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REVIEW

Cognitive function in COPD

J.W. Dodd, S.V. Getov and P.W. Jones

ABSTRACT: In order to characterise the overall clinical picture of chronic obstructive pulmonary disease (COPD) a better understanding of all relevant comorbidities is required. It is increasingly recognised that COPD is a multi-component disease, but little attention has been paid to its effects on cognitive function.

Cognitive dysfunction is associated with increased mortality and disability; however, it remains poorly understood in COPD. This review examines mechanisms of injury and dysfunction to the brain and considers the methods used to evaluate cognition, and assembles evidence concerning the nature and level of cognitive impairment in COPD.

Our main findings are: 1) there may be a pattern of cognitive dysfunction specific to COPD; 2) cognitive function is only mildly impaired in patients without hypoxaemia; 3) the incidence of cognitive dysfunction is higher in hypoxaemia; 4) hypoxaemia, hypercapnia, smoking and comorbidities (such as vascular disease) are unlikely to account for all of the cognitive dysfunction seen in COPD; 5) there is weak or no association between cognitive function and mood, fatigue or health status; 6) cognitive dysfunction may be associated with increased mortality and disability; and 7) there is limited evidence for a significant effect of treatment on cognitive function.

KEYWORDS: Brain, chronic obstructive pulmonary disease, cognitive function, comorbidities, neuropsychological test

AFFILIATIONS
Cardiac and Vascular Medicine
St George's University of London,
London, UK.

CORRESPONDENCE
J.W. Dodd
Respiratory Medicine, Cardiac and
Vascular Sciences
St George's University of London
Cranmer Terrace
London
SW17 0RE
UK
E-mail: jdodd@sgul.ac.uk

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Chronic obstructive pulmonary disease (COPD) is frequently associated with comorbidities, such as cardiovascular disease, anaemia and osteoporosis, leading to the widely accepted view that COPD is a complex multi-component disorder, which is associated with a wide range of psychological and social problems [1]. Measures of disease severity, such as airflow limitation, are poor markers of relevant patient outcomes, largely because they do not reflect the multi-system nature of the disease. Therefore, identification, understanding and assessment of all relevant comorbidities in COPD is needed to better characterise the full clinical spectrum of the disease [2]; cognitive impairment is one such proposed comorbidity.

It is reasonable to regard patients with COPD to be at increased risk of neuronal injury, either through factors related to COPD such as hypoxaemia, or as a result of comorbidities which adversely affect the brain such as vascular disease and smoking (fig. 1).

Cognitive impairment has been demonstrated in 77% of patients with COPD and hypoxaemia [3]. Furthermore, it has been suggested that impaired performance in neuropsychological tests may be a predictor of mortality and disability in certain COPD populations [4–6]. However, despite their potential importance, understanding of cognitive problems in COPD remains incomplete.

COGNITION: DEFINITIONS AND CONCEPTUAL FRAMEWORKS

Cognition is a collective term for high-order neural processes that underpin information handling. These have been variously sub-classified according to conceptual frameworks such as those shown (table 1). In practice, cognitive abilities are mainly inferred from behaviour, which itself is determined by a wide variety of neurological, psychological and emotional factors [7]. The relationships between the many processes involved in an everyday cognitive task are complex, but cognitive ability is usually broken up into discrete domains, although it is rarely possible to study single domains in isolation.

Dementia is defined by the development of multiple cognitive deficits with memory impairment and one or more other cognitive disturbance(s)

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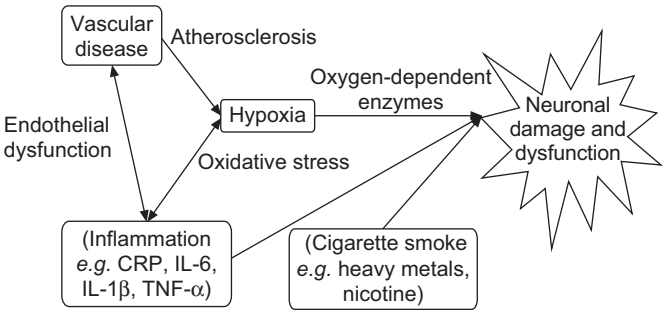

FIGURE 1. Possible mechanisms contributing to neuronal damage in chronic obstructive pulmonary disease. CRP: C-reactive protein; IL: interleukin; TNF: tumour necrosis factor.

that cause significant impairment in social and occupational functioning [8].

Neuropsychological tests aim to provide standardised and objective measurement of the functioning of one or more specific cognitive domains. Performance within each domain depends on one or more of the main classes of cognitive function. The tasks performed as part of neuropsychological testing often closely resemble mental challenges encountered in everyday life.

MECHANISMS OF COGNITIVE IMPAIRMENT

A key mechanism proposed for cognitive dysfunction in COPD is neuronal damage mediated through hypoxia, but it has also been suggested that oxygen-dependant enzymes which are important in the synthesis of neurotransmitters, such as acetylcholine, may be affected [9]. A magnetic resonance spectroscopy study in patients with non-hypoxic severe COPD showed that cerebral metabolism was significantly altered and that the pattern of derangement differed from that seen in heart failure and diabetes [10].

Inflammation may play a role, since there is evidence that C-reactive protein may be associated with cognitive decline, either through a direct neurotoxic effect [11] or an effect on cerebral atherosclerosis. Other inflammatory mediators have also been linked to cognitive dysfunction, including interleukin (IL)-6, IL-1β, tumour necrosis factor-α and α_1-antichymotrypsin [12, 13]. However, these studies suggest an association rather than a causal link [14].

IS THERE EVIDENCE OF COGNITIVE DYSFUNCTION IN COPD?

The majority of studies have shown that patients with COPD have significant cognitive impairment, either globally or in domains such as perception, memory and motor functions (table 2). In the nocturnal oxygen therapy (NOTT) trial, 42% of patients with COPD had moderate-to-severe cognitive impairment compared with 14% amongst controls [3]. In a follow-up of the same cohort, the rate of neuropsychological deficit rose from 27% in mild hypoxaemia to 62% in severe hypoxaemia [31]. In addition, severe COPD cognitive impairment has been reported to worsen over time [32].

However, cognitive impairment in COPD is not always reported. In one study, patients with mild hypoxaemia had worse verbal fluency compared with a control group but, they were still within the normal range [28]. In another study, no difference in mini mental state examination (MMSE) was reported between community-based COPD patients and a healthy group, although the COPD group may have also included cases of asthma [33].

TABLE 1 Cognitive domains and their relationship to cognitive functions tested in practice

Cognitive domain	Description	Cognitive functions
Receptive	Complex sensory reception: central analysis, integration and encoding of stimuli	Perception
	Perception: integration of sensory information into psychologically meaningful constructs, including recognition, discrimination and orientation	Construction
Learning and memory	Implicit (non-declarative) memory: memory of skills and perceptual learning	Memory and learning
	Declarative memory: relating to information, objects and events	Verbal/language
Processing	The ability to relate two or more pieces of information. Includes computation, reasoning, concept formation, abstraction, organisation, planning and problem solving	Memory and learning Verbal/language Reasoning Executive function
Expressive function	The physical expression of cognitive processes (verbal, writing and drawing, manipulation, gestures and movements)	Construction Reasoning Executive function Motor function
Mental activity variables	Attention and consciousness. Not classes of cognition *per se*. Facilitate cognitive processes	Perception Memory and learning Construction Reasoning Executive function Motor function Processing speed

It is important to note that no classification of sub-divisions and domains of cognition is universally accepted; the one presented here is one of many.

FACTORS INFLUENCING COGNITIVE FUNCTION IN COPD

Age and educational level are demographic variables that are thought to strongly relate to neuropsychological performance in all populations [7]. Figure 2 summarises the factors thought to be important in influencing the development of cognitive impairment in both COPD patients and healthy individuals. It shows that, although many factors are shared by both groups, many congregate more frequently within COPD. The influence of each of these factors will be discussed briefly later in the review.

COGNITIVE PERFORMANCE AND LUNG FUNCTION

The association between lung function and cognitive function has been tested in a number of studies in large healthy

TABLE 2 Studies of neuropsychological function in patients with chronic obstructive pulmonary function

First author [Ref.]	Patients n	FEV_1	$\bar{P}_{a,O_2}$ kPa on air	Cognitive function							
				Attention	Perception	Memory and learning	Verbal and language	Construction	Concept formation and reasoning	Executive	Motor
Hypoxaemia											
KROP [15]	10	0.77 L	6.9					●			●
GRANT [3]	203	0.74 L	6.8	●	●	●	●	●	●	●	●
HUPPERT [16]	11	NA	7.9			●					
D'SALLA [17]	28	NA		●							
INCALZI [18]	36	22%	7.9	●		●	●	●	●		
INCALZI [19]	42	34%	6.5			●					
STUSS [20]	18	NA		●		●					
HJALMARSON [21]	10	38%	6.7	●	●	●			●	●	●
ANTONELLI-INCALZI [22]	15/18[#]	NA	7.3/9.3	●		●			●		
KOZORA [23]	20/19[¶]	24%	8.1/7.8	●		●	●			●	●
ANTONELLI-INCALZI [24]	149	37%	7.65	●		●	●	●	●		
Non/mild hypoxaemia											
FIX [25]	66	39%	8.9	●	●	●	●	●	●	●	●
PRIGATANO [26]	100	37%	8.8	●	●	●	●	●	●	●	●
VOS [27]	39	33%	8.9	●							
KOZORA [28]	32	FEV_1/FVC 44%	9.2								
LIESKER [29]	30	49%	10.1	●	●			●		●	●
FAVALLI [30]	20	NA	8.8	●		●	●				●
Proportion of patients demonstrating cognitive dysfunction				**(795/827) 96%**	**(409/430) 95%**	**(709/781) 90%**	**(613/689) 89%**	**(594/648) 92%**	**(579/629) 92%**	**(463/492) 94%**	**(726/776) 94%**

FEV_1: forced expiratory volume in 1 s; $\bar{P}_{a,O_2}$: mean arterial oxygen tension; NA: not applicable; FVC: forced vital capacity. The white shading indicates cognitive function tested and the circles represent demonstration of cognitive function. [#]: 15 non-hypoxaemic and 18 hypoxaemic patients; [¶]: 20 medical therapy and 19 lung volume reduction surgery patients.

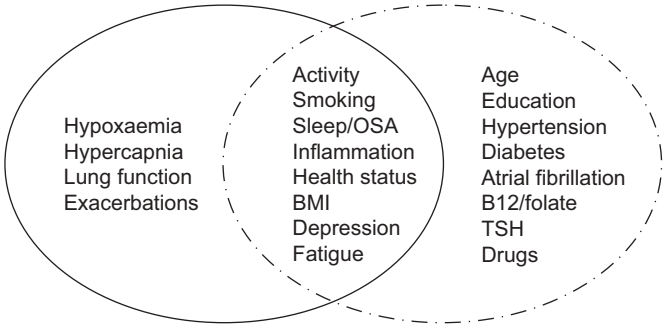

FIGURE 2. Potential factors thought to effect cognitive function in chronic obstructive pulmonary disease. OSA: obstructive sleep apnoea; BMI: body mass index; TSH: thyroid stimulating hormone. ——: chronic obstructive pulmonary disease; · – · – · – ·: general population.

populations, particularly in elderly groups, but the correlations were often weak and confounders were not always adjusted for (table 3). It has been suggested that lung function is actually a marker of physical activity, which itself may account for any associations with cognitive status [41]. Studies investigating the relationship between lung function and cognition in COPD populations have shown even less consistent results, suggesting that lung function is not a reliable predictor of cognitive function in this group (table 4).

COGNITIVE FUNCTION AND HYPOXAEMIA

Table 1 summarises studies of cognitive function and hypoxaemia in COPD, the larger studies suggest global impairment across cognitive domains with the most severe deficits in perception and motor function [3, 25, 26]. Although the majority of studies assessed patients with hypoxaemia, deficits have also been found in non-hypoxaemic patients [29, 30]. It is difficult to draw clear conclusions by comparing these studies, due to differences in disease severity and test methodologies used. The definition of hypoxaemic COPD also varied between studies. However, attention deficits and problems with memory executive and motor functions appear to be common. Perception and language difficulties appear to be less frequently reported.

Correlations between cognitive functions and degree of hypoxaemia

The correlation between cognitive function and arterial oxygen tension (P_{a,O_2}) is weak (r~0.2) [3, 26] and oxygen saturation contributed to just 5% of predicted variance in clinician judged global cognitive performance [3]. These observations from the NOTT and Intermittent Positive Pressure Breathing (IPPB) studies contrast with those from an earlier small study in which P_{a,O_2} correlated with attention, motor function and processing speed (r^2=0.63) [25]. Another study reported that memory was correlated to P_{a,O_2}, but language and perception were not [20]. Nadir nocturnal P_{a,O_2} has been shown to

TABLE 3 Lung function and cognition in healthy populations

First author [Ref.]	Patients n	Description	Measures		Significant associations
			Lung function	Cognition	
COOK [34]	1354	Cross section Healthy elderly	PEFR	NPT	Total cognitive score and memory
ALBERT [35]	1192	Longitudinal Healthy, elderly	PEFR	NPT/MMSE	Second best predictor of decline in MMSE
CHYOU [36]	3036	Longitudinal Japanese American males (3 yrs)	FEV_1	CASI	Baseline FEV_1 (more pronounced in >55 yr olds)
CERHAN [37]	14000	Cross section Middle-aged adults	FEV_1	NPT	Information processing speed and word fluency
EMERY [38]	444	Longitudinal Swedish twin study	FEV_1	NPT	''Fluid intelligence'' but not a predictor of cognitive decline
ANSTEY [39]	2551	Healthy Longitudinal All ages	FEV_1	NPT	Memory Reaction time
ALEMAN [40]	400	Cross section mid age to elderly males	PEFR	NPT/MMSE <26	PEFR associated with MMSE Vascular risk factors associated with processing speed MMSE associated with PEFR
SACHDEV [41]	469	Healthy Cross section	FEV_1	NPT	Information processing Motor dexterity
ALLAIRE [42]	396	Cross section Healthy African American males All ages	PEFR	Telephone cognitive tests	PEFR contributed to 2% variance of cognition in elderly only

PEFR: peak expiratory flow rate; NPT: formal neuropsychological testing; MMSE: mini mental score examination; FEV_1: forced expiratory volume in 1 s; CASI: cognitive ability screening instrument.

TABLE 4 Lung function and cognition in chronic obstructive pulmonary disease (COPD) patients

First author [Ref.]	Patients n	Description	Measures		Correlations
			Lung function	Cognition	
Fix [25]	66	Longitudinal Hypoxic COPD	FEV_1	NPT	Attention, vis-motor and perception
Grant [3]	203	Case control Hypoxaemic COPD	FEV_1	NPT	Nil
Prigatano [26]	100	COPD mild hypoxia form IPPB trial	FEV_1	NPT	Memory
Incalzi [43]	84	Prospective COPD	FEV_1	MMSE	Decline in MMSE worse in severe airflow obstruction
Kozora [28]	32	Mildly hypoxic COPD	Full PFT	NPT	Nil
Etnier [44]	98	Older COPD mild disease and hypoxia	Full PFT	NPT	FVC associated with working memory 6MWT associated with fluid intelligence and processing speed
Antonelli-Incalzi [45]	381	COPD Elderly	GOLD stage	NPT/MMSE	Nil
Liesker [29]	30	Non-hypoxaemic COPD Case control	FEV_1	NPT	Nil
Ohrui [46]	135	Respiratory failure on LTOT *versus* healthy cross section	FEV_1	MMSE	Nil

FEV_1: forced expiratory volume in 1 s; NPT: neuropsychological tests; IPPB: intermittent positive pressure breathing; MMSE: mini mental score examination; PFT: pulmonary function tests; FVC: forced vital capacity; 6MWT: 6-min walk test; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LTOT: long-term oxygen therapy.

correlate with attention, but it is not clear if co-existent obstructive sleep apnoea (OSA) had been excluded [27].

In summary, the exact relationship between cognitive impairment and hypoxaemia remains unclear. Whilst a number of studies have shown a clear association between hypoxaemia and poor cognitive performance, this has been inconsistent and correlations have been weak. There are also inconsistencies as to whether patients with early disease and mild hypoxaemia have significantly impaired cognition. Current evidence would suggest that hypoxaemia alone is not enough to entirely account for the cognitive deficits seen in COPD.

COGNITIVE FUNCTION AND HYPERCAPNIA

Studies have reported a variable correlation between arterial carbon dioxide tension (P_{a,CO_2}) and cognitive function. In patients with hypercapnic respiratory failure, P_{a,CO_2} correlated with memory, complex attention and information processing speed, but not with language, motor function and simple attention [19]. Incalzi *et al.* [18] suggested that P_{a,CO_2} was related to verbal memory and attainment and, in a study of patients awaiting lung transplantation, lower P_{a,CO_2} was significantly correlated to better measures of executive function, attention and verbal memory [47]. In contrast, there was no correlation between cognitive function and hypercapnia in the NOTT and IPPB studies or in studies by Grant *et al.* [31] and Fix *et al.* [25]. Overall the relationship between P_{a,CO_2} and cognitive impairment is even less clear than that for P_{a,O_2}.

EFFECTS OF COPD EXACERBATIONS ON COGNITIVE FUNCTION

Only three studies have directly addressed the impact of exacerbations on cognitive function. In elderly patients admitted with a non-acidotic exacerbation of COPD, MMSE scores were low but unrelated to 6-month mortality [48]. In another study using the MMSE in patients who required mechanical ventilation during the exacerbation, there was significantly impaired cognitive function at the time of discharge, but this had recovered substantially by 6 months [49]. The P300 is an electrophysiological test used as a surrogate marker of information processing, attention and intellect memory [50]. During an exacerbation, COPD patients were reported to have impaired information processing and a tendency to worse attention and memory [51]. It appears that cognitive function is impaired during exacerbation, but may recover.

CORRELATIONS BETWEEN ACTIVITY AND COGNITIVE FUNCTION

A number of studies have shown that physical activity is associated with both the maintenance and improvement in cognitive function in COPD [52–58]. A case–control study of pulmonary rehabilitation showed that if visual attention, verbal memory and visuospatial functions were impaired at baseline, they improved after 3 weeks of treatment. However, practice effects were not addressed and this could have also been due to regression to the mean effect. Furthermore, the

control group had lower exercise capacity, higher oxygen use and took their COPD medications less regularly than the treatment group [59].

Verbal fluency improved significantly with exercise in a randomised control trial of non-hypoxaemic COPD patients that compared exercise training plus education with education alone [53]. Another study showed improvement in verbal fluency after as little as 20 min of exercise [54]. In a group of fit patients with mild COPD, 6-min walk distance and aerobic fitness predicted 83% of the improvement in ''fluid intelligence'' (reasoning and problem solving) amongst COPD patients undergoing short- and long-term exercise programmes [56]. Overall there appears to be a link between exercise and cognitive function and it is important to determine whether improved exercise improves cognitive function.

COGNITIVE FUNCTION IN VASCULAR DISEASE AND OTHER COMORBIDITIES

In the general population, hypertension has been associated with a faster decline in logical reasoning and problem solving, and diabetes has been associated with accelerated decline in executive function tasks [59]. In addition, combined vascular risk factors explained a significant proportion of the variance in information processing capacity and speed, as well as general cognitive status [40]. Given that over 50% of hospitalised patients with COPD have coexistent vascular disease [60], it is likely that this will influence cognitive function. However, the pattern of cognitive dysfunction in COPD has been shown to be different to that found in multi-infarct dementia [18], and memory has been shown to be worse in subjects with chronic cerebrovascular disease than in those with COPD [61]. Therefore, it is unlikely that cognitive dysfunction in COPD is due to vascular comorbidity alone.

SMOKING AND COGNITIVE FUNCTION

In addition to the increased risk of cerebral atherosclerosis, certain particles in cigarette smoke are thought to have a direct neurotoxic effect with heavy metal constituents of smoke being linked to an increased risk of Alzheimer's disease [62, 63]. Smoking may also influence cognitive function by exacerbating cerebral hypoxia due to chronically elevated carbon monoxide causing a left shift of the oxyhaemglobin dissociation curve [3]. A multicentre European cohort showed that yearly decline in MMSE was associated with smoking status, after correcting for baseline MMSE, education and vascular events [64]. Smoking is a risk factor for pre-clinical changes detected on brain computed tomography, and longitudinal studies have found associations with middle-age smoking and cognitive dysfunction in males over a 20-yr period. Cognitive deficits associated with smoking include reduced processing speed, verbal memory and MMSE. However, whilst smoking appears to be an independent factor in cognitive dysfunction, studies have found associations between impaired lung function and cognition that are independent of current and lifetime smoking status [41, 65].

SLEEP AND OBSTRUCTIVE SLEEP APNOEA

Sleep is thought to be important in memory, learning, attention and tracking [31, 66]. COPD patients experience excessive daytime sleepiness and over 50% report long sleep latency [67]. OSA occurs in 20% of individuals with COPD [68], and the conditions share a similar profile of comorbidities [69, 70]. Moderate-to-severe OSA may be associated with impaired cognitive performance, primarily vigilance and executive function with less effect on intellectual and verbal abilities [71]. However, the increase in cognitive deficit appears smaller than the increase in sleepiness [72].

Whilst the degree of cognitive impairment has been reported to be similar in COPD and OSA with shared deficits in complex reasoning, learning and memory, cognitive domains thought to be dependent on sleep, such as attention, were more impaired in OSA, whilst those thought to be affected by hypoxaemia, such as motor skills, were more impaired in COPD [73]. This observation is supported by another small study which showed that patients with severe OSA had a distinctive cognitive profile, *i.e.* a group-specific pattern of cognitive dysfunction compared with COPD, Alzheimer's disease and multi-infarct dementia [74].

DEPRESSION

The prevalence of depression in COPD patients ranges from 10% to 79% [15, 33, 43, 75–79]. Depressive symptoms are present in elderly people with cognitive impairment or dementia [80], but, while it is associated with impairment in executive function, memory and processing speed, it may account for only 1–2% of the variance in cognition in COPD [8, 12]. In the NOTT trial the modest improvement in cognitive function was not associated with improvement in emotional or depressive symptoms [8].

Is there a specific pattern of cognitive deficit in COPD?

A number of studies have explored the presence of a specific pattern of neuropsychological impairment in COPD patients. Most found moderately severe deficits in areas that include attention, memory and executive function (table 1). In particular, the NOTT study suggested a global cognitive deterioration, consistent with age-related physiological decline [3]. In contrast, there is a suggestion from smaller studies that COPD patients may have a specific pattern of deterioration compared with Alzheimer's disease or multi-infarct dementia and healthy controls [18, 28].

Some of the observed heterogeneity in the deficits reported may be due to differences in severity of disease in the populations studied. For example, one study recruited hypoxaemic patients who had never had long-term oxygen [3], whereas a second studied patients who were significantly hypoxaemic and hypercapnic despite many years of oxygen therapy [18]. A third studied patients on oxygen therapy but with only very mild hypoxaemia [28]. Different neuropsychological test batteries were also used in different studies, which is an additional confounding factor. Overall, the main areas of dysfunction in COPD appear to be attention, memory, motor and executive function; this pattern may be different from that seen in Alzheimer's disease or multi-infarct dementia.

Cognitive dysfunction in COPD: does it matter?

In general population studies, cognitive dysfunction has been associated with increased length of stay, mortality, discharge destination [81], instrumental activities of daily living (IADL) [82] and the management of medicines [83].

Few studies have directly examined its impact in COPD. One study suggested a link between poor verbal memory and mortality [6] and, in severe COPD, impaired verbal memory was associated with poor adherence to medications [19]. Incorrect inhaler use has been associated with executive dysfunction, which affects planning and sequencing [84].

A large prospective study in COPD found no link between mortality and MMSE [48]; however, in another study, social isolation, number of medications and comorbidities were the only independent variables associated with length of stay following admission for a COPD exacerbation, not measures of cognitive function [85].

Cognitive problems have been associated with impairment in IADL in COPD [4], although in patients with mild cognitive deficit prevalence of impaired activities of daily living is low [86]. In activity-limited patients using supplementary oxygen, rate of decline in cognitive function may be related to impairment of IADL [32]. However, an earlier study did not find the same relationship [87].

In summary, cognitive dysfunction in COPD may be associated with mortality and other important patient outcomes including functional impairment; however, these associations were not consistent between studies. There appears to be no clear relationship between health status and cognitive impairment [9, 29, 49, 88, 89].

Assessment and treatment of cognitive impairment in COPD

Full neuropsychological testing requires time and specialist training to perform and interpret. A simple and brief clinical assessment would be useful to screen individuals who may need further more comprehensive neuropsychological testing. Recent work suggests that the combination of an MMSE score <24 and dependence in at least one IADL may fulfil this role [24]. Further work is needed to determine if all patients with COPD require screening or whether it should be restricted to those who report cognitive difficulties or who have risk factors for cognitive impairment, such as hypoxaemia, airflow obstruction and vascular comorbidities. Figure 3 illustrates the potential impact of treatment on cognitive function and subsequent patient outcomes.

Oxygen therapy

Acute oxygen therapy has not been shown to improve neuropsychological performance [27, 90] and longer term oxygen therapy has either shown no benefit [18, 21] or modest cognitive improvement when administered for 6 months to hypoxaemic individuals, although much of the improvement was accounted for by practice effects [9, 15, 91]. Whilst oxygen therapy seems to reduce cognitive impairment, it may not prevent it completely. Some longitudinal studies have been performed [6, 9, 47], but longer follow-up periods with larger, more diverse populations of COPD patients are required.

Pulmonary rehabilitation/exercise

A recent meta-analysis of randomised controlled trials of physical activity in the older general population showed that a 14% improvement in aerobic activity coincided with an improvement in cognitive capacity, mostly in motor function

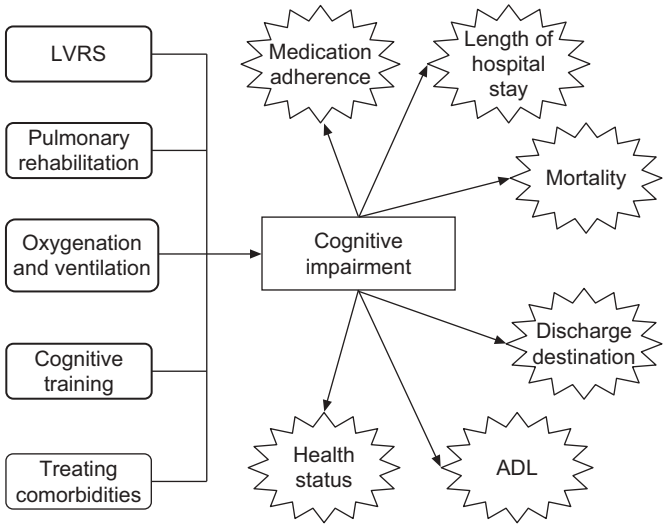

FIGURE 3. Possible treatments and outcomes of cognitive impairment in chronic obstructive pulmonary disease. LVRS: lung volume reduction surgery; ADL: activities of daily living.

and auditory attention, but also in processing speed and visual attention [92]. In COPD patients, evidence is limited, but suggests improvements in verbal fluency after 3 months [56]. It appears that appropriate exercise programmes may have beneficial effects on cognitive functions but it is unclear if these benefits are long term.

Lung volume reduction surgery

Lung volume reduction surgery has been associated with improvement in neuropsychological function as well as measures of depression, anxiety and quality of life over a follow-up period of 6 months [23], but there was no association between cognitive improvements and change in other variables. Even after adjustment for differences in exercise capacity and hypercapnia between the LVRS and control groups, improvement in psychomotor speed and verbal memory remained significant. However, the numbers in this study were small with a test group of only 19 subjects.

Cognitive training

A recent meta-analysis of nine randomised controlled trials assessing cognitive training in the early stages of Alzheimer's and vascular dementia show no evidence of improvement [93]. In COPD patients, cognitive training was not shown to be effective [94].

Addressing comorbidities

The impact on cognitive function of interventions to treat diabetes, hypertension, dyslipidaemia, and vitamin B12 and folate deficiencies has been the subject of several reviews. No benefit has been reported in terms of incidence of dementia or decline in cognitive function. Cognitive impairment was associated with poor response to antidepressant therapy [80].

CONCLUSIONS

Evidence of cognitive impairment in non-hypoxic individuals, together with a consistent pattern of cognitive deficit, suggests that COPD is associated with neuronal damage or dysfunction

that is separate from other comorbidities, such as vascular disease. More work is required to validate methods of assessment, screening and treatment. Cognitive dysfunction may be associated with increased mortality and disability, but despite its potential importance, it remains a poorly understood comorbidity of COPD.

STATEMENT OF INTEREST

Statements of interest for J.W. Dodd and P.W. Jones can be found at www.erj.ersjournals.com/misc/statements.dtl

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