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ATTENTION FUNCTIONS IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A NEUROPSYCHOLOGICAL CASE-CONTROL STUDY

AND CLINICAL RESEARCH PORTFOLIO

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September 2018

Submitted in partial fulfilment of the requirements for the degree of Doctorate in Clinical Psychology



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CHAPTER ONE: SYSTEMATIC REVIEW

Domain-specific Cognitive Dysfunction in Stable Chronic Obstructive Pulmonary Disease: A Systematic Review of the Evidence

Claire Alexander*

Prepared in accordance with authors instructions for the Journal of the International Neuropsychological Society (see Appendix 1.1)

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Chapter One: Systematic Review Contents

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a complex, progressive respiratory condition. There is growing evidence that people with COPD may experience some degree of cognitive dysfunction. Most COPD patients maintain relatively long periods of stable health. Despite this, previous reviews on this topic have included both exacerbating and stable samples and investigations have been limited to examine only general cognitive function. Such approaches reduce the generalisability and clinical utility of findings and confound any conclusions drawn. Therefore, at present, the nature of cognitive dysfunction in stable COPD remains poorly understood.

Objective: To examine the literature comparing domain-specific cognitive function in stable COPD patients and controls.

Methods: After screening 679 potentially relevant articles, 11 met inclusion criteria for this narrative review. All studies were quality rated using a protocol developed from SIGN Methodology Checklist 4.

Results: Stable COPD patients consistently attained significantly lower scores than controls across several cognitive domains, including processing speed, memory, concept formation and abstract reasoning, and executive functions.

Conclusions: COPD patients may be at risk of experiencing cognitive difficulties, even in a stable phase of the disease. While a definitive cognitive profile of stable COPD was not identified, cognitive dysfunction observed in this population may have implications for clinical care.

Key words: Chronic Obstructive Pulmonary Disease; Cognitive Function; Neuropsychological

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory condition marked by irreversible airway inflammation. COPD Is the UK's fifth leading cause of mortality (Snell *et al.*, 2016) and is largely associated with chronic exposure to environmental pollutants or smoking (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2016). Primary symptoms include breathlessness, chronic cough and sputum production. However, more recently, COPD management guidelines are moving towards a multifactorial disease model which extends beyond the lungs. This approach aims to address the interaction of primary disease-specific factors with secondary related issues, such a comorbidities and lifestyle, and wider demographic characteristics.

Comorbidities are common in COPD patients. Secondary cardiovascular problems are frequently observed (Barnes and Celli, 2009) alongside conditions such as diabetes (Feary *et al.*, 2010); cancer (Anthonisen *et al.*, 2002); sleep apnoea (McNicholas, 2016) and mood disorders (Hynninen *et al.*, 2005). Given such circumstances, clinicians are increasingly recognising the necessity of whole-patient approaches, incorporating routine screening and clinical management considerations for all relevant comorbidities (Dodd, Getov and Jones, 2010). In line with these developments, recent attention has been given to the anecdotal accounts of memory problems and "brain fog" which are commonly reported by COPD patients. Indeed, given that primary disease presentation directly influences circulating blood gases, it may be reasonable to expect that some damage or dysfunction to oxygen-sensitive brain regions could arise in this condition (Paola *et al.*, 2008). Several recent neuropsychological literature reviews have explored the relationship between COPD and brain function (Hynninen *et al.*, 2005; Dodd, Getov and Jones, 2010; Schou *et al.*, 2012;

Cleutjens *et al.*, 2014; Lahousse *et al.*, 2015; Torres-Sánchez *et al.*, 2015). However, these studies have varied in methodological approaches and findings have been mixed. Therefore, at present, the pattern and nature of cognitive difficulties arising in this condition are still poorly understood and further investigation is required.

The pathology underlying cognitive dysfunction in COPD is complex and, to date, remains unclear. Several authors have endeavoured to identify the potential mechanisms involved (Borson *et al.*, 2008; Dodd, Getov and Jones, 2010; Cleutjens *et al.*, 2014). While some associations between cognitive abilities and disease severity have been found (Schou *et al.*, 2012), there is mounting literature addressing the role of circulating blood-gases. Several papers have demonstrated a relationship between hypoxemia (abnormally low circulating oxygen levels), and to a lesser extent hypercapnia (abnormally high circulating carbon dioxide levels), and neuropsychological performance (Dodd, Getov and Jones, 2010). Blood-gases have also been linked to changes in cerebral perfusion and neurotransmitter levels (Shim *et al.*, 2001).

The consideration of disease-specific variables is complicated further by the dynamic and phasic nature of COPD. At any one time, the majority of patients are considered "stable", their illness remains well controlled and changes in health, treatment needs or functioning are relatively minor. Indeed, a central aim of COPD management is the maintenance of such stability and prevention of exacerbations: "acute events characterised by a worsening of symptoms beyond normal day-to-day variations" (GOLD, 2016). Exacerbations commonly present as diminished health status marked by increased breathlessness and respiratory infection. These acute episodes usually necessitate periods of close monitoring and additional

treatment, often requiring hospitalisation. While the link between exacerbation and cognitive function is unclear, it has been suggested that physiological dysregulation, as experienced during exacerbation, may increase risk of cognitive difficulties, whether transient or permanent (Dasgupta, 2016). Furthermore, the multifaceted influence of COPD pathology may dynamically interact with comorbidities, many of which may exert independent influence on brain function, marking a complex pathway to cognitive impairment.

Despite the complexity of contributing factors, it is important to understand the nature of any cognitive difficulties arising in COPD. Evidence from other chronic health conditions has demonstrated relationships between cognitive dysfunction and a range of clinical outcomes. Difficulties with disease management and medication adherence has been associated with cognitive problems in heart failure and diabetes (Alosco *et al.*, 2012; Hopkins, Shaver and Weinstock, 2016). Additionally cognitive difficulties have been linked to reductions in activities of daily living in chronic kidney disease (Goto, 2017) and quality of life in multiple sclerosis (Benito-Leon, Morales and Rivera-Navarro, 2002). In the current healthcare landscape of increasing emphasis on self-management, it is important that considerations of cognitive difficulties are incorporated into treatment guidelines. Neglecting to acknowledge such issues may lead to poor disease management causing more frequent exacerbations, related hospital admissions and reliance on care.

Comprehensive neuropsychological assessment should cover a range of cognitive domains, each having a differential impact on functional abilities. A commonly accepted classification system will be used in this study (Lezak *et al.*, 2012). Processing speed is defined as simple mental speed, often measured by reaction times, while working memory and attention tasks

examine an individual's limited attentional capacity. Perception is the ability to take in information from the environment. Memory is the capacity to retain information and later utilise it for adaptive purposes. Tasks examining language and verbal abilities typically involve object naming. Motor abilities are closely linked to processing speed but may also examine abilities of fine-motor dexterity and manipulation, while constructional abilities combine visuospatial perception with motor response. Concept formation involves abstract reasoning and thinking abilities. Executive functions are examined on tasks assessing planning, problem solving, self-monitoring and behavioural regulation.

Previous systematic reviews examining cognitive dysfunction in COPD have varied in scope and methodology (Hynninen *et al.*, 2005; Schou *et al.*, 2012; Torres-Sánchez *et al.*, 2015). Many have taken an inclusive approach to study selection with regards to sample characteristics. Included samples have originated from a wide variety of sources with many recruiting via inpatient respiratory services. As such, a large proportion of participants were exacerbating COPD patients. While insights into cognitive function during exacerbation contribute to the overall picture of this condition, exacerbation phases tend to cover brief periods in the lifecycle of the disease. Furthermore, self-management abilities are likely to have more impact upon outcomes in a stable phase, thus knowledge regarding cognitive function during exacerbation is limited in its clinical utility. Finally, undifferentiated assessment of stable and exacerbating patients introduces a meaningful confound, thus reducing the strength of conclusions drawn. Therefore, this review aims to examine the literature investigating cognitive function in stable COPD and address the following questions: (1) What is the nature of cognitive dysfunction in stable COPD? (2) Is there a relationship

between cognitive dysfunction and disease-specific variables such as lung function and arterial blood-gases (ABGs)?

METHODS

All studies examining cognitive performance in stable COPD were eligible for inclusion in this systematic review. A search of the term "Chronic Obstructive Pulmonary Disease" on PROSPERO found no ongoing systematic reviews on this topic.

Database searches

The search strategy was customised for each database and utilised controlled vocabulary (MeSH) and keywords. The following databases were systematically searched: Medline (via Ovid Medline (R) 1946 to week 1 January 2018 and OVID Medline (R) in-process and other non-indexed citations), EMBASE (via Ovid, 1947 to present, updated daily on 21st January 2018), CINAHL, PsycInfo, Psychology and Behavioural Science Collection (via EBSCOhost 1987 until 21st January 2018), Web of Science (inception date of database until 21st January 2018).

Using Boolean operators 'AND' and 'OR' in-between as specified, the following search terms were used:

- Chronic Obstructive Pulmonary Diseas* OR copd OR Pulmonary Disease, Chronic Obstructive (MeSH)
- Cognitive OR Cognition OR Cognition disorders (MeSH) OR Cognitive defect (MesH) OR Cognition (Mesh) OR neuropsychol* OR Neuropsychological Tests (MesH) OR Neuropsychology (MeSH)
- 3. Stable
- 4. 1 AND 2 AND 3

Hand-searching of included studies reference lists was subsequently conducted to identify any articles not found by electronic searches.

Studies meeting the following criteria were included: (i) published in English, (ii) human adult participants, (iii) original published research, (iv) case-control design, (v) participants have a diagnosis of COPD which is classified as stable, (vi) study provides a neuropsychological measure of function in a specific cognitive domain(s). Studies that reported only general cognitive ability, for example total Montreal Cognitive Assessment scores, were excluded. The article selection process is illustrated in Figure 1. If suitability for inclusion was ambiguous, an independent researcher examined the article.

Quality Rating

Study quality was examined using an adapted version of the Scottish Intercollegiate Guidelines Network (SIGN) Methodology Checklist-4: Case-control studies (2008) [Appendix 1.2]. This protocol consists of nine items covering five methodological issues: study question, subject selection, assessment, confounding factors and statistical analysis. Each item was answered 'yes', 'no' or 'can't say'. The overall methodological quality, dependent upon number of 'yes' responses, was rated as 'high quality' (++) (six or more), 'acceptable' (+) (four or five), or 'low quality' (0) (less than four). A second rater also assessed five of the included papers to ensure reliability. The selected papers were separately rated by each reviewer and disagreements were resolved through discussion with final ratings amended to the consensus. Initial agreement in overall quality was found for four co-rated papers.

Data Synthesis and Extraction

A meta-analysis was not considered appropriate due to variation in methodology, measures of cognitive function and statistical analysis. Therefore, a narrative synthesis was undertaken (Popay *et al.*, 2006). A data extraction form was used to systematically collect information on sample characteristics, recruitment, neuropsychological measures and results for every study [Appendix 1.3]. Statistically significant differences in cognitive performance between COPD and control groups were explored. However, the studies included in this review varied in sample sizes and statistical power. Therefore, data reporting which is limited to only statistically significant between-group differences may lead to inaccurate interpretations of findings. Such results do not speak to the magnitude of the between-group differences and, as such, have limited clinical meaning. To address this issue, Cohen's d effect sizes were also calculated, where possible, for individual cognitive measures within each study.

RESULTS

Search results

As illustrated in Figure 1, the literature search initially identified 679 papers for inclusion. After the exclusion of duplicates and unrelated studies, 96 papers were reviewed at abstract level and 35 full texts were subsequently reviewed. Eleven papers met final inclusion criteria.

Study characteristics

Table 1 summarises the characteristics, quality ratings and main findings of included studies. In addition to stable COPD participants and healthy controls, some studies also included participants during exacerbation (Dodd *et al.*, 2013), Alzheimer's patients and older-healthy volunteers (Incalzi *et al.*, 1997). However, the current review has focussed on results of stable COPD participants and matched controls. A wide range of neuropsychological measures were employed and each domain was explored by at least two papers.

Overall, ten studies reported on disease severity and seven examined the relationship with cognitive performance. Historically, COPD severity has been quantified by degree of airflow limitation, measured by forced expiratory volume in one second (FEV₁) as a percentage of demographic-predicted FEV₁(FEV₁%pred.). Prior to 2011, GOLD promoted the adoption of severity classification ranges (mild to very severe) based on solely FEV₁(%pred.) values. In accordance with these guidelines, two studies reported the number of participants in each severity range (Borson *et al.*, 2008; Zhang *et al.*, 2012), while a further six provided group mean FEV₁(%pred.) values (Incalzi *et al.*, 1997; Liesker *et al.*, 2004; Ortapamuk and Naldoken, 2006; Dodd *et al.*, 2013; Cleutjens *et al.*, 2017; Spilling *et al.*, 2017). However,



Figure 1: Search strategy flow chart

recently revised guidelines introduced the inclusion of self-reported symptoms and exacerbation history into severity gradings (GOLD, 2016). Only one study in this review reported severity in this manner (Karakontaki *et al.*, 2013). Further details of GOLD classification systems are illustrated in Appendix 1.4. The overall range of severity of participants in this review covered 'mild' to 'very severe'. One study analysed results for groups of differing severity separately (Ryu *et al.*, 2013). Three studies included data only for 'moderate' to 'severe' participants (Incalzi *et al.*, 1997; Borson *et al.*, 2008; Ryu *et al.*, 2013) while one examined a 'severe' to 'very severe' sample (Ortapamuk and Naldoken, 2006). The remaining seven papers studied mixed severity groups.

In exploration of the influence of hypoxemia and hypercapnia, eight studies provide mean arterial blood-gas values (ABGs) (Incalzi *et al.*, 1997; Liesker *et al.*, 2004; Ortapamuk and Naldoken, 2006; Zhang *et al.*, 2012; Dodd *et al.*, 2013; Karakontaki *et al.*, 2013; Cleutjens *et al.*, 2017; Spilling *et al.*, 2017). Five studies deliberately controlled for ABGs through sample selection (Grant *et al.*, 1982; Incalzi *et al.*, 1997; Liesker *et al.*, 2004; Ortapamuk and Naldoken, 2006; Karakontaki *et al.*, 2013; Spilling *et al.*, 2017) and one of these studies examined differences between two groups classified by ABGs (Ortapamuk and Naldoken, 2006). Five studies included a hypoxemic sample (Grant *et al.*, 1982; Incalzi *et al.*, 1997; Ortapamuk and Naldoken, 2006; Karakontaki *et al.*, 2013; Spilling *et al.*, 2017), while two included hyercapnic participants (Incalzi *et al.*, 1997; Ortapamuk and Naldoken, 2006). Five studies discuss the relationship between ABGs and neuropsychological performance (Grant *et al.*, 1982; Liesker *et al.*, 2004; Ortapamuk and Naldoken, 2006; Dodd *et al.*, 2013; Karakontaki *et al.*, 2013).

Quality ratings

Two included studies were rated as high quality (++) (Dodd *et al.*, 2013; Cleutjens *et al.*, 2017), with the remaining nine rated as acceptable (+). A summary of item-specific quality scores for each study can be found in Appendix 1.5. Due to variations in study design, neuropsychological measures and confounding variables controlled for, it was not possible to systematically evaluate whether study quality influenced overall findings.

All studies had a clear aim and confirmed cases were clearly differentiated from controls. Five articles ensured that cases and controls came from comparable populations (Grant *et al.*, 1982; Incalzi *et al.*, 1997; Liesker *et al.*, 2004; Dodd *et al.*, 2013; Cleutjens *et al.*, 2017) and six ensured controls were non-cases (Grant *et al.*, 1982; Ortapamuk and Naldoken, 2006; Dodd *et al.*, 2013; Ryu *et al.*, 2013; Cleutjens *et al.*, 2017; Spilling *et al.*, 2017). Seven studies evidenced neuropsychological measure validity and reliability by providing appropriate evaluations or references (Incalzi *et al.*, 1997; Ortapamuk and Naldoken, 2006; Borson *et al.*, 2008; Zhang *et al.*, 2012; Dodd *et al.*, 2013; Karakontaki *et al.*, 2013; Cleutjens *et al.*, 2017). None of the studies reported confidence intervals.

Eight studies clearly stated that the same exclusion criteria were applied to COPD patients and controls (Incalzi *et al.*, 1997; Liesker *et al.*, 2004; Borson *et al.*, 2008; Zhang *et al.*, 2012; Karakontaki *et al.*, 2013; Ryu *et al.*, 2013; Cleutjens *et al.*, 2017; Spilling *et al.*, 2017). Articles were considered to identify the main potential confounders if they provided measures of, and controlled for, the following key variables in their design or analysis: age, gender, premorbid-IQ or education, mental health or mood and smoking status. Only one study controlled for all five variables (Cleutjens *et al.*, 2017). All studies controlled for age and gender and, with the exception of Ryu *et al.*, (2013) and Spilling *et al.*, (2017), also for education or premorbid intelligence. Only two studies controlled for levels of anxiety and depression (Borson *et al.*, 2008; Cleutjens *et al.*, 2017), while four studies controlled for smoking status (Borson *et al.*, 2008; Zhang *et al.*, 2012; Dodd *et al.*, 2013; Cleutjens *et al.*, 2017).

Study	Objective	Sample size and characteristics	Neuropsychological measures	Results	Quality rating
Borson <i>et al.</i> (2008)	To examine the pathways from lung disease to brain dysfunction in COPD patients and controls. To construct a testable model of COPD and the brain.	 n COPD= 18 n Control = 9 Recruitment procedures not stated. <u>Classification of COPD:</u> Moderate to severe GOLD stage (FEV₁%pred.): {(n1 = 0) (n2 = 2) (n3 =8) (n4 = 7)} ABGs not reported. Stable condition not further defined. 	Digit-symbol coding (WAIS-III) Logical memory (WMS-III)	In comparison to controls, COPD patients attained significantly lower scores on tasks examining processing speed and verbal memory.	+
Cleutjens <i>et</i> <i>al.</i> (2017)	To compare general and domain-specific cognitive impairments between COPD patients and controls.	n COPD = 90 n Controls = 90 COPD participants were recruited via pulmonary rehabilitation. Controls were recruited from the local community. Classification of COPD: Mixed disease severity {FEV ₁ %pred.= 54.5 \pm 23.7} {PaO ₂ = 73.5 \pm 12} {PaCO ₂ = 38.3 \pm 6.8} Defined as stable per GOLD guidelines: no exacerbation for 4 weeks.	Stroop Colour-Word Test Concept-shifting Test Letter-digit Substitution Visual-verbal Learning Task Digit Span (WAIS-III) Key Search (BADS) Zoo Map (BADS)	Mean scores on tests examining processing speed, attention, memory, executive functions and concept formation were significantly lower in COPD patients compared to controls. In comparison to control participants without comorbidities (<i>n</i> = 43) COPD participants without comorbidities (<i>n</i> = 18) attained significantly lower scores only in tasks of abstract reasoning and executive function. In the COPD group, prevalence of clinical levels of cognitive impairment (z = <-1SD) was significantly higher than in the control group in the domains of processing speed, memory, executive function and concept formation.	++

Table 1: Summary of included studies with sample characteristics, neuropsychological measures and quality ratings

Study	Objective	Sample size and characteristics	Neuropsychological measures	Results	Quality rating
Dodd <i>et al.</i>	To examine the	n COPD stable = 50	RCFT	Stable COPD patients scored significantly	++
(2013)	cognitive abilities	n COPD exacerbation = 30		lower than controls on tasks examining	
	of COPD patients	n Controls = 30	Word lists (WMS-III)	processing speed, working memory, verbal	
	when stable and			memory, executive function, and	
	during	COPD participants recruited via outpatient	Verbal fluency (DKEFS)	constructional abilities.	
	exacerbation.	clinics. Control participants recruited from			
		local community.	Trails (DKEFS)	Group means for the stable COPD group	
				fell within the 'normal' range for all tests.	
		Classification of COPD:	Letter-number sequencing	However, a significant proportion of this	
		Mixed disease severity	(WAIS-III)	group had 'mild' to 'moderate' (z = <-1 SD)	
		Stable group: {FEV ₁ %pred. = 52 ± 22}		impairment, particularly in measures	
		Exacerbating group: {FEV ₁ %pred. = 40 ± 15 }	Spatial span (WMS-III)	examining executive functions, visual	
				memory and constructional performance.	
		ABG's for stable group:	Digit symbol (WAIS-III)		
		${PaO_2 = 76.5 \pm 13.5}$			
		${PaCO_2 = 37.7 \pm 3.5}$	Symbol search (WAIS-III)		
		Stable: no exacerbation for 8 weeks			
Grant <i>et al.</i>	To determine the	n COPD total sample = 203	Halsted-Reiten Battery:	COPD participants scored significantly	+
(1982)	prevalence, nature	n COPD subsample = 51	 Category test 	lower than controls in tasks examining	
	and severity of	n Controls = 51	 Rhythm test 	processing speed, visual memory, concept	
	neuropsychological		 Speech-sounds 	formation, executive functions, perceptual	
	disturbance in	COPD patients were recruited via hospital	perception test	and motor abilities.	
	hypoxemic COPD	clinic settings and private practice. Control	 Tactual performance 		
	patients.	participants were well matched and	test		
		recruited from the local community.	 Tapping test 		
			 Aphasia Screening Test 		
		Classification of COPD:	 Trail-making Test 		
		Mixed disease severity	 WAIS 		
		Hypoxemic {PaO ₂ <60}			
		Further ABGs not reported	Grooved pegboard		
		Stable: evidenced by consecutive ABGs			
		across one week.	Short story (WMS)		
			Drawings (WMS)		

Study	Objective	Sample size and characteristics	Neuropsychological	Results	Quality
Incalzi <i>et al.</i> (1997)	To clarify the nature of verbal memory impairment in COPD and to explore how this impacts medication adherence.	$n \text{ COPD} = 42$ $n \text{ controls} = 27$ $n \text{ AD} = 31$ $n \text{ older controls} = 26$ COPD participants were recruited frompneumology outpatient clinic. Age-matchedand older controls recruited via minor daysurgery. AD participants recruited vianeuropsychology outpatient clinic.Classification of COPD:Moderate to severe{FEV1%pred. = 34 ± 9 }Hypoxemic {PaO2 = 48.8 ± 7.6 }Hypercapnic {PaCO2 = 56.5 ± 7.2 }Stable condition not further defined.	RAVLT Digit span (WAIS-R)	COPD participants attained significantly lower scores on some, but not all, aspects of a verbal memory test and on a task of working memory. Only 38.1% of COPD patients demonstrated a group-specific memory profile – 19% were classed as controls, 16.7% as AD and 26.2% as older controls.	+
Karakontaki <i>et al.</i> (2013)	To investigate whether: (a) cognitive performance was impaired in COPD patients with subclinical hypoxemia (b) whether cognitive abilities related to driving ability.	n COPD = 35 n controls = 10 Recruitment procedures not stated. $\frac{\text{Classification of COPD:}}{\text{Mixed disease severity}}$ GOLD stage (combined assessment): {(nA = 4) (nB = 7) (nC = 15) (nD = 9)} Mildly Hypoxemic {PaO ₂ > 55} {PaO ₂ = 77± 12} {PaCO ₂ = 41± 6} Stable for 4 weeks minimum.	 <u>Vienna Test System</u> Reaction Time to Single Visual and Acoustic Stimuli Selective Attention Test Permanent Attention Test Tachistoscopic Traffic Test 	COPD patients scored significantly lower than controls tasks of processing speed and perceptual abilities. No significant differences were identified in performance on attention or executive function tests. Significantly less COPD participants than controls were classed as safe to drive.	+

Study	Objective	Sample size and characteristics	Neuropsychological measures	Results	Quality rating
Liesker <i>et al.</i> (2004)	To examine cognitive performance in non-hypoxemic COPD patients.	 n COPD = 30 n controls = 20 COPD participants were recruited via outpatient clinics. Control participants recruited via an electronic database of general practice. <u>Classification of COPD:</u> Mixed disease severity {FEV1%pred. = 49.8±18.7} Non-hypoxemic {PaO2 > 60} {PaO2 = 75.8±8.3} {PaCO2 = 39.8±5.3} Stable according to ATS definition. 	Story recall Trail-making (Halstead-Reitan) Stroop Colour-Word Task Digit-symbol (WAIS) Arithmetic (Groningen Intelligence Test)	COPD patients scored significantly lower than controls in tasks examining processing speed. Significantly lower scores were also identified in this target group in some, but not all, measures of executive functions. No significant differences between the two groups were observed in performance on a verbal memory task.	+
Ortapamuk & Naldoken (2006)	To explore cerebral perfusion patterns and cognitive performance in COPD.	n COPD (hypoxemic) = 8 n COPD (non-hypoxemic) = 10 n Controls = 10Recruitment procedures not stated.Classification of COPD: Severe to very severe {FEV1%pred = 33.9 ± 13}Hypoxemic and hypercapnic {PaO2 = 51.6 ± 4.1} {PaCO2 = 47.6 ± 7.9}Non-hypoxemic and normocapnic {PaO2 = 67.5 ± 4.9} {PaCO2 = 39.9 ± 5.1} Stable condition not further defined	Mental deterioration batteryRAVLTWord fluency and phrase constructionRaven's matricesCopying drawingsTemporal rule inductionWMS - RMental controlFigural memoryLogical memory I&IIVisual and verbal paired associates I&IIVisual reproduction I&IIDigit spanVisual memory spanColour-Trail Test Groove Pegboard	Compared to controls, hypoxemic COPD patients scored significantly lower on tasks exploring memory and attention. Non- hypoxemic COPD patients only scored significantly lower than controls on a test of verbal memory. No significant differences were identified between either COPD groups and controls on measures of constructional abilities, language, concept formation or executive functions.	+

Study	Objective	Sample size and characteristics	Neuropsychological measures	Results	Quality rating
Ryu <i>et al.</i> (2013)	To compare regional microstructural brain changes in COPD patients and controls	 n COPD = 19 n Control = 12 COPD participants were recruited via hospital pulmonary medicine database. Control participant recruitment procedures not stated. <u>Classification of COPD:</u> Moderate <i>n13:</i> {FEV₁%pred. 50-80} Severe <i>n</i>6: {FEV₁%pred. <50} ABGs not reported. Stable condition not further defined. 	 <u>Seoul Neuropsychological</u> <u>Battery:</u> Digit span Boston naming test (Korean) Written calculations RCFT Seoul Verbal Learning Test COWAT Stroop Task 	Compared to both controls and the 'moderate' COPD group, the 'severe' COPD group attained significantly lower scores in tasks of concept formation and executive functions.	+
Spilling <i>et</i> <i>al.</i> (2017)	To examine macroscopic grey and white-matter differences in stable COPD patients with subclinical cognitive impairment.	n COPD = 31 n controls = 24COPD participants were recruited via outpatient clinics. Control participants were recruited from the local community. <u>Classification of COPD:</u> Mixed disease severity {mean FEV1%pred. = 52.1 ± 20.9}Mildly Hypoxemic {PaO2 = 75.8 ± 16.5} Normocapnic {PaCO2 = 37.5 ± 5.3}Stable condition not further defined	RCFT Word lists (WMS-III) Verbal fluency (DKEFS) Trails (DKEFS) Letter-number sequencing (WAIS-III) Spatial span (WAIS-III) Digit symbol (WAIS-III) Symbol search (WAIS-III)	In comparison to controls, COPD participants performed significantly lower in tests examining processing speed, attention, memory and executive function.	+

Study	Objective	Sample size and characteristics	Neuropsychological	Results	Quality
			measures		rating
Zhang et al.	To examine	n COPD = 25	Digit Span	COPD patients had significantly lower	+
(2012)	whether there is	<i>n</i> controls = 25	(WMS-R Chinese)	scores in visual memory tests in	
	brain structural			comparison to controls. No significant	
	alteration in COPD.	COPD participants were recruited via	Visual reproduction	differences were identified between the	
		inpatient rehabilitation. Recruitment	(WMS-R Chinese)	groups on working memory performance.	
		procedures for controls not stated.			
			Figure memory		
			(WMS-R Chinese)		
		Classification of COPD:			
		Mixed disease severity			
		GOLD stage (FEV ₁ %pred.):			
		$\{(n1 = 1) (n2 = 8) (n3 = 7) (n4 = 9)\}$			
		${PaO_2 = 79.9 \pm 23.3}$			
		$\{PaCO_2 = 48.1 \pm 6.0\}$			
		Stable condition not further defined.			

Abbreviations: FEV₁%pred. = forced expiratory volume in one second (FEV₁) as a percentage of demographic-predicted FEV₁; ABGs = arterial blood gases; PaO₂ = Partial pressure of oxygen; PaCO₂ = Partial pressure of carbon dioxide; ATS = American Thoracic Society; WMS-R/III = Wechsler Memory Scale various editions; WAIS-R/III = Wechsler Adult Intelligence Scale various editions; RCFT = Rey Complex Figure Test; DKEFS = Delis-Kaplin Executive Function System; BADS = Behavioural Assessment of Dysexecutive Syndrome; COWAT = Controlled Oral Word Association Test; RAVLT = Rey Auditory Verbal Learning Test;; AD = Alzheimer's Disease. **Note:** All ABGs given as mmHg.

	Processing Speed	Attention & Working Memory	Language	Perception	Constructional	Motor	Memory	Concept Formation & Abstract Reasoning	Executive Functions
Borson (2008)	x						х		
Cleutjens (2017)	x	х					х		Х
Dodd (2013)	х	х			x		х		х
Grant (1982)				х	Х	х	х	х	х
Incalzi (1997)		Х					x		
Karakontaki (2013)	x			x					
Liesker (2004)	x		-					х	x
Ortapamuk (2006)		х					х		
Ryu (2013)								x	x
Spilling (2017)	X	х		-			х		Х
Zhang (2012)							Х		

Table 2: Domain-specific difficulties observed in reviewed studies

= assessed, **X** = difference/impairment found

Summary of overall findings

Cognitive performance

All studies included in this review demonstrated some evidence of cognitive dysfunction in stable COPD patients. Table 2 provides a summary of the domains addressed in each study. Details of domain classification of neuropsychological tests can be found in Appendix 1.6. COPD patients attained significantly lower scores than controls in every study examining processing speed (Liesker *et al.*, 2004; Borson *et al.*, 2008; Dodd *et al.*, 2013; Karakontaki *et al.*, 2013; Cleutjens *et al.*, 2017; Spilling *et al.*, 2017), but only in half of the investigations of attention and working memory (Incalzi *et al.*, 1997; Ortapamuk and Naldoken, 2006; Dodd *et al.*, 2013; Cleutjens *et al.*, 2017; Spilling *et al.*, 2017). No significant between-group differences were identified in either studies assessing language (Grant *et al.*, 1982; Ryu *et al.*, 2013). In contrast, both studies examining perceptual functions found significantly reduced performance in COPD participants in comparison to healthy volunteers (Grant *et al.*, 1982; Karakontaki *et al.*, 2013).

COPD participants scored significantly lower than controls in only one of three studies examining these functions (Grant *et al.*, 1982). Most studies investigating concept formation, abstract reasoning and executive functions found COPD participants performed significantly lower than controls (Grant *et al.*, 1982; Liesker *et al.*, 2004; Dodd *et al.*, 2013; Ryu *et al.*, 2013; Cleutjens *et al.*, 2017; Spilling *et al.*, 2017).

Eight out of ten papers assessing memory performance observed that the COPD group mean scores were significantly lower than the control group (Grant *et al.*, 1982; Incalzi *et al.*, 1997; Ortapamuk and Naldoken, 2006; Borson *et al.*, 2008; Zhang *et al.*, 2012; Dodd *et al.*, 2013;

Cleutjens *et al.*, 2017; Spilling *et al.*, 2017). Distinctions were made between verbal and nonverbal memory in many of these studies, with three (Incalzi *et al.*, 1997; Ortapamuk and Naldoken, 2006; Borson *et al.*, 2008) and two articles (Grant *et al.*, 1982; Zhang *et al.*, 2012) illustrating significantly lower scores for COPD participants in verbal and non-verbal memory tasks in comparison to controls. Interestingly, Incalzi *et al.* (1997) compared the verbal memory profile of COPD patients with aged-matched healthy, Alzheimer's and older healthy participants. This analysis highlighted reduced retrieval efficiency in comparison to age-matched controls. However, COPD patients' memory scores were significantly better than the Alzheimer's group. Discriminant analysis found only 31% of COPD patients conformed to a group-specific profile while 26.2% fell into the older control classification.

Conclusions drawn from specific examination of high quality studies (Dodd *et al.*, 2013; Cleutjens *et al.*, 2017) were in keeping with the overall findings of this review. Each paper demonstrated significantly lower scores for COPD patients in comparison to controls in the domains of processing speed and executive difficulties. Similarly, both studies highlighted significantly lower scores in in attention and memory tasks for COPD participants compared to controls, although this effect became non-significant when adjusting for comorbidities in Cleutjens *et al.* (2017).

Magnitude of cognitive difficulties

Given the variation in sample sizes of studies included in this review, it is possible that relatively minor between group differences may have reached statistical significance. Furthermore, observations of significantly reduced performance in comparison to controls does not confirm

cognitive impairment to the extent of clinical thresholds. Therefore, to better understand the functional impact of any cognitive difficulties in this disease, it is necessary to examine the magnitude cognitive difficulties observed in COPD groups, either in comparison to control groups or standardised norms. A few included studies made some investigation of the severity of cognitive difficulties. Cleutjens et al. (2017) examined compound z-scores across functions of processing speed, planning, working memory, verbal memory and cognitive flexibility. While COPD patients performed significantly worse than controls on these measures, only their cognitive flexibility performance reached levels of clinical impairment (Z-score below -1SD). Another study reported the proportion of different groups to meet classifications for 'moderate to severe' impairment (Dodd et al., 2013). A substantial proportion (>20%) of the COPD group fell within this impaired range (Z-score below -1SD) on subtasks examining memory, mental switching, processing speed and visuospatial function. In contrast, a study exploring drivingrelated attentional performance reported percentiles for COPD participants falling within the 'low average' to 'average' range (Karakontaki et al., 2013) . Nevertheless, the COPD group's scores were significantly lower than controls.

None of the included papers reported effect sizes but these were calculated where possible. Due to data reporting, it was not possible to calculate effect size for four studies (Grant *et al.*, 1982; Liesker *et al.*, 2004; Karakontaki *et al.*, 2013; Ryu *et al.*, 2013). Table 3 summaries all effect sizes (Cohen's d) for between-group differences on individual cognitive measures. Due to the heterogeneity of measures used, overall weighted effect sizes were not calculated. Effect sizes of processing speed tasks ranged from 0.4 to 1.67 (median = 0.93), while those of attention and

working memory tests ranged from 0.09 to 0.97 (median = 0.4). Language and construction task effect sizes were small, respectively ranging from 0.11 to 0.4 (median = 0.25) and 0.06 to 0.32 (median = 0.16). It was only possible to calculate one perception-based effect size which was 0.81. Many effect sizes were calculated for memory tasks with values covering a wide range (0.11 to 1.54, median = 0.54). Similarly, executive function effect sizes were varied, ranging from 0.11 to 1.13 (median = 0.67). Effect sizes of concept formation and abstract reasoning tasks ranged from 0.02 to 0.78 (median = 0.46).

Study	Cognitive Test	Effect Sizes (Cohen's d)	
Borson		<u>02-dependent</u>	Non-O2-dependent
		<u>COPD vs C</u>	<u>COPD vs C</u>
	Digit symbol	1.67	0.40
	Logical memory	1.13	0.52
Cleutjens		<u>COPD vs C</u>	
	SCWT 1	0.48	
	CST – A	0.58	
	LDST written	1.00	
	LDST oral	0.86	
	Key search	0.66	
	Zoo map	0.67	
	VVLT trial 1	0.55	
	DS backwards	0.09	
	VVLT total recall	0.68	
	VVLT delayed recall	0.54	
	VVLT retention	0.39	
	SCWT 3	0.85	
	CST-C	0.78	
Dodd		COPD vs C	
	Memory visual IR	0.43	
	, Memory visual DR	0.44	
	, Memory verbal IR	0.73	
	Memory verbal DR	0.24	
	Trails	1.01	
	Verbal fluency	0.25	
	Working memory index	0.79	
	Processing speed index	1.10	
	Visuospatial	0.81	
Incalzi		COPD vs C	
Inculzi	Immediate recall	0.97	
	Verbal learning	0.41	
	Primacy	0.65	
	Secondary memory	0.93	
	Recency	0.33	
	Delaved recall	0.90	
	Intrusions	0.45	
	True positive recognition	0.53	
	False positive	0.62	
	recognition	0.77	
	Accuracy recognition	0 39	
	Verbal forgetting	0.78	
	Retrieval	0.33	
	DS-forward	0.55	
	DS-backwards	0.00	

Table 3: Summary of Individual Effect Sizes for Cognitive Measures in Studies

Study	Cognitive Test	Effect Sizes	
		(Cohei	n's d)
Ortapamuk		<u>Hypoxemic</u>	<u>Non-hypoxemic</u>
		<u>COPD vs C</u>	<u>COPD vs C</u>
	Verbal memory	0.18	0.11
	Immediate recall	1.10	0.22
	Delayed recall	1.54	0.27
	Delayed recognition	0.36	0.30
	Verbal fluency	0.22	0.11
	Word generation	0.27	0.41
	Copying drawings	0.10	0.06
	Copy with landmarks	0.32	0.21
	DS-forwards	0.09	0.14
	DS-backwards	0.48	0.21
	Raven's matrices	0.59	0.40
	Temporal rule induction	0.02	0.46
Spilling		<u>COPD vs C</u>	
	Executive function	1.13	
	Episodic memory	0.63	
	Processing speed	0.93	
	Working memory	0.92	
Zhang		<u>COPD vs C</u>	
	DS-forwards	0.47	
	DS-backwards	0.12	
	Visual reproduction	0.66	
	Figure memory	0.76	

Abbreviations: C = controls; SCWT = Stroop Colour-Word Task; CST = Card-Sorting Task; IR = immediate recall; DR = delayed recall; Letter-Digit Substitution Test, VVLT = Visual Verbal Learning Task; DS = Digit Span

Cohen's d convention: Small (d = 0.2), Medium (d = 0.5), Large (d = 0.8)

Relationship with disease-related variables

Overall, most studies examining the relationship between arterial blood gases (ABGs) and cognition indicated poorer performance in lower oxygen levels. In hypoxemic groups, significantly lower scores than controls were reported across memory, attention (Incalzi et al., 1997; Ortapamuk and Naldoken, 2006), perceptual, visuospatial and executive domains (Grant et al., 1982). However, in comparing non-hypoxemic groups and controls, significantly poorer scores were also recorded in memory (Ortapamuk and Naldoken, 2006), processing speed and executive skills (Liesker et al., 2004). Significant correlations were demonstrated between neuropsychological performance and partial pressure of oxygen in some studies (Grant et al., 1982; Karakontaki et al., 2013). Although, circulating oxygen levels did not appear to correlate with cognitive scores in a group of non-hypoxemic patients, despite the group performing significantly poorer than controls (Liesker et al., 2004). The impact of oxygen dependence on neuropsychological functioning was unclear with conflicting studies reporting evidence for (Borson et al., 2008) and against (Cleutjens et al., 2017) significantly reduced performance in oxygen-dependent patients, in contrast to controls. The relationship with hypercapnia was examined less often and findings are unclear. Two studies concluded PCO₂ levels made little difference to cognitive scores (Grant et al., 1982; Dodd et al., 2013). However, Karakontaki et al., (2013) identified significantly longer reaction times in hypercapnic patients, compared to controls.

Disease severity seemed to have little relationship with cognitive difficulties. Two studies demonstrated no significant association between overall cognitive performance and disease

severity (Grant *et al.*, 1982; Liesker *et al.*, 2004) while FEV₁(%pred.) explained only modest variations in Dodd *et al.* (2013). However, one study identified significant correlations between lung function, reaction times and visuospatial abilities (Karakontaki *et al.*, 2013). Similarly, in distinguishing between moderate and severe groups, another paper reported significantly reduced overall neuropsychological performance, in comparison to controls, only for the severe group (Ryu *et al.*, 2013).

Relationship with other contributing factors

Despite the widely evidenced influence of mental health on cognitive abilities, many studies neglected this potential confound. For example, Borson *et al.* (2008) reported co-occurring significant differences in measures of mood and cognitive functioning yet did not examine any association between these variables. In a more detailed investigation, Cleutjens *et al.* (2017) reported higher levels of anxiety and depression in COPD participants but did not find any significant differences in cognitive performance when comparing COPD patients above and below clinical thresholds for mood. Similarly, the influence of smoking history was not commonly addressed. One study suggested that smoking history may explain significant but very modest differences in neuropsychological performance (Dodd *et al.*, 2013) but another found no significant relationship (Liesker *et al.*, 2004).
DISCUSSION

The current review asked two questions: (1) What is the nature of cognitive dysfunction in stable COPD? (2) Is there a relationship between cognitive dysfunction and condition-specific variables such as disease severity and arterial blood-gases? Cognitive difficulties in stable COPD patients were identified in every study included in this review, suggesting that COPD patients may be at increased risk of brain dysfunction even in a stable phase of their disease. Due to methodological variation, it is difficult to identify a particular "cognitive profile" of stable COPD. Widespread difficulties across domains may be indicative of general cognitive decline in keeping with suggested theories of an accelerated aging influence of the disease (Grant et al., 1982; Kirkil et al., 2007). Overall, significant group differences and noteworthy effect sizes were most consistently found in the domains of processing speed, concept formation and abstract reasoning, executive functions and memory. Cognitive difficulties seem to have some association with hypoxemia, while hypercapnia and disease severity appear to exert less influence. This was the first review to examine domain-specific cognitive abilities in only stable COPD samples. However, the findings of the current study are in keeping with previous reviews examining general COPD samples, both in terms of cognitive domains affected and relationship with arterial blood gases (Hynninen *et al.*, 2005; Schou *et al.*, 2012; Torres-Sánchez *et al.*, 2015).

Clinical implications

Several studies in this review demonstrated relationships between cognitive performance and functional abilities. Incalzi *et al* (1997) reported significant correlations between medication compliance and long-term memory. Similarly, co-occurring difficulties were also reported in

cognitive scores and activities of daily-living for when comparing COPD participants and controls (Zhang *et al.*, 2012), although the relationship between these abilities was not explored. COPD patients scored lower than controls in five of seven neuropsychological tests assessing driving-related performance, and were classified as safe drivers significantly less than healthy volunteers (Karakontaki *et al.*, 2013). Furthermore, health status and quality of life were found to have a significant positive association with processing speed (Liesker *et al.*, 2004).

Examination of the patterns highlighted in this review may inform recommendations for routine care of stable COPD patients. To allow for slowed processing speed, clinicians should be careful to provide information and instructions at an appropriate speed, in small chunks. Memory difficulties may influence ability to recall treatment schedules or educational information. Compensatory strategies should involve frequent repetitions and reinforcement of educative material. Written guidance and use of electronic reminder systems may be helpful. Difficulties with executive skills may explain a range of presentations commonly observed in COPD patients including reduced motivation or initiation, inflexible behaviour patterns or frequent preventable exacerbations (Hall and Marteau, 2014). Support for self-monitoring and decision-making, through automated-guidance telecare systems, are likely to reduce the demands placed on patients to problem-solve in novel situations.

Methodological limitations of reviewed studies

Given the purpose of this review, compliance with inclusion criteria should be carefully evaluated with particular emphasis on definitions of disease stability. GOLD, (2016) guidelines state that

patients should be classified as in a stable phase of the disease once exacerbation-free for four to six weeks. Only three studies clearly stated compliance with this definition (Liesker *et al.*, 2004; Karakontaki *et al.*, 2013; Cleutjens *et al.*, 2017), while Grant *et al.* (1982) specified a designation of "stable" was accepted after one week of unchanged ABGs. The remaining articles did not further define disease stability and thus it is not possible to definitively confirm all included samples met recognised classification criteria. A further limitation of this review was the wide range of sample characteristics of included studies. These differences in methodological design limit the strength of conclusions drawn on relationships between condition severity, ABGs and neuropsychological performance.

Quality inspection of reviewed studies also raises some concerns around fulfilment of appropriate sample sizes. Only three studies referenced power calculations to justify sample sizes (Incalzi *et al.*, 1997; Dodd *et al.*, 2013; Cleutjens *et al.*, 2017). Therefore, it is possible that inconsistencies in reported findings may be partially explained by inadequate sample sizes. More detailed examination of effect sizes and patterns of significant findings would suggest that most included studies were sufficiently powered. However, two studies with particularly small samples reported few significant differences between COPD and control groups performance (Ortapamuk and Naldoken, 2006; Ryu *et al.*, 2013). Similar results also arose in an article which appeared to include skewed data (Liesker *et al.*, 2004). It was not possible to calculate the effect sizes for these studies. Therefore, sufficient power cannot be assumed and the findings should be interpreted in this context.

Lastly, critical consideration should be given to the principles of neuropsychological assessment and interpretation applied in these studies. Some of the included studies were medically oriented, examining cognitive performance as a secondary outcome of interest. Consequently, application of neuropsychological theory in these studies was limited. In addition, it is important to acknowledge that no singular aspect of cognition can be examined in isolation. Therefore, performance on any task thought to examine a specific cognitive function will also be influenced to varying degrees by additional domains. A wide range of assessment measures were implemented across included studies each varying in psychometric properties. Furthermore, adequate descriptions or references for these tests were lacking in several studies, substantially reducing replicability and critical interpretation. A range of different scoring methods were also implemented including raw and scaled individual subtest scores, and domain-specific index scores. While most studies reported group-comparisons based on subtest scores, others examined frequency of clinical impairment. Finally, while this review aimed to interpret all results with at a significance level of p<0.05, this was not always possible due to data reporting methods. Overall, these differences in neuropsychological practice introduce complex conceptual issues in interpretation.

Future research

Future research should further explore the influence of domain-specific dysfunction on clinical outcomes such as treatment adherence, attrition rates, quality of life and independent living skills. Continuing research into the role of disease-specific variables, including disease phase, is also required to develop greater understanding of biological pathways to brain dysfunction and

identification of at-risk patients. Better awareness of such issues may lead to targeted intervention studies to assess effectiveness of cognitive rehabilitation or assistive technology in identified patient groups. Although, in order to ensure validity of conclusions, careful consideration should be given to the application of neuropsychological theory in this medically driven field. The findings of this review promote the potential benefits of neuropsychological assessment in routine COPD care. However, assessment using comprehensive neuropsychological batteries is time and resource intensive. Therefore, investigation into the sensitivity and specificity of brief cognitive screening tools in this population may be required.

CONCLUSIONS

The findings of this systematic review support the notion that COPD patients may experience some degree of cognitive dysfunction, even in a stable phase of the disease. Due to methodological variation, it was not possible to identify a definitive cognitive profile of COPD, and patients were reported to perform significantly poorer than controls across almost every domain. However, deficits were demonstrated most consistently in the domains of processing speed, executive abilities and memory. Cognitive dysfunction in stable COPD patients seems to worsen in hypoxemia but the relationship with other disease-related variables is unclear. These findings have may have clinical implications for stable COPD treatment guidelines.

REFERENCES

- Alosco, M., Spitznagel, M., Dulmen, M., Raz, N., Cohen, R. and Sweet, L. (2012) 'Cognitive Function and Treatment Adherence in Older Adults with Heart Failure', Psychosomatic Medicine, 74(9), pp. 965–973.
- Anthonisen, N., Cornett, J., Enright, P. and Manfreda, J. (2002) 'Hospitalizations and mortality in the Lung Health Study', American Journal of Respiratory and Critical Care Medicine, 166, pp. 333–339.
- Barnes, P. and Celli, B. (2009) 'Systemic manifestations and comorbidities of COPD', European Respiratory Journal, 33(5), pp. 1165–1185.
- Benito-Leon, J., Morales, J. and Rivera-Navarro, J. (2002) 'Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients.', European Journal of Neurology, 9(5), pp. 497–502.
- Borson, S., Scanlan, J., Friedman, S., Zuhr, E., Fields, J., Aylward, E., Mahurin, R., Richards, T., Anzai, Y., Yukawa, M. and Yeh, S. (2008) 'Modeling the impact of COPD on the brain', International Journal of COPD, 3(3), pp. 429–434.
- Cleutjens, F., Janssen, D., Ponds, R., Dijkstra, J. and Wouters, E. (2014) 'COgnitive-pulmonary disease.', BioMed research international. Hindawi Publishing Corporation, 2014, p.

Cleutjens, F., Franssen, F., Spruit, M., Vanfleteren, L., Gijsen, C., Dijkstra, J., Ponds, R., Wouters, E. and Janssen, D. (2017) 'Domain-specific cognitive impairment in patients with COPD and control subjects', International Journal of Chronic Obstructive Pulmonary Disease. Dove Press, Volume 12, pp. 1–11.

Dasgupta, M. (2016) 'Cognitive Impairment in Hospitalized Seniors', Geriatrics, 1(1), p. 4.

- Dodd, J., Charlton, R., Van Den Broek, M. and Jones, P. (2013) 'Cognitive dysfunction in patients hospitalized with acute exacerbation of COPD', Chest. The American College of Chest Physicians, 144(1), pp. 119–127.
- Dodd, J., Getov, S. and Jones, P. (2010) 'Cognitive function in COPD', European Respiratory Journal, 35(4), pp. 913–922.
- Feary, J., Rodrigues, L., Smith, C., Hubbard, R. and Gibson, J. (2010) 'Prevalence of major
 comorbidities in subjects with COPD and incidence of myocardial infarction and stroke:
 A comprehensive analysis using data from primary care', Thorax, 65(11), pp. 956–962.
- Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016.

Available from: <u>https://goldcopd.org/</u> (Accessed: 25.07.18)

- Goto, Y. (2017) 'Renal rehabilitation in occupational therapy for patients with chronic kidney disease'. Physical Medicine and Rehabilitation Research, 2(5), pp. 1–3.
- Grant, I., Heaton, R., Mcsweeny A., Adams, K. and Timms, R. (1982) 'Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease', Archives of Internal Medicine, 142, pp. 1470–1776.
- Hall, P. and Marteau, T. (2014) 'Executive function in the context of chronic disease prevention: Theory, research and practice', Preventive Medicine. Elsevier Inc., 68, pp. 44–50.
- Hopkins, R., Shaver, K. and Weinstock, R. (2016) 'Management of adults with diabetes and cognitive problems', Diabetes Spectrum, 29(4), pp. 224–237.
- Hynninen, K., Breitve, M., Wiborg, A., Pallsen, S. and Nordus, I. (2005) 'Psychological characteristics of patients with chronic obstructive pulmonary disease: a review.', Journal of Psychosomatic Research, 59(6), pp. 429–443.
- Incalzi, R., Gemma, A., Marra, C., Capparella, O., Fuso, L. and Carbonin, P. (1997) 'Verbal Memory Impairment in COPD', Chest, 112(6), pp. 1506–1513.

- Karakontaki, F., Gennimata, S., Palamidas, A., Anagnostakos, T., Kosmas, E., Stalikas, A., Papageorgiou, C. and Koulouris, N. (2013) 'Driving-related neuropsychological performance in stable COPD patients', Pulmonary Medicine, 2013.
- Kirkil, G., Tug, T., Ozel, E., Bulut, S., Tekatas, A. and Muz, M. (2007) 'The evaluation of cognitive functions with P300 test for chronic obstructive pulmonary disease patients in attack and stable period', Clinical Neurology and Neurosurgery, 109(7), pp. 553–560.
- Lahousse, L., Tiemeier, H., Ikram, M. and Brusselle, G. (2015) 'Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review', Respiratory Medicine, 109, pp. 1371–1380
- Lezak, M., Howieson, D., Bigler, E. and Tranel, D. (2012) Neuropsychological Assessment. 5th edn. New York: Oxford University Press.
- Liesker, J., Postma, D., Beukema, R., ten Hacken, N., van der Molen, T., Riemersma, R., van Zomeren, E. and Kerstjens, H. (2004) 'Cognitive performance in patients with COPD', Respiratory Medicine, 98(4), pp. 351–356.
- McNicholas, W. (2016) 'Chronic obstructive pulmonary disease and obstructive sleep apnoeathe overlap syndrome.', Journal of Thoracic Disease, 8(2), p. 236–242.

- Ortapamuk, H. and Naldoken, S. (2006) 'Brain perfusion abnormalities in chronic obstructive pulmonary disease: Comparison with cognitive impairment', Annals of Nuclear Medicine, 20(2), pp. 99–106.
- Paola, M., Bozzali, M., Fadda, L., Musicco, M., Sabatini, U. and Caltagirone, C. (2008) 'Reduced oxygen due to high-altitude exposure relates to atrophy in motor-function brain areas', European Journal of Neurology, 15(10), pp. 1050–1057.
- Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., Britten, N. Roen, and K. Duffy, S. (2006) 'Guidance on the Conduct of Narrative Synthesis in Systematic Reviews', A Product from the ESRC Methods Programme, (April 2006), pp. 211–219.
- Ryu, C., Jahng, G., Choi, C., Rhee, H., Kim, M., Kim, S., Kim, E. and Choi, W. (2013) 'Microstructural change of the brain in chronic obstructive pulmonary disease: A voxelbased investigation by MRI', COPD: Journal of Chronic Obstructive Pulmonary Disease, 10(3), pp. 357–366.
- Schou, L., Østergaard, B., Rasmussen, L., Rydahl-Hansen, S. and Phanareth, K. (2012) 'Cognitive dysfunction in patients with chronic obstructive pulmonary disease A systematic review', Respiratory Medicine. Elsevier Ltd, 106(8), pp. 1071–1081.

Shim, T., Lee, J., Kim, S., Lim, T., Kim, S., Kim, D. and Kim, W. (2001) 'Cerebral Metabolic Abnormalities in COPD Patients Detected by Localized Proton Magnetic Resonance Spectroscopy', Chest, 120(5), pp. 1506–1513.

SIGN, (2008) Methodology checklist 4: case-control studies. Available at: <u>http://www.sign.ac.uk/checklists-and-notes.html</u>. (Accessed: 26.7.18)

- Snell, N., Strachan, D., Hubbard, R., Gibson, J., Gruffydd-Jones, K. and Jarrold, I. (2016) 'S32 Epidemiology of COPD in the UK: Findings from the British Lung Foundation's "Respiratory Health of the Nation" Project', Thorax, 71(Suppl 3), p. A20.1-A20.
- Spilling, C., Jones, P., Dodd, J. and Barrick, T. (2017) 'White matter lesions characterise brain involvement in moderate to severe chronic obstructive pulmonary disease, but cerebral atrophy does not', BMC Pulmonary Medicine. BMC Pulmonary Medicine, 17(1), p. 92.
- Torres-Sánchez, I., Rodríguez-Alzueta, E., Cabrera-Martos, I., López-Torres, I., Moreno-Ramírez, M. and Valenza, M. (2015) 'Cognitive impairment in COPD: a systematic review', Jornal Brasileiro de Pneumologia, 41(2), pp. 182–190.
- Zhang, H., Wang, X., Lin, J., Sun, Y., Huang, Y., Yang, T., Zheng, S., Fan, M. and Zhang, J. (2012) 'Grey and white matter abnormalities in chronic obstructive pulmonary disease: A casecontrol study', BMJ Open, 2(2).

CHAPTER TWO: MAJOR RESEARCH PROJECT

Attention Functions in Stable Chronic Obstructive Pulmonary Disease: A Neuropsychological Case-control Study

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Prepared in accordance with authors instructions for the Journal of the International Neuropsychological Society (see Appendix 2.1)

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PLAIN ENGLISH SUMMARY

Background: Chronic Obstructive Pulmonary Disease (COPD) is an umbrella term for several conditions causing progressive and irreversible damage to the airways. There is evidence to suggest that COPD patients may experience some difficulties with processing information (cognition). A recent study explored attention in people with COPD (Klein et al., 2009). Attention is the brain's way of processing information which we take in from the environment through our senses (for example, through seeing or hearing things). There are different types of attention, the most well-known types are: how we select information from the environment to attend to; and how long we can concentrate on something. Klein et al's previous study used a tool, the Attention Network Test (Fan et al., 2002), which was developed to examine a well-known theoretical model of attention (Petersen & Posner, 1990, 2012). Klein et al. (2009) found that COPD patients performed worse than controls on certain aspects of the Attention Network Test but not all. A limitation of Klein et al's study was that it only examined patients while they were staying in hospital and were acutely unwell. There are several ways that this might influence attention and these participants would not match the majority COPD patients, as most maintain a relatively stable condition living in the community.

Objective: The current study aimed to examine whether COPD patients in a stable phase of their condition, differ in their performance on attention tasks from healthy control participants. **Methods:** Twenty-three participants with stable COPD and twenty-three healthy volunteers took part. Participants first provided some demographic information and then completed three tasks designed to examine different components of attention. The Attention Network Task involved looking at a computer screen and pressing a key, as quickly as possible, to indicate whether

arrows on the screen were pointing left or right. This test uses reaction times to examine three different aspects of attention: alerting, orienting and response inhibition. Alerting is "achieving and maintaining an alert state" and was measured by differences in reaction times depending on whether a warning cue was presented or not. Orienting is "the selection of information from sensory input" and was investigated by examining reaction times when the warning cue was presented in different locations. Response inhibition involves "resolving conflict among responses, overcoming a strong automatic response". This aspect of attention was measured by presenting the target arrow, to which the participant was to respond, accompanied by four flanking arrows. Response inhibition was measured by comparing reactions times for when the flanking arrows were pointing in the same or different direction as the target arrow. Two other tasks were used to examined response inhibition in different ways. In one, participants were asked to read aloud information from a sheet of paper as quickly as possible. The first part was colour words printed in black ink. The second part was patches of colour. The last part involved participants stating the colour of ink which colour words were printed in. For example, the correct response to "red" printed in blue ink would be "blue". The final measure of response inhibition asked participants to first complete sentences with words that made sense and then words that did not fit sensibly and were completely unrelated.

Results: The people with stable COPD who were included in this study had more difficulty maintaining alertness (alerting) and suppressing a natural and automatic response (response inhibition) than healthy volunteers. However, for most, these difficulties were mild and not statistically significant.

Conclusions: The findings of this study suggest that stable COPD patients may experience mild difficulties with some aspects of attention. For the majority of these patients, such difficulties are unlikely to have a substantial impact on their day-to-day life or ability to manage their condition. However, for a small number of individuals, attention difficulties may be severe enough to require additional support. Attention difficulties seem to be worse in COPD patients who are very unwell, in comparison to those whose condition is stable.

References

- Fan, J., Mccandliss, B., Sommer, T., Raz, A. and Posner, M. (2002) 'Testing the Efficiency and Independence of Attentional Networks', Journal of Cognitive Neuroscience, 14(3), pp. 340-347.
- Klein, M., Gauggel, S., Sachs, G., & Pohl, W. (2009). Impact of chronic obstructive pulmonary disease (COPD) on attention functions. *Respiratory Medicine*, *104*, 52–60.
- Posner, M. & Petersen, S. (1990). The Attention System of the Human Brain. Annual Review of Neuroscience, 13, 25–42.
- Petersen, S. and Posner, M. (2012) 'The Attention System of the Human Brain: 20 Years After', Annual Review of Neuroscience, 21(35), pp. 73–89.

ABSTRACT

Background: Previous studies have demonstrated some attentional difficulties in exacerbating COPD inpatients. However, such findings are of limited clinical utility and raise issues with generalisability to the majority of COPD patients whose condition is stable. This study aimed to build on, and offer a comparison to, previous investigations by examining attention functions in stable COPD.

Methods: Performance of 23 stable COPD patients and 23 matched controls were compared on three attention-based tasks: Attention Network Test, Stroop Colour-Word Task and Hayling Sentence Completion Task. Performance on these tasks was used to examine alerting and orienting attention and response inhibition.

Results: No significant differences were identified in between-group comparisons of individual subtest scores. Inspection of between-group effect sizes suggested a slight reduction in alerting and response inhibition abilities in the COPD group. However, the study was underpowered to detect effects at the level observed. Impairment analysis suggested a small-subgroup of COPD participants experienced response inhibition difficulties beyond the threshold for clinical impairment.

Conclusions: For most stable COPD patients, any attention difficulties experienced are mild and unlikely to have a notable difference on everyday functioning. However, a small sub-group may be at risk of clinically relevant levels of attentional impairment, which may influence health outcomes.

Key words: Chronic Obstructive Pulmonary Disease; Neuropsychological; Attention; Executive Function

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory condition, regarded as a leading cause of disability worldwide (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2016). Airflow limitation to the lungs, causing breathlessness, typically results from inflammatory responses to noxious environmental particles or smoking. However, the impact of this disease may not be limited only to pulmonary problems. Recent literature has aimed to examine the many factors influencing the development, progression, management and prognosis of this disease.

One thread of investigation has identified increasing evidence that people with COPD may experience some degree of cognitive dysfunction (Hynninen *et al.*, 2005; Dodd, Getov and Jones, 2010; Cleutjens *et al.*, 2014; Lahousse *et al.*, 2015; Torres-Sánchez *et al.*, 2015). To date, the prevalence of cognitive difficulties in this group remains unclear, with estimates ranging from 3.9% (Chang *et al.*, 2012) to 77% (Grant *et al.*, 1982). Cognitive dysfunction has been reported across multiple domains and, as such, a disease-specific cognitive profile has yet to be identified. Nonetheless, cognitive difficulties arising in this condition may have substantial impact on clinical outcomes such as activities of daily living (Perneczky *et al.*, 2006) and quality of life (Roncero *et al.*, 2016). Furthermore, poor medication adherence (Incalzi *et al.*, 1997) and impaired self-management abilities (Allen *et al.*, 2003) may lead to frequent exacerbations, hospital admissions and reliance on care.

The challenges to understanding cognitive difficulties in COPD arise through the multifactorial nature of the condition. Several studies have explored the pathology underlying this issue (Borson *et al.*, 2008; Dodd, Getov and Jones, 2010; Cleutjens *et al.*, 2014). Primary disease presentation of reduced lung function often leads to circulating blood-gas imbalance. Evidence suggests that hypoxemia, and to a lesser extent hypercapnia, may have a role in mediating brain dysfunction in COPD (Stuss *et al.*, 1997; Ortapamuk and Naldoken, 2006). Hypoxemia has been associated with localised reductions in cerebral perfusion, metabolic activity and neurotransmitter production (Grant *et al.*, 1982; Incalzi *et al.*, 2003; Ortapamuk and Naldoken, 2006). Inflammatory cytokines and oxidative stress are also suggested to cause systemic changes which may influence brain function in this disease (Borson *et al.*, 2008).

Increasing severity of COPD has been inconsistently linked with worsening cognitive difficulties (Schou *et al.*, 2012). Interpretation of these findings is complicated by short-term changes in symptoms. Although most COPD patients maintain long periods of a relatively stable condition, exacerbations are common. GOLD (2016) define an exacerbation as an "acute event characterised by a worsening of symptoms beyond normal day-to-day variations". Recent studies have suggested that, in comparison to those in a stable phase, exacerbating patients experience significantly more cognitive difficulties (Dodd *et al.*, 2013; López-Torres *et al.*, 2016). However, due to a lack of prospective studies, it is currently unclear whether these cognitive changes are transient or continue post-exacerbation. Co-morbidities are also the norm in COPD. Patients with the disease often present with co-existing cardiovascular disease, diabetes, stroke (Feary *et al.*, 2010), anxiety or depression (Hynninen *et al.*, 2005), each of which may exert an independent

influence on cognitive function. To adequately examine brain function in this condition it is important to include consideration of these disease-related variables and comorbidities into research design.

Given the complex pathology of this disease is dominated by reduced circulating oxygen, cognitive impairment may be expected to arise through damage or dysfunction of oxygensensitive neuroanatomical regions, namely the hippocampus, basal ganglia and frontal cerebral cortex (Paola *et al.*, 2008). In keeping with this theory, difficulties have been identified most consistently in the cognitive domains of attention (Klein *et al.*, 2009; Dodd *et al.*, 2013; Spilling *et al.*, 2017), memory (Fioravanti *et al.*, 1995; Incalzi *et al.*, 1997), processing speed (Liesker *et al.*, 2004; Borson *et al.*, 2008; Dodd *et al.*, 2013; Cleutjens *et al.*, 2017) and executive functions (Incalzi *et al.*, 2003; Dodd *et al.*, 2015; Cleutjens *et al.*, 2017; Spilling *et al.*, 2017). However, many medically-oriented studies reporting on cognitive function have examined this as a secondary outcome of interest. These investigations have lacked a theoretically driven approach to neuropsychological investigation and findings have often been inappropriately generalised.

In an investigation of COPD inpatients, Klein *et al.* (2009) utilised the Attention Network Test (ANT) (Fan *et al.*, 2002) to examine functioning of distinct attention systems proposed by Peterson and Posner (1990, 2012). Neuropsychological definitions of attention vary; however, this function is broadly viewed as the processing of information or stimuli from the environment (Lezak *et al.*, 2012). The ANT examines three different attention-based functions: alerting "achieving and maintaining an alert state"; orienting "the selection of information from sensory

input" otherwise known as selective attention; and executive control "resolving conflict among responses, overcoming a strong habitual, pre-potent response" also termed response inhibition. This previous study highlighted prolonged reaction times and significantly reduced alerting and orienting effects in COPD patients compared to controls. Despite this, no significant differences in the executive attention function of response inhibition were identified. These findings are similar to the intact response inhibition observed in a previous study examining Stroop Colour-Word Task (SCWT) performance in stable COPD patients (Liesker *et al.*, 2004). However, a more robust study, also utilising the SCWT, identified contrasting results (Cleutjens *et al.*, 2017).

Klein *et al's* (2009) study limited recruitment of COPD participants to individuals admitted to hospital during exacerbation. All task procedures were completed during the inpatient stay, when patients were medically unstable. Such sample selection introduces multiple physiological confounds which may have influenced cognitive performance. Furthermore, the conclusions drawn from inpatient studies cannot be generalised to the stable, community dwelling COPD patients who make up the majority of the population. Therefore, the current study aimed to build on the theoretically driven approach taken by Klein *et al.* (2009) to examine attention functions in a group of clearly defined stable COPD patients and healthy age-matched controls. This study offers a useful comparison to existing literature by examining alertness, orienting and response inhibition (conflict) using the ANT. Given the findings of Klein *et al.* (2009), use of additional measures of response inhibition, namely the SCWT and Hayling Sentence Completion task (HSCT), provide further exploration of this function.

Hypotheses

- 1. Performance on attention tasks will be significantly reduced in COPD patients, in comparison to controls.
 - a. On the attention network test, COPD patients will show significantly reduced alerting and orienting effects in comparison to controls and will experience a greater detrimental influence of conflicting stimuli on reaction times (response inhibition)
 - b. Compared to controls COPD patients will attain significantly lower scores on other measures of response inhibition (HSCT and SCWT).
- 2. Attention task performance will negatively correlate with increasing age, disease severity, smoking history and levels of anxiety and depression.

METHODS

Ethical Approval

Ethical approval for this study was granted by South Birmingham NRES Committee [Appendices 2.2 & 2.3]. NHS Highland and NHS Forth Valley Research and Development Departments granted management approval [Appendices 2.4 - 2.6]. Participation in the study was voluntary and all participants provided written informed consent.

Participants

Twenty-three COPD patients were recruited via respiratory care teams, in NHS Highland and NHS Forth Valley, during attendance at pulmonary rehabilitation or routine review appointments. Inclusion criteria for COPD participants were: (i) a diagnosis of COPD, (ii) COPD is considered clinically stable in accordance with GOLD (2016) guidelines (i.e. exacerbation-free for 6 weeks). Twenty-three control participants were recruited as a convenience sample from the local community. All participants were one-to-one matched for age and, where possible, gender. Exclusion criteria for all participants were: (i) history of neurological illness or event (e.g. dementia, multiple sclerosis, stroke); (ii) significant sensory impairment or co-morbid health conditions which may affect participation (e.g. visual or hearing impairment or severe motor impairment); (iii) diagnosis of major psychiatric disorder; (iv) non-native English speaker.

Justification of sample size

In their examination of COPD inpatients, Klein *et al.* (2009) found medium effect sizes in alerting and orienting effects (d = 0.48-0.61). However, Cleutjens *et al.* (2017) identified an effect size of d=0.85 on differences between stable COPD patients and controls in SCWT performance.

Consideration was given to recruitment feasibility and methodological differences within these previous investigations. Final sample size estimation was based on and the findings of Cleutjens *et al.* (2017), as this sample closely fitted the population of interest in the current study. Using G*power with power set at 0.8, alpha at 0.05 (two tailed) d = 0.85, a minimum of 23 participants per group was required. Taking a more conservative approach, the target sample size was 30 per group.

Design

A between-subjects design was used to examine differences in attention functions between COPD and control participants. A within-subjects design was used to examine the association between attention performance and: age; education; smoking pack-years; anxiety; depression; years since diagnosis; lung-function and MRC score.

Procedure

COPD participants were recruited by respiratory clinicians during routine contact. Screening, to ensure participants fit study criteria, was initially conducted by respiratory clinicians and later confirmed by the researcher. Control participants contacted the researcher using contact details on a poster and were screened at this point. A single participation appointment was held in an NHS clinic room or as a home visit. Prior to participation, all participants provided written informed consent, including granting access to most recent spirometry results for COPD patients [Appendices 2.7-2.10]. Spirometry data were collected from respiratory clinicians postparticipation. Demographic information was collected for all participants (gender, age, education, smoking history and health information). Additionally, COPD participants provided information on years of illness and current treatment. COPD patients also provided ratings of breathlessness and impact on function on a commonly used self-report measure, the Medical Research Council (MRC) Breathlessness Scale (Fletcher, 1960) [Appendix 2.12]. Subsequently all participants completed the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). This self-report measure was designed for use with non-psychiatric hospital patients. It has good reliability and validity with internal consistency of 0.8, concurrent validity of 0.6–0.8 and both specificity and sensitivity of 0.8 (Bjelland *et al.*, 2002).

All participants then performed three neuropsychological tests as described below:

Attention Network Test (ANT) (Fan et al., 2002)

The ANT is a computer-based choice reaction time (RT) task developed to examine phasic alertness, spatial selective attention and response inhibition. Through pressing corresponding buttons on a computer keyboard, participants were required to indicate whether a central arrow, presented on a screen, pointed left or right. The stimuli (one central arrow or one central arrow accompanied by four flanking arrows) appeared either above or below a fixation point. The arrows were presented under several different conditions to manipulate alerting, orienting and executive factors. There were four warning conditions (asterisk cues) indicating the imminent appearance of the target: (a) no cue (only fixation cross), (b) centre cue, (c) double cue, and (d) spatial cue. The alerting effect is calculated by subtracting double cue mean RT from no cue mean RT. The orienting effect is calculated by subtracting spatial cue.

RT. To influence level of conflict, a central target arrow was presented with flanker arrows which were congruent or incongruent with the target arrow direction. The conflict effect is calculated by subtracting congruent mean RT from incongruent mean RT. The ANT includes a practice block of 24 trials and three assessment blocks totalling 288 trials. Immediate feedback is given in the practice block (correct, incorrect, no response) but not in the assessment blocks. For further details of ANT instruction and stimuli see Appendices 2.13 and 2.14.

Hayling Sentence Completion Test (HSCT) (Burgess and Shallice, 1996)

As with the conflict component of the ANT, the HSCT aims to detect difficulties with response inhibition. It is commonly used in neuropsychological evaluation and is composed of two sections. The first section asks the participant to complete a series of sentences with a sensible, meaningful word. The participant is then required to complete a second series of sentences with an irrelevant word that does not "fit" sensibly in the sentence and is completely unrelated. Performance scores are calculated based on response time and errors made. The HSCT has been found to have good test-retest reliability (r=0.72–0.93), and internal consistency (α =0.62–0.76), in a range of patients with neurological disorders (Burgess and Shallice, 1996).

Stroop Colour-Word Task (SCWT) (Golden and Freshwater, 2002)

The SCWT is another measure of response inhibition. There are several variations of the Stroop task available. The version used in this study is the most commonly used English language format, which has three parts. In the first section participants are asked to read aloud, as quickly as possible, a page of colour-words (red, blue or green) which are printed in black ink. In the second section, participants are asked to identify patches of colours. Lastly, participants are asked to

state the colour of ink in which the colour-word is printed, the ink being a different colour to the word itself e.g. the correct response to the word "red" printed in blue ink would be "blue". There is a 45 second time limit for each section. Number of correct responses provided is taken as the raw score. An interference scores is calculated by subtracting a predicted colour-word score, based on performance in the first two sections, from the observed colour-word score. The SCWT has been found to have good test-retest reliability (r=0.73-0.89) (Golden, 1975) and a similar version of this measure has been shown to be sensitive to response inhibition difficulties in COPD patients (Cleutjens *et al.*, 2017).

Data Analysis

Distribution of all variables were examined to assess normality and descriptive statistics were calculated. For each participant ANT data was pre-processed in line with Klein *et al.* (2009) to exclude invalid or outlier trials, further details are available in Appendix 2.16. To compare variables between groups, independent-t tests or Mann-Whitney U tests were utilised as appropriate. Effect sizes were reported as Cohen's d. Impairment analysis for HSCT and SCWT was conducted in relation to published test norms. As no normative data was available for the ANT, impairment classifications were based on deviations from control group means. Cut offs for clinical impairment were as follows: HSCT (scaled score \leq 3); SCWT mild (T < 40), moderate (T < 30); ANT Accuracy (<90%); ANT overall RT and conflict effect, mild (>1SD), moderate (>2SD) above control mean; ANT alerting and orienting mild (>1SD), moderate (>2SD) below control mean. Chi-square analysis was conducted to examine between-group frequency of clinical impairment. Correlational analysis was exploratory and corrections were not made for multiple

comparisons. Due to heterogeneity in variable distributions Spearman correlations coefficients were used to examine relationships between task performance and participant characteristics. Statistical significance was accepted at p<0.05.

RESULTS

Descriptive Characteristics

Data were collected for 23 COPD and 23 control participants. Demographic and clinical characteristics of each group are outlined in Table 1. There were no significant differences in gender $x^2 = 0.093$, age (t(df 44) = -0.136), years of education (t(df 44) = -1.719), or levels of anxiety (z = -0.875) between the groups. More COPD participants had a history of smoking, and the COPD group reported significantly more smoking pack-years (number of packs per day x years smoking) (z = -5.176). Significant between-group differences were also identified in levels of depression (z = -2.722), with COPD participants self-reporting more depressive symptoms on the HADS.

Regarding disease status of COPD patients, median number of years since diagnosis was six (IQR 3 - 15). Multiple measures of disease severity were recorded. Mean FEV₁(%predicted) for these individuals was 55.0 ± 23. Severity classifications of airflow restriction (GOLD 1-4), MRC score (1-4) and combined severity grade (GOLD A-D) are also displayed in the table. Additional details for these classification systems can be found in Appendix 2.17. Overall, most COPD participants fell within the 'moderate' to 'severe' range of disease severity. The majority of COPD participants were on a treatment regimen of long-acting bronchodilators, inhaled corticosteroids and anticholinergics. Only three participants required long-term oxygen therapy.

	COPD Participants Control Participants		P value					
	(n = 23)	(n = 23)						
Age	68.9 ± 8.2	69.2 ± 9.1	0.892					
Gender			0.760					
Female	15	14						
Male	8	9						
Years of Education	13.1 ± 3.0	14.7 ± 3.3	0.093					
Smoking status & history								
Never	1 (4.3%)	12 (52.2%)	0.006*					
Former	21(91.3%)	11 (47.8%)						
Current	1 (4.3%)	0 (0%)						
Smoking pack years	37.5 [28.0 - 45.5]	0.10 [0.0 - 9.0]	<0.001*					
HADS								
Anxiety	6[3 - 7]	5[3 - 6]	0.382					
Depression	4 [3 - 9]	2[1 - 4]	0.006*					
	DISEASE SEVERITY	(COPD only n = 23)						
Lung funct	tion	Self-reported breathle	essness (MRC score)					
FEV ₁ (%predicted) 55.5 ±	23.0	·	,					
		1	2					
GOLD Classificatio	n	2	7					
1 (Mild)	1	3	6					
2 (Moderate)	12	4	8					
3 (Severe)	7							
4 (Very Severe)	3							
	GOLD combined sev	verity classification						
	(Lung funct	ion & MRC)						
	Α	2						
	В	11						
	C	0						
	D	10						
long-term ovugen therenu	12	Long-term beta-2-agonist						
Long torm antichalinarsies	12	Combination compound	(ICC + I ARA) 70					
Systemic Corticostoroide	03 17	Theonhylling						
Inhaled Corticosteroids (ICG	12 12	Mucolytic	ອ າງ					
Short-term Bronchodilators	5 78	Leukotriene antagonist	9					

Table 1: Participant Demographic and Clinical Information

Note: values are mean ± standard deviation, median [lower-upper interquartile range] or n. p values for Gender and Smoking Status were computed using chi-square and yates' chi square respectively. *statistically significant difference between COPD and control participants.

Group Comparisons of Attention Task Performance

Table 2 summarises between-group comparisons of attention task performance. Although COPD participants generally performed poorer on most measures of attention, none of these differences reached statistically significance. Notably, the COPD group scores covered larger ranges in the SCWT, HSCT and ANT RTs. All effect sizes fell within the small to medium range. Largest effect sizes, indicating reduced performance in the COPD group compared to controls, were identified in alerting (d = -0.52), raw total HSCT scores (d = -0.49) and SCWT (d= -0.44).

Table 3 details the frequency of clinical levels of impairments identified in each group. Chi-square analysis indicated significantly more COPD participants were observed as having mild impairment on the SCWT. No other significant differences were noted and comparable proportions of each group were impaired across the majority of remaining measures. For both COPD and control groups, several participants demonstrated response inhibition errors suggestive of impairment on the HCST. More COPD participants than controls were considered impaired on ANT accuracy, alerting and conflict, although it is unclear whether these findings are clinically important.

	COPD	Control	p-value	Effect size	
	(n = 23)	(n = 23)		(95% confidence interval)	
<u>SCWT</u>					
Colour-Word	43.7 ± 9.8	47.3 ± 5.7	0.144	-0.44	
Interference (T score)				(-1.03 to 0.14)	
нѕст					
Time 1 SS ^a	5.96 ± 0.56	6.13 ± 0.55	0.294	-0.31	
				(-0.89 to 0.28)	
Time 2 SS ^a	6 13 + 0 55	6 17 + 0 78	0 828	-0.06	
	0.10 2 0.00	0.17 2 0.70	0.020	(-0.64 to 0.52)	
a ia ash		1			
Converted Errors SS [®]	6 [2-8]	7 [6 - 7]	0.360	-0.27	
Total (sum of SS) ^b	18 [15 - 20]	19 [18 - 20]	0.103	-0.49	
cob			0.054		
Total SS ⁻	6 [5 - 7]	6 [6 - 7]	0.251	-0.34	
ΔΝΤ					
Overall RT(ms) ^a	769.6 ± 102.1	757.0 ± 86.9	0.654	0.13	
a u a caub				(-0.45 to 0.71)	
Overall Accuracy (%) [°]	98.6 [96.5 – 99.3]	99.0 [94.8 – 99.7]	0.732	-0.10	
Relative Alerting ^a	2.98 ± 4.7	5.41 ± 4.6	0.084	-0.52	
No cue (ms)	785 9 + 98 9	780 2 + 89 2		(-1.11 to 0.07)	
Double cue (ms)	764 2 +106 3	739 6 + 89 8			
	707.2 ±100.3	, 55.0 ± 65.0			
Relative Orienting ^a	5.85 ± 4.4	6.3 ± 5.2	0.778	-0.09	
				(-0.67 to 0.49)	
Centre cue (ms)	771.7 ± 96.2	763.1 ± 93.0			
Spatial cue (ms)	728.7 ± 110.0	714.6± 80.4			
Relative Conflict ^b	21 0 [17 8 <u>-</u> 24 E]	19 6 [17 4 - 22 9]	0 / / 9	-0.22	
	21.0 [17.0 - 24.5]	19.0 [17.4 - 23.8]	0.440	-0.22	
Incongruent (ms)	897 [851 – 1014]	874 [811 – 967]			
Congruent (ms)	745.3 [702 - 795]	718 [687 - 811]			

Table 2: COPD and control performance on attention tasks

Note: values are mean ± standard deviation, median [lower-upper interquartile range]. Abbreviations: SS = scaled score; RT = reaction time

Effect size given as Cohen's d. Confidence intervals provided for normally distributed data. ^a = t-test; ^b = Mann-Whitney U.

	COPD	Control	P value	Chi-square	
	(n = 23)	(n = 23)			
SCWT					
Mild	8 (34.8)	2(8.7)	0.032*	4.600	
Moderate	1(4.3)	0 (0.0)	1.000+	0.000	
HSCT Errors	8(34.8)	5(21.7)	0.326	0.965	
HSCT Total	0(0.0)	1(4.3)	1.000†	0.000	
ANT Accuracy (<90%)	2(8.7)	0(0)	0.523†	0.470	
ANT Overall RT					
Mild	3(13.0)	2(8.7)	1.000+	0.000	
Moderate	1(4.3)	1(4.3)	0.470+	0.523	
Alerting					
Mild	6(26.1)	4(17.4)	0.475	0.511	
Moderate	1 (4.3)	0(0.0)	1.000+	0.000	
Orienting					
Mild	3 (13.0)	3(13.0)	0.661†	0.192	
Moderate	1(4.3)	0(0.0)	1.000+	0.000	
Conflict					
Mild	5(21.7)	3(13.0)	0.151†	0.698	
Moderate	2 (8.7)	1(4.3)	1.000+	0.000	

Table 3: Frequency of clinical impairment

Note: Values are n (% of group) classified as clinically impaired.

p-values based on chi-square and yate's chi-square⁺.

*statistically significant

Correlational analysis

Table 4 provides a summary of exploratory correlational analyses examining relationships between participant characteristics and attention measure performance. Few significant correlations were observed. However, age (r = 0.453, p =0.03) and self-reported levels of depression (r = 0.415, p = 0.049) were found to correlate with increasing RTs in control participants. Similarly, a positive correlation was identified between years of education and ANT accuracy (r = 0.419, p = 0.047), while increased anxiety correlated with better SCWT performance (r = 0.449, p = 0.032). These relationships were not observed in COPD participants. However, a negative relationship was identified between age and ANT accuracy (r = -0.503, p = 0.009) in this target group. The orienting effect also appeared to correlate positively with length of time since diagnosis (r = 0.479, p= 0.021) and negatively with self-reported anxiety (r = -0.492, p = 0.017). However, as these analyses were not corrected for multiple correlations, caution in interpretation is required.

		SCWT	HSCT	HSCT	ANT	ANT	ANT	ANT	ANT
			Errors	Total	Grand RT	Accuracy	Alerting	Orienting	Conflict
AGE									
COPD									
	p-value	0.131	0.087	0.100	0.484	0.009*	0.862	0.183	0.441
	rho	-0.324	-0.365	-0.351	0.154	-0.530	0.038	0.288	0.169
Control	S								
	p-value	0.067	0.381	0.639	0.030*	0.295	0.796	0.127	0.791
	rho	-0.388	-0.192	-0.103	0.453	-0.228	0.057	0.328	-0.059
EDUCAT	ION								
COPD									
	p-value	0.937	0.570	0.554	0.250	0.199	0.823	0.347	0.614
	rho	0.017	0.125	0.130	-0.250	0.278	0.049	0.205	0.111
Control	S								
	p-value	0.219	0.375	0.531	0.590	0.047*	0.741	0.512	0.182
	rho	0.266	0.194	0.138	0.119	0.419	0.073	-0.144	0.288
PACK YE	ARS								
COPD									
	p-value	0.338	0.790	0.895	0.614	0.354	0.846	0.889	0.529
	rho	-0.209	0.059	0.029	0.111	-0.203	0.043	0.031	-0.138
Control	S								
	p-value	0.231	0.220	0.206	0.641	0.911	0.332	0.149	0.105
	rho	0.260	0.266	0.274	-0.103	-0.025	-0.212	-0.311	-0.347
ANXIET	Y								
COPD									
	p-value	0.749	0.403	0.687	0.637	0.285	0.295	0.017*	0.698
	rho	-0.071	-0.183	-0.089	0.104	0.233	0.228	-0.492	0.085
Control	S								
	p-value	0.032*	0.714	0.365	0.617	0.816	0.398	0.861	0.200
	rho	0.449	-0.081	-0.198	0.110	-0.051	-0.185	-0.039	0.278

Table 4: Correlations between measures of attention and participant characteristics

	SCWT	HSCT	HSCT	ANT	ANT	ANT	ANT	ANT
		Errors	Total	Grand RT	Accuracy	Alerting	Orienting	Conflict
DEPRESSION								
COPD								
p-value	0.404	0.546	0.606	0.248	0.138	0.682	0.626	0.479
rho	0.183	-0.133	-0.113	0.251	0.319	-0.090	-0.107	0.155
Controls								
p-value	0.723	0.637	0.177	0.049*	0.259	0.583	0.567	0.777
rho	0.078	-0.104	-0.291	0.415	-0.246	0.121	-0.126	0.063
COPD ONLY								
DURATION								
p-value	0.310	0.771	0.872	0.725	0.919	0.208	0.021*	0.987
rho	-0.221	0.064	-0.035	0.078	-0.022	-0.273	0.479	0.003
MRC								
p-value	0.387	0.556	0.457	0.161	0.856	0.203	0.359	0.555
rho	0.189	-0.129	-0.163	0.302	-0.040	-0.276	-0.200	0.130
FEV ₁ (%pred.)								
p-value	0.232	0.570	0.823	0.573	0.316	0.503	0.717	0.396
rho	-0.259	-0.125	-0.049	0.124	-0.219	-0.147	-0.080	-0.186

Note: values are spearman's rho.

*statistically significant

DISCUSSION

The current study investigated differences in attention-based performance between stable COPD participants and healthy age-matched controls. Direct comparison of individual subtest scores found no significant differences between the two groups.

Examination of ANT reaction times highlighted prolonged RTs across both groups, in comparison to the participants in Klein et al. (2009). This difference may be best explained by the impact of aging on the older samples included in the present study. Nonetheless, a smaller between-group effect size was noted. This suggests that, although COPD may generally have a slightly negative influence on response speed, the extent of response slowing seems more substantial during exacerbation. These patterns are consistent with a recent study comparing healthy controls to stable and exacerbating groups (Dodd et al., 2013). While both patient groups performed poorer than controls, processing speed in the exacerbating participants was significantly slower than the stable group. This prospective investigation also observed some improvement of these difficulties three months after exacerbation. Nevertheless, processing speed difficulties in stable cohorts have been reported previously (Liesker et al., 2004; Karakontaki et al., 2013). The SCWT has also been used to examine this function, evaluating the speed at which participants read a simple word list aloud (Liesker et al., 2004; Cleutjens et al., 2017). However, critical interpretation of this subtest highlights the confound of breathlessness on speaking rate in a COPD population. Therefore, slower reading speeds observed in this group may be independent of processing speed issues and, for this reason, the SCWT was not used for this purpose in the current study.
Compared to the findings of Klein *et al.* (2009), the small effect size of ANT accuracy suggests stable patients may make less errors than exacerbating counterparts on simple visual perception tasks. However, further examination of individual participant scores identified two patients whose accuracy rates were particularly low (<75%). As no such outliers were observed in the control group, these difficulties with response accuracy in a small sub-group of this stable sample may be noteworthy. This observation also gives weight to a previous study which demonstrated "concentration faults" in stable COPD participants on a driving-based assessment (Orth *et al.*, 2008).

Between-group effect sizes in ANT alerting were relatively equivalent to those identified in Klein *et al.* (2009). Such similar findings would suggest that COPD patients, in any disease phase, may be less vigilant than their peers and gain less benefit from alarm cues. In contrast, the current study's selective attention (orienting) results, assessed by the spatial orienting effect, differ from those of Klein *et al.* (2009). While this study of exacerbating patients demonstrated a small to medium negative effect size, the current investigation identified little between-group difference. Equivalent proportions of each group were deemed as mildly impaired on this subtask and, while performance of one COPD participant was suggestive of moderate impairment, it is unclear whether this result is clinically meaningful. Relatively intact selective attention abilities in stable COPD have also been illustrated elsewhere (Karakontaki *et al.*, 2013). These findings suggest that exacerbation may have a differential impact on spatial selective attention.

The current study utilised two additional measures, alongside the ANT conflict component, to examine response inhibition. Firstly, the substantial variability observed in individual

participant's conflict effects should be noted. The distribution of these scores, particularly for the COPD group, necessitated non-parametric analyses. Nevertheless, consistent with the findings of Klein *et al.* (2009), between-group negative effect sizes on this measure of executive attention were small. Interestingly, condition-specific accuracy analysis identified that the two COPD participants marked as impaired for overall accuracy, demonstrated very poor accuracy (<20%) and substantially prolonged RTs in the incongruent condition. Similar patterns were also observed in the HSCT with response inhibition errors indicating impairment in several participants across both groups, although impairment was slightly more common in the COPD group (34.8% vs 21.7%). Given the demographic characteristics of the sample, such high frequencies of impairment may be explained by the influence of higher education levels in the original HSCT normative sample. Alternatively, these findings may be related to age, which is not addressed in the scoring procedures of this test. As the between-group differences in occurrence of impairment are relatively small across both these measures, it is unclear whether these findings have clinical importance.

In examination of SCWT performance, a small to medium negative effect size was observed when comparing the two groups. In addition, significantly more COPD patients than controls were marked as mildly impaired on this task. Findings of other studies utilising the SCWT in stable COPD groups have been mixed. While Cleutjens *et al.* (2017) reported significantly reduced performance in COPD patients, in comparison to controls, a similar study did not support these findings (Pereira *et al.*, 2011). Notably, both Liesker *et al.* (2004) and Ryu *et al.* (2013) identified significantly diminished performance only in a sub-group of participants with severe COPD. No difficulties were reported in the moderate group. Executive attention dysfunction on the attentional switching sub-task of the Trail-making test has also been

indicated by several studies (Grant *et al.*, 1982; Liesker *et al.*, 2004; Dodd *et al.*, 2013). However, this trend did not appear to generalise to a more complex task examining drivingrelated executive abilities (Karakontaki *et al.*, 2013). These findings, taken together with those of the current study, seem to suggest that stable COPD participants may be at some increased risk of experiencing executive attention difficulties and, in particular, a small proportion may experience impairment sufficient to impact on day-to-day functioning.

However, as previously mentioned, care is required when interpreting SCWT results in respiratory groups. Most studies utilising this measure examined response inhibition as the number of correct responses in a given time, compared to age normed data. Due to the impact of breathlessness on speaking rate, this method does not adequately examine response inhibition in COPD patients. This issue was given some consideration by Cleutjens *et al.*, (2017) through calculation of an interference score, subtracting the mean score of the Colour-Word trial from the Colour and Word subtest scores. However, only the current study utilised the interference calculation recommended by Golden and Freshwater, (2002). This method accounts for individual variability in reading speed through the discrepancy between a predicted colour-word score, calculated using the previous subtest scores, and observed performance.

The main findings of the current study are insufficient to support hypothesis one. No statistically significant differences were identified in between-group comparisons of attention task performance. However, examination of effect sizes suggested reduced alerting and response inhibition in the COPD group. Furthermore, for a small subgroup, these difficulties met criteria for clinical impairment. The attention performance observed in this stable COPD cohort is somewhat discordant with patterns detected on similar tasks in an exacerbating

group (Klein *et al.*, 2009). However, consistent with this previous investigation, all effect sizes observed in the present study indicated some detrimental influence of COPD across all attention components investigated. This may suggest a graded detrimental impact of worsening health status, which differentially influences subcomponents of attention. Such patterns are supported by the findings of a prospective study (Dodd *et al.*, 2013). Interestingly, in comparison to Klein *et al.* (2009), larger negative effect sizes were observed across all measures of response inhibition. This pattern would suggest that stable COPD participants may experience greater difficulties with executive attention than exacerbating counterparts. However, the observed effect sizes on ANT conflict relatively small in both studies. Therefore, it seems likely that other measures, particularly the SCWT, may have increased sensitivity for executive attention abilities when appropriately applied in this health group.

The results of this study do little to support hypothesis two. Few correlations were identified between participant characteristics and attention scores. Despite the observation of some significant correlations in demographics and performance of the control group, these were not noted in the COPD group. This may suggest that the factors influencing attention abilities in this group may be more complex. However, few significant relationships were observed between attention task performance and disease-related variables. Therefore, based on the findings of the current study, the pathology underlying any attention-based difficulties in stable COPD patients remains unclear.

Clinical Implications

The findings of this study suggest that, for most stable COPD patients, any attention difficulties experienced are unlikely to have a meaningful impact upon everyday functioning. Therefore, routine screening of attention abilities may not be warranted in this population. However, respiratory clinicians should be aware that a small sub-group are at risk of experiencing attentional impairment. For these individuals, additional support and adaptations to routine care may aid self-management abilities and improve clinical outcomes. Allowing additional processing time and providing repetition of small chunks of information may support treatment compliance and patient's awareness of their condition. Confirmation of understanding during clinical conversations may highlight any information lost through concentration lapses. Difficulties with response inhibition may imply impaired impulse control. Clinicians should be mindful of the influence of this problem on health behaviour change. Targeted support and encouragement for lifestyle changes may prove beneficial for these individuals.

Limitations

Given the observed effect sizes, the sample size of the present study was not large enough to identify significant differences between groups. Recruitment of additional participants, as initially planned, may have led to stronger conclusions. However, examination of the largest effect size on the ANT (d = 0.52), would suggest the initial target would still be insufficient and a sample of 60 participants per group would be required. The ANT itself has some limitations, with indications that split-half reliabilities may be low for alerting and orienting effects, though moderately high for executive control (MacLeod *et al.* 2010). Participants in this study also reported mental fatigue due to the repetitive nature of this measure, this was not

addressed in experimental design. A shortened version of this test is available but has not yet been fully validated. Therefore, to allow useful comparison with the findings of Klein *et al.* (2009), the original ANT was deemed most suitable for the current investigation. The use of the HSCT may also be criticised as it has not been validated for use in a respiratory population. However, it is routinely used in neuropsychological assessments of older adults.

Limitations of the impairment analyses should also be noted. Firstly, no published norms are available for the ANT. Classification of impairment on this task was limited to deviations from control groups means. It is not possible to determine how closely these scores fit a larger sample of the general population. Furthermore, classification of impairment varied somewhat between attention measures and HSCT sten scores provide a crude classification system. A relatively low Z-score cut off (>1SD below mean) for mild impairment classification may explain why clinical levels of difficulties were identified in some controls. For this reason, Z-scores of >2SD below means were also employed to explore differences in magnitude of impairment between groups.

It should be noted that this study did not account for the influence of circulating blood gases or history of exacerbations which, as previously documented, may have a role in mediating cognitive dysfunction. However, methodological and resource constraints, in addition to problems with patient self-report, prevented the collection of this data. Lastly, recruitment for this study took place at a secondary care level despite most interventions for stable COPD being provided within primary care settings. Due to the presumed reduction in health status of the patients in this study, cognitive difficulties in primary care patients may be less likely.

Future Research

Although this investigation has taken some steps to explore the correspondence in attention functions between exacerbating and stable phases of COPD, it is not possible to effectively establish whether these findings were influenced by individual premorbid abilities. Future research should aim to address this issue by conducting prospective studies examining cognitive abilities prior to, during and post-exacerbation. Given the executive problems suggested by this study, further examination of other higher-order abilities, such as planning and self-monitoring, may highlight clinically useful implications for COPD care.

CONCLUSIONS

The current study was the first investigation to take a theoretically driven approach to examine attention functions in stable COPD. Direct comparison of individual subtest scores identified no significant between-group differences. Trends in effect sizes and frequency of impairment indicated that stable COPD patients may have some mild difficulties in attention tasks. However, a small subgroup may experience substantial impairment that negatively influences functional abilities and clinical outcomes.

REFERENCES

- Allen, S., Jain, M., Ragab, S. and Malik, N. (2003) 'Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects', Age and Ageing, 32(3), pp. 299–302.
- Bjelland, I. Dahl, A., Haug, T. and Neckelmann, D. (2002) 'The validity of the Hospital Anxiety and Depression Scale', Journal of Psychosomatic Research, 52, pp. 69–77.
- Borson, S., Scanlan, J., Friedman, S., Zuhr, E., Fields, J., Aylward, E., Mahurin, R., Richards, T., Anzai, Y., Yukawa, M. and Yeh, S. (2008) 'Modeling the impact of COPD on the brain', International Journal of COPD, 3(3), pp. 429–434.
- Burgess, P. and Shallice, T. (1996) 'Response supression, initiation and strategy use following frontal lobe lesions', Neuropsychologica, 34(4), pp. 263–272.
- Chang, S., Chen, S., McAvay, G. and Tinetti, M. (2012) 'Effect of coexisting chronic obstructive pulmonary disease and cognitive impairment on health outcomes in older adults', Journal of the American Geriatrics Society, 60(10), pp. 1839–1846.
- Cleutjens, F., Janssen, D., Ponds, R., Dijkstra, J. and Wouters, E. (2014) 'COgnitive-pulmonary disease.', BioMed research international. Hindawi Publishing Corporation, 2014, p. 697825.

Cleutjens, F., Franssen, F., Spruit, M., Vanfleteren, L., Gijsen, C., Dijkstra, J., Ponds, R.,

Wouters, E. and Janssen, D. (2017) 'Domain-specific cognitive impairment in patients with COPD and control subjects', International Journal of Chronic Obstructive Pulmonary Disease. Dove Press, Volume 12, pp. 1–11.

- Dodd, J., Charlton, R., Van Den Broek, M. and Jones, P. (2013) 'Cognitive dysfunction in patients hospitalized with acute exacerbation of COPD', Chest. The American College of Chest Physicians, 144(1), pp. 119–127.
- Dodd, J., Novotny, P., Sciurba, F. and Benzo, R. (2015) 'Executive function, survival, and hospitalization in chronic obstructive pulmonary disease: A longitudinal analysis of the national emphysema treatment trial (NETT)', Annals of the American Thoracic Society, 12(10), pp. 1473–1481.
- Dodd, J., Getov, S. and Jones, P. (2010) 'Cognitive function in COPD', European Respiratory Journal, 35(4), pp. 913–922.
- Fan, J., Mccandliss, B., Sommer, T., Raz, A. and Posner, M. (2002) 'Testing the Efficiency and Independence of Attentional Networks', Journal of Cognitive Neuroscience, 14(3), pp. 340-347.
- Feary, J., Rodrigues, L., Smith, C., Hubbard, R. and Gibson, J. (2010) 'Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: A comprehensive analysis using data from primary care', Thorax, 65(11), pp. 956–962.

- Fioravanti, M., Nacca, D., Amati, S., Buckley, A. and Bisetti, A. (1995) 'Chronic obstructive pulmonary disease and associated patterns of memory decline', Dementia, 6(1), pp. 39–48.
- Fletcher, C. (1960) 'Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis', BMJ, (2), p. 1665. Available at: <u>https://mrc.ukri.org/research/facilitiesand-resources-for-researchers/mrc-scales/mrc-dyspnoea-scale-mrc-breathlessnessscale/</u> (Accessed: 26.07.18)
- *Global Strategy for the Diagnosis, Management and Prevention of COPD*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available from: <u>https://goldcopd.org/</u> (Accessed: 25.07.18)
- Golden, C. (1975) 'The measurement of creativity by the Stroop Color and Word Task', J Pearson Assessment, 39(5), pp. 502–506.
- Golden, C. and Freshwater, S. (2002) The Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Chicago, IL: Stoelting.
- Grant, I., Heaton, R., Mcsweeny A., Adams, K. and Timms, R. (1982) 'Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease', Archives of Internal Medicine, 142, pp. 1470–1776.

- Hynninen, K., Breitve, M., Wiborg, A., Pallsen, S. and Nordus, I. (2005) 'Psychological characteristics of patients with chronic obstructive pulmonary disease: a review.', Journal of Psychosomatic Research, 59(6), pp. 429–443.
- Incalzi, R., Gemma, A., Marra, C., Capparella, O., Fuso, L. and Carbonin, P. (1997) 'Verbal Memory Impairment in COPD', Chest, 112(6), pp. 1506–1513.
- Incalzi, R., Marra, C., Giordano, A., Calcagni, M., Cappa, A., Basso, S., Pagliari, G. and Fuso, L. (2003) 'Cognitive Impairment in Chronic Obstructive Pulmonary Disease: A Neuropsychological and SPECT study', Journal of Neurology, 250, pp. 325–332.
- Karakontaki, F., Gennimata, S., Palamidas, A., Anagnostakos, T., Kosmas, E., Stalikas, A., Papageorgiou, C. and Koulouris, N. (2013) 'Driving-related neuropsychological performance in stable COPD patients', Pulmonary Medicine, 2013.
- Klein, M., Gauggel, S., Sachs, G. and Pohl, W. (2009) 'Impact of chronic obstructive pulmonary disease (COPD) on attention functions', Respiratory Medicine, 104, pp. 52–60.
- Lahousse, L., Tiemeier, H., Ikram, M. and Brusselle, G. (2015) 'Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review', Respiratory Medicine, 109, pp. 1371–1380

- Lezak, M., Howieson, D., Bigler, E. and Tranel, D. (2012) Neuropsychological Assessment. 5th edn. New York: Oxford University Press.
- Liesker, J., Postma, D., Beukema, R., ten Hacken, N., van der Molen, T., Riemersma, R., van Zomeren, E. and Kerstjens, H. (2004) 'Cognitive performance in patients with COPD', Respiratory Medicine, 98(4), pp. 351–356.
- López-Torres, I., Valenza, M., Torres-Sánchez, I., Cabrera-Martos, I., Rodriguez-Torres, J. and Moreno-Ramírez, M. (2016) 'Changes in Cognitive Status in COPD Patients Across Clinical Stages', COPD: Journal of Chronic Obstructive Pulmonary Disease, 13(3), pp. 327–332.
- Macleod, J., Lawrence, M., McConnell, M., Eskes, G., Klein, R. and Shore, D. (2010) 'Appraising the ANT: Psychometric and theoretical considerations of the Attention Network Test.', Neuropsychology, 24(5), pp. 637–651.
- Ortapamuk, H. and Naldoken, S. (2006) 'Brain perfusion abnormalities in chronic obstructive pulmonary disease: Comparison with cognitive impairment', Annals of Nuclear Medicine, 20(2), pp. 99–106.
- Orth, M. Diekmann, C., Suchan, B., Duchna, H., Widdig, W., Schultze-Werninghaus, G., Rasche, K. and Kotterba, S. (2008) 'Driving performance in patients with chronic obstructive pulmonary disease', Journal of Physiology and Pharmacology, 59 Suppl 6, pp. 539–547.

- Paola, M., Bozzali, M., Fadda, L., Musicco, M., Sabatini, U. and Caltagirone, C. (2008)
 'Reduced oxygen due to high-altitude exposure relates to atrophy in motor-function brain areas', European Journal of Neurology, 15(10), pp. 1050–1057.
- Pereira, E., Viana, C., Tauny, T., Sales, P., Lima, J. and Holanda, M. (2011) 'Improvement of cognitive function', Lung, (189), pp. 279–285.
- Perneczky, R., Pohl, C., Sorg, C., Hartmann, J., Komossa, K., Alexopoulos, P., Wagenpfeil, S. and Kurz, A. (2006) 'Complex activities of daily living in mild cognitive impairment: Conceptual and diagnostic issues', Age and Ageing, 35(3), pp. 240–245.
- Petersen, S. and Posner, M. (2012) 'The Attention System of the Human Brain: 20 years After', Annual Review of Neuroscience, 21(35), pp. 73–89.
- Posner, M. and Petersen, S. (1990) 'The Attention System of the Human Brain', Annual Review of Neuroscience, 13, pp. 25–42.
- Roncero, C. Campuzano, A., Quintano, J., Molina, J., Pérez, J. and Miravitlles, M. (2016) 'Cognitive status among patients with chronic obstructive pulmonary disease', International Journal of Chronic Obstructive Pulmonary Disease, p. 543.
- Ryu, C., Jahng, G., Choi, C., Rhee, H., Kim, M., Kim, S., Kim, E. and Choi, W. (2013) 'Microstructural change of the brain in chronic obstructive pulmonary disease: A

voxel-based investigation by MRI', COPD: Journal of Chronic Obstructive Pulmonary Disease, 10(3), pp. 357–366.

- Schou, L., Østergaard, B., Rasmussen, L., Rydahl-Hansen, S. and Phanareth, K. (2012) 'Cognitive dysfunction in patients with chronic obstructive pulmonary disease - A systematic review', Respiratory Medicine. Elsevier Ltd, 106(8), pp. 1071–1081.
- Spilling, C., Jones, P., Dodd, J. and Barrick, T. (2017) 'White matter lesions characterise brain involvement in moderate to severe chronic obstructive pulmonary disease, but cerebral atrophy does not', BMC Pulmonary Medicine. BMC Pulmonary Medicine, 17(1), p. 92.
- Stuss, D., Peterkin I., Guzman D., Guzman C. and Troyer AK. (1997) 'Chronic obstructive pulmonary disease: Effects of hypoxia on neurological and neuropsychological measures', Journal of Clinical and Experimental Neuropsychology, 19(4), pp. 515–524.
- Torres-Sánchez, I., Rodríguez-Alzueta, E., Cabrera-Martos, I., López-Torres, I., Moreno-Ramírez, M. and Valenza, M. (2015) 'Cognitive impairment in COPD: a systematic review', Jornal Brasileiro de Pneumologia, 41(2), pp. 182–190.
- Zigmond, A. and Snaith, R. (1983) 'The Hospital Anxiety and Depression Scale', Acta Psychiatry Scandanavia, 67, pp. 361–370.

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Appendix 1.1

JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY

Instructions for Contributors

Aims and Scope The Journal of the International Neuropsychological Society is the official journal of the International Neuropsychological Society, an organization of over 4,500 international members from a variety of disciplines. The Journal of the International Neuropsychological Society welcomes original, creative, high quality research papers covering all areas of neuropsychology. The focus of articles may be primarily experimental, applied, or clinical. Contributions will broadly reflect the interest of all areas of neuropsychology, including but not limited to: development of cognitive processes, brain-behavior relationships, adult and pediatric neuropsychology, neurobehavioral syndromes (such as aphasia or apraxia), and the interfaces of neuropsychology with related areas such as behavioral neurology, neuropsychiatry, genetics, and cognitive neuroscience. Papers that utilize behavioral, neuroimaging, and electrophysiological measures are appropriate.

To assure maximum flexibility and to promote diverse mechanisms of scholarly communication, the following formats are available in addition to Regular Research Articles: Brief Communications are shorter research articles; Rapid Communications are intended for "fast breaking" new work that does not yet justify a full length article and are placed on a fast review track; Neurobehavioral Grand Rounds are theoretically important and unique case studies; Critical Reviews and Short Reviews are thoughtful considerations of topics of importance to neuropsychology, including associated areas, such as functional brain imaging, genetics, neuroepidemiology, and ethical issues; Dialogues provide a forum for publishing two distinct positions on controversial issues in a point-counterpoint format; Symposia consist of several research articles linked thematically: Letters to the Editor respond to recent articles in the Journal of the International Neuropsychological Society; and Book Reviews. Critical Reviews, Dialogues, and Symposia are typically invited by the Editor-in-Chief or an Associate Editor. Book Reviews are considered but are no longer solicited.

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Brief and Rapid Communications: Maximum of 2,500 words (not including abstract, tables, figures, or references) and a 200 word abstract, with a maximum of two tables or two figures, or one table and one figure, and 20 references. Brief and Rapid Communications are shorter research articles.

Neurobehavioral Grand Rounds: Maximum of 3,500 words with an informative literature review (not including abstract, tables, figures, or references) and a 200 word abstract. Neurobehavioral Grand Rounds are unique case studies that make a significant theoretical contribution.

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Scientific Article:

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Book:

Lezak, M.D., Howieson, D.B., Bigler, E.D., Tranel, D. (2012). *Neuropsychological Assessment*. New York: Oxford University Press.

Book Chapter:

Mahone, E.M. & Slomine, B.S. (2008). Neurodevelopmental disorders. In J.E. Morgan, & J.H. Ricker (Eds.), *Textbook of Clinical Neuropsychology* (pp. 105–127). New York: Taylor & Francis.

Report at a Scientific Meeting:

Weintraub, S. (2012, June). Profiles of dementia: Neuropsychological, neuroanatomical and neuropathologic phenotypes. International Neuropsychological Society, Oslo, Norway.

Manual, Diagnostic Scheme, etc.:

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Menual Disorders (4th ed.). Washington, DC: American Psychiatric Association Press.

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Appendix 1.2

QUALITY RATING PROTOCOL

Author and year:

SECTION 1: INTERNAL VALIDITY

Study question

		Circle respo	onse	
1.1	The study addresses an appropriate and clearly	Yes	No	
	focussed question	Can't say		

Selection of subjects

1.2	The cases and controls are taken from	Yes		No
	comparable populations		Can't say	
1.3	The same exclusion criteria are used for both			
	cases and controls			
		Yes		No
	Controls will differ in one exclusion criteria with		Can't say	
	regards to disease status e.g. will not have			
	diagnosis of Chronic Obstructive Pulmonary			
	Disease or any other respiratory disease.			
1.4	Comparison is made between participants (cases			
	and controls) and non-participants (eligible to			
	participate but did not take part) to establish	Yes		No
	their similarities or differences.		Can't say	
1.5	Cases are clearly defined and differentiated from	Yes		No
	controls		Can't say	
1.6	It is clearly established that controls are non-	Yes		No
	cases		Can't say	

Assessment

1.7	Evidence from other sources is used to				
	demonstrate that the method of outcome	Yes	No		
	assessment is valid and reliable.	Can't say			

Confounding

1.8	The main potential confounders are identified	Yes	No
	and taken into account in the design and analysis.	Can't	say

Statistical Analysis

1.9	Confidence intervals are provided.	Yes	No

SECTION 2: OVERALL STUDY

2.1	 How well was the study done to reduce the risk of confounding or bias? High quality (++) = Majority of criteria met (6 or more yes responses). Little or no risk of bias. Results unlikely to be changed by further research. Acceptable (+) = Most of criteria met (4 or more yes responses). Some flaws in the study with an associated risk of bias. Conclusions may change in the light of other studies. Unacceptable (0) = Either most criteria not met or significant flaws relating to key aspects of study design. Conclusions likely to change in the light of further studies. 	High quality (++) Acceptable (+) Unacceptable (0)
2.2	Taking into account clinical considerations, your evaluation of the methodology used and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes No Can't say
2.3	Are the results of this study directly applicable to the patient group targeted by this review?	Yes No

<u>NOTES</u>

Add any comments on your own assessment of the study and the extent to which it answers your question. Mention any areas of uncertainty raised above.

Appendix 1.3

Data Extraction Proforma

AUTHOR:	YEAR:			
TITLE:				
STUDY CHARACERISTICS				
Purpose/aims of study:				
PARTICIPANT CHARACTERISTICS				
Type of COPD and Disease Stage:				
Age Range for COPD group:				
Age Range for Control Group:				
Gender COPD Group:				
Gender Control Group				
Matching:				
RECRUITMENT				
Number of COPD participants:				
Number of control participants:				
Recruitment method of COPD participants:				
Recruitment method of control participants:				
INCLUSION/EXCLUSION				
Inclusion criteria:				
Exclusion criteria:				
MEASURES				
What were the measures of cognitive function	on?			
RESULTS				
What type of analysis was used?				
What were the results?				
CONCLUSIONS				
What were the main findings/conclusions of	f the study?			
Limitations:				
QUALITY RATING				

GOLD Severity Assessment Guidelines

Classification	Severity of airflow limitation	FEV ₁ (% predicted)
GOLD 1	Mild	≥ 80
GOLD 2	Moderate	50 -79
GOLD 3	Severe	30 - 49
GOLD 4	Very severe	<30

Prior to 2011: Assessment solely based on degree of airflow limitation (FEV1%pred)

2011 onwards: Combined assessment of severity. Degree of airflow limitation above, in addition to number of exacerbations per year and self-report of symptoms (Medical Research Council Breathlessness Scale score)

	Characteristic	Spirometric	Exacerbations	
		classification	per year	MRC
А	Low risk	GOLD 1-2	≤ 1	0-1
	Less symptoms			
В	Low risk	GOLD 1-2	≤ 1	≥ 2
	More symptoms			
С	High risk	GOLD 3-4	≥ 2	0 -1
	Less symptoms			
D	High risk	GOLD 3-4	≥ 2	≥ 2
	More symptoms			

Appendix 1.5

Quality Rating Scores

	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.1	2.2	2.3	Yin1
Borson	Y	CS	Y	Ν	Y	CS	Y	N	N	+	Y	Y	4
Cleutjens	Y	Y	Y	N	Y	Y	Y	Y	N	++	Y	Y	7
Dodd	Y	Y	CS	Y	Y	Y	Y	Ν	Ν	++	Y	Y	6
Grant	Y	Y	CS	CS	Y	Y	CS	Ν	Ν	+	CS	Y	4
Incalzi	Y	Y	Y	Ν	Y	Ν	Y	Ν	Ν	+	Y	Y	5
Karakontaki	Y	CS	Y	Ν	Y	CS	Y	Ν	Ν	+	Y	Y	4
Liesker	Y	Y	Y	CS	Y	CS	CS	Ν	Ν	+	Y	Y	4
Ortapamuk	Y	CS	CS	CS	Y	Y	Y	Ν	Ν	+	CS	Y	4
Ryu	Y	CS	Y	Ν	Y	Y	CS	Ν	Ν	+	CS	Y	4
Spilling	Y	CS	Y	N	Y	Y	CS	N	N	+	Y	Y	4
Zhang	Y	CS	Y	N	Y	N	Y	N	N	+	Y	Y	4

Y = yes, N = No, CS = Can't say

Appendix 1.6

Cognitive domain	Test names			
Processing speed	Digit symbol/coding			
	Symbol search			
	Letter-digit substitution			
	Reaction Time to Single Visual and Acoustic Stimuli			
Attention/working memory	Digit span			
	Spatial span			
	Visual memory			
	Letter-number sequencing			
	Mental control			
	Selective attention test			
Perception	Rhythm test			
	Speech-sound perception test			
	Sensory examination			
	Tachistoscopic Traffic Test			
Language	Boston naming test			
	Aphasia screen			
Construction	Rey Complex Figure Test (Copy)			
	Coping drawings with and without landmarks			
	Tactual performance test (spatial relations)			
Motor	Tapping test			
	Groove peg board			
Memory				
Verbal	Word lists			
	Story recall/logical memory			
	Verbal paired associated			
	Verbal visual learning task			
Non-verbal	Rey Complex Figure Test			
	Visual paired associated			
	Visual reproduction			
	Figural memory			
	Tactual performance test			
Concept formation and abstract reasoning	Raven's progressive matrices			
	Temporal rule induction			
	Category test			
	Arithmetic			
Executive functions	Verbal fluency			
	Trail making test			
	Stroop task			
	Concept shifting test			
	Zoo Мар			
	Key Search			
	Permanent Attention Test			
NB: A number of different versions/variations of	many of these measures are available and were			
utilised across different studies. This table provides a simplified summary.				

Appendix 2.1

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Manuscript Preparation and Style The entire manuscript should be typed double-spaced throughout using a word processing program. Unless otherwise specified, the guideline for preparation of manuscripts is the *Publication Manual of the American Psychological Association* (6th edition) except for references with 3 or more authors (see References section). This manual may be ordered from: APA Order Dept, 750 1st St. NE, Washington, DC 20002-4242 USA.

Pages should be numbered sequentially beginning with the Title Page. The Title Page should contain the full title of the manuscript, the full names and institutional affiliations of all authors; mailing address, telephone and fax numbers, and e-mail address for the corresponding author; and the word count for the abstract and manuscript text (excluding title page, abstract, references, tables, and figures). At the top right provide a short title of up to 45 characters preceded by the lead author's last name. Example: Smith-Memory in Parkinson's Disease. This running head should be repeated at the top right of every following page.

Page 2 should include an Abstract and a list of at least six keywords or mesh terms. Note: structured abstracts must be included with papers submitted after January 1, 2014. A structured abstract must include four header labels: *Objective, Method, Results, and Conclusions.* A total of six mesh terms (http://www.nlm.nih.gov/mesh/) or keywords should be provided and should not duplicate words in the tide.

The full text of the manuscript should begin on page 3. For scientific articles, including Regular Research Articles, Brief Communications, Rapid Communications, and Symposia, the format should include a structured Abstract, Introduction, Method, Results, and Discussion. This should be followed by Acknowledgments, References, Tables, Figure Legends, Figures, and optional Appendices and Supplemental Material.

The use of abbreviations, except those that are widely used, is strongly discouraged. They should be used only if they contribute to better comprehension of the manuscript. Acronyms should be spelled out at first mention. Metric system (SI) units should be used.

Appendices and Supplemental Materials may be submitted. Appendices include material intended for print and should be included with the manuscript file. Supplementary material will appear only online and should be submitted as a separate file.

The Acknowledgements Section should include a disclosure of conflicts of interest (see above) and all sources of financial support for the paper. In documenting financial support, please provide details of the sources of financial support for all authors, including grant numbers. For example, "This work was supported by the National Institutes of Health (grant number XXXXXXX)". Multiple grant numbers should be separated by a comma and space and where research was funded by more than one agency, the different agencies should be separated by a semicolon with "and" before the final funding agency. Grants held by different authors should be identified using the authors' initials. For example, "This work was supported by the Wellcome Trust (A.B., grant numbers XXXX, YYYY), (C.D., grant number ZZZZ); the Natural Environment Research Council (E.F., grant number FFFF); and the National Institutes of Health (A.B., grant number GGGG), (E.F., grant number HHHH)."

Tables and Figures should be numbered in Arabic numerals. Figures should be numbered consecutively as they appear in the text. Figures should be twice their intended final size and authors should do their best to construct figures with notation and data points of sufficient size to permit legible photo reduction to one column of a two-column format.

Please upload figure(s) in either a .doc or .pdf format. There is no additional cost for publishing color figures. When uploading figures (color or black and white) they need only be a high enough resolution for the reviewers and editors to identify the information you are trying to convey.

The approximate position of each table and figure should be provided in the manuscript: [INSERT TABLE 1 HERE]. Tables and figures should be on separate pages. Tables should have short titles and all figure legends should be on separate pages.

References should be consistent with the Publication Manual of the American Psychological Association (6th Edition). In-text references should be cited as "... Given the critical role of the prefrontal follows: cortex (PFC) in working memory (Cohen et al., 1997; Goldman-Rakic, 1987; Perlstein et al., 2003a, 2003b) " with multiple references in alphabetical order. Another example: "...Cohen et al. (1994, 1997), Braver et al. (1997), and Jonides and Smith (1997) demonstrated ... " References cited in the text with two authors should list both names. References cited in the text with three, four, or five authors, list all authors at first mention; with subsequent citations, include only the first author's last name followed by et al. References cited in the text with six or more authors should list the first author et al. throughout. In the reference section, for works with up to seven authors, list all authors. For eight authors or more, list the first six, then ellipses followed by the last author's name. Examples of the APA reference style are as follows

Online/Electronic Journal Article with DOI:

Dikmen, S., Machamer, J., Fann, J. & Temkin, N. (2010). Rates of symptom reporting following traumatic brain injury. Journal of the International Neuropsychological Society, 16, 401–411. doi:10.1017/ S1355617710000196

Scientific Article:

Giovannetti, T., Britnell, P., Brennan, I., Siderowf, A., Grossman, M., Libon, D.J., Seidel, G.A. (2012). Everyday action impairment in Parkinson's disease dementia. Journal of the International Neuropsychological Society, 18, 787-798.

Book:

Lezak, M.D., Howieson, D.B., Bigler, E.D., Tranel, D. (2012). Neuropsychological Assessment. New York Oxford University Press.

Book Chapter:

Mahone, E.M. & Slomine, B.S. (2008). Neurodevelopmental disorders. In J.E. Morgan, & J.H. Ricker (Eds.), Textbook of Clinical Neuropsychology (pp. 105–127). New York: Taylor & Francis.

Report at a Scientific Meeting:

Weintraub, S. (2012, June). Profiles of dementia: Neuropsychological, neuroanatomical and neuropathologic phenotypes. International Neuropsychological Society, Oslo, Norway.

Manual, Diagnostic Scheme, etc.:

American Psychiatric Association (1994). Diagnostic and Statistical Manual of Mental Disorders (4th ed.), Washington, DC: American Psychiatric Association Press.

English Editing The Research and Editing Consulting Program (RECP) within the International Neuropsychological Society's International Liaison Committee is designed to provide English language editing and statistical consulting to international colleagues who wish to publish their research in English language journals. For additional information see http://www.the-ins.org/the-research-and-editingconsulting-program.

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Open Access Papers In consideration of payment of the Open Access fee specified by Cambridge University Press, the contribution will be published in the Journal of the International Neuropsychological Society within an Open Access environment, freely accessible to those who wish to browse, read, print, save, copy, display or further disseminate the contribution. Please see the Open Access Transfer of Copyright Agreement for the proper procedures at http://journals.cambridge.org/acion/displayMoreInfo? jid=INS&type=tcr. The processes will depend on your source of funding, permissions to use material owned by an outside source, etc.



West Midlands - South Birmingham Research Ethics Committee

The Old Chapel Royal Standard Place Nottingham NG1 6FS

14 August 2017

Ms Claire Alexander Trainee Clinical Psychologist NHS Highland Psychological Services New Craigs Hospital, Leachkin Road Inverness IV2 8NP

Dear Ms Alexander

Study title:	An Investigation of Attentional Functions in Stable
-	Chronic Obstructive Pulmonary Disease (COPD)
REC reference:	17/WM/0320
IRAS project ID:	229888

The Proportionate Review Sub-Committee of the West Midlands - South Birmingham Research Ethics Committee reviewed the above application on 14 August 2017.

Provisional opinion

The Sub-Committee would be content to give a favourable ethical opinion of the research, subject to clarification of the following issues and/or the following changes being made to the documentation for study participants:

- Please remove the wording regarding contacting GPs from the Health Volunteer Participant Information Sheet together with the relevant sections of the Healthy Volunteer Consent Form.
- Please reword the section 'What is the purpose of the study?' sentence six of both Participant Information Sheets to be reworded to ensure they are understandable.
- Please correct the Recruitment Email 'recruit matched health control participants' to 'recruit matched healthy control participants'

When submitting a response to the Sub-Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion/ Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

Authority to consider your response and to confirm the final opinion on behalf of the Committee has been delegated to Ms Philippa Burgon.

Please contact the REC Manager at <u>nrescommittee.westmidlands-</u> <u>southbirmingham@nhs.net</u> if you need any further clarification or would find it helpful to discuss the changes required with the lead reviewer.

The Committee will confirm the final ethical opinion within 7 days of receiving a full response. A response should be submitted by no later than 13 September 2017.

Summary of discussion at the meeting

 Informed consent process and the adequacy and completeness of participant information

The PR Sub Committee queried the necessity of informing GPs of healthy volunteer participation. Members requested the wording regarding contacting GPs be removed from the Health Volunteer Participant Information Sheet together with the relevant sections of the Healthy Volunteer Consent Form.

The PR Sub asked for the section 'What is the purpose of the study?' sentence six of both Participant Information Sheets to be reworded to ensure they are understandable.

Suitability of supporting information

The PR Sub Committee asked for the Recruitment Email to be corrected from 'recruit matched health control participants' to 'recruit matched healthy control participants'

Documents reviewed

The documents reviewed were:

Document	Version	Date
Copies of advertisement materials for research participants [Recruitment poster]	2	01 July 2017
Copies of advertisement materials for research participants [Recruitment e-mail]	1	10 July 2017
Covering letter on headed paper [Cover Letter]	1	31 July 2017
GP/consultant information sheets or letters [GP letter]	1	26 June 2017
IRAS Checklist XML [Checklist_31072017]		31 July 2017
IRAS Checklist XML [Checklist_02082017]		02 August 2017
Letters of invitation to participant [Invitation letter]	1	21 June 2017
Other [Stroop Task]	1	20 June 2017
Other [Attention Network Test]	1	20 June 2017
Other [Hayling]	1	20 June 2017
Other [Data Collection Form COPD]	1	26 June 2017

Other [Data Collection Form - Controls]		26 June 2017
Other [CV - Sue Tumbul]		12 July 2017
Participant consent form [Consent form - COPD]	2	26 June 2017
Participant consent form [Consent form - controls]	2	26 June 2017
Participant consent form [Consent to contact form]	1	26 June 2017
Participant information sheet (PIS) [Information sheet - COPD]	2	01 July 2017
Participant information sheet (PIS) [Information sheet - controls]	2	01 July 2017
REC Application Form [REC_Form_02082017]		02 August 2017
Referee's report or other scientific critique report [Proposal feedback]	1	13 March 2017
Referee's report or other scientific critique report [Proposal approval]	1	09 June 2017
Research protocol or project proposal [Proposal]	4	21 June 2017
Summary CV for Chief Investigator (CI) [CV - Claire Alexander (CI/student)]	1	21 June 2017
Summary CV for supervisor (student research) [CV - Jon Evans]	1	12 July 2017
Validated questionnaire [HADS]	1	20 June 2017
Validated questionnaire [MRC]	1	20 June 2017

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

17/WM/0320	Please quote this number on all correspondence	
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Yours sincerely

Professor Paula McGee Chair

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Email:	NRESCommittee.WestMidlands-SouthBirmingham@nhs.net
Enclosures:	List of names and professions of members who took part in the review
Copy to	Ms Frances Hines, NHS Highland



West Midlands - South Birmingham Research Ethics Committee

The Old Chapel Royal Standard Place Nottingham NG1 6FS

<u>Please note</u>: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

30 August 2017

Ms Claire Alexander Trainee Clinical Psychologist NHS Highland Psychological Services New Craigs Hospital, Leachkin Road Inverness IV2 8NP

Dear Ms Alexander

Study title:	An Investigation of Attentional Functions in Stable Chronic Obstructive Pulmonary Disease (COPD)
REC reference:	17/WM/0320
IRAS project ID:	229888

Thank you for your letter of 22 August 2017, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact <u>hra.studyregistration@nhs.net</u> outlining the reasons for your request.

prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	Version	Date
Copies of advertisement materials for research participants [Recruitment poster]	2	01 July 2017
Copies of advertisement materials for research participants [Recruitment e-mail]	2	18 August 2017
Covering letter on headed paper [Cover Letter]	1	31 July 2017
GP/consultant information sheets or letters [GP letter]	1	26 June 2017
Letters of invitation to participant [Invitation letter]	1	21 June 2017
Other [Stroop Task]	1	20 June 2017
Other [Attention Network Test]	1	20 June 2017
Other [Hayling]	1	20 June 2017
Other [Data Collection Form COPD]	1	26 June 2017
Other [Data Collection Form - Controls]	1	26 June 2017
Other [CV - Sue Turnbull]	1	12 July 2017
Participant consent form [Consent form - COPD]	2	26 June 2017
Participant consent form [Consent to contact form]	1	26 June 2017
Participant consent form [Consent form - controls]	2	18 August 2017
Participant information sheet (PIS) [Information sheet - COPD]	3	18 August 2017
Participant information sheet (PIS) [Information sheet - controls]	3	18 August 2017
REC Application Form [REC_Form_02082017]		02 August 2017
Referee's report or other scientific critique report [Proposal feedback]	1	13 March 2017
Referee's report or other scientific critique report [Proposal approval]	1	09 June 2017
Research protocol or project proposal [Proposal]	4	21 June 2017
Summary CV for Chief Investigator (CI) [CV - Claire Alexander (CI/student)]	1	21 June 2017
Summary CV for supervisor (student research) [CV - Jon Evans]	1	12 July 2017
Validated questionnaire [HADS]	1	20 June 2017
Validated questionnaire [MRC]	1	20 June 2017

Statement of compliance

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, <u>www.hra.nhs.uk</u> or at <u>http://www.rdforum.nhs.uk</u>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact <u>hra.studyregistration@nhs.net</u>. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers' gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/guality-assurance

We are pleased to welcome researchers and R & D staff at our RES Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/WM/0320	Please guote this number on all correspondence	

With the Committee's best wishes for the success of this project.

Yours sincerely

Professor Paula Chair	McGee
Email:	NRESCommittee.WestMidlands-SouthBirmingham@nhs.net
Enclosures:	"After ethical review – guidance for researchers"
Copy to:	Ms Frances Hines

Appendix 2.4



Professor Angus Watson Research & Development Director NHS Highland Research & Development Office Room S101 Centre for Health Science Old Perth Road Inverness IV2 3JH



Tel: 01463 255822 Fax: 01463 255838 E-mail: angus.watson@nhs.net

05 September 2017

NHS Highland R&D ID: 1321 NRSPCC ID: NA

Ms Claire Alexander Psychological Services New Craigs Hospital, Leachkin Road Inverness IV2 8NP

Dear Ms Alexander,

Management Approval for Non-Commercial Research

I am pleased to tell you that you now have Management Approval for the research project entitled: 'An Investigation of Attention Functions in Stable COPD'. [Protocol Version 4, 21 June 2016].

I acknowledge that:

- The project is sponsored by NHS Highland.
- The project does not require external funding.
- Research Ethics approval for the project for the project has been obtained from the West Midlands – South Birmingham Research Ethics Committee (Reference Number: 17/WM/0320).
- The project is Site-Specific Assessment exempt.

The following conditions apply:

The responsibility for monitoring and auditing this project lies with NHS Highland

This study will be subject to ongoing monitoring for Research Governance purposes and may be audited to ensure compliance with the Research Governance

Headquarters: NHS Highland, Assynt House, Beechwood Park, Inverness, IV2 3HG

Chairman: David Alston Chief Executive: Elaine Mead Framework for Health and Community Care in Scotland (2006, 2nd Edition), however prior written notice of audit will be given.

- Any researchers coming into NHS Highland for the purposes of carrying out research will require the submission of a Research Passport, Occupational Health approval and Letter of Access before starting the study at this site. Please contact Anna McIver (<u>anna.mciver@nhs.net</u>) for further assistance, if this is required
- The paperwork concerning all incidents, adverse events and serious adverse events, thought to be attributable to participant's involvement in this project should be copied to the NHS Highland R&D Office. Please email documents to Anna McIver, RD&I Facilitator (anna.mciver@nhs.net).
- If applicable, monthly recruitment rates should be notified to the NHS Highland Research and Development Office, detailing date of recruitment and the participant trial ID number. This should be done by e-mail on the first week of the following month, to Debbie McDonald, Data Manager (debbie.mcdonald@nhs.net). Please quote your RD&I Highland reference number (Highland 1321).
- Please report any other changes in resources used, or staff involved in the project, to the NHS Highland Research and Development Manager, Frances Hines (01463 255822, <u>frances.hines@nhs.net</u>).

Please quote your RD&I Highland reference number (Highland 1321), on all correspondence.

1

Yours sincerely,

Frances Hines R&D Manager

cc <u>Frances Hines</u>, R&D Manager, NHS Highland Research, Development & Innovation Division, Phase 3, The Centre for Health Science, Old Perth Road, Inverness, IV2 3JH **NHS Forth Valley**

Research and Development Office Acute Division Headquarters Westburn Avenue Falkirk FK1 5SU Tel 01324 677564 Email: FV-UHB.RandD-depart@nhs.net Forth Valley



Date 10 April 2018 Your Ref Our Ref

Direct Line: 01324214690 Email: FV-UHB.RandD-depart@nhs.net

PRIVATE & CONFIDENTIAL

Ms Claire Alexander Trainee Clinical Psychologist NHS Highland **Psychological Services** New Craigs Hospital Leachkin Road Inverness IV2 8NP

Dear Ms Alexander

Letter of Access: Study title: An investigation of Attentional Functions in Stable Chronic Obstructive Pulmonary **Disease (COPD)** REC reference: 17/WM/0320 FV number: FV1092

This letter confirms your right of access to conduct research through NHS Forth Valley for the purpose and on the terms and conditions set out below. This right of access commences when you return a signed copy of this Letter and ends on 1 July 2018 unless terminated earlier in accordance with the clauses below

DETAILS OF ACCESS

You have a right of access to conduct such research as confirmed in writing in the letter of permission for research from this NHS organisation. Please note that you cannot start the research until the Chief Investigator for the research project has received a letter from us giving permission to conduct the project.

The information supplied about your role in research at NHS Forth Valley has been reviewed and you do not require an honorary research contract with this NHS organisation. We are satisfied that such pre-engagement checks as we consider necessary have been carried out. If your current role or involvement in research changes, or any of the information provided in your Research Passport changes, you must inform your employer through their normal procedures. You must also inform your nominated manager in this NHS organisation.



Chairman: Alex Linkston CBE Chief Executive: Cathie Cowan

Forth Valley NHS Board is the common name for Forth Valley Health Board Registered Office: Carseview House, Castle Business Park, Stirling, FK9 4SW

www.nhsforthvalley.com

Your activities in NHS Forth Valley under this agreement will be consenting participants, collecting demographic information and administering neuropsychological assessment measures. Your named contact for the duration of the study will be Olwyn Lamont, clinical contact and Dr Rosemary Wilson, R&D contact

CONDUCT

You must carry out your duties under this contract in accordance with policies, practices and procedures established by the Board and varied from time to time. NHS Forth Valley Board manages all research in accordance with the requirements of the Scottish Executive Research Governance Framework for Health and Community Care. While carrying out research within NHS Forth Valley you must comply with all reporting requirements, systems and duties of action put in place by the Board to deliver research governance where this is relevant to your work with the Board. You are also required to comply with all laws and statutes applicable to the performance of the study including, but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Medicines Act 1968, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical trials from time to time in force including, but not limited to, the ICH GCP and the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version). You are required to co-operate with NHS Forth Valley in discharging its duties under the Health and Safety at Work etc Act 1974 and other health and safety legislation and to take reasonable care for the health and safety of yourself and others while on NHS Forth Valley premises. You must observe the same standards of care and propriety in dealing with patients, staff, visitors, equipment and premises as is expected of any other contract holder and you must act appropriately, responsibly and professionally at all times.

You are required to ensure that all information regarding patients or staff remains secure and strictly confidential at all times. You must ensure that you understand and comply with the requirements of the NHS Confidentiality Code of Practice and the Data Protection Act 1998. Furthermore you should be aware that under the Act, unauthorised disclosure of information is an offence and such disclosures may lead to prosecution. In the course of your duties you may have access to information about staff or patients or other aspects of the Board's activities, about which you have a duty to maintain confidentiality at all times. In common with all other staff you have, in addition, a responsibility to ensure that information relating to your work and the operation of the Board in general is kept and maintained securely and you are obliged to receive, store and dispose of data in accordance with Board policies and good practice. In particular, the disclosure of commercial or other confidential information which may affect the Board's business interests or endangers the survival of any of its services will be regarded as a fundamental breach of the mutual confidence which must exist between the Board and yourself. You should seek advice from the Medical Director or the Board's Data Protection Officer if you are in any doubt whatsoever. Unauthorised disclosure or removal of information may lead to consideration of termination of the honorary appointment. You are further obligated under this agreement to report to your R&D Office contact person any infringements either by accident or otherwise which constitute a breach of confidentiality. The R&D Office contact person will then be responsible for notifying the data-protection officer for NHS Forth Valley.

You should ensure that, where you are issued with an identity or security card, a bleep number, email or library account, keys or protective clothing, these are returned upon termination of this arrangement. Please also ensure that while on the premises you wear your ID badge at all times, or are able to prove your identity if challenged. Please note that this NHS organisation accepts no responsibility for damage to or loss of personal property, with the exception of property handed over and accepted on behalf of the Board for safe custody. You are therefore advised to cover yourself against any such risk by taking out appropriate insurance.

The Board operates a "Tobacco Policy". Smoking is not permitted anywhere within Board premises, grounds or Board vehicles. Failure to comply with this policy will be considered a disciplinary matter.
While undertaking research through NHS Forth Valley you will remain accountable to your employer **NHS Highland** but you are required to follow the reasonable instructions of **Olwyn Lamont** in this NHS organisation or those given on her/his behalf in relation to the terms of this right of access.

LEGAL POSITION AND INDEMNITY

You are considered to be a legal visitor to NHS Forth Valley premises. You are not entitled to any form of payment or access to other benefits provided by this NHS organisation to employees and this letter does not give rise to any other relationship between you and this NHS organisation, in particular that of an employee. This agreement does not affect the terms and conditions of any other employment you may currently hold with another employer, who will remain responsible for you and for any disciplinary matters that may arise.

Your substantive employer will remain liable for your acts or omissions in the course of the research project covered by this letter, and must ensure they maintain appropriate indemnity insurance for this purpose. Where any third party claim is made, whether or not legal proceedings are issued, arising out of or in connection with your right of access, you are required to co-operate fully with any investigation by this NHS organisation in connection with any such claim and to give all such assistance as may reasonably be required regarding the conduct of any legal proceedings.

We may terminate your right to attend at any time either by giving seven days' written notice to you or immediately without any notice if you are in breach of any of the terms or conditions described in this letter or if you commit any act that we reasonably consider to amount to serious misconduct or to be disruptive and/or prejudicial to the interests and/or business of this NHS organisation or if you are convicted of any criminal offence. Where required by law, your employer will initiate your Independent Safeguarding Authority (ISA) registration, and thereafter, will continue to monitor your ISA registration status via the on-line ISA service. Should you cease to be ISA-registered, this letter of access is immediately terminated. Your employer will immediately withdraw you from undertaking this or any other regulated activity. You MUST stop undertaking any regulated activity.

Your substantive employer is responsible for your conduct during this research project and may in the circumstances described above instigate disciplinary action against you.

NHS Forth Valley will not indemnify you against any liability incurred as a result of any breach of confidentiality or breach of the Data Protection Act 1998. Any breach of the Data Protection Act 1998 may result in legal action against you and/or your substantive employer.

If you agree to accept this agreement on the terms indicated above, please sign the statement of acceptance and return one copy contract to me at the address above, retaining the other for your own reference. Please also forward a copy to **your academic supervisor** for your records.

Yours sincerely

Dr Rosemary Wilson Research and Development Officer cc: **NHS Forth Valley**

Carseview House Castle Business Park Stirling FK9 4SW



Telephone: Fax:

Date 10 April 2018 Your Ref Our Ref

Direct Line: 01324214690 Email: <u>FV-UHB.RandD-depart@nhs.net</u> R&D ref: FV1092

Ms Claire Alexander Trainee Clinical Psychologist NHS Highland Psychological Services New Craigs Hospital Leachkin Road Inverness IV2 8NP

Dear Ms Alexander

Study title: An investigation of Attentional Functions in Stable Chronic Obstructive Pulmonary Disease (COPD) NRES number: 17/WM/0320

Following the favourable opinion from the West Midlands-South Birmingham Research Ethics Committee on 30 August 2017, I am pleased to confirm that I formally gave Management Approval to the study above on 10 April 2018. This approval is subject to the following conditions:

• Provision of a suitable letter of access for yourself

This approval is granted subject to your compliance with the following:

1. Any amendments to the protocol or research team must have Ethics Committee and R&D approval (as well as approval from any other relevant regulatory organisation) before they can be implemented. Please ensure that the R&D Office and (where appropriate) NRS are informed of any amendments as soon as you become aware of them.

2. You and any local Principal Investigator are responsible for ensuring that all members of the research team have the appropriate experience and training, including GCP training if required.

3. If someone working within NHS Forth Valley is recruiting participants, those figures **MUST** be recorded on the EDGE research management system. If you have not used EDGE before, you should already have been offered training on the system. If recruitment is all being handled outside Forth Valley, you will be contacted monthly for the latest recruitment figures.



Chairman: Alex Linkston CBE Chief Executive: Cathie Cowan

Forth Valley NHS Board is the common name for Forth Valley Health Board Registered Office: Carseview House, Castle Business Park, Stirling, FK9 4SW

www.nhsforthvalley.com



3. All those involved in the project will be required to work within accepted guidelines of health and safety and data protection principles, any other relevant statutory legislation, UK Policy Framework for Health and Social Care Research and IHC-GCP guidelines. A copy of the Framework can be accessed at: http://www.nhsresearch%20v11.pdf

and ICH-GCP guidelines may be found at http://www.ich.org/LOB/media/MEDIA482.pdf

4. As custodian of the information collected during this project you are responsible for ensuring the security of all personal information collected in line with NHS Scotland IT security policies, until the destruction of this data.

5. You or the local Principal Investigator will be required to provide the following reports and information during the course of your study:

- A progress report annually
- Report on SAEs and SUSARs if your study is a Clinical Trial of an Investigational Medicinal Product
- Any information required for the purpose of internal or external audit and monitoring
- Copies of any external monitoring reports
- Notification of the end of recruitment and the end of the study
- A copy of the final report, when available.
- Copies of or full citations for any publications or abstracts

The appropriate forms will be provided to you by the Research and Development office when they are needed. Other information may be required from time to time.

Yours sincerely

pp MR. ANDREW MURRAY Medical Director

CC: Jonathan.evans@gla.ac.uk





Centre Number: Study Number: Patient Identification Number for this trial:

CONSENT FORM

(For those with a diagnosis of Chronic Obstructive Pulmonary Disease)

Title of Project: "An Investigation of Attentional Functions in Stable COPD"

Name of Researcher: Claire Alexander

- 1. I confirm that I have read and understand the information sheet dated (version) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
- 2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Health Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
- 4. I consent to the researchers obtaining my most recent spirometry (lung function) results from my clinical care team
- 5. I agree to take part in the above study.

Please initial box











Name of Patient	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature
If you would like your GP to be inf contact details below.	ormed of your partici	pation in the study please provide their
Name of GP Practice:		
Address:		

If you would like to receive a written summary report of the study findings, please provide details for where this should be mailed to below.

Name:

Address:

Postcode:





Centre Number: Study Number: Patient Identification Number for this trial:

CONSENT FORM

(For Healthy Volunteers)

Title of Project: "An Investigation of Attentional Functions in Stable COPD"

Name of Researcher: Claire Alexander

6. I confirm that I have read and understand the information sheet dated (version) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

- 7. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 8. I agree to take part in the above study.

Please initial box







Name of Patient	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

If you would like to receive a written summary report of the study findings, please provide details for where this should be mailed to below.

Name:	
Address:	
-	
Postcode:	





"An Investigation of Attentional Functions in Stable COPD"

Participant Information Sheet

(For those with a diagnosis of Chronic Obstructive Pulmonary Disease)

Invitation to take part in the research

You are invited to take part in a research project. We are looking for adults aged 18 and over who have a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) which is currently stable, have had no previous neurological conditions (e.g. Traumatic Brain Injury; Stroke), do not have severe sensory deficits (e.g. partial or complete blindness), and do not have other health conditions which significantly impact on their ability to engage with the tasks.

Before deciding whether you want to participate or not it is important to understand why this research is being carried out and what taking part will involve. This information is outlined below. Please take the time to read this carefully and, if you wish, discuss it with others. If there is anything that is unclear or you would like more information on, please do not hesitate to ask. Take time to decide whether you would like to take part. Thank you for taking the time to read this information sheet.

Who is conducting the research?

The research project is being conducted by Claire Alexander (Trainee Clinical Psychologist), Dr Jim Law (Clinical Psychologist, NHS Highland), Dr Sue Turnbull and Professor Jonathan Evans from the Institute of Health and Well-being at the University of Glasgow. The study is being carried out to fulfil academic requirements for the University of Glasgow's Doctorate in Clinical Psychology degree course.

What is the purpose of the study?

(i)Background

Chronic Obstructive Pulmonary Disease (COPD) is predominantly a respiratory condition. However, many people with COPD also experience several other difficulties including high blood pressure, reduced mobility and anxiety. Difficulties vary a lot between people with COPD, and not everyone has difficulties in all these areas. In this project, we are particularly interested in how COPD might impact on brain functioning (cognition). There is emerging evidence that COPD may have some impact on the brain

structure and function and this could affect how information is processed. Specifically, we are interested in a kind of brain function, attention. Attention is the brain's way of processing information which we take in from the environment through our senses (for example, through seeing or hearing things). There are different types of attention, the most well-known types are: how we select information from the environment to attend to; and how long we can concentrate on something. Previous work by other researchers has suggested that some people with COPD may have difficulties with some types of attention. However, as this research is still in its infancy it is difficult to draw helpful conclusions from these studies. Several studies have also focussed on examining cognitive functioning while COPD patients are acutely unwell and staying in hospital. For this project, we wanted to examine COPD patients whose condition is currently stable as this represents most COPD patients. Problems with cognition during a stable phase of COPD may have important implications on patient's quality of life. If we find that attention is affected in stable COPD, this may therefore help us identify strategies that help people with COPD manage their treatment and daily activities.

In this project we will measure different types of attention using a few different tasks. These will involve looking at a computer screen and responding to some visual stimuli, reading some words on a card and completing some sentences. Each of these tasks focus on particular components of attention based on established neuropsychological models of attention. In addition, we will investigate whether attention varies with disease severity and other important factors such as age or anxiety.

<u>(ii) Aims</u>

To investigate: (1) Whether individuals with stable COPD perform differently on attention tasks compared to people who do not have COPD; and (2) If there is a relationship between attention performance and other relevant factors such as disease severity.

What does taking part involve?

If you would like to take part, we will arrange a time convenient to you to come along and meet our researcher. Typically, the appointments would take place in an NHS building however if necessary it may be possible for the researcher to visit you at home.

Participation involves completing some assessment measures which, in total, will take approximately 30-60 minutes. First, we will collect some demographic information such as age and any medication you might be taking. With your permission, we would also like to access information about your most recent lung function tests. We will use this information, to see if whether your lung functioning has any relationship with your performance on the tasks. We will also ask you to complete a short questionnaire about your mood.

You will then be asked to complete three different tasks. One task will involve looking at a computer screen and responding to visual stimuli which is presented. A second task will involve reading information from a sheet of paper. The last task will involve completing several sentences which will be read out to you. With your permission, we will also inform your GP that you are participating in this study.

What are the possible benefits of taking part?

Research gives us the opportunity to improve our knowledge about various difficulties people with COPD may experience. Your participation in this study will help us increase our knowledge about cognition and attention in individuals with COPD and help us make improvements to treatment in the future.

What are the possible risks or disadvantages of taking part?

There are no significant risks or disadvantages of taking part in this study. Although we do not predict that participating in this study will cause you any distress, if this were to happen we would help you access appropriate support.

Do I have to take part?

It is up to you whether you decide to take part in this study. If you decide you want to take part, you will be given a copy of this information sheet to keep and be asked to sign a consent form. Although you will be signing the consent form, please be aware that you are free to withdraw from the study at any time. A decision to withdraw from the study or not take part at all will have absolutely no impact on the standard of care you receive.

Will my information be confidential?

All information collected about you during the study will be kept strictly confidential. If any information about you was required to leave the hospital, your name and address will be removed so that you cannot be recognised from it.

What happens to the information?

Your personal information and identity will be kept strictly confidential and known only by the researchers. Information will be stored within a locked filing cabinet in the locked Psychology Department. All information will be held in accordance to the Data Protection Act (1998), meaning that it be stored securely and not shared with other people without your permission. If any findings from this study are published, your identity will be anonymised so you are not identifiable.

What will happen to the results of the study?

At the end of the study, the finished report will be submitted to the University of Glasgow. We hope that the findings will be published in a medical journal and through other sources to make sure the general public know what the study found. If you wish, you will be sent a written summary report of the findings. Your identity and personal information will not be reported or published following this study.

Who is funding the research?

The research is funded by the Doctorate in Clinical Psychology course at the University of Glasgow.

Who has reviewed the study?

The study has been reviewed by Glasgow University to make sure that it meets standards outlined regarding scientific conduct. The Proportionate Review Sub-

Committee of the NRES Committee West-Midlands South Birmingham has also reviewed this study to make sure that it meets standards outlined regarding ethical conduct.

Who can I contact for further information?

If you would like any additional information or have any questions, please do not hesitate to contact a member of the research team on the below contact details. Alternatively, if you would like to speak to someone independent to the study please use the below contact details. Please also use the independent contact information if you wish to raise a complaint.

RESEARCH TEAM:		
Name	Role	Contact
Claire Alexander	Trainee Clinical	Drumossie Unit,
	Psychologist,	New Craigs Hospital,
	NHS Highland	Inverness,
		IV3 8NP
		Tel: 01463 704683
Dr Sue Turnbull and	Academic	University of Glasgow
Professor Jon Evans	Supervisors,	1st Floor, Administration Building,
	University of Glasgow	Gartnavel Royal Hospital,
		1055 Great Western Road, Glasgow,
		G12 0XH
		Tel: 0141 211 0607
Dr Jim Law	Field Supervisor,	Drumossie Unit,
	NHS Highland	New Craigs Hospital,
		Inverness,
		IV3 8NP
		Tel: 01463 704683

INDEPENDENT CONTACT:			
Name	Role	Contact	
Professor Thomas McMillan	Independent Contact, University of Glasgow	University of Glasgow 1st Floor, Administration Building, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH Tel: 0141 211 0607	





"An Investigation of Attentional Functions in Stable COPD"

Participant Information Sheet

(For Healthy Volunteers)

Invitation to take part in the research

You are invited to take part in a research project. This project is investigating attention in people with Chronic Obstructive Pulmonary Disease (COPD), but in addition, we need a group of healthy people with whom to compare the participants with COPD. We are looking for adults aged 18 and over who do not have a diagnosis of Chronic Obstructive Pulmonary Disease (COPD) have had no previous neurological conditions (e.g. Traumatic Brain Injury; Stroke), do not have severe sensory deficits (e.g. partial or complete blindness), and do not have other health conditions which significantly impact on their ability to engage with the tasks.

Before deciding whether you want to participate or not it is important to understand why this research is being carried out and what taking part will involve. This information is outlined below. Please take the time to read this carefully and, if you wish, discuss it with others. If there is anything that is unclear or you would like more information, please do not hesitate to ask. Take time to decide whether you would like to take part. Thank you for taking the time to read this information sheet.

Who is conducting the research?

The research project is being conducted by Claire Alexander (Trainee Clinical Psychologist), Dr Jim Law (Clinical Psychologist; NHS Highland), Dr Sue Turnbull and Professor Jonathan Evans from the Institute of Health and Well-being at the University of Glasgow. The study is being carried out to fulfil academic requirements for the University of Glasgow's Doctorate in Clinical Psychology degree course.

What is the purpose of the study?

(i)Background

Chronic Obstructive Pulmonary Disease (COPD) is predominantly a respiratory condition. However, many people with COPD also experience several other difficulties including high blood pressure, reduced mobility and anxiety. Difficulties vary a lot between people with COPD, and not everyone has difficulties in all these areas. In this project, we are particularly interested in how COPD might impact on brain functioning (cognition). There is emerging evidence that COPD may have some impact on the brain structure and function and this could affect how information is processed. Specifically, we are interested in a kind of brain function, attention. Attention is the brain's way of processing information which we take in from the environment through our senses (for example, through seeing or hearing things). There are different types of attention, the most well-known types are: how

we select information from the environment to attend to; and how long we can concentrate on something. Previous work by other researchers has suggested that some people with COPD may have difficulties with some types of attention. However, as this research is still in its infancy it is difficult to draw helpful conclusions from these studies. Several studies have also focussed on examining cognitive functioning while COPD patients are acutely unwell and staying in hospital. For this project, we wanted to examine COPD patients whose condition is currently stable as this represents most COPD patients. Problems with cognition during a stable phase of COPD may have important implications on patient's quality of life. If we find that attention is affected in stable COPD, this may therefore help us identify strategies that help people with COPD manage their treatment and daily activities.

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(ii) Aims

To investigate: (1) Whether individuals with stable COPD perform differently on attention tasks compared to people who do not have COPD; and (2) If there is a relationship between attention performance and other relevant factors such as disease severity.

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If you would like to take part, we will arrange a time convenient to you to come along and meet our researcher. Typically, the appointments would take place in an NHS building however if necessary it may be possible for the researcher to visit you at home.

Participation involves completing some assessment measures which, in total, will take approximately 30-60 minutes. First, we will collect some demographic information such as age and any medication you might be taking. We will also ask you to complete a short questionnaire about your mood.

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There are no significant risks or disadvantages of taking part in this study. Although

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Professor Thomas McMillan	Independent Contact, University of Glasgow	University of Glasgow 1st Floor, Administration Building, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow, G12 0XH Tel: 0141 211 0607	

Major Research Project Proposal

An Investigation of Attentional Functions in Stable COPD

Matriculation No: XXXXXXXX

Date of Submission: 21/06/2017

Version Number: 4

Word Count: 3,400

An Investigation of Attentional Functions in Stable COPD

Abstract

Background: There is growing evidence to suggest that patients with Chronic Obstructive Pulmonary Disease (COPD) may experience some cognitive difficulties across several different domains. Due to the complex nature of the condition and co-morbidities, the underlying pathological mechanisms influencing cognition remains unclear. In addition, variation in experimental design has led to inconsistent findings. A previous study found significant differences between COPD patients and controls in attentional functions. However, the study recruited an inpatient population of medically unwell COPD patients. **Aims:** This study aims to take a theoretically driven approach to examine of attentional and executive functions in stable COPD patients.

Methods: A between-subjects design will be used to compare cognitive performance between COPD patients and controls on the Attentional Network Task, Colour-Word Stroop Task and Hayling Sentence Completion task.

Practical applications: Clinical management of COPD may be better informed by greater awareness of cognitive abilities of COPD patients. Exploring strategies to compensate for difficulties in attention may help with treatment compliance, symptom management and quality of life.

Introduction

Chronic obstructive pulmonary disease (COPD) is an umbrella term for several conditions causing progressive and irreversible damage to the airways. These conditions predominantly include chronic bronchitis and emphysema, typically associated with inflammatory responses to noxious particles through cigarette smoking or occupational exposure (GOLD, 2016). There is growing evidence to suggest that cognitive impairments may be noted in COPD patients. Such difficulties may impair activities of daily living (Antonelli-Incalzi & Corsonello, 2008) and coexist with problems in treatment compliance (Allen et al, 2003).

Reports on the occurrence of cognitive impairment in COPD range between 3.9% (Chang et al, 2012) to 77% (Grant et al, 1982). Deficits have been suggested across multiple cognitive domains (Cleutjens et al., 2017; Dodd et al., 2010; Lahousse et al, 2015; Torres-sánchez et al., 2015). However, the research appears to have taken an exploratory approach, examining cognition as one of many disease related variables and its influence on outcomes such as admissions, rehabilitation and morbidity. While these studies have led to interesting conclusions, findings seem inconsistent and variation in experimental design has led to difficulties in interpretation.

The complexity of assessing cognitive impairment in COPD arises in the interaction of disease related variables and co-morbidities. Several studies have aimed to explore the underlying pathology of deficits noted with multifactorial models of cognitive impairment proposed (Andreou et al, 2014; Dodd et al, 2010). Primary disease presentation is reduced lung function, often leading to imbalance of circulating blood gases. Evidence suggests that hypercapnia, abnormally elevated blood carbon-dioxide level, and hypoxemia, abnormally

low blood oxygen concentration, may have a role in mediating cognitive impairment in the disease (Borson et al., 2008; Grant et al., 1987; Klein et al, 2009; Ortapamuk & Naldoken, 2006; Stuss et al, 1997). Studies have also found reduced cerebral perfusion and metabolic activity within frontal, subcortical and parietal areas during hypoxemia (Incalzi et al., 2003; Ortapamuk & Naldoken, 2006). MRI studies revealed atrophy in several brain regions including cortex, hippocampus, and striatum, suggesting that chronic hypoxemia may influence cognition through hypoxic neuronal damage (Maiti et al, 2008). In addition, hypoxemia may affect neural signalling, impacting oxygen dependent enzymes required for neurotransmitter synthesis (Grant et al, 1987).

Suggestions have been made that the physiological circumstances of COPD may induce systemic cerebral changes through oxidative stress, inflammatory cytokines and increased thrombotic factors (Borson *et al.*, 2008) and exacerbate co-existing risk of cerebral atherosclerosis, commonly related to smoking history. Co-morbid cardiovascular disease is common in COPD, occurring in more than half of hospital admissions (Fioravanti, 1995). Therefore, primary disease presentation may influence cerebrovascular risk factors, a notion supported by evidence on the influence of COPD in small vessel disease (Lahousse *et al.*, 2015). Lastly, several cognitive deficits have been noted in Obstructive Sleep Apnoea (Incalzi et al., 2003; Grant et al., 1987) frequently co-existing with COPD. It has been suggested that nocturnal hypoxemia and sleep disruption may explain shared cognitive impairment. Therefore, COPD may facilitate chronic haemodynamic imbalance.

Given such a presentation, cognitive impairment in COPD may be expected in relation to oxygen sensitive neuroanatomical regions, namely the hippocampus, basal ganglia and cerebral cortex (Paola *et al.*, 2008). To date, the literature suggests cognitive impairments in the domains of perception (Anontelli-Incalzi et al., 2006), attention (Orth *et al.*, 2006), memory (Antonelli-Incalzi & Corsonello, 2008; Fioravanti et al., 1995) and executive function (Incalzi et al, 2003; Grant et al, 1982). Yet many of these studies have lacked a theoretically driven approach to neuropsychological investigation and findings have been inappropriately generalised.

Klein et al (2009) utilised the Attentional Network Test (Fan et al, 2002) to explore attentional networks of alerting, orienting and executive control proposed by Posner and Petersen (2012). The paper defined alerting as achieving and maintaining an alert state; orienting is the selection of information from sensory input. Executive control is defined as resolving conflict among responses, overcoming a strong habitual, pre-potent response. Klein (2009) found prolonged reaction times and significant impairment in alerting and orienting in COPD patients compared to controls. No significant differences were found between groups for executive control. Similarly, a study by Liesker et al (2004) found no significant differences between controls and COPD patients on the Colour-Word Stroop Task. However, the validity of these results is unclear as the findings were adjusted based on normative data which is not identified. In contrast, a recent study, utilising a simpler scoring system found strong effect sizes of COPD on Stroop task performance (Cleutjens et al., 2017).

Therefore, there is emerging but inconsistent evidence suggesting attentional deficits may arise in COPD. However, a key criticism of Klein et al's (2009) study is its limitation of inpatient participant recruitment. There are several physiological factors which may influenced cognitive performance in such a medically unstable sample and may confound the results. Such a sampling method limits the generalisability of findings and neglects the most common, stable and community dwelling COPD population. Due to its increased influence on community outcomes, it is important that cognition in COPD is examined during stable disease stage. Therefore, the current study aims to build on the existing neuropsychological literature in COPD by examining attentional functions in community dwelling stable COPD patients.

Hypotheses

- Performance on attentional tasks will be significantly poorer in COPD patients than controls
 - a. COPD patients will show significant impairment in alerting, orienting and executive components of the attention network test in comparison to controls
 - b. COPD patients will perform poorer than controls on other measures of response inhibition (Hayling and Stroop)
 - c. Cognitive performance will negatively correlate with increasing age, disease severity and levels of anxiety and depression

Plan of Investigation

Participants

Participants will be persons with a diagnosis of COPD and control subjects matched for age and gender. The study aims to recruit 30 participants in each group. COPD patients will be recruited via community respiratory nurses. Control participants will include a convenience sample of friends/family of COPD participants and others may be recruited through NHS emails, hospital/community noticeboards.

Inclusion and Exclusion Criteria

- Inclusion criteria for COPD participants:
 - Diagnosis of COPD diagnosed prior to participation, according to GOLD
 (2016) guidelines
 - Have attended annual COPD review and completed lung function tests
 - COPD is considered clinically stable, classified in line with the GOLD (2016) strategic document
- Exclusion criteria for COPD and controls:
 - Presence of major psychiatric disorders
 - History of neurodegenerative disease or neurological disorder or event e.g.
 stroke
 - Significant sensory impairment or co-morbid health conditions which may affect participation
 - Non-native English speaker

Recruitment

Individuals who have a diagnosis of COPD, and are under the care of community respiratory nurses, will be invited to participate in the study. Participants who meet participation criteria will be informed of the study by a respiratory nurse during routine appointments. If the individual consents, the researcher will contact potential participants to provide them with more information. Arrangements will then be made for task administration. All participants will be given an information sheet outlining the project procedures.

Participants will be informed that they can withdraw from the study at any time. If they

choose to take part, participants will complete written consent forms.

Measures

Administered at appointment:

- Demographic information collection:
 - Age, gender, education, occupation, medical history, current medication,

smoking history

- Current treatment, onset and years of illness COPD patients only
- Medical Research Council Breathlessness Scale COPD patients only
- Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983)
- Attention Network Test (Fan et al., 2002)
- Hayling Sentence Completion Test (Burgess and Shallice, 1996)
- Stroop Colour-Word Test (Golden, 1978; 2002)

Collected via respiratory care team:

NHS Highland complies with GOLD (2016) COPD management guidelines, ensuring annual respiratory review via primary care. Utilising this care pathway, this study will collect up to date spirometry (lung function) data. As the participants will be under the care of respiratory nurses, it is expected that the spirometry data will be accessed via these clinicians. However, there may be a small number of cases where that data must be sought from primary care clinicians.

Design

A between-subjects design will be used to examine differences in attentional and executive functions between COPD and control participants. A within-subjects design will be used to examine the association between: lung-function; MRC score; smoking pack years; age; depression; anxiety and attention performance.

Test procedures

Informed consent will be obtained from each participant, including consent to access respiratory data.

The researcher will ensure that COPD participants have taken their respiratory treatment (e.g. bronchodilator inhaler) as prescribed, ensuring optimum respiratory functioning during testing procedures.

Demographic Information

At the task administration appointment, demographic information will be collected first. In addition, the Hospital Anxiety and Depression Scale will be completed. COPD patients will also be asked to complete the MRC breathlessness scale questionnaire.

Attention Network Test (ANT)

All participants will then be asked to complete the Attention Network Test. The ANT is a computer based reaction time task for assessing alerting, orienting and executive components of attention. Through pressing arrows on a computer keyboard, participants will be required to indicate whether an arrow presented on a screen points left or right. This arrow will be presented under several different conditions to manipulate alerting, orienting and executive factors. To examine alerting the arrow will be presented at varying delays from cue presentation. To influence orienting the arrow will be presented following varying spatial cues. To influence conflict (executive component) the arrow will be presented with flankers which are congruent or incongruent with the target arrow direction. The ANT includes a practice block then three assessment blocks. A critical appraisal of the psychometric properties of the test has been conducted by (Macleod et al., 2010). Split half reliabilities of reaction times were found to be low for alerting and orienting and moderate high for executive control. There is also some evidence to suggest that the networks examined may interact. Therefore, the ANT may be somewhat limited in examining the attentional networks proposed by Posner and Petersen. However, we would argue the ANT is useful to make comparisons with Klein (2009).

Colour-Word Stroop Task

All participants will then be asked to complete the Stroop Colour-Word Test, another measure of response inhibition. There are several variations available of the Stroop task. The version administered by Cleutjens et al (2017) is not available in English. Therefore, it is proposed that this study utilise (Golden, 1978; 2002), the most commonly used format in English, which has three parts. In the first trial participants are asked to read aloud names of colours which are printed in black ink. In the second the participants are asked to name patches of colours. Lastly, participants are asked to state the colour which the word is printed in which is different from the word itself. e.g. the correct response to the word "red" printed in blue ink would be "blue". Scoring will correspond with the method used in Cleutjen's (2017) Errors and completion time for trials are measured. The time needed for the last card will be subtracted from the mean score for the first and second cards to obtain an interference score.

Hayling Test

All participants will then be asked to complete the Hayling test. This test is made up of two parts and aims to detect difficulties with response inhibition. The first part requires the participant to complete a series of sentences with a meaningful word. Next, the participant is asked to complete the sentence with an irrelevant word that does not "fit" sensibly in the sentence.

The Hayling test has been found to have good test-retest reliability (r=0.72–0.93) and internal consistency (α =0.62–0.76) in a range of patients with neurological disorders (Burgess & Shallice, 1997).

It is estimated that testing will take approximately 30 to 60 minutes.

Data Analysis

- Descriptive statistics will be produced to describe the data.
- Independent Samples T tests, Mann-Whitney U and Chi-Square tests will be used as appropriate to compare COPD and control groups on demographic information, and to compare groups on attentional task performance.
- Pearson Correlation coefficients (r) or non-parametric equivalents will be used to explore relationships between lung function, MRC scale, HADs, age, pack years, and attention scores.

Justification of sample size

In their examination of attentional function in an inpatient COPD population, Klein et al (2009) found medium effect sizes in examining alerting and orienting (d = 0.48-0.61). Using G Power, with power set at 0.8, alpha at 0.05 (two-tailed), d=0.61, sample size estimations suggest that 44 participants per group are required. However, examining a stable outpatient COPD patients, Cleutjens et al (2017) a found an effect size of d=0.85 on Stroop Task performance. Using G power under these conditions generates a sample size requirement of 23 participants per group. We would note that the Cleutjen's(2017) sample fits more closely with the population of interest in this study. Therefore, considering recruitment feasibility and methodological variations within these previous investigations, we would conservatively propose aiming to recruit 30 participants for this study.

Settings and Equipment

Efforts will be made to ensure task administration will occur within a clinic room within NHS Highland. However, if participants are unable to travel, home visits may be necessary. The Attention Network Test is presented electronically through E-prime on a computer, it will be necessary to borrow a University laptop for this purpose.

Health and Safety

Researcher safety

Home visits will be avoided if possible. If necessary, NHS Highlands procedures and the University of Glasgow guidance on lone working procedures will be followed. Please see appendix 1 for more details.

Participant safety

The task does not involve physical exertion. However, should the participant become distressed or breathless the task will be stopped. Permission will be sought for the researcher to contact an appropriate clinician should the participant present with significant exacerbation of COPD symptoms and participation would be terminated. If the participant presents with symptoms of anxiety or other mental health concerns the researcher will signpost them to local support.

For full details of Health and Safety Issues see appendix 1.

<u>Ethics</u>

Ethical approval will also be sought through the NHS Integrated Research Approval System. Data collection, storage and analysis will occur while following the principles of the Data Protection Act (1998), NHS Highland and the University of Glasgow guidelines.

Financial Issues

For full details of expenses see appendix 2.

Timetable

For full timetable please see appendix 4.

Practical Applications

If cognitive impairment affecting attention difficulties is noted for individuals with COPD, it will be necessary to take this into consideration in clinical practice. Exploring strategies to compensate for this difficulty may help with treatment compliance, symptom management and quality of life.

References

- Allen, S. C., Jain, M., Ragab, S., & Malik, N. (2003). Acquisition and short-term retention of inhaler techniques require intact executive function in elderly subjects. Age and Ageing, 32(3), 299–302. https://doi.org/10.1093/ageing/32.3.299
- Andreou, G., Vlachos, F., & Makanikas, K. (2014). Effects of Chronic Obstructive Pulmonary Disease and Obstructive Sleep Apnea on Cognitive Functions: Evidence for a Common Nature. https://doi.org/10.1155/2014/768210
- Antonelli-Incalzi, R., & Corsonello, A. (2008). Correlation between cognitive impairment and dependence in hypoxemic COPD. Journal of Clinical and Experimental Neuropsychology, 30(2), 141–150. https://doi.org/10.1080/13803390701287390
- Antonelli-Incalzi, R., Incalzi Camillo, M., G, A., Calcagni, M. L., Cappa, A., Basso, S., ... Fuso, L. (2003). Cognitive impairment in chronic obstructive pulmonary disease A neuropsychological and spect study. J Neurol, 250, 325–332.
 https://doi.org/10.1007/s00415-003-1005-4
- Borson, S., Scanlan, J., Friedman, S., Zuhr, E., Fields, J., Aylward, E., ... Yeh, S. (2008). Modeling the impact of COPD on the brain. International Journal of COPD, 3(3), 429– 434.
- Burgess, P. W., & Shallice, T. (1996). Response supression, initiation and strategy use following frontal lobe lesions. Neuropsychologica, 34(4), 263–272. Retrieved from https://www.sissa.it/cns/Articles/BurgessHayling.pdf
- Chang, S. S., Chen, S., McAvay, G. J., & Tinetti, M. E. (2012). Effect of Co-existing Chronic Obstructive Pulmonary Disease and Cognitive Impairment on Health Outcomes in Older Adults. J Am Geriatr Soc, 60(10), 1839–1846. https://doi.org/10.1111/j.1532-

- Cleutjens, F. A., Franssen, F. M., Spruit, M. A., Vanfleteren, L. E., Gijsen, C., Dijkstra, J. B., ... Janssen, D. J. (2017). Domain-specific cognitive impairment in patients with COPD and control subjects. International Journal of Chronic Obstructive Pulmonary Disease, Volume 12, 1–11. https://doi.org/10.2147/COPD.S119633
- Dodd, J. W., Getov, S. V., & Jones, P. W. (2010). Cognitive function in COPD. European Respiratory Journal, 35(4), 913–922. https://doi.org/10.1183/09031936.00125109
- Fan, J., Mccandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the Efficiency and Independence of Attentional Networks.

Fioravanti, M., Nacca, D., Amati, S., Buckley, A. E., & Bisetti, A. (1995). Chronic obstructive pulmonary disease and associated patterns of memory decline. Dementia (Basel, Switzerland), 6(1), 39–48. Retrieved from

http://www.ncbi.nlm.nih.gov/pubmed/7728218

- GOLD. (2016). Global Initiative for Chronic Obstructive L ung D isease GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE UPDATED 2016.
- Golden, C. J. (1978). Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Chicago, IL: Stoelting Co.
- Golden, C. J., & Freshwater, S. M. (2002). The Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Chicago, IL: Stoelting.e.
- Grant, I., Heaton, R. K., Mcsweeny, A. J., Adams, K. M., & Timms, R. M. (1982). Neuropsychologic Findings in Hypoxemic Chronic Obstructive Pulmonary Disease.
- Grant, I., Prigatano, G. P., Heaton, R. K., Mcsweeny, A. J., Wright, E. C., & Adams, K. M. (1987). Progressive Neuropsychologic Impairment and Hypoxemia Relationship in Chronic Obstructive Pulmonary Disease.

- Klein, M., Gauggel, S., Sachs, G., & Pohl, W. (2009). Impact of chronic obstructive pulmonary disease (COPD) on attention functions. Respiratory Medicine, 104, 52–60. https://doi.org/10.1016/j.rmed.2009.08.008
- Lahousse, L., Tiemeier, H., Arfan Ikram, M., & Brusselle, G. G. (2015). Chronic obstructive pulmonary disease and cerebrovascular disease: A comprehensive review. Respiratory Medicine, 109, 1371–1380. https://doi.org/10.1016/j.rmed.2015.07.014
- Liesker, J. J. W., Postma, D. S., Beukema, R. J., ten Hacken, N. H. T., van der Molen, T., Riemersma, R. A., ... Kerstjens, H. A. M. (2004). Cognitive performance in patients with COPD. Respiratory Medicine, 98(4), 351–356.

https://doi.org/10.1016/j.rmed.2003.11.004

Macleod, J. W., Lawrence, M. a, McConnell, M. M., Eskes, G. a, Klein, R. M., & Shore, D. I. (2010). Appraising the ANT: Psychometric and theoretical considerations of the Attention Network Test. Neuropsychology, 24(5), 637–651. https://doi.org/10.1037/a0019803

Maiti, P., Singh, S. B., Mallick, B., Muthuraju, S., & Ilavazhagan, G. (2008). High altitude memory impairment is due to neuronal apoptosis in hippocampus, cortex and striatum. Journal of Chemical Neuroanatomy, 36(3–4), 227–238.

https://doi.org/10.1016/j.jchemneu.2008.07.003

- Ortapamuk, H., & Naldoken, S. (2006). Brain perfusion abnormalities in chronic obstructive pulmonary disease: comparison with cognitive impairment. Annals of Nuclear Medicine, 20(2), 99–106.
- Orth, M., Kotterba, S., Duchna, K., Widdig, W., Rasche, K., Schultze-Werninghaus, G., & Duchna, H.-W. (2006). Kognitive Defizite bei Patienten mit chronisch-obstruktiver Atemwegserkrankung (COPD). Pneumologie, 60(10), 593–599.

https://doi.org/10.1055/s-2006-944251

- Paola, M. D., Bozzali, M., Fadda, L., Musicco, M., Sabatini, U., & Caltagirone, C. (2008).
 Reduced oxygen due to high-altitude exposure relates to atrophy in motor-function brain areas. European Journal of Neurology, 15(10), 1050–1057.
 https://doi.org/10.1111/j.1468-1331.2008.02243.x
- Petersen, S. E., & Posner, M. I. (2012). The Attention System of the Human Brain: 20 Years After. https://doi.org/10.1146/annurev-neuro-062111-150525
- Posner, M. L., & Petersen, S. E. (1990). THE ATTENTION SYSTEM OF THE HUMAN BRAIN. Annu. Rev. Neurosci, 13, 25–42.
- Stuss, D. T., Peterkin, I., Guzman, D. A., Guzman, C., & Troyer, A. K. (1997). Chronic obstructive pulmonary disease: Effects of hypoxia on neurological and neuropsychological measures. Journal of Clinical and Experimental Neuropsychology, 19(4), 515–524. https://doi.org/10.1080/01688639708403741
- Torres-sánchez, I., Rodríguez-alzueta, E., Cabrera-martos, I., López-torres, I., Morenoramírez, M. P., & Valenza, M. C. (2015). Review Article, 41(61), 182–190.

MRC	Dyspnoea Scale
1	Breathless only with strenuous exercise
2	Short of breath when hurrying on the level or up a slight hill.
3	Slower than most people of the same age on a level surface or Have to stop when walking at my own pace on the level.
4	Stop for breath walking 100 meters or After a walking few minutes at my own pace on the level
5	Too breathless to leave the house.

ATTENTION NETWORK TASK INSTRUCTIONS:

This is an experiment investigating attention.

You will be shown an arrow on the screen pointing either to the left or right.

	\rightarrow

Your task is to press the left arrow key on your keyboard when the central arrow points left and the right arrow key when it points right.

On some trials the central arrow will be flanked by two arrows to the left and two arrows to the right.

Your task is to respond to the direction of only the <u>CENTRAL</u> arrow.



Please make sure you respond as **quickly** and **accurately** as possible.

Use your left <u>index finger</u> for the left arrow key and your right index finger for the right arrow key.

There will be a cross ("+") in the centre of the screen and the arrows will appear either above or below the cross. You should try to fixate on the cross throughout the experiment. Please do not move your eyes to the target.

On some trials there will be asterisk (*) cues indicating when or where the arrow will occur. Try to maintain fixation on the cross ("+") at all times.

The experiment contains 4 blocks

The <u>first</u> block is for <u>practice</u> and takes about 2 minutes The other three blocks are experimental blocks and each takes about 5 minutes.

After each block there will be a message "take a break" and you may take a rest.

Press the space bar to begin the next block. The whole experiment takes about 20 minutes. Any questions?

If you understand the instructions, you may start the practice session The practice trial will tell you whether your response is correct or incorrect.





Flanker conditions

Congruent



Incongruent



ANT data pre-processing procedures

Only trial data from the experimental assessment blocks were included in the analysis. Overall accuracy and condition accuracy were calculated. Subsequently incorrect trials and trials with a reaction time <200ms or >2000ms were removed. Outlier analysis was also conducted with trials above or below 2SDs of the participant specific condition mean removed. Then mean, median and SD were calculated for each individual and condition.
Appendix 2.17

GOLD Severity Assessment Guidelines

Classification	Severity of airflow limitation	FEV ₁ (% predicted)	
GOLD 1	Mild	≥ 80	
GOLD 2	Moderate	50 -79	
GOLD 3	Severe	30 - 49	
GOLD 4	Very severe	<30	

Prior to 2011: Assessment solely based on degree of airflow limitation (FEV1%pred)

2011 onwards: Combined assessment of severity. Degree of airflow limitation above, in addition to number of exacerbations per year and self-report of symptoms (Medical Research Council Breathlessness Scale score)

	Characteristic	Spirometric classification	Exacerbations per year	MRC
A	Low risk Less symptoms	GOLD 1-2	<u> </u>	0-1
В	Low risk More symptoms	GOLD 1-2	≤1	≥2
С	High risk Less symptoms	GOLD 3-4	≥ 2	0 -1
D	High risk More symptoms	GOLD 3-4	≥ 2	≥ 2