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Benefits of Pulmonary Rehabilitation in COPD patients with mild cognitive impairment – A pilot study

Vasileios Andrianopoulos¹, Rainer Gloeckl¹, Tessa Schneeberger¹, Inga Jarosch¹,
Ioannis Vogiatzis², Emily Hume², Rembert A. Koczulla^{1,3,4}, Klaus Kenn^{1,3,4}

Affiliations

¹Institute for Pulmonary Rehabilitation Research; Schoen Klinik Berchtesgadener Land; Schoenau am Koenigssee, Germany ²Department of Sport, Exercise and Rehabilitation, Faculty of Health and Life Sciences, Northumbria University Newcastle, United Kingdom ³Department of Pulmonary Rehabilitation, Philipps University Marburg, Marburg, Germany ⁴German Centre of Lung Research (DZL), Giessen-Marburg, Germany

Email addresses of authors:

Dr. Vasileios Andrianopoulos: vasileios.andrianopoulos@web.de

Dr. Rainer Gloeckl: RGloeckl@schoen-klinik.de

Ms. Tessa Schneeberger: TSchneeberger@schoen-klinik.de

Dr. Inga Jarosch: IJarosch@schoen-klinik.de

Prof. Dr. Ioannis Vogiatzis: ioannis.vogiatzis@northumbria.ac.uk

Miss Emily Hume: emily.c.hume@northumbria.ac.uk

Prof. Dr. Rembert A. Koczulla: RKoczulla@schoen-klinik.de

Prof. Dr. Klaus Kenn: KKenn@schoen-klinik.de

Corresponding author information

Vasileios Andrianopoulos, PhD

Institute for Pulmonary Rehabilitation Research; Schoen Klinik Berchtesgadener Land; Schoenau am Koenigssee, Germany. Tel: +49 (0)8652 93-1524 - Fax: +49 8652 93-1800

Email: vasileios.andrianopoulos@web.de

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Abstract

BACKGROUND: Cognitive impairment might interfere with the efficacy of Pulmonary Rehabilitation (PR) in Chronic Obstructive Pulmonary Disease (COPD). We aimed to identify differential responses to PR between cognitively impaired (CI) and cognitively normal (CN) COPD patients by assessing health status and exercise capacity.

METHODS: Sixty patients (FEV_1 : $47 \pm 15\%$) were classified as CI or CN according to the Montreal Cognitive Assessment ($MoCA \leq 25$ points) and completed a 3-week inpatient PR program. Cognitive function (neuropsychological battery), health-status (36-Item Short Form Survey [SF-36]), and exercise capacity (six-minute walk test [6MWT], cycle-endurance test [CET]) were assessed before and after PR. Responsiveness to PR was estimated by mean change (delta-value [Δ]) and the *d*-Effect Size (ES).

RESULTS: Twenty-five COPD patients (42%) presented evidence of mild CI prior to PR. Both, CI and CN patients significantly improved global cognitive function, health status (the majority of SF-36 components), and exercise capacity (6MWT and cycle endurance) in response to PR. Compared to CN, CI patients did not improve SF-36 subdomains of “role emotional” and “bodily pain”, and demonstrated a lower magnitude of improvement in 6MWT ($[\Delta]$: 25m; ES: 0.21) compared to CN ($[\Delta]$: 46m; ES: 0.54).

CONCLUSIONS: PR had favorable effects on global cognitive function, health status, and exercise capacity in both CI and CN COPD patients. There was no concrete evidence to indicate interference of cognitive impairment to PR effectiveness.

Key-words: Cognitive function, health status, exercise capacity, chronic pain, Chronic Obstructive Pulmonary Disease

Introduction

Pulmonary rehabilitation (PR) is recommended as a core component of standard comprehensive care for patients with chronic obstructive pulmonary disease (COPD) [1]. The main components of this multidisciplinary therapeutic approach include exercise training, education, emotional and nutritional support, which are designed to improve health, functional status, and health-related quality of life [2, 3]. There is compelling evidence that PR improves clinical symptoms, health-related quality of life, exercise capacity and participation in physical and social activities [4-6]. However, to obtain the optimal benefits from PR and reverse the systemic consequences of COPD, it requires patients to engage both physically and psychologically Patients' engagement with PR, however, requires physical and psychological investment to gain the optimal benefits and reverse the systemic consequences of COPD [7]. Although many studies ~~have~~ reported the benefits ~~beneficial effects~~ of PR in COPD patients who complete the program [6, 8], different patient characteristics and comorbid conditions, such as COPD-related cognitive impairment, may lead to differential responses to PR interventions [9, 10].

Previous literature highlights the higher prevalence of cognitive impairment in COPD patients ~~reports higher prevalence of cognitive impairment in COPD patients~~ (ranging from 10% to 61%, with an average of 36%) compared to the normal population (ranging from 5% to 24%, with an average of 12%), reflected by based on lower cognitive performance scores ~~in comparison to normative scores~~ [11-13]. Cognitive impairment (CI) in COPD patients is likely multifactorial, involving factors such as hypoxemia, lung inflammation (increased C-reactive protein levels), and a decrease in physical functioning [14, 15]. CI is usually manifested with frequent memory loss, functional disability, poor physical and psychological well-being, and faster cognitive decline over time [16-18]. Furthermore,

~~studies show a strong association between cognitive impairment and chronic pain [19, 20], with higher bodily pain hindering physical activities and negatively impacting health-related quality of life in COPD [21]. These factors all have the potential to interfere with the effectiveness of PR programs. Previous research looking specifically at PR, highlights lower adherence and higher dropout rates in COPD patients with CI, compared to those without [22]. Additionally, CI has been linked to poorer disease self-management [23], as well as an increased risk of hospitalization and mortality. Moreover, CI has been linked to an increased risk of hospitalization and mortality [23, 24]. Additionally, CI patients often have a reduced ability to manage their disease [22], along with lower adherence and higher dropout rates to PR [19], compared to cognitively normal (CN) patients with COPD. Furthermore, a strong association between cognitive impairment and chronic pain has been reported, with higher bodily pain hindering physical activities and negatively impacting health-related quality of life in COPD [21]. Engagement with PR can provide elicit significant physical and mental health benefits to in COPD patients [20, 25, 26], however coexisting cognitive impairment has the potential to might limit the effectiveness of PR.~~

To date, the impact of cognitive impairment on the responsiveness to PR in health, functional, and mental status has not been extensively investigated. Therefore, we aimed to investigate whether cognitive impairment influences PR outcomes in COPD patients.

Materials and methods

Setting and participants

Sixty-two patients with clinically stable COPD, who were referred to a comprehensive 3-week inpatient PR program (Schoen Klinik Berchtesgadener Land, Germany), were recruited. Data from sixty patients (n=60), who completed the study, were analysed. Inclusion criteria for the study were: diagnosed GOLD stage II-IV, aged 40 to 85 years old at the time of eligibility screening. We excluded patients with resting hypoxia ($\text{PaO}_2 < 55\text{mmHg}$), resting hypercapnia ($\text{PaCO}_2 > 45\text{mmHg}$), exacerbation of COPD within the past 4 weeks, chronic heart failure, history of stroke, increased cognitive impairment or dementia (MoCA < 17 points), other diagnosed neuropsychiatric symptoms. The study was approved by the Bavarian ethical committee in Munich (ID: 15134) and was conducted in accordance with the guidelines of the Helsinki Declaration. All subjects provided written, signed, informed consent.

Assessment

As part of the pre-rehabilitation clinical routine assessment, patients underwent physical examination, anthropometric and lung function measurements, blood gas analysis at rest under ambient conditions, and screening of medical history and comorbidities. Furthermore, patients completed self-administered questionnaires including the 36-Item Short Form Survey (SF-36) [27], the COPD Assessment Test (CAT) [28], the St. George's Respiratory Questionnaire (SGRQ) [29], the Hospital Anxiety and Depression Scale (HADS) [30], and performed a six-minute walk test (6MWT)

according to the international guidelines [31, 32]. For the post-rehabilitation assessment, the SF-36 [21] and 6MWT were repeated under the same conditions.

The study protocol consisted of four assessment visits (two-visits at PR admission and two-visits at PR discharge; see online figure 1). On visit 1 (V1), a comprehensive cognitive assessment was performed providing global and domain-specific cognitive evaluation of patients' mental status (See below for details). On the second visit (V2), patients performed a symptom-limited cycle endurance test (CET) at 75% of the estimated peak Work Rate (WR_{peak}; see online supplement for details). A re-assessment of global and domain-specific cognitive function (V3) and cycle-ergometer exercise parameters (V4) were conducted on PR discharge for examining differences between baseline and post-PR measurements.

Patient Questionnaires

The self-administered questionnaires used in the current study were all in German language and validated for their purposes. Patients were strongly advised to ask for clarifications, when they could not clearly comprehend a question and, in some cases, partners or relatives helped them during this procedure. In specific Specifically, we used the self-administered SF-36 Health Survey that is validated in German as part of the IQOLA project[33]; the CAT, with scores ranging from 0 to 40 (a score of 0 indicating no impairment), translated using a standardised and validated procedure into German [34]; the SGRQ in its German validated version consisting of 50 questions about symptoms, activity and the

impact of COPD [29]; and the HADS for detecting states of depression and anxiety by using 14-items ranging from 0 to 21, with higher scores indicating greater anxiety and depression levels more severe distress [35].

Neuropsychological Tests

Cognitive status/impairment was assessed at PR admission and discharge using a comprehensive neuropsychological assessment battery, which included: 1) Standardized Mini-Mental Status Examination (SMMSE) [36], 2) Addenbrooke's Cognitive Examination-Revised (ACE-R; v.2007) [37], 3) Montreal Cognitive Assessment (MoCA) [38], and 4) Interview for Cognitive Status (T-ICS) administered by face-to-face interview [39]. The screening for cognitive impairment and groups' categorization (Groups: CI; CN) was performed by the MoCA test according to the suggested cut-off point of ≤ 25 points [40, 41]. This MoCA threshold score has been found as optimal for the detection of cognitive impairment in COPD patients, with 81% sensitivity, 72% specificity, and 76% correctly diagnosed cases [40]. After categorization to cognitively impaired (CI) and cognitively normal (CN) patients, cognitive function (global and domain-specific evaluation) was assessed by SMMSE, ACE-R, and T-ICS clinical instruments.

Besides the global cognitive assessment, a domain-specific cognitive evaluation of six key-domains as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [42] was performed at PR admission and discharge. Domain-specific cognitive evaluation included: A) orientation ability, B) memory, C) attention/concentration, D) language and executive, E) fluency, and F) visuospatial skills.

The percentage (%) of correctly matched items on each of the cognitive domains determined cognitive performance.

Pulmonary Rehabilitation program

Patients attended a comprehensive 3-week pulmonary rehabilitation (PR) program. Exercise training was performed 4 times per week (at least 12 sessions) with each session lasting around 50 minutes, plus 30 minutes activities of daily living (Online table 1). Exercise sessions were supervised by physicians and exercise physiologists, and consisted of cycle ergometry, treadmill walking and resistance exercises, with time and workload progressively increased as tolerated, based on breathlessness and leg discomfort assessment using the 0-10 Borg scale [43]. In addition, each patient received education about COPD self-management and physical activity counselling.

Examination of Responsiveness

To address the question of differential responses to PR between CI and CN patients, we compared scores from SF-36, cognitive tests, and the exercise performance before and after PR in both groups. Normal distribution of data was assessed before conducting multiple comparisons to examine responsiveness (Online table 2). We employed: a) the significance of delta values [Δ] (differences on clinical parameters from admission to PR discharge) and the Cohen's *d* effect size (ES). Additionally, the index of percentage of responders (%R) was used. The percentage of responders (%R) was calculated from the number of patients who achieved improvements according to the minimal clinical important difference (MCID). MCID for the SF-36 subdomains and the exercise capacity (6MWD, CET)

were adopted from the HSR: Health Services Research 2005 [44], and the ERJ official systematic review 2014 [31], respectively. The remaining MCID thresholds (non-existing in the literature) were estimated by multiplying the standard deviation of patients' measures at baseline by 0.5 [45]. The ES was calculated by taking the mean change and dividing it by the pooled SD of both measurements (Cohen's *d*) appropriately weighted, when the sample sizes were not equal [46]. Higher ES represents greater responsiveness, with scores greater than 0.20, 0.50 and 0.80 representing "small", "moderate" and "large" changes [47], respectively (Online table 3).

Addressing ceiling effect

Ceiling effects needs to be considered as these may lead to artefactual estimates in the analyses of data derived from clinical instruments with a certain scoring range (i.e. SF-36 and cognitive tests). It occurs when a high proportion (>20%) of patients grade themselves at baseline with scores possessing a distinct upper limit for potential responses [48]. Consequently, we considered the occurrence of a ceiling effect when more than 20% of patients had higher baseline scores than the derivative of "maximum scores minus the minimal important difference (MID) or estimates", to ensure that scoring captured the full range of potential responses. In cases where a ceiling effect was present, non-parametric analyses were used (Online table 4).

Statistical analysis

All statistical analyses were carried out using SPSS v.19.0, Stata/SE v.12 and MedCalc v.12. Data are presented as mean \pm standard deviation or proportion, as appropriate. Data distribution was assessed

by two methods; the D'Agostino & Pearson omnibus normality test and the Jarque-Bera test, matching the skewness and kurtosis for the baseline residual values in CN and CI patients (Online table 2). Non-normally distributed data detected by *at least* one method (i.e. D'Agostino test or Jarque-Bera test), were analyzed using non-parametric analyses. Differences *between* groups at baseline were assessed using an independent t-test or Mann-Whitney *U*-test, and differences *within*-group and *between*-groups following PR were evaluated by paired-samples *T*-tests or Wilcoxon signed rank test, as appropriate. Responsiveness to PR between CI and CN patients for several outcomes was evaluated and compared using paired samples *T*-test analysis and the delta [Δ] values (pre and post PR) as well as the effect size (ES). The comparisons of %R were conducted using chi-square test. Multivariate models based on a stepwise multiple linear regression were used to determine the interaction between bodily pain and PR. Pearson's correlation coefficients were also used to assess bivariate relationships. Two-sided level of significance was set at $P < 0.05$.

Results

Feasibility of the study protocol

We report that the study protocol was feasible. In brief, the majority of the patients who were contacted in the phase of during study recruitment were willing to participate, after receiving a detailed explanation of the research project and were informed for the potential benefits of participating in this project (i.e. cognitive evaluation and additional functional assessments). Initially, self-completed questionnaires (HADS, CAT, CRQ, SF-36) were given to participants and a researcher explained the tasks. Nevertheless, there were some items that patients missed out, possibly because

Commented [e1]: Do we need to add numbers/percentage here?

~~they skipped and forgot the question or were not sure of the answer. When this occurred, We contacted patients were contacted again to ensure all answers were fully completed patients so as to get all the answers. Moreover, some participants faced difficulties in understanding their tasks in cognitive tests. To overcome this problem the tests were explained to the participant multiple times, until the researcher was confident that the participant had full understanding of the task. This ensured that the results of each test reflected the participant's cognitive performance, rather than confusion derived from poor understanding of the cognitive test tasks. This problem was overcome after explaining the tests to the participant multiple times until we were confident that they had fully understood the tasks and the results of each test reflected more the pure cognitive performance rather than confusion derived from a poor understanding of the cognitive test tasks [49]. Participants needed ~50 minutes to perform all the cognitive tests, with while a well-trained researcher present was next to them to recording correct answers and evaluateing responses (visuospatial skills, language/executive, and fluency). We had only There were only two dropouts from the in this study, because of which were due to a lack of interest to complete the study.~~

Patient characteristics

Sixty patients with COPD (n=60) were included in the analysis, since two patients (one with CI and one with CN) dropped out ~~because of lack of interest to complete the study~~. Patients (age range: 49-85; mean: 67.7 years; 42% women) had a normal body-mass index, severe airflow limitation, resting lung hyperinflation (RV/TLC), and mild resting hypoxemia. Patients exhibited increased chronic dyspnea in daily life (assessed by mMRC), intense COPD-related symptoms (rated by CAT) and demonstrated a severely impaired health-related quality of life (rated by SGRO; Table 1).

Twenty-five out of sixty patients (42%) presented evidence of cognitive impairment (MoCA \leq 25 points). Almost all patients exhibited mild cognitive impairment based on MoCA scores, except one who scored below 18 points reflecting a moderate stage of cognitive impairment [41] (Figure 1). The cognitively impaired (CI) group was acceptably balanced with the cognitively normal (CN) group in respect to important demographics (sex, age, BMI) and COPD-related symptoms (mMRC, CAT; Table 1). CI patients had significantly lower blood oxygen levels at rest, a trend ($p= 0.15$) for smaller Forced Vital Capacity (FVC) and for higher number of comorbidities ($p= 0.12$), compared to cognitively normal (CN) counterparts (Table 1). CI patients were less educated, presented poorer global cognition function as assessed by the cognitive tests included in the neuropsychological testing battery, but had comparable levels of anxiety and depression (HADS; Table 2). In regard to health and functional status, CI patients had comparable baseline values in SF-36, exercise capacity and physical activity levels, compared to their CN counterparts (Table 2). There was no difference in the history of acute exacerbation of COPD one year prior to entering the study between CI and CN counterparts.

Changes in health status (SF-36)

Normal distribution was rejected for the SF-36 in two out of the eight subdomains and there was a ceiling effect in bodily pain, social functioning, and in role limitations due to emotional problems (Role Emotional) dimensions (Online tables 2 and 3). Following the PR intervention, both CI and CN patients significantly improved Physical- and Mental- Summary scores and the following SF-36 subdomains: Physical Functioning, General Health, Vitality, Social Functioning, and Mental Health ($p < 0.05$; Table 3), with small to moderate effect sizes demonstrated from PR admission to discharge (Online table 3).

Different responses to PR between CI and CN patients were detected for the following subdomains: a) bodily pain (Effect Size: 0.21 and 0.70, respectively) and b) role limitations due to personal or emotional problems (role emotional; Effect Size: 0.15 and 0.43), respectively (Table 3, online table 3).

Changes in cognitive function

The MoCA cognitive test was used solely for the categorization of patients to CN and CI groups. Normal distribution was rejected for the T-ICS in CN patients only and the ceiling effect was only detected in CN patients for the S-MMSE and ACE-R scores (Online table 2). Both CI and CN patients significantly improved global cognition in response to PR, as assessed by the clinical instruments of S-MMSE, T-ICS, and ACE-R (all $p < 0.05$; Table 3 and Figure [1A2A](#)), with moderate effect sizes shown (Online table 3). Regarding the domain-specific cognitive evaluation, a moderate increase in memory ($p < 0.001$) in response to PR was observed in both CI and CN patients. Moreover, CI patients had small to moderate improvements (all $p < 0.05$) in fluency and in visuospatial skills, whilst CN patients presented better language and executive skills after PR completion (all $p < 0.05$; Table 3, online table 3 and Figure [1B2B](#)). A relationship between CI and the changes of bodily pain in association with the disease burden (SGRQ impact) after PR intervention was significant (Table 4).

Changes in exercise capacity

Following the PR program, both CI and CN patients exhibited a comparable improvement in exercise capacity evaluated by the six-minute walk distance (6MWD; CI: $[\Delta] = 25 \pm 59\text{m}$, $p < 0.001$ and CN: $[\Delta] = 46 \pm 48\text{m}$, $p < 0.05$) and cycle endurance time (CET; CI: $[\Delta] = 140 \pm 142\text{s}$, $p < 0.001$ and CN: $[\Delta] = 117$

$\pm 166s$, $p < 0.001$; Table 3). Effect sizes demonstrated small to moderate changes from PR admission to discharge (Table 3 and online table 3).

Percentages of responders

On average, each patient completed a total of 12 (± 4) PR sessions, with an all-participants adherence of 92% (sessions assigned / sessions attended) and similar adherence for both CI and CN (92 $\pm 16\%$ and 91 $\pm 17\%$, respectively). Based on the MCID [50], a large proportion (%R ≥ 50) of both CI and CN patients improved health status (SF-36), which encompasses Physical Functioning, Social Functioning, and the mental component summary score (Table 3 and online table 5). Similarly, a high percentage of both CI and CN patients increased exercise capacity assessed through the 6MWT (43% and 53%) and CET (54% and 41%), respectively (Table 3 and online table 5). Moreover, the majority of CI patients (54%) presented clinically important improvements in global cognitive function based on ACER-R multi-domain cognitive test. The domain of memory seemed to gain the most benefits from PR in CI patients, as half of them (50%) demonstrated a significant improvement (Table 3 and online table 5). Proportional differences in responders (%R) of CI and CN groups were detected in the ACE-R test and the cognitive domains of orientation, attention, and fluency (Table 3 and Online table 5).

Discussion

The current study shows that PR is beneficial for COPD patients with and without cognitive impairment ~~gain significant benefits from participating in PR~~, with both groups exhibiting improvements in respect to cognitive function, health status, and exercise capacity. ~~It is also important~~Importantly, mild cognitive impairment does not appear to significantly limit the improvements in exercise capacity and ~~SF-36 scores~~health related quality of life after a comprehensive 3-week PR program, when compared to CN patients. Although ~~it is suggested that~~ PR ~~is appears~~ comparably effective for CI and CN patients with COPD, persisting bodily pain in CI patients as assessed by the effect size, might have affected the magnitude of improvement in the 6MWT. Consequently, PR programs undertaken by COPD patients with CI may require special attention/consideration regarding the assessment and amelioration of bodily pain.

Cognitive impairment in COPD has been shown to be highly prevalent, affecting around 40% of patients referred to PR without resting hypoxemia [51]. Although its occurrence is not always linked with disease severity, patients with COPD often have significantly worsened cognitive status in the advanced and acute stages of disease [52]. Evidence suggests that chronic hypoxemia in COPD patients is a likely mechanism for hippocampal atrophy, which plays a key role in cognitive impairment [53, 54]. ~~has shown that chronic hypoxemia aggravates the prevalence and progress of cognitive impairment [54], and is accountable for the small hippocampal volume in hypoxemic COPD patients which, in turns, may be associated with cognitive deficits [53].~~ From a clinical perspective, this evidence-based hypothesis [53, 54] is important but usually not tested in the typical clinical settings. Moreover, hypoxemic-hypercapnic COPD has been suggested as an original model of cognitive decline ~~in these patients~~ [55]. In the current study, CI patients demonstrated worse

~~respiratory sufficiency as indicated by lower resting PaO₂ levels, along with slightly lower FVC and a higher number of comorbidities compared to CN counterparts (Table 1). These findings indicate a relationship between worse clinical status and cognitive impairment, which is in agreement with previous literature [54-57]. A worse clinical condition associated with cognitive impairment was also observed in patients of the current study. Specifically, CI patients demonstrated worse respiratory sufficiency as indicated by lower resting PaO₂ levels, whilst also presenting with slightly lower FVC and a higher number of comorbidities compared to CN counterparts (Table 1). These findings indicate a relationship between worse clinical status and cognitive impairment, which is in agreement with previous literature.~~

The consequences of COPD-related cognitive impairment can be detrimental, and may interfere with the course of respiratory treatment [58]. It has also been demonstrated that cognitive decline correlates with and predicts functional decline [59], and that CI patients with COPD may require assistance in several aspects of daily living [57]. Moreover, cognitive impairment may have a negative impact on treatment adherence and self-management [22], along with an increased risk of dropping out of a PR program in COPD [60]. Difficulties ~~in~~ with memory, impaired psychological profile, excessive conscientiousness, lack of social support, and weak ability to communicate and understand could constitute reasons for dropping out from PR [58, 61]. Despite this, in the current study, adherence and completion of PR was high and comparable between CI and CN patients, with only one drop out in each group. This is likely due to the current study implementing inpatient rehabilitation rather than outpatient rehabilitation, leading to greater PR adherence and completion. ~~Therefore, cognitive impairment in COPD seems not to be a factor adversely affecting adherence to inpatient PR.~~

Although previous research [62] suggests that the clinical characteristics of cognitive impairment in COPD may restrict PR benefits, the current study found that CI patients with mild levels of cognitive impairment, can benefit from a comprehensive 3-week inpatient PR program, in terms of cognitive, health and functional status. CI patients achieved small to moderate improvements in the majority of the assessed outcomes and presented a comparable overall responsiveness to PR with CN patients, as estimated by several responsiveness indices (Figure 23). This is in line with a recently conducted study [63] in severe COPD patients exhibiting mild cognitive dysfunction. Several physiological mechanisms may have contributed to these improvements, such as the ability of beneficial effect of exercise in increasing to increase neurotransmitter release and perfusion of the cerebral cortex to improve cognition [64] or even in increasing hippocampal subfield volumes [65]. Indeed, significant favourable changes were observed in the majority of the SF-36 subdomains and the SF-36 summary components of physical and mental status, selected neuropsychological measures, and functional status (Table 3). CI and CN patients improved their overall health status, global cognitive function, memory skills, and exercise capacity (6MWT and CET duration). Although an improvement in cognitive performance in COPD patients has already been evidenced after a three-month PR program [25, 60, 62], it is promising that we also observed better memory performance in our short-term PR program of 3 weeks.

Despite the overall benefits of PR, differences between CI and CN patients were detected in the role limitations due to emotional problems (Role Emotional) and bodily pain (BP) domains of the SF-36, as well as the magnitude of increase in the 6MWT (Table 3 and Figure 23). A smaller proportion of CI

patients (%R) improved the SF-36 RP domain based on the MCID, whereas less magnitude of improvement (ES) was detected for SF-36 bodily pain and 6MWD (Table 3 and Figure 23). These findings led us to perform a multivariate model analysis to control for potential confounders in the observed differential responses to PR between CI and CN patients. A stepwise linear regression allowed us to confirm the impact of cognitive impairment on certain outcomes when several other factors were included (Table 4). A relationship between the changes in bodily pain in association with the disease burden (SGRQ impact) and the existence of cognitive impairment remained significant (Table 4). This finding reveals that bodily pain as a non-pulmonary factor may lower the improvement in the 6MWD [66] for the CI patients compared to CN counterparts.

Intriguingly, CI patients in the current study did not show any improvement in the SF-36 bodily pain domain following the PR program, unlike the CN patients (Table 3). Pain is a common experience in patients with COPD which is intensified by breathlessness and anxiety [67], and has also been associated with cognitive deficit [68]. Research into structural brain changes in COPD patients showed reductions in grey matter volume, in the areas of the brain responsible for the processing of dyspnea, fear and antinociception Recently, substantial nigra degradation in brain areas including the cingulate cortex, hippocampus, and amygdala that are relevant for the processing of dyspnea and fear perception, and antinociception has been demonstrated in COPD [69]. Indeed, Additionally, in non-hypoxemic COPD patients, MRI techniques revealed substantial reductions in both white matter integrity and gray matter functional activation assessed through MRI techniques, which may contribute to cognitive impairment in these patients may be associated with cognitive impairment in non-hypoxemic COPD patients [70]. Evidence has shown that the loss of substantial nigra in cognitive

impairment might also be the reason for the pending pain suppression [71]. Although the mechanisms linking bodily pain to cognitive impairment are not clearly defined and may be multifaceted and interrelated, it seems that bodily pain is more prevalent in CI patients with COPD.

Study limitations

The small number of studied COPD population (n=60) did not provide us with a wide distribution of values regarding PR responses and, thus, our results may be minimized and not generalizable to all COPD patients. [Further multi-centre studies are guaranteed.](#) Moreover, we did not differentiate CI patients according to the subtype of cognitive impairment (amnesic/ non-amnesic), however we can report that all CI patients included in this study presented multiple-domain cognitive impairment and a global lower cognitive performance (Table 2 and Figure 23). Furthermore, bodily pain was assessed only by the SF-36 (2-items) and not by additional clinical instruments. Although pain is a difficult outcome to measure due to its multifaceted and subjective nature, SF-36 is an accepted tool for tracking pain-related treatment outcomes [72]. [CAT and the SGRQ were assessed only at baseline as a part of the standard patients' assessment to facilitate the initial evaluation for physicians and other health professionals in our clinic.](#)

Despite these limitations, this study shows that cognitive impairment is not a contraindication for participating in PR and, thus, PR programs for CI patients with COPD should be recommended. This is

in line with the recommendation of an earlier investigation by our group demonstrating that rehabilitative exercise training in CI with mild to moderate desaturation does not reduce cerebral oxygen availability and therefore is unlikely to interfere with the progression of training load during PR [51]. Moreover, PR is an integrated approach for personalised management of patients with COPD [73], and according to the findings of the current study, we believe that special consideration regarding the efficient amelioration of bodily pain in CI patients should be given.

Conclusions

PR is an effective treatment in COPD patients including cases with coexisting mild cognitive impairment. Participation in a comprehensive 3-week inpatient PR program has favorable effects on global cognitive function, health status, and exercise capacity in CI patients with COPD. Persisting bodily pain of CI patients may need special consideration within the frame of a PR program.

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Tables

Table 1. Demographics and clinical characteristics

Baseline characteristics	All Patients (n=60)	CN (n=35, 58%)	CI (n=25, 42%)	P value
Women, n, (%)	25 (42)	16 (46)	9 (36)	NS
Age, years	67.7 ±8.4	67.8 ±8.9	67.6 ±7.8	NS
BMI kg·m ²	24.2 ±4.6	24.5 ±5.1	23.9 ±3.8	NS
FEV ₁ , %pred.	46.7 ±15.4	47.0 ±16.6	46.4 ±13.8	NS
FVC, %pred.	69.7 ±18.0	72.5 ±18.6	65.8 ±16.5	0.154
RV/TLC, %	65.8 ±9.2	65.5 ±8.7	66.3 ±10.3	NS
PaO ₂ , mmHg	66.0 ±7.4	67.7 ±7.6	63.5 ±6.6	0.031
PaCO ₂ , mmHg	36.0 ±3.8	36.1 ±3.2	35.9 ±4.7	NS
pH, mmHg	7.42 ±0.03	7.42 ±0.02	7.43 ±0.03	NS
GOLD Stage II	16 (27)	11 (31)	5 (20)	NS
GOLD Stage III	26 (43)	14 (40)	12 (48)	NS
GOLD Stage IV	18 (30)	10 (29)	8 (32)	NS
Comorbidities, n	2.6 ±1.7	2.3 ±1.7	3.0 ±1.5	0.116

MMRC, index	1.5 ±0.9	1.6 ±0.8	1.4 ±1.0	NS
CAT, score	21.2 ±6.9	20.7 ±5.7	22.0 ±8.4	NS
SGRQ total, score	47.3 ±18.4	46.9 ±15.4	47.9 ±22.4	NS
LTOT, n	16 (27)	8 (23)	8 (32)	NS
Former smokers, n	55 (92)	32 (91)	23 (92)	NS
Smoking history, packs/year	37.2 ±23.1	36.7 ±20.7	37.8 ±26.6	NS

Table 1: Data are mean ± SD unless specified otherwise. Level of significance was set at $p < 0.05$.

Table 2. Cognitive function, health-related quality of life and psychological characteristics				
Baseline assessment	All Patients (n=60)	CN (n=35, 58%)	CI (n=25, 42%)	P value
Cognitive / Psychological status				
Education, years, ±SD	12.4 ±2.3	13.1 ±2.3	11.4 ±2.2	0.007
MoCA [/30], score	25.6 ±2.8	27.4 ±1.4	23.1 ±2.5	<0.001
S-MMSE [/30], score	27.8 ±1.4	28.5 ±1.1	27.0 ±1.3	<0.001
T-ICS [/41], score	34.3 ±2.5	35.5 ±1.9	32.6 ±2.3	<0.001
ACE-R [/100], score	88.0 ±7.1	92.5 ±3.6	81.7 ±5.9	<0.001
HADS Anxiety, score	5.3 ±4.0	5.1 ±4.1	5.5 ±3.8	NS
HADS Depression, score	5.4 ±4.0	5.4 ±3.8	5.3 ±4.4	NS
Health status (SF-36)				
Physical Functioning, %	34.2 ±21.8	34.1 ±18.9	34.4 ±25.7	NS
Role Physical health, %	18.7 ±33.4	18.6 ±32.3	19.0 ±35.6	NS
Bodily Pain, %	64.7 ±32.0	65.4 ±27.3	63.6 ±38.1	NS
General Health, %	37.2 ±16.0	39.3 ±15.2	34.2 ±16.9	NS
Vitality, %	42.7 ±19.5	42.5 ±17.1	43.0 ±22.6	NS
Social Functioning, %	58.8 ±30.7	62.3 ±28.9	54.0 ±33.0	NS
Role Emotional, %	52.0 ±45.6	51.0 ±45.9	53.3 ±46.1	NS

Mental Health, %	58.6 ±23.0	61.6 ±22.2	54.6 ±24.0	NS
Physical total, %	39.5 ±17.7	40.0 ±15.4	38.7 ±20.7	NS
Mental total, %	48.6 ±17.9	50.5 ±17.7	46.0 ±18.2	NS
Functional status				
6MWD, m, ±SD	370 ±99	364 ±86	378 ±114	NS
6MWD, %predicted	58.3 ±16.0	58.0 ±14.9	58.8 ±16.8	NS
CET 75%WRpeak, s	667 ±356	719 ±347	598 ±362	NS
PASE activity, score	107.7 ±66.5	112.9 ±63.6	99.4 ±71.6	NS

Table 2: Data are mean ±SD unless specified otherwise. Within brackets the maximal score of each cognitive test is reported. Level of significance was set at $p < 0.05$.

Table 3. Responsiveness to PR program from admission to discharge

Cognitive status	CN patients (n=35, 58%)					CI patients (n=25, 42%)				
	Post value	Mean change	%R	ES	ES	Post value	Mean change	%R	ES	ES
S-MMSE [/30]	29.0 ±0.8	0.5 ±1.2*	21.2	0.58	27.8	27.8 ±1.2†	0.7 ±1.1*	20.8	0.58	0.58
T-ICS [/41]	36.5 ±1.6	1.1 ±1.7*	18.2	0.68	33.9	33.9 ±2.3†	1.1 ±1.9*	20.8	0.51	0.51
ACE-R [/100]	94.1 ±3.0	1.8 ±2.9*	15.2	0.54	86.4	86.4 ±5.1†	4.4 ±4.6*	54.2	0.80	0.80
Visuospatial skills	89.9 ±10.6	0.4 ±12.9	24.2	0.03	79.8	79.8 ±16.0†	7.5 ±14.4*	37.5	0.48	0.48
Memory	83.2 ±6.3	4.2 ±5.8*	33.3	0.67	74.0	74.0 ±8.9†	6.0 ±9.3*	50.0	0.75	0.75
Orientation	99.3 ±2.8	0.9 ±6.7	6.1	0.19	97.2	97.2 ±5.4	0.3 ±6.7	25.0	0.06	0.06
Attention	95.2 ±5.4	-0.1 ±4.1	3.0	0.01	89.6	89.6 ±10.0†	2.5 ±8.0	33.3	0.27	0.27
Language/executive	97.0 ±2.6	1.9 ±3.4*	24.2	0.62	91.6	91.6 ±5.0†	2.1 ±5.9	33.3	0.36	0.36
Fluency	83.9 ±11.4	0.9 ±9.5	18.2	0.08	67.2	67.2 ±19.7†	8.3 ±16.0*	50.0	0.44	0.44
Health status (SF-36)										
Physical Functioning	49.3 ±23.4	15.1 ±18.5*	67.6	0.72	47.6	47.6 ±31.7	13.2 ±20.2*	64.0	0.47	0.47
Role Physical health	30.7 ±41.2	12.1 ±43.0	40.0	0.33	23.0	23.0 ±34.5	4.0 ±17.2	16.0	0.12	0.12
Bodily Pain	82.1 ±20.4	16.6 ±18.8*	60.0	0.70	70.8	70.8 ±32.6	7.2 ±26.3	48.0	0.21	0.21
General Health	45.8 ±16.0	6.6 ±13.5*	40.0	0.43	42.6	42.6 ±19.4	8.4 ±16.7*	44.0	0.47	0.47
Vitality	54.0 ±18.4	11.5 ±14.3*	41.2	0.65	56.0	56.0 ±25.1	13.0 ±16.8*	44.0	0.56	0.56
Social Functioning	78.3 ±22.5	15.6 ±23.3*	64.7	0.61	68.5	68.5 ±33.3	14.5 ±29.5*	52.0	0.45	0.45

Role Emotional	69.6 ±41.3	18.6 ±42.0*	32.4	0.43	60.0 ±47.1	6.7 ±43.0	28.0	0.15
Mental Health	71.5 ±19.7	10.0 ±18.1*	42.9	0.48	69.8 ±21.7	15.2 ±15.5*	60.0	0.68
Summary Physical	52.9 ±17.7	13.4 ±15.0*	60.6	0.81	48.6 ±22.8	9.9 ±13.4*	48.0	0.46
Summary Mental	60.4 ±17.1	10.2 ±12.6*	56.3	0.59	58.5 ±20.5	12.4 ±12.4*	72.0	0.66
Functional status								
6MWD, m, ±SD	410 ±85	46 ±48*	53.3	0.54	403 ±128	25 ±59*	43.5	0.21
6MWD, %predicted	65.1 ±14.5	7.1 ±7.3*	46.7	0.49	62.4 ±18.5	3.6 ±9.3	39.1	0.20
CET 75%WRpeak, s	836 ±344	117 ±166*	41.4	0.34	737 ±399	140 ±142*	54.5	0.37

Table 3: Asterisks denote significant difference between baseline and after PR measurement (Paired t-tests; *: $p < 0.05$). Crosses denote significant difference between post values in CN and CI patients (Independent t-tests; †: $p < 0.05$).

Table 4. Relationship between changes [Δ] in bodily pain and cognitive impairment					
Multivariate model	Coefficient	Std. error	95% CI		P value
Bodily Pain, [Δ]					
Cognitive Impairment	-12.6	6.09	-24.79	-0.34	0.044
SGRQ impact	0.36	0.16	0.04	0.68	0.030

Table 4: Relationship between changes [Δ] in bodily pain and cognitive impairment, adjusted for potential confounders amongst COPD patients (n=60). Fourteen potential confounders were included to a stepwise linear regression (confounders: Education, Sex, BMI, FEV₁%, number of Comorbidities, SGRQ -Symptoms; -Activity; -Impact; -Total score, HADS -Anxiety; -Depression, PR adherence, Smoking packs/year, LTOT). A multivariate model including cognitive impairment was detected only

for the changes in bodily pain after PR. The existence of cognitive impairment and the value of SGRQ impact explained the 16% of variance ($R= 0.40$; $R^2= 0.16$).

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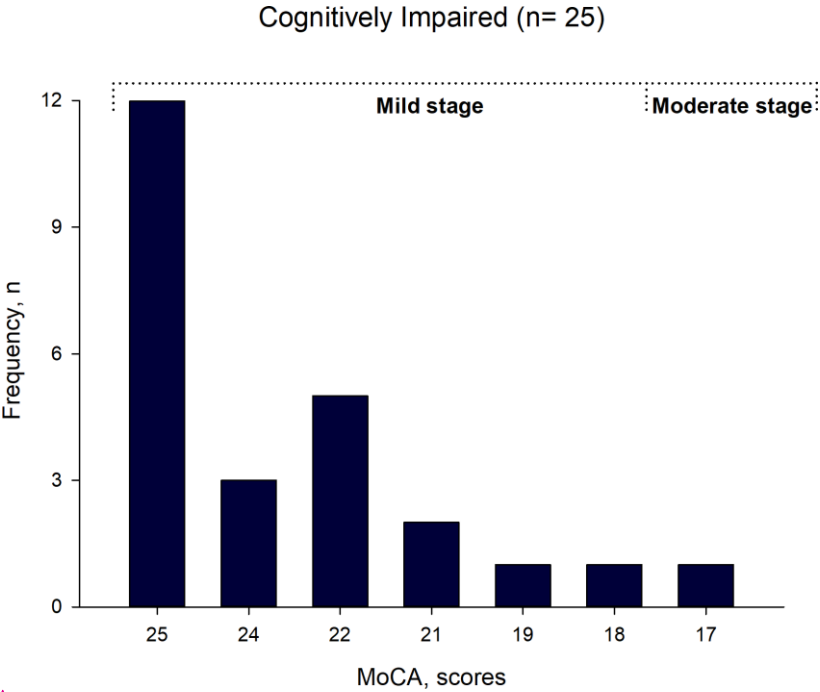
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Figure 1



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Figure 1. Stratification of CI patients based on the severity of Cognitive Impairment. The following ranges may be used to grade severity: 18-25 = mild stage of cognitive impairment, <18 = moderate to severe stage of cognitive impairment. [41]

Figure 12

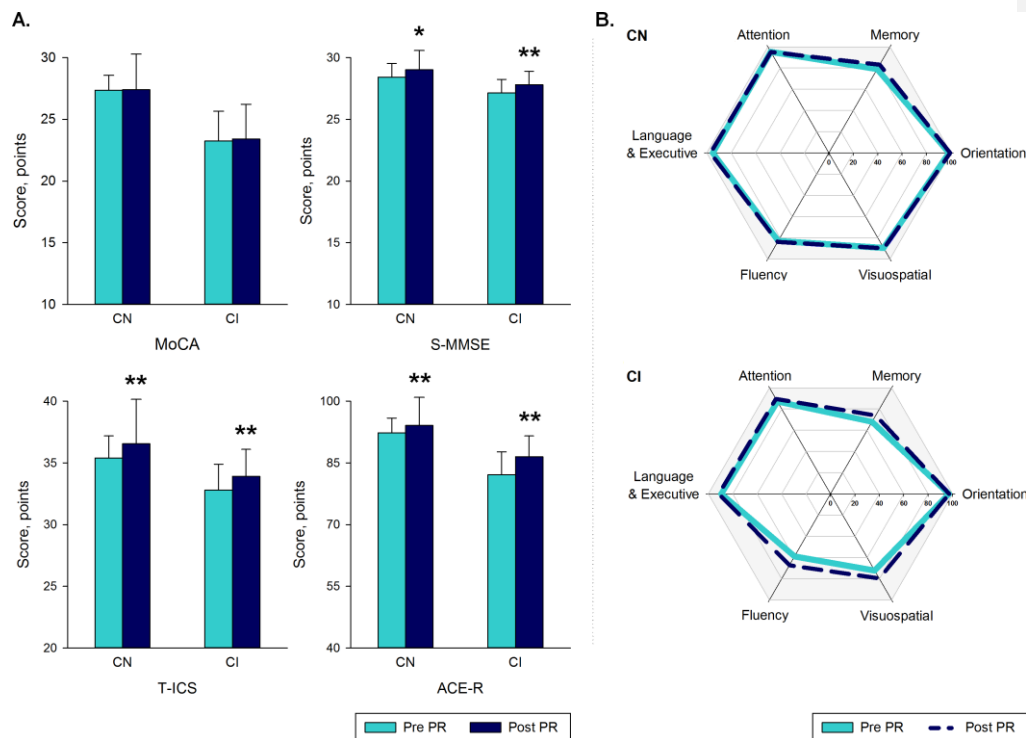


Figure 12. Changes in global cognitive function and domain-specific cognitive performance in CI and CN patients with COPD. On the left panel (A), scores derived from the cognitive assessment tools of MoCA, S-MMSE, T-ICS, and ACE-R show cognitive performance before and after PR within CI and CN groups. On the right panel (B), domain-specific cognitive function evaluation as expressed by percentage (%) of correctly matched items derived from MoCA, S-MMSE, T-ICS, and ACE-R tests in CN and CI patients with COPD. Lines represent cognitive performance (%) for six main cognitive domains. Statistical significant improvements following PR were detected in CI group on the domains of fluency and visuospatial skills (all $p < 0.05$), and in CN group only on the domain of language & executive skills (all $p < 0.05$).

Figure 23

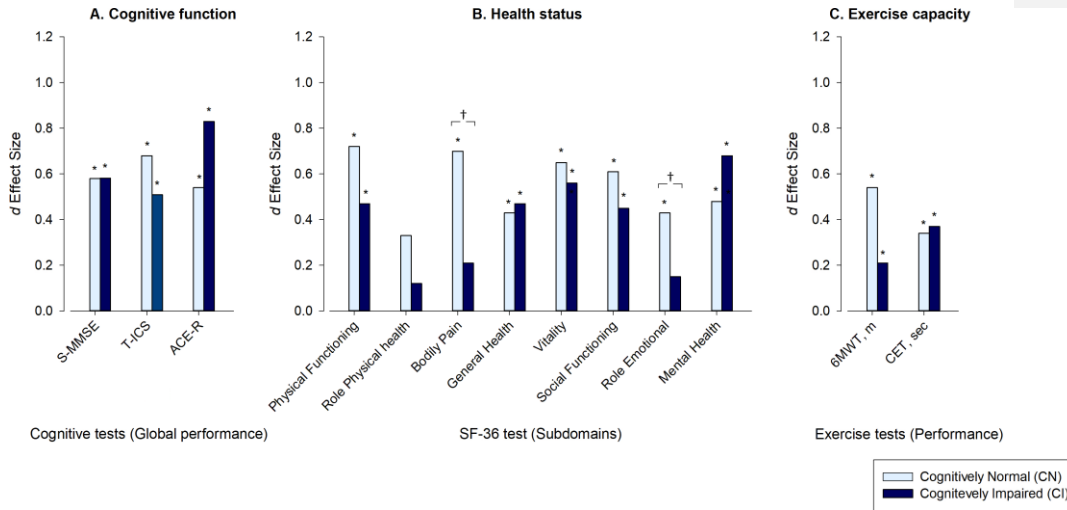


Figure 23. The magnitude of changes in (A) cognitive function, (B) health status, and (C) exercise performance in response to PR between cognitively impaired and cognitively normal patients with COPD. Asterisks (*) denote significant changes in response to PR. Crosses (+) denote differences in changes between CI and CN patients.