ORIGINAL ARTICLE
COPD

Improvements in functional and cognitive status following short-term pulmonary rehabilitation in COPD lung transplant recipients: a pilot study

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ABSTRACT

Background: Pulmonary rehabilitation (PR) following lung transplantation (LTx) is considered part of the optimal treatment in chronic obstructive pulmonary disease (COPD) for favourable post-operative outcomes. We investigated the effects of a PR intervention in the post-transplant phase with regard to lung function, exercise responses and cognitive function in COPD LTx recipients.

Methods: 24 COPD LTx recipients (mean±SD forced expiratory volume in 1 s 75±22% predicted) were assigned to a comprehensive 3-week inpatient PR programme. Changes from PR admission to discharge in lung function variables, 6-min walk test-derived outcomes and cognitive function were assessed and examined for several factors. The magnitude of changes was interpreted by effect size (ES).

Results: In response to the PR intervention, LTx recipients had improved lung function with regard to diffusing capacity of the lung for carbon monoxide (+4.3%; p=0.012) and static hyperinflation (residual volume/total lung capacity −2.3%; p=0.017), increased exercise capacity (6-min walk test +86 m; p<0.001), and had small to large improvements (ES range 0.23–1.00; all p⩽0.34) in 50% of the administered cognitive tests. Learning skills and memory ability presented the greatest benefits (ES composite scores 0.62 and 0.31, respectively), which remained similar after stratification by single or bilateral LTx and sex.

Conclusions: PR is an effective treatment for LTx recipients in the post-transplant phase, improving lung function, exercise responses, and domains of cognitive function of learning, memory and psychomotor speed. PR may facilitate the course of post-operative treatment and should be recommended in LTx.

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Pulmonary rehabilitation (PR) demonstrates beneficial effects on functional and cognitive status in COPD LTx recipients. Even a short PR programme of 3 weeks may improve memory ability, learning skills and psychomotor speed in the post-transplant phase. http://bit.ly/2xbRViD

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Introduction

Pulmonary rehabilitation (PR) is a multidisciplinary therapeutic approach including exercise training that aims to restore patients' independent functioning, decrease disability, relieve symptoms and enhance quality of life [1, 2]. Its integral role in preparing patients with advanced lung disease for lung transplantation (LTx), facilitating their recovery and optimising long-term benefits in the post-transplant phase has already been well documented [3–7]. Despite vast improvement in lung function, a number of LTx recipients may present persisting impairment in exercise capacity and skeletal muscle function [8–10] due to reduced capacity for skeletal muscle oxidative metabolism, extended hospital and intensive care unit stay, prolonged body inactivity, immunosuppressant medication, and episodes of allograft rejection [11–13]. Moreover, LTx seems to be associated with cognitive decline in a subset of older patients [14], likely due to immunosuppressant toxicity [13–15] and/or central nervous system events [16]. Given the fact that transplantation is limited by the shortage of available organ donors, patients with chronic obstructive pulmonary disease (COPD) selected to undergo LTx should be candidates with an expected good long-term outcome [17–20].

Intact cognitive function is a critical prerequisite for optimal post-operative handling, in particular when dealing with a complex drug regimen and decision-making abilities [21, 22], whereas reduced cognitive function after LTx could undermine the goals of LTx and result in poor long-term outcomes [23]. Evidence has shown that 39% of cognitively intact patients who underwent LTx exhibited cognitive deficits after surgery, when cognitive function was assessed at hospital discharge [14, 23]. This could further suggest the important role of PR in cognitive status for optimising the long-term outcomes in LTx [24].

To date, the beneficial effects of PR programmes in the post-transplant phase, especially in cognitive function, which is the primary outcome of the current study, are not clear and merit further investigation. The objectives of this pilot study were to determine the feasibility of the current study protocol, and to investigate changes in lung function, exercise capacity and cognitive function after a comprehensive 3-week PR programme in COPD LTx recipients. In addition to the expected improvements in functional status, we assumed that PR provides COPD LTx recipients with a beneficial effect on cognitive function in the post-transplant phase.

Methods

Study design and patients

LTx recipients at least 1 month following LTx and referred to PR at the Schoen Klinik Berchtesgadener Land (Schoenau am Koenigssee, Germany) were asked to participate in this pilot study. A comprehensive

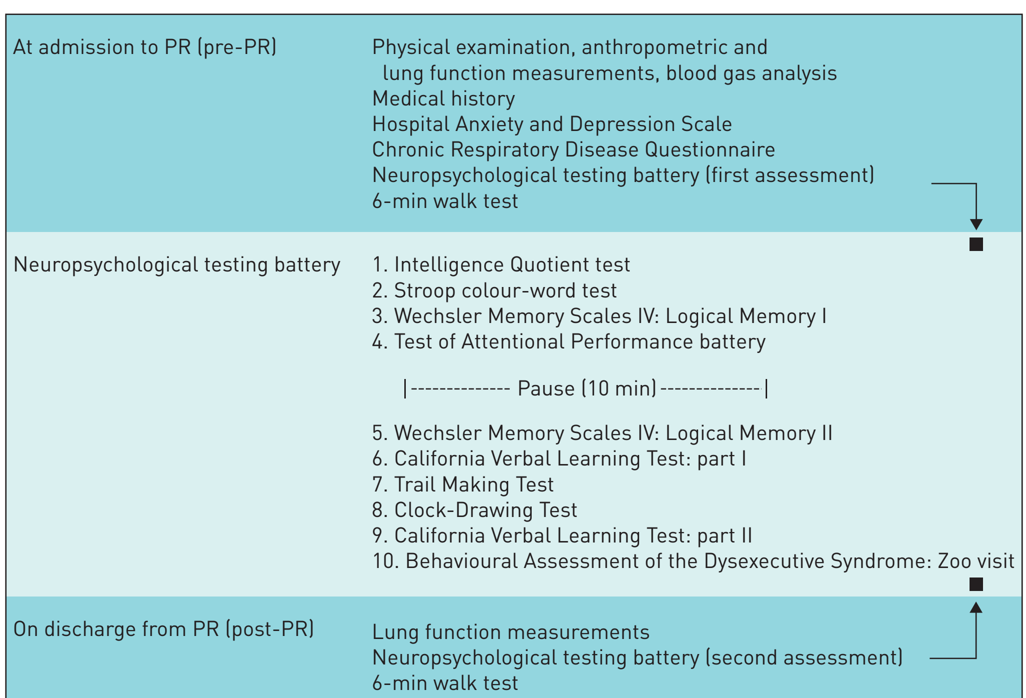

FIGURE 1 Flowchart of study methodology. PR: pulmonary rehabilitation.

assessment of neurocognitive function was performed on PR admission and at discharge. These measurements were part of a larger exercise trial in LTx recipients [25] and were approved by the Bavarian Ethics Committee (approval 11051). Participants met the following inclusion criteria: 1) single or bilateral LTx for COPD and 2) stable health condition (⩾4 weeks). Exclusion criteria were: 1) post-operative complications (pathological: acute organ rejection, infection, persisting pulmonary oedema and cardiovascular events; surgical: wound dehiscence) and 2) neurological or psychiatric conditions.

Assessment

As part of the pre-PR clinical routine assessment, LTx recipients underwent physical examination, anthropometric and lung function measurements, and blood gas analysis, and their medical history was taken. Additionally, they completed self-administered questionnaires (Hospital Anxiety and Depression Scale (HADS) and Chronic Respiratory Disease Questionnaire (CRQ)) and performed the 6-min walk test (6MWT) according to international guidelines [26, 27]. Furthermore, they underwent a comprehensive cognitive function assessment by a complete neuropsychological testing battery (figure 1 and see supplementary material for details), including the Intelligence Quotient (IQ) test [28] and the Stroop colour-word test [29]. After a 3-week PR programme, the measurements were repeated under the same conditions (post-PR assessment) to detect differences between pre- and post-PR values (figure 1).

PR programme

Exercise training was a core component in the PR [30], performed 5–6 times per week (at least 15 sessions), with each session lasting ∼50 min, plus 30 min training of daily living activities. Patients performed supervised exercise on stationary bicycles, treadmills and fitness equipment during each session. Workload and duration were progressively increased as tolerated for the bicycles, treadmills and fitness equipment, reaching exercise at 70% of peak work rate for 20 min. In addition to the aerobic training, patients performed lightweight body training with upper and lower limb strengthening exercises. Exercise intensity was progressed with the aim of reaching dyspnoea and leg fatigue scores of 5 and 6 on a 10-point Borg scale, respectively (see supplementary table S2 for more details).

Statistical analysis

All statistical analyses were carried out using SPSS Statistics version 19.0 (IBM, Armonk, NY, USA). Data are presented as mean with standard deviation or proportion, as appropriate. Paired-sample t-tests were used to detect differences between pre- and post-PR measurements; Pearson's correlation coefficient (r) was used to assess bivariate relationships. Effect size (ES) was calculated by taking the mean change between pre- and post-PR values and dividing it by the pooled standard deviation of both measurements (Cohen's *d*) [31]. Higher values of ES represent higher responsiveness, with scores greater than 0.20, 0.50 and 0.80 representing "small", "moderate" and "large" changes, respectively [32]. The average value of different ES means derived from several domain-specific cognitive evaluation outcomes was tested against zero (test value=0) by the one-sample t-test to detect a directional trend significance. Changes in lung and cognitive function and exercise capacity after PR were estimated in the total patient population and after stratification for LTx type (single *versus* bilateral) and sex (male *versus* female). A two-sided level of significance was set at $p \leqslant 0.05$.

Results

Feasibility of the study protocol

A researcher involved in this study was responsible for the recruitment, which usually required ∼5–10 min for explaining the research project and obtaining consent from the participants. Initially, self-completed questionnaires (HADS and CRQ) were given to participants, but there were some items that they missed, possibly because they skipped and forgot the question or were not sure of the answer. Moreover, some participants faced difficulties in understanding their tasks in cognitive tests. 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. Participants needed ∼90 min to perform all the cognitive tests, including a 10 min break (figure 1), while most of the tasks/test questions were not standardised by time. The long duration of our comprehensive cognitive testing battery caused mental fatigue to the participants; however, the large number of cognitive tests was necessary in order to have a complete multiple domain-specific cognitive evaluation. We did not have any dropout during the cognitive function tests, the 6MWTs or the PR programme. The exclusion criteria of post-operative complications and neurological or psychiatric conditions were set to eliminate the possibility of an adverse event during exercise and to secure the study in better reflecting PR effectiveness in COPD LTx recipients.

Recruitment of subjects

24 LTx recipients (age range 39–70 years; 42% female) were included in this study. They had normal range body mass index, mild airflow limitation, moderately reduced diffusing capacity of the lung for carbon monoxide (D_{LCO} <60% predicted) and elevated unresolved hyperinflation (residual volume (RV)/ total lung capacity (TLC) >50% predicted). LTx recipients were characterised by mildly impaired health-related quality of life (rated by CRQ), with normal anxiety and depression levels (rated by HADS), while they had completed on average 8 years of education and presented a normal IQ score. The majority (67%) had undergone bilateral LTx for COPD, with 33% being diagnosed with α_1-antitrypsin deficiency (table 1).

Data entry and analysis

LTx recipients had impaired exercise capacity (6MWD <350 m) with a moderate exercise-induced arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) decline during the 6MWT (ΔS_{pO_2} −3.9 percentage points), mild elevation in heart rate (ΔHR 21 beats·min^{-1}), and weak physical condition as indicated by the low ratio of the distance–saturation product (DSP) and the limited ability to keep a continuous pace during the 6MWT (unintended stop point 340 m) (table 2). In addition, LTx recipients demonstrated reduced cognitive performance in several clinical instruments of cognitive function assessment according to the respective normative values (table 3 and supplementary figure S1). They presented reduced to average memory (Wechsler Memory Scales IV: Logical Memory I and II) and learning skills (California Verbal Learning Test tasks) as indicated by low scores, and poor performance in attention and flexibility (Test of Attentional Performance (TAP) battery: speed–accuracy index at the 25th percentile of normative values) with limited shared attention ability (table 3 and supplementary figure S1). By contrast, LTx recipients presented a normal IQ (score 110), normative range values in psychomotor speed (Stroop colour-word test values 40–60), average visuospatial and processing speed/praxis ability (TAP and Clock-Drawing Test scores in the 25th to 75th percentile of norms), and average range behavioural activation (Behavioural Assessment of the Dysexecutive Syndrome) (table 3 and supplementary figure S1). Moreover, there were weak or no associations between cognitive function and mental health (HADS) as well as health status (CRQ) for the majority of the tests (supplementary table S3), while changes in cognitive function and changes in exercise capacity (6MWT) after the PR programme did not show any significant correlation (supplementary figure S2).

TABLE 1 Demographics and clinical characteristics of the lung transplantation (LTx) recipients

Subjects	24
Female	10 (42)
Age years	58.2±6.3
BMI kg·m^{-2}	22.0±3.5
FEV_1 % pred	75.4±22.0
FEV_1/VC % pred	75.0±14.1
D_{LCO} % pred	53.5±16.4
RV/TLC % pred	55.6±12.1
CRQ domain score	
Dyspnoea	4.7±2.1
Fatigue	4.9±1.5
Emotion	5.5±1.4
Mastery	5.8±1.4
HADS domain score	
Anxiety	4.4±4.2
Depression	3.8±3.5
Education years	8.0±2.6
IQ score	110.0±12.4
Single or bilateral LTx	
Single	8 (33)
Bilateral	16 (67)
α_1-antitrypsin deficiency	8 (33)

Data are presented as n, n (%) or mean±SD. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; VC: vital capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; RV: residual volume; TLC: total lung capacity; CRQ: Chronic Respiratory Disease Questionnaire; HADS: Hospital Anxiety and Depression Scale; IQ: Intelligence Quotient.

TABLE 2 Lung function and exercise responses before and after the pulmonary rehabilitation (PR) programme in the 24 lung transplantation recipients

	Pre-PR	Post-PR	Mean difference	ES	p-value
FEV_1 % pred	75.4±22.0	76.6±22.7	1.2±5.2	0.06	NS
D_{LCO} % pred	53.5±16.4	57.8±17.5	4.3±4.6	0.27	0.012
RV/TLC % pred	55.6±12.1	53.3±11.9	−2.3±3.2	0.20	0.017
Exercise data					
6MWD m	346±127	432±113	86±77	0.73	<0.001
6MWD % pred	51.0±17.7	64.0±14.7	13.0±10.6	0.81	<0.001
S_{pO_2} baseline %	96.5±1.4	97.0±1.4	0.5±1.5	0.36	NS
S_{pO_2} end-exercise %	92.6±6.3	93.9±3.9	1.3±5.1	0.08	NS
ΔS_{pO_2} percentage points	−3.9±5.7	−3.1±3.3	0.8±4.8	0.17	NS
HR baseline beats·min^{-1}	87±13	87±12	0±12	0.01	NS
HR end-exercise beats·min^{-1}	108±18	116±17	8±10	0.47	0.002
ΔHR beats·min^{-1}	21±19	29±14	8±15	0.49	0.029
DSP m%	326±124	406±109	80±63.9	0.70	<0.001
Unintended stop point m	340±130	424±115	84±75.6	0.70	<0.001

Data are presented as mean±SD, unless otherwise stated. ES: effect size; FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; RV: residual volume; TLC: total lung capacity; 6MWD: 6-min walk distance; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; HR: heart rate; DSP: distance–saturation product. Level of significance was set at p⩽0.05; NS: nonsignificant.

Effect of PR on lung functioning and exercise responses

Overall, LTx recipients improved lung diffusing capacity (D_{LCO}) and static hyperinflation (RV/TLC) after the PR intervention, demonstrating small but significant improvements in lung function (ΔD_{LCO} 4.3%; p=0.012 and ΔRV/TLC −2.3%; p=0.017) (table 2). Moreover, substantial increases in exercise capacity (Δ6MWD 86 m; p<0.001) and HR peak during the 6MWT (ΔHR 8 beats·min^{-1}; p=0.029) were observed after the PR programme. The minimum clinically important difference for the 6MWD (⩾30 m) was reached or surpassed by 71% of LTx recipients. Furthermore, they significantly increased the 6MWT-derived variables of DSP (ΔDSP 80 m%; p<0.001) and unintended stop point during the 6MWT (distance where the first pause to rest was usually noticed: 84 m; p<0.001) (table 2). A strong correlation between improvements in DSP and unintended stop points (r=0.79; p<0.001) was detected.

Effect of PR on cognitive functioning

Overall, LTx recipients demonstrated improvements in cognitive function according to several domain-specific cognitive tests after the PR programme (figure 2). Specifically, they presented better performance in 10 out of 20 cognitive tests (50%), demonstrating small to large significant improvements (ES range 0.23–1.00; all p⩽0.34) (table 3). Cognitive domains of learning, memory and psychomotor speed showed significant small to moderate improvements (ES 0.62, 0.31 and 0.23, respectively), whereas the global performance (composite scores) for the rest did not present any significant change in response to PR (table 3 and figure 2a).

A posteriori *analyses*

After stratification for the type of LTx (single or bilateral), changes in the 6MWT [19] and the assessed cognitive domains were studied. We demonstrated that PR is particularly beneficial for exercise capacity (6MWD) and cognitive function (learning skills, memory ability and psychomotor speed) during the post-transplant phase for both single and bilateral LTx recipients (figure 2b and c). Although similar improvements in the 6MWD were recorded for both single and bilateral LTx recipients (63±54 *versus* 90±76 m; p=0.38), differences in cognitive performance on specific domains were detected. Bilateral LTx recipients improved to a greater extent in the domains of learning skills and memory, demonstrating moderate improvements compared with single LTx recipients who obtained smaller benefits (figure 2b and c). However, single LTx recipients also presented small improvements in visuospatial and processing speed in contrast to bilateral LTx recipients (figure 2b and c). Moreover, sex-related differences were also examined for PR effectiveness on cognitive function, demonstrating a beneficial effect on learning skills and memory, irrespective of sex. Nevertheless, small differences were observed in the domains of psychomotor speed and visuospatial processing in favour of males and females, respectively (figure 2d and e).

Furthermore, we controlled for the influence of time interval to PR intervention (time between LTx and PR admission) on the improvement in cognitive function including as total all of the assessed cognitive

TABLE 3 Cognitive function assessment before and after the pulmonary rehabilitation (PR) programme in the 24 lung transplantation recipients

Domain-specific evaluation	Pre-PR	Post-PR	Mean difference	ES	p-value
Memory ability					
WMS Logical Memory I score	11.0±2.7	12.9±2.4	1.9±2.7	0.76	0.004
WMS Logical Memory II score	9.7±3.0	11.9±3.8	2.2±2.9	0.66	0.003
CVLT Free recall: list 1 score	30.4±28.2	51.7±34.7	21.3±28.5	0.69	0.003
CVLT Free recall: list 2 score	33.3±31.1	47.8±34.1	14.5±26.0	0.45	0.022
CVLT Recall with help: list 1 score	38.7±26.6	50.9±33.6	12.2±31.6	0.41	NS
CVLT Recall with help: list 2 score	38.5±28.7	50.7±30.9	12.2±23.9	0.42	0.034
CVLT Repeating errors score	68.6±21.8	70.9±27.5	2.3±26.4	0.09	NS
Composite score	32.7±29.2	42.1±33.6	9.3±23.6	0.31	0.001
Learning skills					
CVLT Learning ability %	33.4±31.8	57.1±33.9	23.7±28.2	0.74	0.020
CVLT Passage 1 %	32.1±23.4	61.0±34.2	28.9±34.9	1.00	0.001
CVLT Passage 5 %	20.8±25.4	40.3±34.6	19.5±24.2	0.66	0.001
CVLT List B %	23.0±28.4	25.6±22.0	2.6±28.2	0.10	NS
Composite score	27.5±27.5	46.4±34.2	18.9±30.4	0.62	0.001
Attention and flexibility					
TAP Speed/accuracy %	56.2±31.5	56.5±32.9	0.3±27.6	0.01	NS
TAP Shared attention ability %	50.4±28.3	45.8±28.9	−4.6±33.0	0.16	NS
Composite score	54.1±29.8	51.3±31.1	−2.8±30.1	0.09	NS
Visuospatial and processing speed					
TMT-A score	42.8±14.9	38.3±20.1	−4.5±27.9	0.26	NS
TMT-B score	99.0±52.2	84.9±35.2	−14.1±36.9	0.32	NS
Composite score	70.9±47.4	61.6±36.9	−9.3±32.7	0.22	NS
Visuospatial and praxis ability					
CDT Clock test score	13.1±1.2	13.1±1.3	0.0±0.7	0.01	NS
Psychomotor speed					
Stroop colour-word read points	48.5±7.5	51.3±7.7	2.8±4.9	0.38	0.015
Stroop colour recognition points	54.4±8.1	57.4±9.3	3.0±6.0	0.35	0.027
Stroop interference points	55.0±9.7	55.3±9.3	0.3±7.7	0.03	NS
Composite score	52.6±8.8	54.6±9.0	2.0±6.3	0.23	0.012
Behavioural activation					
BADS version 1 score	6.8±1.6	6.1±1.6	−0.7±2.6	0.42	NS
BADS version 2 score	7.6±0.7	7.6±0.7	−0.0±0.9	0.01	NS
Composite score	7.1±1.3	6.8±1.4	−0.3±1.9	0.23	NS

Data are presented as mean±SD, unless otherwise stated. ES: effect size; WMS: Wechsler Memory Scales IV; CVLT: California Verbal Learning Test; TAP: Test of Attentional Performance; TMT: Trail Making Test; CDT: Clock-Drawing Test; BADS: Behavioural Assessment of the Dysexecutive Syndrome. Positive values (better scores) determine improvement for memory ability, learning skills, psychomotor speed (points) and visuospatial/praxis ability, while negative values (faster responses) determine improvement (expressed as positive ES) for behavioural activation, visuospatial and processing speed, and attention/flexibility. Level of significance was set at $p \leqslant 0.05$; NS: nonsignificant.

domains (mean ES). Thereby, we report that the mean ES was significantly larger than zero after stratification for 1–2, 2–12 and >12 months between LTx and the PR intervention, indicating directional trends for the beneficial PR effects on cognitive function (table 4).

Discussion

Initially, we report that the proposed study protocol is feasible according to this pilot study. With regard to the study outcomes, COPD LTx recipients gain significant benefits participating in PR with regard to lung and cognitive function as well as exercise capacity. Participation in a 3-week comprehensive PR programme was associated with multidimensional favourable effects on the post-transplant phase, which may lead to a faster and optimal recovery after surgery. Moreover, improvements in health and functional status, including less metabolic/cardiovascular morbidities [33] and greater exercise capacity [34], and an enhanced cognitive function associated with better adherence to therapy [35], after PR might improve long-term prognosis in COPD LTx recipients [33–37].

In COPD patients undergoing PR programmes, mild improvements in lung function and slower respiratory decline over time have been observed compared with patients treated only with medication [38, 39].

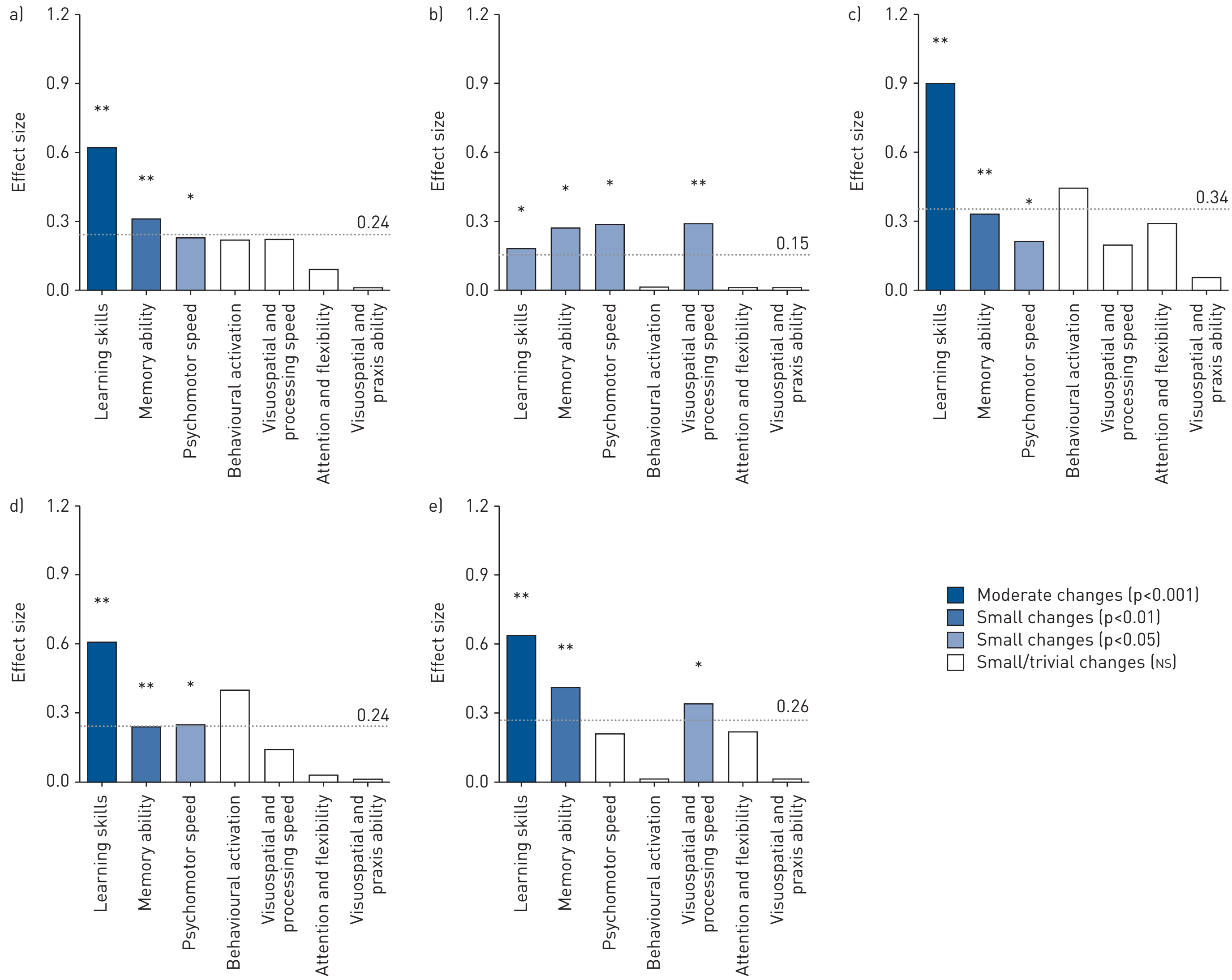

FIGURE 2 The effects of pulmonary rehabilitation on cognitive function in lung transplantation (LTx) recipients: a) total population (n=24), b) single LTx recipients (n=8 (33%)), c) bilateral LTx recipients (n=16 (66%)), d) male LTx recipients (n=14 (58%)) and e) female LTx recipients (n=10 (42%)). The dashed line indicates the mean effect size. *: p<0.05; **: p<0.001; NS: nonsignificant.

Comprehensive PR programmes including exercise training may improve skeletal muscle function, enhancing both respiratory and peripheral muscles [40], and increase D_{LCO} [41] and exercise capacity [42]. With regard to cognitive function, beneficial effects of PR programmes in COPD are well documented

TABLE 4 Mean effect sizes (ESs) for the relationship between the magnitude of improvement in cognitive function and the time interval between lung transplantation (LTx) and the pulmonary rehabilitation (PR) programme

Time to PR months	LTx recipients n	t	ES		p-value
			Mean±SD	95% CI	
1–2	6	3.66	0.15±0.11	0.05–0.25	0.011
2–12	5	2.67	0.28±0.28	0.02–0.54	0.037
>12	13	3.12	0.34±0.28	0.07–0.60	0.020

Mean ES was defined as the mean value of all cognitive domain ESs. A significant mean ES indicates a directional trend of global improvement in cognitive function.

[24, 43, 44]. Pereira *et al.* [44] demonstrated that participation in a 3-month comprehensive PR programme in COPD led to significant improvements in a range of cognitive tests after adjusting for age, sex, tobacco consumption and educational level. Indeed, cognitive deficits may counteract with treatment course and fast recovery in LTx recipients, and result in poorer adherence to self-care practices and complex medication regimens [22, 45]. PR programmes during the post-transplant phase are important to improve lung function, exercise capacity and cognitive function [46].

Comparison with other studies

In the current study, we found that LTx recipients significantly improved D_{LCO}, static hyperinflation (RV/TLC) and functional capacity as assessed by the 6MWT after a comprehensive 3-week PR programme (table 2). In terms of exercise tolerance, the impaired baseline walking capacity (<350 m) in LTx recipients as a consequence of the prior COPD condition, poor health status and extended hospital unit stay along with prolonged sedentary time was increased by 86 m on PR discharge. This large gain is similar to the finding of Munro *et al.* [47], who reported an increase of 95 m after a 7-week outpatient post-LTx PR programme in lung disease LTx recipients. Despite the longer duration of the PR programme in the Munro *et al.* [47] study, the observed 6MWD increase in response to PR was comparable. Plausible explanations could be that our LTx patients were more debilitated at baseline (mean 6MWD 346 *versus* 451 m) and that our 3-week inpatient PR programme was comparatively more intensive. Indeed, lower baseline walking capacity is associated with higher increases in 6MWD after PR [48–50]. The 6MWD increase in our LTx recipients (from 346 to 432 m; $p<0.001$) might also indicate a better long-term prognosis as the walking threshold of ⩽350 m, which is associated with higher risk of all-cause mortality [51, 52], was surpassed at PR discharge. Furthermore, LTx recipients reached higher HR levels as they were able to walk more in the 6MWT, with increased DSP and reduced unintended stop points during walking that might also advocate for better long-term prognosis (table 2) [53].

Cognitive function performance of the studied LTx recipients was lower according to normative values (supplementary figure S1), as expected due to cognitive deficits that are prevalent in some patients with end-stage COPD disease before and after LTx [54]. In addition, LTx-related factors such as prolonged sedentary time/inactivity and immunosuppressive drugs [13–15], which may have a negative impact on cognitive function, and the COPD-related pathology could further increase the risk for cognitive decline. Indeed, COPD patients with mild and advanced hypoxaemia tend to display progressively poorer performance on multiple cognitive domains, including perceptual learning, problem solving, memory, cognitive flexibility, planning, psychomotor speed and simple motor functions [55–57], while mild cognitive impairment is present in the majority of patients after LTx [58]. Furthermore, Torres-Sanchez *et al.* [59] reported that verbal memory and learning constitute the second most commonly impaired cognitive domain in COPD, and Dodd *et al.* [60] demonstrated weak or no association between cognitive function and mood, fatigue or health status. In accordance with these findings, memory and learning skills, next to attention ability, were also the most impaired cognitive domains in COPD LTx recipients, while we found only a weak or no association for the vast majority of cognitive tests with the mental (HADS) and health (CRQ) status tests (supplementary table S3).

In the current study, we report for the first time that LTx recipients obtained significant benefits in cognitive function after PR intervention as assessed by multidomain cognitive tests (figure 2a). Engagement with a comprehensive PR programme including exercise training [30] may offer several physiological and psychological positive effects on cognitive function [61]. Consistent with previous reports, we found that COPD LTx recipients, who had poor performance in memory and executive skills, significantly improved the cognitive domains of learning, memory and psychomotor speed through their participation in PR (figure 2a). Indeed, the mechanism by which a PR programme benefits COPD LTx recipients is multifactorial and difficult to define; however, some favourable alterations to cognitive function have been noted on the effects of exercise [62, 63]. Exercise training may mitigate COPD-related adverse effects on cognitive function both by improving low arterial oxygen levels, elevated carbon dioxide tension and systemic inflammation [64, 65], and by increasing cerebral neural activation through body activity [66–68].

However, since most of our LTx recipients were not hypoxaemic or hypercapnic and the 3-week PR duration could not be an adequate time period to cause, through exercise, long-term vascular adaptations (*e.g.* improved vascular physiology and neurovascular coupling) [69], which in turn could offer long-term benefits in brain health, the observed improvements in cognitive function cannot be explained solely by the short-term exercise adaptations. Moreover, we did not detect any significant correlation between changes in exercise capacity (6MWT) and changes in the performance of several cognitive domains (supplementary figure S2). Nevertheless, we believe that the favourable effect on cognitive function after our PR programme can likely be mostly attributed to a cumulative result of improvements rather than a single-factor outcome [70]. Improvements in lung function and physiological indices (table 2) along with potentially improved mental health (mood and self-efficacy) after the completion of the associated intervention, even though short term, may increase the levels of arousal, confidence and energy, and thus set the stage for individuals to meet and overcome task demands [71, 72].

Interestingly, one further novelty of the current study is that we detected differences in the effectiveness of PR on cognitive function after stratification by single or bilateral transplantation (figure 2b). The cognitive domains that improved after PR in both single and bilateral LTx recipients were learning skills, memory ability and psychomotor speed, but it seems that bilateral LTx recipients improved more likely because they were younger and had better baseline lung function (supplementary table S4) [73]. However, both single and bilateral LTx recipients presented similar improvements in 6MWD, confirming previous findings from our laboratory [19]. Obviously, future trials are needed to investigate potential changes in the effectiveness of PR between single and bilateral LTx recipients.

Implications and future perspectives

The findings of the current study may promote the value of PR in COPD LTx recipients as they demonstrate improvements not only in functional status but also in cognitive function, which is a critical factor for optimal post-operative outcomes [21, 22]. Indeed, we believe that the effect of our PR programme, even though of only 3 weeks duration, could be strong enough to make a difference in the post-transplant phase of COPD LTx recipients. Additionally, our study may provide information that will be helpful in designing future relevant studies with large cohorts of LTx recipients.

Study limitations

The small number of LTx recipients (n=24) in the current pilot study did not provide us with a wider distribution of values regarding the beneficial effects of PR in health, functional and cognitive status. Moreover, a typical 3-week PR programme (the standard PR duration covered by insurance in Germany) may reflect only the short-term PR effects in LTx as smaller but clinically significant improvements have been found to be continued in the second month of PR in LTx recipients [47]. Nevertheless, we detected significant benefits in health, functional and cognitive status of LTx recipients even after this short-term PR programme. Moreover, peripheral muscle strength was not assessed even though quadriceps strength has been described as an independent predictor of exercise performance post-transplantation [74]. Another limitation of this study is the different time intervals from LTx to PR admission across some participants (ranging from 1 to 294 months; median 17 months). Nevertheless, we assessed baseline cognitive evaluation just before PR engagement and immediately after PR completion in all cases. Additionally, we controlled for the effect of different time intervals to PR admission after LTx by stratifying participants in different groups, demonstrating that the PR effect has a significant positive directional trend in all groups, irrespective of the time interval between LTx and PR engagement (table 4).

Despite these limitations and the fact that a number of important clinical questions remain unanswered, including the most effective type of exercise training, the intensity and progression of exercise bouts, and the duration of the PR programme, the current study demonstrates for the first time the benefits of PR in cognitive function of COPD LTx recipients. Further understanding of the impact of the LTx procedure on cognitive function may provide an opportunity to improve post-operative outcomes and prognosis by adopting PR at the post-transplant phase in LTx recipients.

Conclusions

COPD LTx recipients obtain significant benefits from engagement in a 3-week inpatient PR programme, improving lung function, exercise capacity and specific domains of cognitive function (*e.g.* learning, memory and psychomotor speed) in the post-transplant phase. These improvements may facilitate post-operative treatment and might have a positive impact on prognosis. Therefore, PR programmes, even with a short duration, should be recommended in the post-transplant phase in COPD LTx recipients.

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References

1 Rochester CL, Vogiatzis I, Holland AE, *et al.* An Official American Thoracic Society/European Respiratory Society Policy Statement: enhancing implementation, use, and delivery of pulmonary rehabilitation. *Am J Respir Crit Care Med* 2015; 192: 1373–1386.
2 Andrianopoulos V, Klijn P, Franssen FM, *et al.* Exercise training in pulmonary rehabilitation. *Clin Chest Med* 2014; 35: 313–322.
3 Takaoka ST, Weinacker AB. The value of preoperative pulmonary rehabilitation. *Thorac Surg Clin* 2005; 15: 203–211.
4 Langer D, Gosselink R, Pitta F, *et al.* Physical activity in daily life 1 year after lung transplantation. *J Heart Lung Transplant* 2009; 28: 572–578.
5 Gloeckl R, Halle M, Kenn K. Interval versus continuous training in lung transplant candidates: a randomized trial. *J Heart Lung Transplant* 2012; 31: 934–941.
6 Li M, Mathur S, Chowdhury NA, *et al.* Pulmonary rehabilitation in lung transplant candidates. *J Heart Lung Transplant* 2013; 32: 626–632.
7 Yosuke I, Harada T, Kohzuki M. Rehabilitation in patients undergoing lung transplantation (LTx). *Pulm Res Respir Med Open J* 2017; 2: S57–S62.
8 Bartels MN, Armstrong HF, Gerardo RE, *et al.* Evaluation of pulmonary function and exercise performance by cardiopulmonary exercise testing before and after lung transplantation. *Chest* 2011; 140: 1604–1611.
9 Wilkens H, Weingard B, Lo Mauro A, *et al.* Breathing pattern and chest wall volumes during exercise in patients with cystic fibrosis, pulmonary fibrosis and COPD before and after lung transplantation. *Thorax* 2010; 65: 808–814.
10 Reinsma GD, ten Hacken NH, Grevink RG, *et al.* Limiting factors of exercise performance 1 year after lung transplantation. *J Heart Lung Transplant* 2006; 25: 1310–1316.
11 Studer SM, Levy RD, McNeil K, *et al.* Lung transplant outcomes: a review of survival, graft function, physiology, health-related quality of life and cost-effectiveness. *Eur Respir J* 2004; 24: 674–685.
12 Mathur S, Janaudis-Ferreira T, Wickerson L, *et al.* Meeting report: consensus recommendations for a research agenda in exercise in solid organ transplantation. *Am J Transplant* 2014; 14: 2235–2245.
13 Martinez-Sanchis S, Bernal MC, Montagud JV, *et al.* Effects of immunosuppressive drugs on the cognitive functioning of renal transplant recipients: a pilot study. *J Clin Exp Neuropsychol* 2011; 33: 1016–1024.
14 Hoffman BM, Blumenthal JA, Carney RC, *et al.* Changes in neurocognitive functioning following lung transplantation. *Am J Transplant* 2012; 12: 2519–2525.
15 Grimm M, Yeganehfar W, Laufer G, *et al.* Cyclosporine may affect improvement of cognitive brain function after successful cardiac transplantation. *Circulation* 1996; 94: 1339–1345.
16 Goldstein LS, Haug MT, Perl J, *et al.* Central nervous system complications after lung transplantation. *J Heart Lung Transplant* 1998; 17: 185–191.
17 Kenn K, Gloeckl R, Soennichsen A, *et al.* Predictors of success for pulmonary rehabilitation in patients awaiting lung transplantation. *Transplantation* 2015; 99: 1072–1077.
18 Hook JL, Lederer DJ. Selecting lung transplant candidates: where do current guidelines fall short? *Expert Rev Respir Med* 2012; 6: 51–61.
19 Schneeberger T, Gloeckl R, Welte T, *et al.* Pulmonary rehabilitation outcomes after single or double lung transplantation in patients with chronic obstructive pulmonary disease or interstitial lung disease. *Respiration* 2017; 94: 178–185.
20 Weill D, Benden C, Corris PA, *et al.* A consensus document for the selection of lung transplant candidates: an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2015; 34: 1–15.
21 Gaviria M, Pliskin N, Kney A. Cognitive impairment in patients with advanced heart failure and its implications on decision-making capacity. *Congest Heart Fail* 2011; 17: 175–179.
22 Andrianopoulos V, Gloeckl R, Vogiatzis I, *et al.* Cognitive impairment in COPD: should cognitive evaluation be part of respiratory assessment? *Breathe* 2017; 13: e1–e9.
23 Diamond JM, Mikkelsen ME. From research to clinical practice. Cognitive trajectory after lung transplantation. *Ann Am Thorac Soc* 2014; 11: 1604–1605.
24 Kozora E, Tran ZV, Make B. Neurobehavioral improvement after brief rehabilitation in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2002; 22: 426–430.
25 Gloeckl R, Heinzelmann I, Seeberg S, *et al.* Effects of complementary whole-body vibration training in patients after lung transplantation: a randomized, controlled trial. *J Heart Lung Transplant* 2015; 34: 1455–1461.
26 Singh SJ, Puhan MA, Andrianopoulos V, *et al.* An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J* 2014; 44: 1447–1478.
27 Holland AE, Spruit MA, Troosters T, *et al.* An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; 44: 1428–1446.
28 Lehrl S, Triebig G, Fischer B. Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol Scand* 1995; 91: 335–345.
29 Jensen AR, Rohwer WD. The Stroop color-word test: a review. *Acta Psychol* 1966; 25: 36–93.
30 Vogiatzis I. Prescription of exercise training in patients with COPD. *Curr Respir Med Rev* 2008; 4: 288–294.
31 Field A. Discovering Statistics Using SPSS. 3rd edn. London, Sage, 2009.
32 Smith HJ, Taylor R, Mitchell A. A comparison of four quality of life instruments in cardiac patients: SF-36, QLI, QLMI, and SEIQoL. *Heart* 2000; 84: 390–394.
33 Langer D, Burtin C, Schepers L, *et al.* Exercise training after lung transplantation improves participation in daily activity: a randomized controlled trial. *Am J Transplant* 2012; 12: 1584–1592.
34 Smith PJ, Byrd R, Lusby M, *et al.* Depressive symptoms, exercise capacity, and clinical outcomes after lung transplantation. *Psychosom Med* 2018; 80: 403–409.
35 Hayes TL, Larimer N, Adami A, *et al.* Medication adherence in healthy elders: small cognitive changes make a big difference. *J Aging Health* 2009; 21: 567–580.

36 Myaskovsky L, Dew MA, McNulty ML, *et al.* Trajectories of change in quality of life in 12-month survivors of lung or heart transplant. *Am J Transplant* 2006; 6: 1939–1947.
37 Gerbase MW, Soccal PM, Spiliopoulos A, *et al.* Long-term health-related quality of life and walking capacity of lung recipients with and without bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2008; 27: 898–904.
38 Stav D, Raz M, Shpirer I. Three years of pulmonary rehabilitation: inhibit the decline in airflow obstruction, improves exercise endurance time, and body-mass index, in chronic obstructive pulmonary disease. *BMC Pulm Med* 2009; 9: 26.
39 Incorvaia C, Russo A, Foresi A, *et al.* Effects of pulmonary rehabilitation on lung function in chronic obstructive pulmonary disease: the FIRST study. *Eur J Phys Rehabil Med* 2014; 50: 419–426.
40 McCarthy B, Casey D, Devane D, *et al.* Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2015; 2: CD003793.
41 Santus P, Radovanovic D, Balzano G, *et al.* Improvements in lung diffusion capacity following pulmonary rehabilitation in COPD with and without ventilation inhomogeneity. *Respiration* 2016; 92: 295–307.
42 Spruit MA, Pitta F, McAuley E, *et al.* Pulmonary rehabilitation and physical activity in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015; 192: 924–933.
43 Emery CF, Schein RL, Hauck ER, *et al.* Psychological and cognitive outcomes of a randomized trial of exercise among patients with chronic obstructive pulmonary disease. *Health Psychol* 1998; 17: 232–240.
44 Pereira ED, Viana CS, Taunay TC, *et al.* Improvement of cognitive function after a three-month pulmonary rehabilitation program for COPD patients. *Lung* 2011; 189: 279–285.
45 Campbell NL, Boustani MA, Skopelja EN, *et al.* Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. *Am J Geriatr Pharmacother* 2012; 10: 165–177.
46 Smith PJ, Blumenthal JA, Hoffman BM, *et al.* Postoperative cognitive dysfunction and mortality following lung transplantation. *Am J Transplant* 2018; 18: 696–703.
47 Munro PE, Holland AE, Bailey M, *et al.* Pulmonary rehabilitation following lung transplantation. *Transplant Proc* 2009; 41: 292–295.
48 Garrod R, Marshall J, Barley E, *et al.* Predictors of success and failure in pulmonary rehabilitation. *Eur Respir J* 2006; 27: 788–794.
49 Vagaggini B, Costa F, Antonelli S, *et al.* Clinical predictors of the efficacy of a pulmonary rehabilitation programme in patients with COPD. *Respir Med* 2009; 103: 1224–1230.
50 Moore LE, Byers BW, Fuhr DP, *et al.* Cardiovascular benefits from standard pulmonary rehabilitation are related to baseline exercise tolerance levels in chronic obstructive pulmonary disease. *Respir Med* 2017; 132: 56–61.
51 Spruit MA, Polkey MI, Celli B, *et al.* Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. *J Am Med Dir Assoc* 2012; 13: 291–297.
52 Celli B, Tetzlaff K, Criner G, *et al.* The 6-minute-walk distance test as a chronic obstructive pulmonary disease stratification tool. Insights from the COPD Biomarker Qualification Consortium. *Am J Respir Crit Care Med* 2016; 194: 1483–1493.
53 Andrianopoulos V, Wouters EF, Pinto-Plata VM, *et al.* Prognostic value of variables derived from the six-minute walk test in patients with COPD: results from the ECLIPSE study. *Respir Med* 2015; 109: 1138–1146.
54 Andreou G, Vlachos F, Makanikas K. Effects of chronic obstructive pulmonary disease and obstructive sleep apnea on cognitive functions: evidence for a common nature. *Sleep Disord* 2014; 2014: 768210.
55 Stuss DT, Peterkin I, Guzman DA, *et al.* Chronic obstructive pulmonary disease: effects of hypoxia on neurological and neuropsychological measures. *J Clin Exp Neuropsychol* 1997; 19: 515–524.
56 Antonelli-Incalzi R, Corsonello A, Trojano L, *et al.* Correlation between cognitive impairment and dependence in hypoxemic COPD. *J Clin Exp Neuropsychol* 2008; 30: 141–150.
57 Cleutjens FA, Franssen FM, Spruit MA, *et al.* Domain-specific cognitive impairment in patients with COPD and control subjects. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 1–11.
58 Cohen DG, Christie JD, Anderson BJ, *et al.* Cognitive function, mental health, and health-related quality of life after lung transplantation. *Ann Am Thorac Soc* 2014; 11: 522–530.
59 Torres-Sanchez I, Rodriguez-Alzueta E, Cabrera-Martos I, *et al.* Cognitive impairment in COPD: a systematic review. *J Bras Pneumol* 2015; 41: 182–190.
60 Dodd JW, Getov SV, Jones PW. Cognitive function in COPD. *Eur Respir J* 2010; 35: 913–922.
61 Mandolesi L, Polverino A, Montuori S, *et al.* Effects of physical exercise on cognitive functioning and wellbeing: biological and psychological benefits. *Front Psychol* 2018; 9: 509.
62 Zhu N, Jacobs DR, Schreiner PJ, *et al.* Cardiorespiratory fitness and cognitive function in middle age: the CARDIA study. *Neurology* 2014; 82: 1339–1346.
63 Gutierrez-Arias R, Gaete-Mahn MC, Osorio D, *et al.* Exercise training for adult lung transplant recipients. *Cochrane Database Syst Rev* 2016; 8: CD012307.
64 van Beers M, Janssen DJA, Gosker HR, *et al.* Cognitive impairment in chronic obstructive pulmonary disease: disease burden, determinants and possible future interventions. *Expert Rev Respir Med* 2018; 2018: 1–14.
65 Emtner M, Wadell K. Effects of exercise training in patients with chronic obstructive pulmonary disease – a narrative review for FYSS (Swedish Physical Activity Exercise Prescription Book). *Br J Sports Med* 2016; 50: 368–371.
66 Soya H, Okamoto M, Matsui T, *et al.* Brain activation via exercise: exercise conditions leading to neuronal activation. *J Exerc Nutrition Biochem* 2011; 15: 1–10.
67 Hyodo K, Dan I, Suwabe K, *et al.* Acute moderate exercise enhances compensatory brain activation in older adults. *Neurobiol Aging* 2012; 33: 2621–2632.
68 Soya H, Okamoto M, Jangsoo Y, *et al.* [Mild exercise results in robust brain activation and increased memory function]. *Brain Nerve* 2018; 70: 745–752.
69 Barnes JN. Exercise, cognitive function, and aging. *Adv Physiol Educ* 2015; 39: 55–62.
70 Hill K, Vogiatzis I, Burtin C. The importance of components of pulmonary rehabilitation, other than exercise training, in COPD. *Eur Respir Rev* 2013; 22: 405–413.
71 Marmeleira J. An examination of the mechanisms underlying the effects of physical activity on brain and cognition. *Eur Rev Aging Phys Act* 2013; 10: 83–94.
72 Tomporowski P. The effects of physical and mental training on the mental abilities of older adults. *J Aging Phys Act* 1997; 5: 9–26.

73 Singh-Manoux A, Dugravot A, Kauffmann F, *et al*. Association of lung function with physical, mental and cognitive function in early old age. *Age* 2011; 33: 385–392.
74 Mathur S, Levy RD, Reid WD. Skeletal muscle strength and endurance in recipients of lung transplants. *Cardiopulm Phys Ther J* 2008; 19: 84–93.