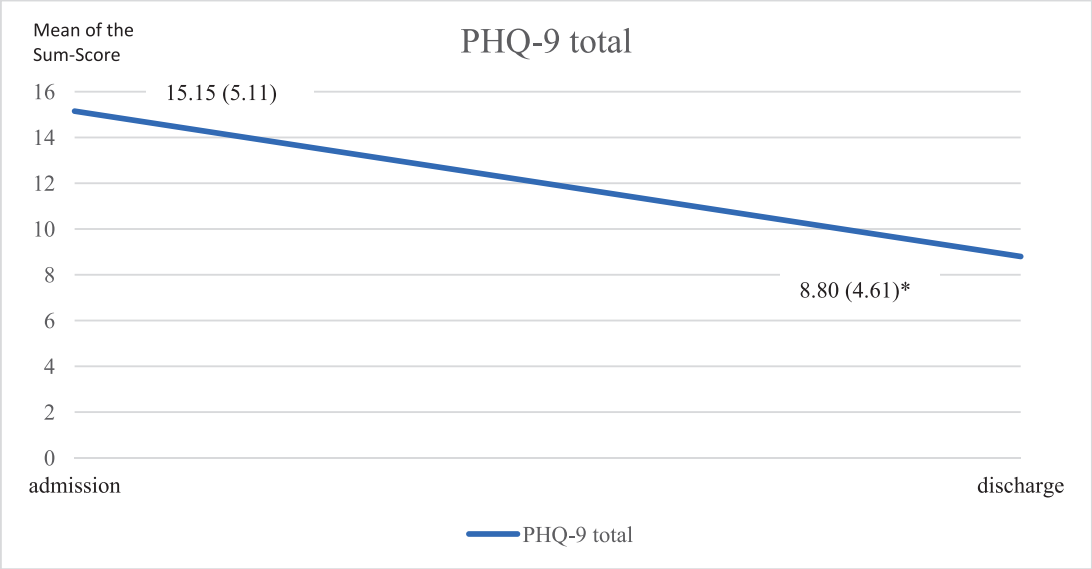

Fig. 1. PHQ-9: Depressive symptoms - differences within the groups from admission to discharge.
Note. Higher values mean a poorer result; * significant. The values represent the mean and the standard deviation in brackets.

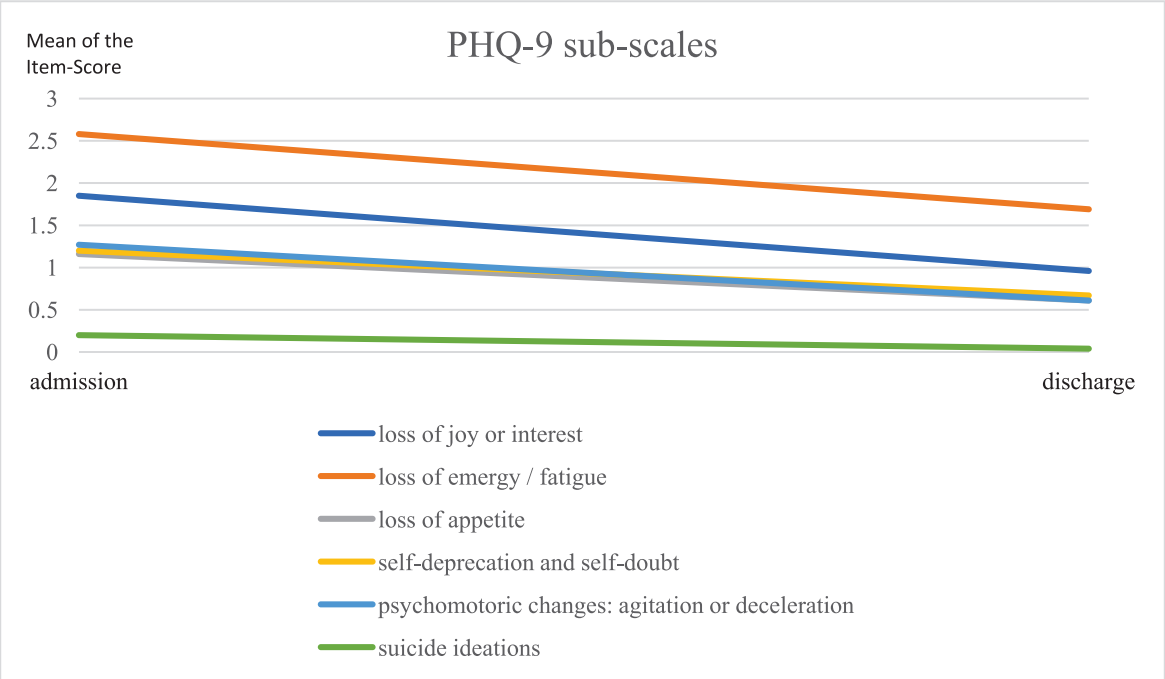

Fig. 2. PHQ-9: Depressive symptoms - differences within the groups from admission to discharge.
Note. Higher values mean a poorer result; * significant. The values represent the mean and the standard deviation in brackets.

show that the depressive symptoms of post-COVID patients improved after the rehabilitation programme, but the cognitive impairments persisted.

Some studies on cognitive impairment after SARS-CoV-2 infection have been published [3,17–21]. Data show that approximately 1 in 5 individuals exhibited cognitive impairment for 12 or more weeks following a COVID-19 diagnosis [34] and approx. 78% of young patients who had recovered from a mild to moderate COVID-19 disease reported sustained mild cognitive deficits and performed worse in a screening test for mild cognitive impairment compared to age-matched healthy controls [35]. There are also studies showing links between neuro-immunological changes or other somatic abnormalities and cognitive deficits after SARS-CoV-2 infection [34,36,37]. For example, an elevation of pro-inflammatory markers associated with functional impairment can be detected [34]. A review [38] on cognitive impairment in patients with previous COVID-19 infection found that neurological and respiratory conditions were often reported in association with cognitive deficits. At the same time, results on psycho-affective conditions were inconclusive due to the low frequency of reported data.

As far as we know, this study is the first to look at the cognitive impairment of post-COVID patients in a psychosomatic post-COVID rehabilitation setting and the extent to which cognitive deficits (TAP results) are independent of depression (PHQ-9 results). As already explained, post-COVID patients in psychosomatic post-COVID

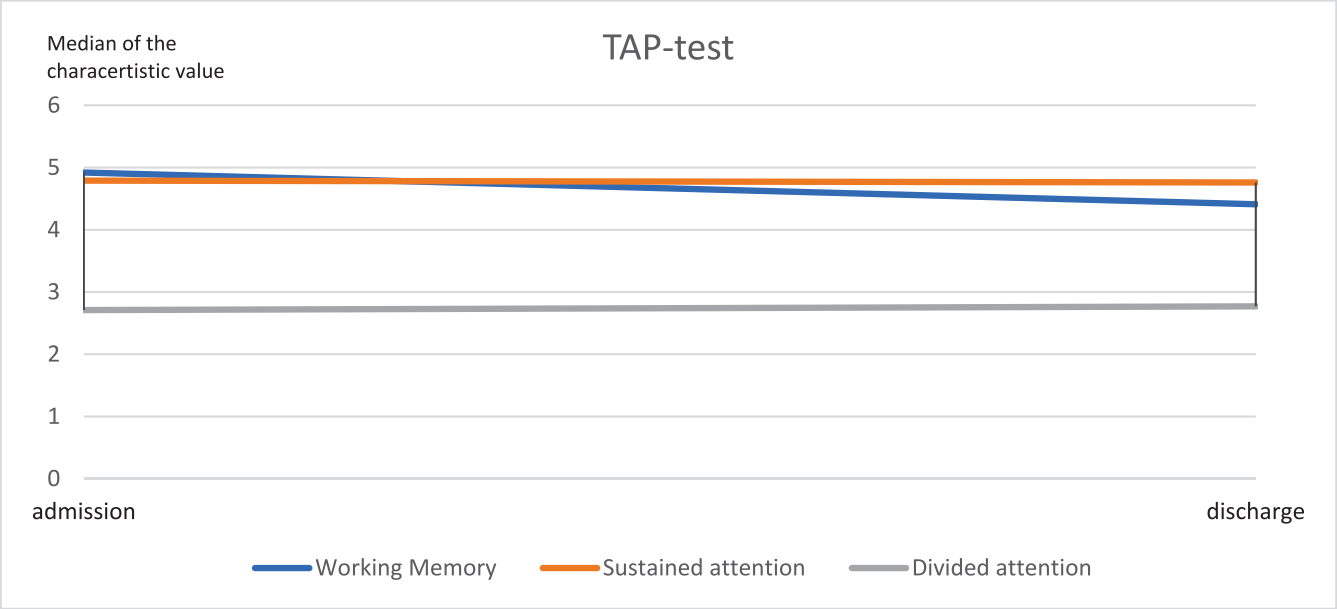

Fig. 3. TAP test: Cognitive impairment - differences within the groups from admission to discharge.
Note. Higher values mean a poorer result. * significant, ns not significant. The values represent the median and the standard deviation in brackets.

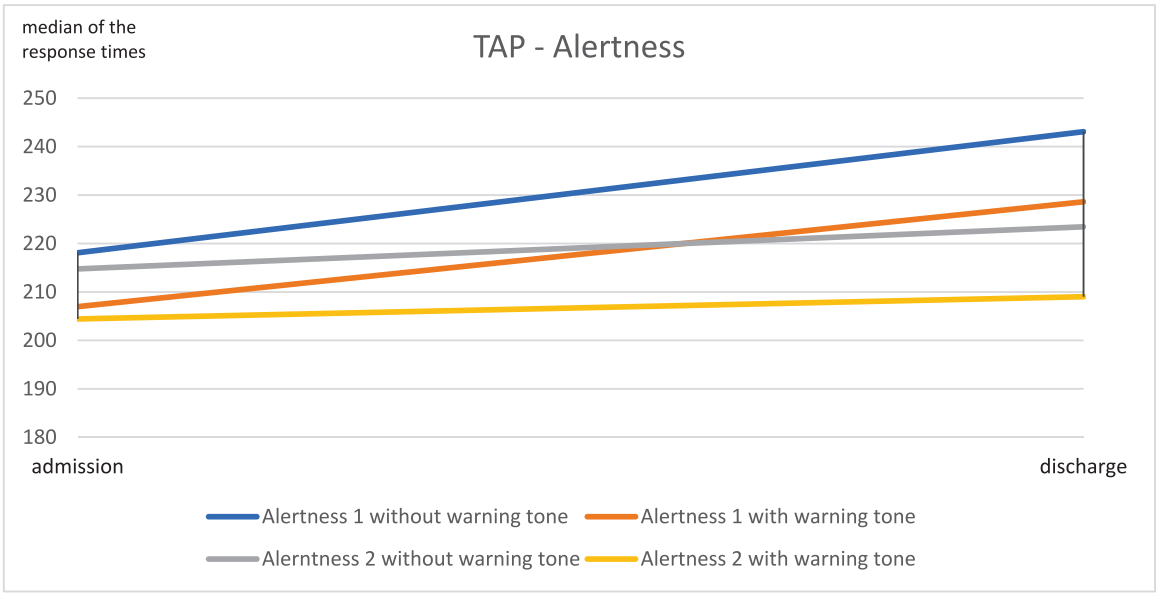

Fig. 4. Sub-TAP test Alertness: Reaction time and degree of alertness - differences within the groups from admission to discharge.
Note. Higher values mean a poorer result. * significant ($p < .05$). The values represent median of response time and standard deviation.

Table 3
TAP test: Cognitive impairment - differences within the groups from admission to discharge.

Sub-test	Mistakes made						Not processed / omissions					
	T1	PR	T2	PR	p	Cohen's d	T1	PR	T2	PR	p	Cohen's d
	MDN (SD)		MDN (SD)				MDN (SD)		MDN (SD)			
Working memory	4.92 (7.71)	16–21	4.41 (6.12)	16–21	0.613	–	4.18 (18)	14–16	3.28 (3.66)	24–27	0.157	–
Sustained attention	4.79 (8.34)	16–21	4.76 (8.94)	16–21	0.918	–	10.71 (8.78)	0	9.29 (9.27)	0	0.348	–
Divided attention	2.71 (7.79)	42–50	2.77 (5.65)	42–50	0.348	–	4.94 (5.39	10–12	4.68 (5.39)	10–12	0.086	–

Note. T1 Test No. 1 on admission, T2 Test No. 2 on discharge, PR percentile, p significance level, MDN median, SD standard deviation

Table 4
Sub-TAP test Alertness: Reaction time and degree of alertness - differences within the groups from admission to discharge.

	T1					T2					
Sub-TAP test Alertness	Without warning tone		With warning tone			Without warning tone	With warning tone				
	MDN (SD)		MDN (SD)	indicator	PR	MDN (SD)	MDN (SD)	indicator	PR	p	Cohen's d
Alertness 1	218.09 (30.46)		206.97 (29.10)	0.089 (0.17)	66	243.08 (41.50)	228.61 (41.94)	0.026 (0.14)	38	0.012	d = 0.32
Alertness 2	214.76 (29.40)		204.43 (28.05)	0.098 (0.13)	66–69	223.45 (32.49)	209.02 (30.45)	0.079 (0.18)	58–62	0.471	–
Difference Alertness 1 & Alertness 2	3.33 (2.41)	2.54 (1.05)	–	– 19.63 (9.01)	19.59 (11.49)	– –	–	–			

Note. MDN median of the response times, SD standard deviation of the response time, PR percentile, p significance level
Characteristic value: calculation of the indicator for the phasic alertness reaction: difference in the reaction time medians with and without warning tone divided by the reaction time median of all individual stimuli. A value above zero indicates an increase in the level of attention in the sense of phasic alertness. The registered number of "omissions" reflects the frequency with which a critical stimulus was not responded to by pressing a key. It is an indicator of inattentiveness.

rehabilitation show clinically relevant depression scores at the beginning of rehabilitation, which improve over the course of rehabilitation. Cognitive impairment is also part of depressive symptoms, so there is a possibility that cognitive impairment occurs in the context of a reactive depressive disorder due to COVID-19, or is a pure post-COVID symptom independent of depression. Whether the persistence or worsening of the cognitive impairment in the individual cognitive sub-components we found is a reliable result needs to be proved by follow-up studies. Potentially this change for the worse could be explained by the fact that the testing at the beginning of rehabilitation was carried out under the condition of a relatively mild cognitive load, and at the end of rehabilitation under the condition of an increased cognitive load, meaning that even short tests of simple reactions may eventually become affected. Another explanation could be that the second test was carried out at a different time of day (e.g. in the afternoon) or after emotionally or cognitively demanding therapies (e.g. after group psychotherapy) and that the patients were therefore already mentally and emotionally stressed. We checked this potential explanation, but found no consistent differences between T1 and T2 in testing times or type of treatment that was experienced before being tested.

The results of the correlation and regression analyses support the thesis that cognitive deficits in post-COVID syndrome are probably not an artefact of a reactive depressive disorder. If the cognitive impairments were symptoms of reactive depression, we would assume that they would also remit with resolution of depressive symptomatology. The results of this study show a different picture: the depressive symptoms remit, the cognitive impairments persist. Also, no significant correlations between the depressive symptoms and the cognitive disorders could be found. Again, several explanations exist, two of which will be mentioned: either the depression lingers in the form of persistent cognitive impairment, or the cognitive impairment goes beyond depressive mood and perhaps could be interpreted as a rather independent neuropsychological deficit. Data [39] show that cognitive impairment can persist for a considerable time even after remission of depressive symptoms (affective components and changes in drive). Nevertheless, there is a lot to suggest that the cognitive disturbances are probably a neurological rather than a psychosomatic problem [40–42]. In this case, an even more intensive and longer-term cognitive training than offered in this post-COVID rehabilitation setting (2× per week 45 min over 5 weeks) might be necessary to adequately reduce the cognitive symptomatology. Study data have already shown that cognitive training has produced good results for cognitive impairment in conditions other than post-COVID [43,44]. A meta-analysis [45] of short-term and long-term effects of cognitive training demonstrated large training effects for trained outcomes. Further analyses of immediate effectiveness found significant, small training effects for executive function, fluid intelligence, memory and visuospatial domain performance, but not for attention or processing speed. The results of a large-scale, cross-sectional study on the efficacy of brain training [46] suggest an efficacy for brain training over an extended period of time which increases with duration (months – one year – more than one year) and the intensity (monthly – weekly – daily basis). The greatest effect was seen for those who were trained on a weekly basis for >1 year.

Positive results were also reported for cognitive training in combination with exercise therapy [47]. However, with respect to therapy intensity, individualised therapy programmes adapted to the patients' endurable load may be best suited to this patient group as, for example, intolerance to heightened cognitive load or exercises and related post exertional malaise can be part of the post-COVID syndrome [48].

The results of our study suggest that patients with post-COVID syndrome benefit significantly from post-COVID rehabilitation in terms of PHQ-9. Especially in loss of joy or interest and loss of energy, large effects could be found; in loss of appetite, self-deprecation and self-doubt and psychomotoric changes, there were medium effects. Post-COVID patients did not improve significantly in terms of cognitive deficits, such as alertness, attention and working memory. These appear to be independent of depressive symptoms, which can include cognitive deficits, and persisted despite cognitive training, which usually achieves good results in other neuropsychological disorders [43,44].

It can therefore be argued that further research is needed to elucidate the mechanism of cognitive impairment following SARS-CoV-2, particularly as cognitive impairment is a major factor in long-term sick leave and poses a significant threat to activity and participation, as well as earning capacity.

4.1. *Strength and limitations*

The current study provided the opportunity to examine post-COVID patients in a psychosomatic rehabilitation setting with regard to depressive symptoms, their course and at the same time the course and interaction with cognitive disorders.

Also, limitations of this study should be addressed. Firstly, the present study consists of a retrospective data evaluation. Also, this is a single-centre study that has an allocation bias due to the psychosomatic post-COVID setting. Therefore, we can only draw conclusions about the psychosomatic post-COVID sub-group that was considered in the post-COVID rehabilitation conducted here. With regard to the measurement instruments used here, it should be mentioned that both the PHQ-9 and the MoCa are quite simple test procedures that cannot provide a comprehensive picture, but are rather to be understood as screening instruments. In future investigations, differentiated measures should be used, which, for example, deal with a more comprehensive assessment of short-term memory encoding. In some studies on cognitive impairment in post-COVID, attention has been identified as a key functional

area that is impaired. In addition, problems in other areas such as memory and executive functions have been documented, so that an extended assessment and more in-depth neuropsychological examinations with regard to resilience seem to be useful [49]. A comprehensive neuropsychological test battery could also be considered, as was used in a studies of cognitive disorders in adults with post-COVID syndrome [50,51].

Also, with regard to cognitive impairment, we are faced with the base-rate problem: since no baseline data are available from before the disease, the assessment of cognitive impairment had to be based on reference data from a normative sample delivered with the test battery. Another point to be considered is previous studies demonstrating that cognitive impairment can persist even after remission of depressive symptoms and intensify with the number of episodes [39]. In addition, medication, which can also have an influence on cognitive performance, was not systematically recorded. Thus, causal statements on the actual effectiveness of rehabilitation are not possible, but they were not the aim of this study. Another limitation is the restriction of the data evaluation to certain parameters of the TAP and to the PHQ-9. While our results are of scientific value and can contribute to unveiling the complex characteristics of post-COVID syndrome, in future studies it would be advisable to consider further parameters for a more comprehensive picture.

5. Conclusion

The results of this study imply that rehabilitation patients with post-COVID condition who report clinically relevant depressive symptoms at the beginning of rehabilitation can improve significantly during the course of rehabilitation. At the same time, cognitive deficits are present at the start of rehabilitation and persist throughout the course of rehabilitation. Although post-COVID rehabilitation seems to contribute to improvement in psychological complaints, the cognitive performance seems to be unaffected by the psychosomatic post-COVID rehabilitation programme.

To sum up, it can be said that:

1. Post-COVID rehabilitation inpatients are clinically relevantly depressed at the start of rehabilitation, and the depressive symptoms improve over the course of rehabilitation.
2. The post-COVID patients examined in this study show clinically relevant cognitive impairments that persist throughout the rehabilitation period despite treatment.
3. In the post-COVID patients studied here, the cognitive impairments seem to be independent of depressive mood.

Although there has been some research on cognitive deficits in patients suffering from post-COVID syndrome, knowledge is still lacking about the mechanisms and how to treat the syndrome effectively. In addition, the lack of studies with good methodological quality focusing on interventions especially for post-COVID condition calls for further research. There is a strong need to support this population adequately, due to their high levels of mental distress and risk of dropping out of social life.

Statement of ethical approval and consent to participate

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Data were obtained as part of the PoCoRe study and are not part of routine diagnostics. The research was approved by the ethics committee of the Centre for Clinical Research, University Hospital Regensburg (identification 22–2814-101) in February 2022. Prior to study participation, patients were informed about the study objectives and the study procedure in a personal information consultation and received standardised participant information sheets. After this, voluntary written informed consent for study participation and storage, evaluation and transfer of study-related data were obtained from each study participant by research associates. Withdrawal of written consent is possible at any time, without giving reasons or disadvantages to their treatment.

Author contributions

AK: Conceptualisation, wrote the original draft, conceived and designed the analysis, collected the data, performed the statistical analysis. TH: Review. MJ: Review & supervision. JR: Review & supervision. THL: Review & supervision. VK: Conceptualisation, review & editing, supervision. †THL and †VK share senior authorship.

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Declaration of Competing Interest

The authors whose names are listed below declare that there are no conflicts of interests.

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