Cognitive complaints in obstructive sleep apnea

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"I wrote it for myself, but I also wrote it
for other people to inspire other people
to get through whatever kind of things they go
through in their personal lives
'cause none of us are perfect,
we're all human."

Mariah Carey

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CHAPTER 1

General Introduction

OBSTRUCTIVE SLEEP APNEA

Obstructive Sleep Apnea (OSA) is a prevalent sleep disorder characterized by repetitive interruptions of breathing due to collapse of the upper airway during sleep. These interruptions can be complete (apneas) or partial (hypopneas), lasting from 10 seconds to minutes. Such events lead to oxygen desaturation and brief arousals, shifting the sleep into lighter stages and resulting in fragmented, non-restorative sleep [1].

The severity of OSA is quantified using the apnea-hypopnea index (AHI), which is the average number of apneas and hypopneas per hour of sleep. The golden standard for diagnosing OSA is a full overnight sleep study in the form of polysomnography (PSG) [1]. During a PSG several physiological functions are measured: brain waves (elektroencephalogram, EEG), eye movements, muscle activity, heart rate, respiratory airflow and effort and blood oxygen levels. These measures are used to evaluate sleep architecture and detect sleep disruption [2].

The American Academy of Sleep Medicine (AASM) defines OSA as an AHI ≥ 15 or an AHI ≥ 5 combined with clinical symptoms[1]. The prevalence of OSA is estimated at 3-7% for men and 2-5% in women [3,4]. In the Netherlands, estimates indicate that around 2-3% of the adult population may have a diagnosed form of OSA [5], though prevalence is likely higher when undiagnosed cases are included. Importantly, some patients with an AHI < 5 may still present clinical symptoms [6], and not all patients with an AHI ≥ 15 report symptoms [4,7], suggesting that OSA exists on a continuum rather than as a discrete syndrome [8].

Obesity is a significant risk factor for OSA [9], as excess fat around the neck and upper abdomen increases the likelihood of airway collapse, especially in a supine position [10]. Other risk factors include a naturally narrow airway [11], male gender [3] and older age [12]. OSA has serious health implications, including increased risks of hypertension [13], heart attack [14], stroke [15], and type 2 diabetes [16], comparable to the risks associated with smoking [17].

Nighttime symptoms of OSA include loud snoring, gasping [18], sweating [19], nocturia [18], and nocturnal awakenings, sometimes accompanied by panic attacks [20]. The core daytime symptom is excessive sleepiness [21], leading to a higher likelihood of falling asleep at work [22] and an increased risk of motor vehicle accidents [23]. Other daytime symptoms include morning headaches [24], dry mouth [25], reduced libido [26], fatigue [27], anxiety [28], depressed mood [28] and irritability [29]. OSA patients also report complaints of memory loss [30], concentration difficulties [31] and may have cognitive impairments [32].

COGNITIVE IMPAIRMENTS IN OSA

Recent systemic reviews and meta-analysis indicate that OSA is associated with cognitive impairments across several domains, as measured by standard neuropsychological tests [33], with particular deficits in vigilance [34], attention, memory and executive functioning [32,35].

Several theories have been proposed to explain the relationship between OSA and cognitive impairments. Initial models proposed that cognitive deficits were primarily due to poor sleep quality and hypoxemia resulting from apneic events [32,36]. Disruptions in sleep quality can lead to decreased alertness and executive functioning [37], as well as impaired long-term memory formation [38] in healthy adults. In OSA, changes in sleep architecture have been linked to overall reduced cognitive performance [39]. In OSA changes in the electrical activity of the brain during sleep (as measured with EEG) are associated with impaired vigilance[40] and executive functioning [41]. Large changes in sleep cycles further correlate with memory impairments observed in OSA patients [42,43].

Hypoxemia, resulting from intermittent oxygen desaturation, can cause long-term brain damage through oxidative stress [36]. Studies have shown that white matter damage in the brain is associated with cognitive impairments in OSA [44]. However, hypoxemia alone does not account for all cognitive problems observed in OSA patients [45]. Evidence linking cognitive impairments directly to AHI or hypoxemia is inconclusive [46-48].

More recent theories propose that cognitive impairments in OSA may also stem from comorbid medical or psychiatric conditions [32,49]. OSA patients frequently have obesity [9], hypertension [13], stroke [15], diabetes [16], depression [28] or alcohol abuse [50], all of which independently contribute to cognitive impairments.

COGNITIVE COMPLAINTS IN OSA

Cognitive complaints are self-reported difficulties with cognitive functioning, rather than objective deficits measured by neuropsychological tests. As such, cognitive complaints are distinct from cognitive impairments. Although cognitive complaints can be an early indicator of dementia [51], they may also arise from medical or psychiatric conditions, such as stroke [52] or depression[53]. These complaints are also common in healthy adults [54,55], often linked to stress [56,57], sleep disturbances [58,59], anxiety [60,61], depressed mood [62] and neuroticism [63]. Among older adults, cognitive complaints are a major reason for seeking medical care [64], while in younger adults, they are associated with permanent work disability [65], increased healthcare costs [66] and reduced quality of life [67].

Cognitive complaints can be assessed through interviews or validated questionnaires including the Cognitive Failure Questionnaire (CFQ)[68] and the Behavior Rating Inventory for Executive Functioning for Adults (BRIEF-A)[69].

In OSA research, cognitive complaints have received less attention than objective cognitive impairments. Most OSA studies focus on neuropsychological testing [32], often assuming these tests capture cognitive complaints [70], which they do not. Limited studies employing cognitive complaint questionnaires indicate that, particularly in attention [31] and vigilance [71], they are more prevalent and severe in OSA compared to healthy controls, snorers [72] and patients with narcolepsy [71]. The literature on cognitive complaints related to memory and executive function in OSA remains inconclusive [30,72,73].

Cognitive complaints show a poor correlation with objective cognitive impairments in healthy adults and in various medical conditions [30,74–76]. In OSA, a disconnect between cognitive complaints and objective impairments has also been noted. For instance, OSA patients with cognitive impairments report fewer complaints than patients with mild cognitive impairment (MCI) without OSA[77]. Some studies suggest more severe cognitive impairments are associated with fewer cognitive complaints[78], while others find no correlation at all [30].

TREATMENT OF OSA

Various treatments are available for OSA including Continuous Positive Airway Pressure (CPAP), Mandibular Advancement Devices (MADs), weight loss, surgical treatments, positional therapy and hypoglossal nerve stimulation [79]. CPAP and MAD are the most recommended treatments for OSA [80]. CPAP keeps the airway open by delivering continuous pressured air through a mask during sleep [81]. CPAP effectively reduces AHI [82], subjective sleepiness [82], fatigue [83], and symptoms of depression and anxiety [84]. However, CPAP compliance is low (30-60%)[85] due to discomfort, inconvenience and claustrophobia [86]. MADs mechanically move the jaw and tongue forward to maintain an open airway during sleep [87]. Though CPAP appears slightly more effective than MADs in reducing AHI [88,89], both treatments perform equal on functional outcome measures such as subjective sleepiness[87] due to higher compliance of MAD[90]

Studies on the effect of CPAP on objective cognitive impairments indicate small improvements [91], with cognitive impairments often persisting even after successful treatment [92,93]. There are fewer studies with MAD, but results appear comparable to CPAP [88]. The impact of CPAP or MAD on cognitive complaints is unclear. The few CPAP studies that explored cognitive complaints as a patient outcome measure found that cognitive complaints persist after treatment for some, but not all patients [78,94]. The effectivity of CPAP and MAD on sleep

quality, subjective sleepiness and depressive symptoms, however, do suggest potential benefits for cognitive complaints as well.

AIMS AND OUTLINE OF DISSERTATION

The primary aim of this dissertation is to deepen the understanding of cognitive complaints in OSA, focusing on their prevalence, severity, nature and associations with factors like cognitive impairments, subjective sleepiness, anxiety, depression, fatigue and coping styles. The impact of treatment of OSA on these complaints will be evaluated as well. Although cognitive complaints do not always align with objective cognitive impairments, they strongly affect quality of life, productivity and healthcare costs. Clarifying cognitive complaints in OSA could help guide clinicians toward more personalized diagnostic and treatment approaches, when patients express concerns about their cognition.

- Chapter 2 reviews literature on cognitive complaints in OSA, comparing prevalence and characteristics to both healthy controls and other conditions. Also related factors such as sleepiness, mood and objective impairments are reviewed.
- Chapter 3 compares the prevalence and severity of cognitive complaints in OSA patients from sleep centers to other neurological and respiratory conditions. The relationship between cognitive complaints, cognitive impairments, anxiety and depression are explored across these conditions.
- Chapter 4 examines the nature and severity of cognitive complaints in patients referred to an OSA clinic for suspected OSA, compared to healthy controls. It explores associations with OSA severity, subjective sleepiness, fatigue, anxiety, depression, and objective cognitive impairments.
- Chapter 5 investigates how coping styles relate to cognitive complaints in diagnosed OSA patients.
- Chapter 6 evaluates the effect of CPAP and MAD on cognitive complaints compared to healthy controls, examining links between improvement in complaints, apnea severity, and sleepiness.
- Chapter 7 concludes with a summary, implications for clinical practice, and recommendations for future research.

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CHAPTER 2

Cognitive Complaints In Obstructive Sleep Apnea

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ABSTRACT

Obstructive sleep apnea (OSA) is associated with impairments in cognitive functioning. Although cognitive complaints are related to quality of life, work productivity and health care expenditures, most research and all reviews have focused exclusively on objective cognitive functioning so far. In this systematic review, we assessed the available literature on subjective measures of cognition in adult OSA patients. Concentration complaints were consistently found to be more severe in untreated OSA patients as compared to primary snorers and healthy controls. The same seems to be true for memory and executive function problems, but firm conclusions cannot be made as of yet, due to methodological limitations of the available studies. Cognitive complaints appear to be at least partially related to subjective sleepiness. Importantly, they are not necessarily a sign of objective cognitive impairment. Additional research is needed to explore the relation between cognitive complaints, sleepiness and mood problems using validated and norm-referenced questionnaires for cognitive complaints. In addition, the impact of CPAP treatment on cognitive complaints in OSA warrants further study.

1. INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep disorder estimated to affect up to 5% of adults in the Western world[1]. In OSA, episodes of (partial) obstruction of the upper airway cause intermittent hypoxemia and arousals during sleep[2], disrupting the sleep architecture and causing an overall poor quality of sleep. OSA results in significant impairments in daytime functioning, including excessive sleepiness, fatigue and mood problems[3]. Moreover, OSA patients often report cognitive complaints[4-6].

Cognitive functioning in OSA may be assessed objectively -using formal neuropsychological tests to assess cognitive performance- or subjectively, using self-report measures to assess daytime cognitive complaints. So far research in OSA has focussed primarily on objective cognitive functioning. Studies using objective measures of cognition in untreated OSA patients show impairments in memory function[7-10] as well as in attention and executive function [8,11-15]. Effect sizes range from moderate to large depending on the selection of cognitive tests and the control group[8,16]. Treatment with continuous positive airway pressure (CPAP) has been shown to improve performance on objective attention measures with medium effect sizes[17]. Improvements on objective measures for memory and executive function have not been found consistently, indicating that impairments in memory and executive function may persist, even after successful CPAP treatment[17,18].

Although widely used to study cognitive impairments in OSA, the ecological validity of objective measures of cognition is notoriously low[19,20]. Objective cognitive functioning often correlates poorly with cognitive complaints[21-27] and measures of quality of life[28,29]. In contrast, cognitive complaints (i.e. subjective cognitive functioning) have been found to relate to quality of life, health care utilisation and work productivity in both the general population[30-32] and several medical conditions such as cancer[22,33,34]. In OSA, subjective daytime symptoms including cognitive complaints, were shown to influence treatment compliance[35] and health service expenditures[36]. Cognitive complaints may therefore serve as an important patient outcome measure next to objective cognitive functioning.

This review will give an overview of our current knowledge of cognitive complaints in patients with OSA, including their prevalence and type in different OSA populations. In addition, possible factors associated with cognitive complaints are reviewed, including objective cognitive functioning, daytime sleepiness and mood problems.

2. METHODS

We reviewed published studies examining cognitive complaints in patients with OSA. Studies were included when adult patients were assessed (18 years and older) with OSA confirmed by polygraphy or polysomnography, in the absence of medical comorbidity, and in which cognitive complaints were measured with at least one subjective or self-report measure of cognition. Searches were limited to papers written in English. MEDLINE, Cochrane and PsychINFO databases were searched for articles from 1960 until May 2013 using the key terms "sleep apnea/OSAS/sleep disordered breathing/ sleep related breathing disorder" in combination with "cognition/memory/ attention" or "subjective/neuropsychological/cognitive/neurobehavioural" and "functioning/complaints/symptoms".

The initial search yielded 1997 hits. Titles and abstracts were scanned for the inclusion criteria. If the abstract did not provide sufficient information, a full-text version was collected in which the method section and appendices were assessed. Studies using a quality of life scale as a measure of complaints, were only included if the results from subscales or items directly related to cognition were reported separately. Only 10 studies used a measure for cognitive complaints, all of them meeting our inclusion criteria. The reference lists of these articles yielded an additional two articles. A total of 12 articles were included for the review. Data from the articles was extracted using word processing software.

To assess the quality of the included studies, we constructed a 13-item checklist (see table 1), based on quality criteria used in recent reviews on cognitive complaints in other medical populations[37,38]. Two authors (TJAV, MMS) rated each item, giving one point for each criterion fulfilled. Disagreement was solved by discussion.

Table 1. Scale for methodological quality assessment

Each items is scored 1 (present) or 0 (absent)
Study sample
A. Inclusion and exclusion criteria are reported.
B. OSA is confirmed by poly(somno)graphic evaluation.
C. OSA severity is described using polysomnographic variables (at least AHI or RDI).
D. Demographic variables of participants are described (at least age and gender).
E. If CPAP treatment is studied, dropout rates are included.
Study design:
F. Data collection is sufficiently described to replicate the study.
G. Cognitive complaints are a primary or secondary outcome measure.
H. Cognitive complaints are measured using a validated questionnaire.
I. Cognitive complaints in OSA patients are compared to at least one other group.
J. At least one factor associated with cognitive complaints is studied (objective cognitive functioning, sleepiness or mood)
Results
K. Recognized statistical techniques are used to analyze cognitive complaints.

AHI = apnea-hypopnea index; RDI = respiratory disturbance index, CPAP = continuous positive airway pressure

3. RESULTS

3.1 Included studies

3.1.1 Study characteristics

The characteristics of the included studies are summarized in table 2. OSA populations differed across studies. In two studies OSA patients were recruited from the general community [6,39-41] and in 10 studies patients were recruited in sleep centers[4,5,42-49]. Four studies compared cognitive complaints in OSA patients to healthy controls[4,5,43,49], two studies compared OSA patients to a general community sample without OSA [6,39-41] and four studies compared OSA patients to other disorders (narcolepsy[43], attention deficit hyperactive disorder, ADHD [46], primary snorers [47,48]). Two studies did not include a control group[44,45].

Six studies reported on memory complaints [4-6,42,43,49], seven studies on concentration complaints [4,6,42,46-49] and two on complaints about executive function[4,45]. Two studies only reported on cognitive complaints in general, without differentiating between specific types[41,44].

Table 2. Study characteristics

Study	Design	Primary objective	OSA Population	Comparison group	Measure	Cognitive domain		
						Memory	Attention	Executive function
Chen et al. (2012) [43]	case-control	cognitive complaints in OSA	sleep center	healthy control	SCIRS	x	x	x
Daurat et al. (2010) [44]	case-control	memory complaints in OSA	sleep center	healthy control	MIA	x		
Flemons & Reimer (1998) [45]	longitudinal, case-control	change in quality of life in OSA after CPAP	sleep center	snorers	yes/no-item	x		
							x	
Hood & Bruck (1997) [46]	case-control	memory complaints in narcolepsy	sleep center	healthy control narcolepsy	MIA	x		
Jennum & Sjol (1994)[39]	case-control	cognitive complaints in snorers and OSA	community	community without OSA	yes/no-item	x		
					yes/no-item		x	
Moore et al. (2001) [47]	descriptive, uncontrolled	PSG measures and quality of life in OSA	sleep center	-	MOS QOL*			
Mulgrew et al. (2007) [48]	longitudinal, uncontrolled	sleepiness and work limitations in OSA before and after CPAP	sleep center	-	WLQ			x
Sangal & Sangal (2004) [49]	case-control	inattention and sleepiness in OSA and ADHD	sleep center	ADHD	ADHDRS		x	
Sforza et al. (2010) [42]	cross-sectional	cognition and OSA in healthy elderly	community	community without OSA	CDS*			

Stoohs et al. (2008) [50]	case-control	clinical features of sleep disorders	sleep center	snorers OSA without sleepiness	VAS-scale	x
Ulfberg et al. (1996) [51]	case-control	sleepiness, subjective work performance in snorers and OSA	sleep center	snorers	Likert-scale	x
Vernet et al. (2011) [52]	case-control	phenotype of residual sleepiness in OSA	sleep center	healthy control	CAARS	x
					yes/no-item x	

* only assesses cognitive complaints in general, without specifying type of cognitive complaint. CAARS = conners' adult attention deficit-hyperactivity disorder rating scale; SCIRS = subjective cognitive impairment rating scale; CDS = cognitive difficulties scale (McNair-R); FLP = functional limitations profile; MIA = metamemory index for adults; MOS QOL = medical outcome study quality of life; PSG = polysomnography; WLQ = work limitations questionnaire.

3.1.2 Demographic and clinical characteristics

Demographic and clinical characteristics are summarized in table 3, with a separation between community and sleep center studies. As only two studies reported in sufficient detail on nocturnal oxygen desaturations as a marker for OSA severity [5,49], these data are not listed.

There was an important variation in sample size: the majority of studies included between 19 and 65 OSA patients. Three studies included larger numbers with Stoohs et al including an exceptional number of 1610 patients[47]. In most studies, the number of controls roughly matched the number of patients, except for the studies by Stoohs et al (OSA patients: controls 10:1)[47] and Jennum et al (OSA patients:controls 1:10)[6].

Of the two community studies, one specifically targeted elderly OSA patients (>60 years old) [40,41]. OSA severity in this study was moderate (apnea-hypopnea index [AHI]=30,4±13,1), but with notably low sleepiness scores (Epworth sleepiness scale [ESS]=6.2±3.7). The second community study included adult patients (>30 years old), but did not provide information on OSA severity. Extrapolation of the findings of the community studies should therefore be made with caution.

The average age of OSA patients from the 10 sleep center studies varied from 41 to 61 years old. Three sleep center studies did not provide information on OSA severity (either AHI, respiratory disturbance index [RDI] or ESS)[42,43,48]. The 7 studies reporting information on OSA severity showed moderate to severe OSA based on AHI (study means ranging from 21.4 to 48.9), RDI (means ranging from 25.6 to 59.2) and ESS (means ranging from 10.1 tot 16.4), indicating that representative samples of OSA patients consulting sleep centers were included.

Table 3. Demographic and clinical characteristics

Study	Group	N	Age (y)	Diagnostics	AHI (events/h)	RDI (events/h)	ESS
Community studies							
Jennum & Sjol[39]	OSA COM	65 683	30-60	PG, RDI≥5	-	-	-
Sforza et al. [42]	OSA COM	445 382	>68	PG, AHI≥15	30.4±13.1 8.7±4.1	-	6.2±3.7 5.1±3.4
Sleep center studies							
Chen et al.[43]	OSA HC	19 19	41,7±7.5 41.6±8.3	PSG, RDI>15	-	59.2±24.5	12.6±2.4 5.8±3.0
Daurat et al.[44]	OSA HC	26 27	52.7±1.5 50.6±1.2	PSG, AHI≥5	24.2±17.2		12.4±3.8 8.9±4.8
Hood & Bruck[46]	OSA HC NC	23 29 33	48.5±11.8 49.6±12.7 55.2±14.4	Sleep laboratory, not specified	-	-	-
Flemons & Reimer[45]	OSA SNR	113 50	49.5±10.6 44.9±9.9	Sleep laboratory, not specified	-	-	-
Moore et al.[47]	OSA	39	48.0±9.0	PSG, RDI>20	-	46.0±26.9	11.0±5.0
Mulgrew et al.[48]	OSA	428	49.3	PSG	21.4±22.0		10.1±5.4
Sangal & Sangal[49]	OSA ADHD	38 18	48.7±15.5 31.9±12.2	PSG, RDI>5	-	-	12.9±5.1 8.3±5.6

Table 3. Demographic and clinical characteristics (continued)

Study	Group	N	Age (y)	Diagnostics	AHI (events/h)		RDI (events/h)	ESS	
Stoohs et al.[50]	OSA	1610	51.5±11.7	PSG,RDI>5	-		25.6±20.9	9.9±4.9	
	SNR	157	48.7±11.8				2.2±1.3	5.6±3.4	
	OSA-	562	53.0±12.3				23.1±18.0	5.9±3.3	
Ulfberg et al.[51]	OSA	62	49.7	PG, ODI>6	-		-	-	
	SNR	289	47.1						
Vernet et al.[52]	OSA+	20	61.1±9.9	PSG, AHI≥15	CPAP-	CPAP+	-	CPAP-	CPAP+
	OSA-	20	61.8±9.0		40.7±17.3	2.4±2.3		15.9±5.5	16.4±3.0
	HC	20	55.6±10.0		48.9±19.0	2.7±3.9		13.2±3.4	6.2±9.2
						7.6±5.8			5.7±2.7

AHI = apnea-hypopnea Index; COM = community population without OSA; CPAP- = before CPAP treatment; CPAP+ = after CPAP treatment; ESS = Epworth sleepiness scale; HC = healthy controls; NC = narcolepsy; ODI = oxygen desaturation index; OSA- = OSA without residual sleepiness after CPAP; OSA+ = OSA with residual sleepiness after CPAP; PG = polygraphy; PSG = polysomnography; RDI = respiratory disturbance index; SNR = primary snorer.

3.1.3 Methodological study quality

For a full overview of the quality ratings of the included studies, see table 4. All studies reported in- and exclusion criteria, reported the study design in sufficient detail and included cognitive complaints as a primary or secondary outcome. The most common limitations were a lack of a validated questionnaire for cognitive complaints, and a failure to report on the relation between cognitive complaints and objective cognitive functioning, sleepiness or mood problems.

Table 4. Quality assessment of the included studies

Study	Criterion											
	A	B	C	D	E	F	G	H	I	J	K	Total
Chen et al. (2012) [4]	1	1	1	1	NA	1	1	0	1	1	1	9
Daurat et al. (2010) [5]	1	1	1	1	NA	1	1	1	1	1	1	10
Flemons & Reimer (1998) [42]	1	0	0	1	NA	1	1	0	0	0	0	4
Hood & Bruck (1997) [43]	1	0	0	1	NA	1	1	1	1	0	1	7
Jennum & Sjol (1994)[6]	1	0	0	0	NA	1	1	0	1	0	1	5
Moore et al. (2001) [44]	1	1	1	1	NA	1	1	0	0	1	1	8
Mulgrew et al. (2007) [45]	1	1	1	1	1	1	1	0	0	1	1	9
Sangal & Sangal (2004) [46]	1	1	1	0	NA	1	1	1	1	1	1	9
Sforza et al. (2010) [41]	1	0	0	1	NA	1	1	1	1	1	1	8
Stoohs et al. (2008) [47]	1	1	1	1	NA	1	1	1	1	1	1	10
Ulfberg et al. (1996) [48]	1	1	1	0	NA	1	1	0	1	0	1	7
Vernet et al. (2011) [49]	1	1	1	1	NA	1	1	1	1	1	1	10
Total	12	8	8	9	1	12	12	6	9	8	11	

NA = not applicable

3.2 Prevalence of cognitive complaints in OSA

3.2.1 Untreated OSA patients versus general community controls

Jennum and Sjol[6] found a significant higher number of OSA patients from a community sample to report concentration problems (23%) compared to a community sample without OSA (14%). The percentage of OSA patients reporting memory problems was not significantly higher (OSA 59%, non-OSA: 45%). The generalizability of the findings of this study may be limited, as no validated questionnaires were used for cognitive complaints and details on OSA severity were not provided. Flemons and Reimer[42] found 69% of OSA patients from a sleep center reporting concentration difficulties and 58%

experiencing memory problems. Unfortunately, no formal comparisons were made for these problems with their control group. Sforza et al. administered the validated cognitive difficulties scale (CDS) in an elderly community population (age over 60 years), and did not find a difference between OSA patients and subjects without OSA.[41] It should be noted however that the CDS evaluates aspects of cognition that are typically affected in dementia or stroke patients, such as praxis and temporal orientation. This may have resulted in underestimating or masking cognitive complaints more typically related to OSA.

3.2.2 Untreated OSA patients from sleep centers versus healthy controls

Findings on cognitive complaints in sleep center samples comparing OSA to healthy controls are summarized in table 5. Compared to healthy controls OSA patients were more likely to report difficulties concentrating on new tasks, performing monotonous tasks[48] and reported their life to be more impacted by problems with attention and vigilance[4]. Also OSA patients experienced more difficulties with memory, learning in general [4] and learning new tasks [48]. Findings on more specified memory complaints were inconsistent. Daurat et al.[5] found OSA patients to experience a decline in memory over time and to be more anxious about their memory compared to healthy controls. Hood and Bruck[43] could not replicate these findings however using the same questionnaire in their study design. Both studies failed to find a significant difference in subjective memory capacity between OSA patients and healthy controls. The inconsistent findings for these more specified memory complaints may be attributed to lack of statistical power in both studies due to small sample sizes (N=26 and N=23 respectively). With regard to executive function Chen et al.[4] found OSA patients to report more complaints regarding emotional control and motivation, but not regarding abstract thinking and problem solving.

3.2.3 Untreated OSA versus other disorders

Findings on OSA patients compared to other disorders are summarized in table 6. Compared to primary snorers, OSA patients reported more concentration complaints, complaints performing monotonous tasks[47,48] and complaints learning and concentrating on new tasks[48]. Compared to narcolepsy patients, OSA patients perceived their memory to have a higher capacity and experienced less memory decline over time[43]. The only study comparing OSA patients to a non-sleep disorder group found that OSA patients experienced less inattention complaints than people with ADHD[46]. It should be noted that even though a validated questionnaire was used, this questionnaire is not designed to assess general attention complaints but attention complaints typically found in ADHD.

Table 5. Cognitive complaints in OSA patients compared to healthy controls

Study	Cognitive complaints		p	Comment
concentration problems				
Chen et al.[4]	attention & vigilance	↑	.01	
Ulfberg et al.[48]	concentrating on new tasks	↑	<.05	odds ratio 7.5
	performing monotonous tasks	↑	<.05	odds ratio 20
memory complaints				
Chen et al.[4]	memory & learning	↑	.02	
Daurat et al.[5]	memory capacity		.10	
Hood & Bruck[43]			ns	
Daurat et al.[5]	memory stability	↑	.012	cohen's d=.75
Hood & Bruck[43]			ns	
Daurat et al.[5]	anxious about memory	↑	.009	cohen's d=.85
Hood & Bruck[43]			ns	
Ulfberg et al.[48]	learning new tasks	↑	<.05	odds ratio 9.1
executive function complaints				
Chen et al.[4]	emotional control & motivation	↑	0.01	
	abstract thinking & problem solving		.07	

↑ = more severe cognitive complaints compared to healthy controls; ns = non significant with no exact p-values provided in the paper.

Table 6. Cognitive complaints in untreated OSA from sleep centers compared to other disorders

Study	Comparison group	Cognitive complaint		p
Hood & Bruck[43]	narcolepsy	memory capacity	↓	<.05
		memory stability	↓	<.05
		anxious about memory		ns
Sangal & Sangal[46]	ADHD	inattention	↓	<.001
Stoohs et al.[47]	primary snorers	concentration	↑	<.001
Ulfberg et al.[48]	primary snorers	concentrating on new tasks	↑	<.05
		learning new tasks	↑	<.05
		performing monotonous tasks	↑	<.05

ADHD = attention deficit hyperactive disorder; ↑ = more severe cognitive complaints compared to comparison group; ↓ = less severe cognitive complaints compared to comparison group; ns = non significant with no exact p-values provided in the paper.

3.2.4 Cognitive complaints after CPAP-treatment

Only two studies reported on the effect of CPAP on cognitive complaints. Mulgrew et al. [45] approached 100 patients, who were prescribed CPAP, from their initial 428 OSA patients included at baseline for a two year follow-up survey. Thirty-eight of the patients completed the follow-up. After two years, 33 patients were still using CPAP (age=49, AHI=28±20, ESS=9.3) and reported less complaints with time-management ($p<.001$) and cognitive work tasks ($p<.05$). No information on OSA severity or CPAP usage was available at follow-up, nor was a control group included. However, five of the 38 patients that completed follow-up had discontinued CPAP and did not report improvements on time-management ($p=.54$) and cognitive work tasks ($p=.46$) . These findings suggest a possible positive effect of CPAP on cognitive complaints.

In contrast, a study by Vernet et al.[49] showed that cognitive complaints may remain after CPAP treatment. They compared OSA patients with residual sleepiness after CPAP (n=20, age=61±10, AHI=4±2, ESS=16±3) to patients without residual sleepiness (n=20, age=62±9, AHI=4±2, ESS=6±3) and healthy controls (n=20, age=66±10, ESS=6±3). In both OSA groups, memory complaints were significantly more frequent than in healthy controls (prevalence of 95% with residual sleepiness, and 65% without residual sleepiness). Both OSA groups also reported more inattention complaints compared to healthy controls. These data show that cognitive complaints may persist even after successful CPAP treatment.

3.3 Factors associated with cognitive complaints

Although cognitive complaints are common among OSA patients, clearly not every patient is affected to the same degree and reports the same type of cognitive dysfunction. Next, we will review possible determinants of cognitive complaints, focusing on the relation with objective cognitive functioning, daytime sleepiness and mood problems.

3.3.1 Cognitive complaints versus objective cognitive functioning

Research in healthy subjects as well as non-sleep disorder patient populations (such as cerebrovascular disease) has shown that the relation between cognitive complaints and objective cognitive functioning is often rather weak or even absent[22,24,50]. Studies in OSA patients support this finding [4,5,49]. Daurat et al.[5] did not find significant correlations between the performance on an episodic memory test and subjective ratings for memory capacity ($r=.09$, $p=.68$), subjective memory stability ($r=.08$, $p=.68$) or anxiety about memory ($r=.06$, $p=.77$). Chen et al. studied possible correlations between cognitive tests for attention, memory, and executive function and subjective ratings for attention, vigilance, memory, learning, abstract thinking, problem solving,

emotional control and motivation. [4] Of the resulting 252 Pearson correlation coefficients, none were significant. As reported earlier Vernet et al.[49] found that even after successful CPAP treatment, patients still often reported memory and inattention complaints. Interestingly, this was in the absence of objective impairments on tests for memory, attention and executive function. No correlations were calculated between subjective and objective measures of cognition in this study.

3.3.2 Cognitive complaints and sleepiness

Findings on correlations between cognitive complaints and sleepiness scores are summarized in table 7. Both Chen et al.[4] and Sangal & Sangal[46] found complaints on attention to correlate with subjective sleepiness (with r-values above .41). Findings for memory complaints were less consistent. Chen et al.[4] found memory complaints and learning problems to correlate with subjective sleepiness (r=.33). In contrast, Daurat et al.[5] failed to find correlations between memory complaint ratings and subjective sleepiness. Regarding executive function, correlations were found for emotional control, motivation problems, abstract thinking and problem solving (r>.35). Mulgrew et al.[45] used multivariable logistic regression analyses and found that subjective sleepiness predicted complaints of time management difficulties in OSA patients. Unfortunately, none of the studies explored the association between cognitive complaints and objective measures of sleepiness.

Findings comparing cognitive complaints between OSA patients with and without daytime sleepiness are summarized in table 8. Subjects in the reported studies were matched for AHI or RDI. Patients with sleepiness were more likely to report complaints about concentration[47] and difficulties with time management and cognitive work tasks [45]. After successful CPAP treatment, memory and inattention complaints were elevated in patients with residual sleepiness, compared to non-sleepy patients [49].

Table 7. Relation between cognitive complaints and sleepiness

Study	Cognition complaints	ESS	
		r	slope
Chen et al.[4]	attention & vigilance problems	.414**	
	memory & learning problems	.332**	
	emotional control & motivation problems	.363**	
	abstract thinking & problem solving problems	.350**	
Daurat et al.[5]	memory capacity	ns	
	memory stability	ns	
	anxious about memory	ns	
Mulgrew et al.[45]	time management difficulties		1.22***
	difficulties cognitive work tasks		1.09***
Sangal & Sangal[46]	attentional deficits	.49***	
Sforza[41]	subjective cognitive difficulties	.51***	

r = Pearson correlation coefficient; slope = multivariable logistic regression; ** = p<.01; *** = p<.001; ESS = Epworth sleepiness scale; ns = non significant with no exact p-values provided in the paper.

Table 8. Cognitive complaints in OSA with sleepiness compared to OSA without sleepiness

Study	Group	ESS	Cognitive domain	p
Mulgrew et al.[45]	OSA with sleepiness	18-24[1]	time management	↑ <.001
	OSA without sleepiness	0-5[1]	cognitive work tasks	↑ <.001
Stoohs et al.[47]	OSA with sleepiness	9.9±4.9	concentration	↑ <.001
	OSA without sleepiness	5.9±3.3		
Vernet et al.[49]	OSA with residual sleepiness after CPAP	16.4±3.0	memory	↑ <.10
			inattention	↑ <.10
	OSA without residual sleepiness after CPAP	6.2±2.9		

ESS = Epworth sleepiness scale; [1] only ranges were provided, no means;↑ = more severe cognitive complaints in OSA with sleepiness compared to OSA without sleepiness.

3.3.3 Cognitive complaints and mood problems

Cognitive complaints, particularly memory complaints, have often been associated with mood problems in the general population and in non-sleep disorder patients[22,23]. In these groups mood problems were shown to be an even stronger predictor for memory complaints than actual impairments in objective memory function [24,51-53]. It is therefore surprising that no study to date has reported on possible associations between cognitive complaints and mood problems in OSA. As more than a quarter of OSA patients report significant depressive symptoms and 20% are estimated to suffer from a depressive syndrome[54], it is not unlikely that mood problems may be a mediator of cognitive complaints in OSA as well.

4. DISCUSSION

Cognitive complaints have repeatedly been linked to quality of life, work productivity and health care utilization in the general population[30-32] and medical populations such as cancer patients[22,33,34]. In addition to indicators of objective cognitive functioning, cognitive complaints are therefore an important patient outcome measure in OSA. In this paper, we reviewed the current knowledge on cognitive complaints in OSA. Several studies showed an increased prevalence of concentration complaints in OSA patients. The same may be true for memory and executive function problems, but firm conclusions are not possible due to methodological limitations of the (few) available studies. OSA patients with higher level of subjective sleepiness seem to report cognitive complaints more often. Importantly, cognitive complaints are not necessarily a sign of objective cognitive impairment.

The results of the review stress the importance of differentiating between objective cognitive functioning and cognitive complaints. In accordance with findings in other medical populations, no evidence was found for a relation between objective cognitive functioning and cognitive complaints in OSA. In fact, cognitive complaints in OSA may be reported in the absence of objective cognitive impairments. There are several possible explanations for this lack of relation. Firstly, current validated objective tests for cognition are designed to detect cognitive impairments in brain-injured patients and not to specifically assess cognitive impairments in OSA. For example, alertness may fluctuate across different environmental circumstances in OSA patients, while most objective cognitive tests only assess cognitive performance under maximum levels of alertness, potentially masking everyday cognitive failures in sleep apnea. Secondly, cognitive complaints are typically rated over a longer time period, including different circumstances, whereas objective measures only assess cognition at one point in time and under conditions often not comparable to everyday life. Finally, cognitive complaints may

be secondary to other daytime symptoms in OSA and not purely related to objective impairments in cognitive performance. So far, only the relation between subjective sleepiness and cognitive complaints has been studied. In other medical populations it has been proposed cognitive complaints are a sign of psychological distress rather than objective cognitive impairments[37]. This hypothesis certainly warrants further exploration in OSA, for it could potentially guide treatment strategies for persisting cognitive complaints.

Meta-analyses have shown that CPAP improves objective cognitive functioning[17], and reduces sleepiness complaints [55,56] and mood problems[56]. No randomized controlled trial on CPAP has used cognitive complaints as an outcome measure. Only one of the reviewed studies[45] performed follow-up after CPAP therapy, showing a positive effect of the intervention on cognitive complaints. A large dropout rate and lack of a control group made it however unclear whether CPAP was the primary cause of this improvement. A study by Vernett et al.[49] showed that even after successful CPAP cognitive complaints may persist, underscoring the importance of improving our understanding of the effect of CPAP on cognitive complaints.

The number of studies on cognitive complaints in OSA is still limited. Moreover, methodological limitations of the available studies limit the extent to which firm conclusions can be drawn. Only concentration complaints were consistently found to be more severe in untreated OSA patients as compared to primary snorers and healthy controls. Findings on OSA and memory complaints were inconsistent, most likely due to the various types of outcome parameters used for memory complaints, small sample sizes and different types of control groups. Subjective measures for executive function were used in only two studies, yielding inconsistent findings on its relation with OSA.

Given the clinical importance of cognitive complaints, there is a clear need for future studies on this topic in OSA. It will be important that severity measures are included, both for the number of noctural respiratory events and daytime symptoms, especially sleepiness. As cognitive complaints are prevalent in other medical populations and even the general population, the inclusion of well-specified control groups is of paramount importance. Most importantly however would be the use of more unified measures for cognitive complaints, that cover domains typically affected in OSA. Validated questionnaires covering various aspects of subjective cognitive dysfunction are available, with cut-off scores that distinguish normal levels of cognitive complaints from clinically significant complaints based on general population norms. Examples include the Multifactorial Memory Questionnaire (MMQ)[57,58] for memory complaints, and the Behavior Rating Inventory of Executive Function (BRIEF)[59] for complaints related to executive function.

We have shown that the literature on cognitive complaints in OSA is far less extensive than studies on objective cognitive functioning. Because of

methodological limitations, only firm conclusions can be drawn regarding an increase in concentration problems in OSA, although memory complaints and subjective executive dysfunction may also be affected. Cognitive complaints appear to be at least partially related to subjective sleepiness and may not necessarily be a sign of objective cognitive impairment. Future studies are needed to address the impact of CPAP and explore the relation between cognitive complaints, sleepiness and mood problems. This will improve our understanding of the determinants of cognitive complaints in OSA and help to find effective treatment strategies for those cognitive complaints that endure even after successful (CPAP) treatment.

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CHAPTER 3

Cognitive Complaints In Patients With Untreated Obstructive Sleep Apnea Versus Patients With Neurological And Respiratory Diseases: Prevalence, Severity And Risk Factors

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ABSTRACT

Purpose: Little is known about cognitive complaints (self-reported problems in cognitive functioning) in patients with Obstructive Sleep Apnea (OSA). We compared the prevalence and severity of cognitive complaints in patients with untreated OSA to patients with neurological and respiratory diseases. We also studied risk factors for cognitive complaints across these diseases, including OSA.

Methods: We used a convenience sample to compare untreated OSA patients (N=86) to patients with stroke (n=166), primary brain tumor (N=197) and chronic obstructive pulmonary disease (COPD, N=204) on cognitive complaints (Cognitive Failure Questionnaire, CFQ), anxiety and depression (Hospital Anxiety and Depression Scale, HADS) and cognitive impairments using neuropsychological tests. We combined all patient groups (OSA, stroke, brain tumor and COPD) and studied potential risk factors (demographic variables, anxiety, depression and cognitive impairments) for cognitive complaints across all patient groups using regression analysis.

Results: The prevalence of cognitive complaints was higher in OSA patients and complaints of forgetfulness and distractibility were more severe compared to stroke and primary brain tumor patients, but similar to or lower than COPD patients. Regression analysis for the combined sample of all patient groups showed that cognitive complaints were most strongly associated with symptoms of anxiety and depression.

Conclusion: A high rate of OSA reported clinically significant cognitive complaints, comparable to other respiratory and neurological patients. Symptoms of anxiety and depression are important risk factors for cognitive complaints in patients with various neurological and respiratory diseases. Future studies should examine the relation between anxiety, depression and cognitive complaints in patients with OSA.

1. INTRODUCTION

Obstructive Sleep Apnea (OSA) is a sleep disorder characterized by intermittent obstruction of the airway during sleep. OSA is associated with cognitive impairments as verified with neuropsychological testing [1]. Causes for cognitive impairments in OSA are multifactorial and include disruption of sleep and nighttime blood gas abnormalities (hypoxemia). More recent studies show that fragmented sleep and hypoxemia may be insufficient to cause cognitive impairments [2–4]. These studies show that comorbid conditions, such as overweight, hypertension, stroke, diabetes and emotional problems may worsen or even be the primary cause of cognitive impairments [5,6]. Impairments in cognition in OSA might therefore be similar to or have overlap with those other medical diseases [5]. OSA is often treated with continuous positive airway pressure (CPAP). While CPAP improves cognition, residual cognitive impairments may persist post-treatment[6,7].

Fundamentally different from objectively tested cognitive impairments are cognitive complaints. These are subjective self-reported problems in cognitive functioning (with or without objective cognitive impairment). Cognitive complaints are concerns patients express about their daily life cognitive functioning and are an important reason patients seek medical help for their cognition. They can be assessed relatively easily through an interview or by validated questionnaires. Evaluating cognitive complaints alongside objective cognitive impairments is crucial, as they correlate to overall well-being [8] , other self-reported outcomes[10,11], and absence from work due to sickness [9].

Cognitive complaints are common in patients with neurological diseases, such as stroke [12], and brain tumors [11], and respiratory diseases, such as chronic obstructive pulmonary disease (COPD)[13]. The limited studies in untreated OSA indicate more severe concentration problems compared to healthy controls [14]. To our best knowledge, no study has compared the prevalence and severity of cognitive complaints in patients with untreated OSA to other patients with neurological or respiratory diseases.

Associated with cognitive complaints include/are symptoms of anxiety and depression [15], objective cognitive impairments [10], and a chronic (versus acute) phase of the disorder [16]. Here, the acute phase typically refers to the early onset of symptoms (days to weeks) whereas the chronic phase refers to the months or years in which symptoms remain relatively stable. Given the chronic nature of OSA, and that it is often accompanied by depression, anxiety symptoms [17], and objective cognitive impairments [18], it is expected that cognitive complaints in OSA may be as prevalent and severe as those in patients with other diseases.

To test this hypothesis, we performed a retrospective study using available datasets on cognitive complaints in patients with OSA, stroke, primary brain

tumors and COPD. We are aware that some of these medical diseases share comorbidities, such as hypertension or even OSA. However, our purpose is not to determine the unique contribution of OSA on cognitive complaints in various diseases but to compare cognitive complaints between untreated OSA patients and patients with other neurological and respiratory diseases, regardless of underlying pathophysiological causes of cognitive complaints or shared comorbidities. Additionally, we studied potential risk factors (sociodemographic characteristics, anxiety and depression symptoms and cognitive impairments) for cognitive complaints across all four patient groups.

2. METHODS

2.1 Participants

OSA patients were recruited from the sleep units of two general hospitals in the Netherlands (VieCuri Medical Center, Venlo; and Reinier de Graaf Hospital, Delft). OSA diagnosis followed the clinical guidelines of the adult OSA taskforce of the American Academy of Sleep Medicine: apnea-hypopnea index (AHI) of ≥15 or AHI of ≥5 according to a polysomnography (PSG) with significant daytime symptoms [20]. Patients were assessed before they started treatment.

We compared OSA patients (N=86) to three separate medical diseases (these three groups were previously recruited for other studies). These were patients three months after a stroke without major communication difficulties (N=166)[21] and patients three months after surgery for a primary brain tumor: low grade glioma (N=85)[22], or meningioma (N=112)[10]. All neurological patients were recruited at the general hospital where they received their treatment. Our third group comprised patients suffering from COPD (N=204) [23]. They were recruited at a tertiary center for pulmonary rehabilitation. The majority of these patients had severe to very severe airway obstruction global initiative for chronic obstructive lung disease stage of III–IV based on pulmonary function parameter [24]. Exclusion criteria for OSA, stroke, COPD and brain tumor patients were a history of a psychiatric or (other) neurological disorder and the use of medication/substances impacting cognition. All studies were conducted in accordance with the declaration of Helsinki and approved by nationally certified medical ethical committees (OSA: NL37795.068.11; stroke: NL21642.008.08; low grade glioma + meningioma: NL41351.008.12; COPD: NL33713.008.10).

2.2 Measures

2.2.1 Sociodemographic characteristics

Data on age, sex and educational level were collected for all patient groups. Educational level was rated according to the Dutch Verhage system: a 7-point scale similar to the International Standard Classification of Education [25], but adapted to the Dutch educational system.

2.2.2 Cognitive complaints

Cognitive complaints were assessed using the Cognitive Failure Questionnaire (CFQ) [26]. The CFQ is a validated and reliable instrument that assesses the severity of everyday cognitive complaints in the last three months and consists of 25 items. Every item is rated on a 5-point Likert-scale (ranging from "never" to "very often"). Higher scores indicate a higher severity of everyday cognitive complaints. Scores were classified as clinically significant if they were one standard deviation above the mean for a healthy Dutch norm sample (>68)[27].

Rast and colleagues found a stable factor structure of the CFQ across different ages in a Dutch population consisting of three subscales: "forgetfulness" (sum of 8 items, score range 0-32), "distractibility" (sum of 8 items, score range 0-32) and "false-triggering" (sum of 8 items, score range 0-32)[28]. The subscale forgetfulness contains items related to memory slips. The subscale distractibility contains items related to attentional misses, such as absentmindedness. The subscale false-triggering contains items related to blunders or slips in thinking or motor actions. If one item was missing on any of the CFQ subscales it was replaced by the average score of the same subscale. If more than one item was missing on any of the CFQ subscales that subscale was labeled as missing (see figure 1).

2.2.3 Depression and anxiety symptoms

Depression and anxiety symptoms were measured using the depression (sum of 7 items, score range 0-21) and anxiety subscales (sum of 7 items, score range 0-21) of the Hospital Anxiety and Depression Scale (HADS), a reliable and validated questionnaire for mood problems in a medical setting[29]. If one item was missing on any of the HADS subscales the average score of the subscale replaced it. If more than one item was missing on any of the two subscales, the subscale was labeled as missing (see Figure 1). A score of 8 or higher on either of the subscales indicates clinical symptoms of depression or anxiety.

2.2.4 Cognitive impairments

Neuropsychological tests were used to assess cognitive performance. We defined cognitive impairments using the Cognitive Impairment Non-Dementia

(CIND) criteria[30]. These criteria were selected because previous studies have shown CIND criteria to be useful in defining cognitive impairments in various medical diseases [31]. According to these criteria, a cognitive domain is impaired if the norm-corrected Z-score is below -1.65 after adjusting for age, sex and educational level (the lowest 5% of the normal population). For brain tumor patients, scores were also corrected for practice effects [32], as this group had already taken the same tests three months prior. See table 1 for all cognitive tests and scores per domain used for the different patient groups.

Table 1. Cognitive tests and scores used per cognitive domain for all patientgroups

Cognitive domain	Test	Scores used*	Patientgroup
Verbal memory	RAVLT-DR [50]	Total number of correct responses on delayed recall	OSA
	WMS-PA-DR [36]	Total number of correct responses on delayed recall	Stroke
	CNSVS-VM [51]	Total number of correct responses on delayed recall	Brain tumor, COPD
Cognitive flexibility	CNSVS-CF [51]	Total number of correct responses and errors on the Shifting Attention Test and the number of commission errors of the Stroop test	OSA, brain tumor, COPD
	SCWT [37]	Interference score: based on the time to complete the interference part of the SCWT corrected for an estimated time based on the naming part of the SCWT test.	Stroke
Processing speed	CNSVS-PS [51]	Number of correct responses minus the number of errors on the Symbol Digit Coding test (an adaptation of the pen-and-paper Digit Symbol Substitution Test).	OSA, brain tumor, COPD
	WAIS-SDST [36]	number of correctly coded symbols	Stroke

* All scores were corrected for age, sex and educational level using available Dutch norm groups, except for WMS-PA-DR and WAIS-SDST, for these scores only age corrected norm scores were available CNSVS-CF = Central Nervous System Vital Signs Cognitive Flexibility Domain, CNSVS-PS = Central Nervous System Vital Signs Processing Speed Domain, CNSVS-VM = Central Nervous System Vital Signs Verbal Memory Domain, RAVLT-DR = Rey Auditory Verbal Learning Test Delayed Recall, SCWT = Stroop Color Word Test, WAIS-SD = Wechsler Adult intelligence Scale III Symbol Digit Substitution Test, WMS-PA-DR = Wechsler Memory Scale III Paired Association Delayed Recall.

2.2.4.1 Verbal memory

In OSA patients, verbal memory was measured using the delayed recall score (total number of correct responses) of the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT-DR) [33]. For COPD and brain tumor patients, the Verbal Memory domain score of Central Nervous System Vital Signs (CNSVS-VM) was used [34]. The CNSVS is a computerized neurocognitive test battery developed as a routine clinical screening instrument. This verbal memory test is based on an adaptation of the Rey Auditory Verbal Learning Test [35] and is recognition-based. Correct responses are summed to generate the composite Verbal Memory domain score. In stroke patients, the delayed recall score (total number of correct responses) of the Verbal Paired Association subtest of the Wechsler Memory Test (WMS-PA-DR) third edition[36] was used. For WMS-PA-DR only age- (not sex and educational level) corrected norms were available.

2.2.4.2 Cognitive flexibility

In OSA, COPD and brain tumor patients, cognitive flexibility was measured using the Cognitive Flexibility domain of Central Nervous System Vital Signs (CNSVS-CF) [32]. The score on this domain is based on the total number of correct responses and errors on the Shifting Attention Test (a measure of cognitive flexibility) and the number of commission errors of the Stroop test (a computerized version of the pen-and-paper Stroop Color Word Test, SCWT). In stroke patients, the interference score of the pen-and-paper SCWT was used as a measure for cognitive flexibility [37]. The SCWT consists of a reading, naming and interference part. The interference score was based on the time to complete the interference part corrected for an estimated time based on the naming part of the test [38].

2.2.4.3 Processing speed

In OSA, COPD and brain tumor patients processing speed was measured using the Processing Speed domain of Central Nervous System Vital Signs (CNSVS-PS) [32]. The score of this domain is based on the number of correct responses minus the number of errors on the Symbol Digit Coding test (an adaptation of the pen-and-paper Digit Symbol Substitution Test). In stroke patients, processing speed was measured using the pen-and-paper Digit Symbol Substitution Test of the Wechsler Adult Intelligence Scale (WAIS-DSST) third edition [36]. The score is based on the number of correctly coded symbols. For WAIS-DSST only age- (not sex and educational level) corrected norms were available.

2.3 Statistical analysis

Patients with untreated OSA were compared to patients with stroke, brain tumor and COPD on sociodemographic variables (age, sex and educational

level), prevalence of cognitive complaints (percentage of patients with significant elevated total CFQ scores), severity of cognitive complaints (scores on CFQ subscales for forgetfulness, distractibility and false triggering), anxiety and depression symptoms (scores on HADS) and cognitive impairments (impaired scores on tests for verbal memory, cognitive flexibility and processing speed). For continuous variables we used independent samples t-tests and for categorical variables Chi-square tests.

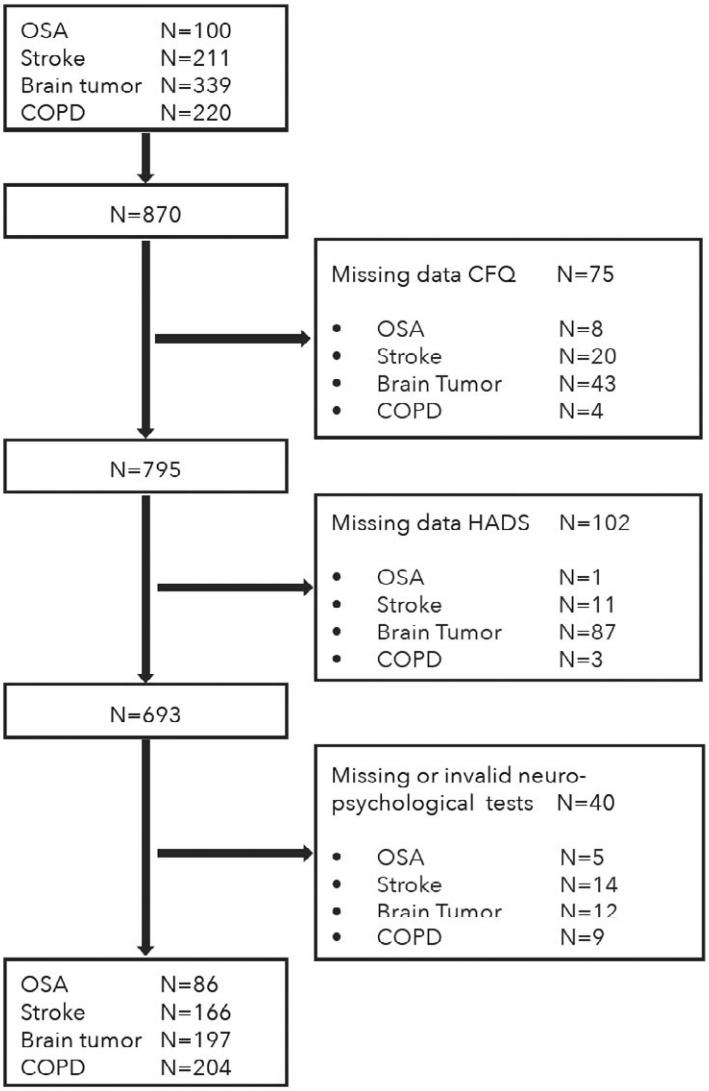
We combined all patient groups and performed separate multiple linear regression analyses for the three CFQ subscales. As predictors we used age, sex, educational level, HADS depression, HADS anxiety and cognitive impairments. Standardized regression coefficients (β) were used to indicate the strength of the associations. We only examined component measures if the overall multivariate effect was significant. Two-sided p-values are reported and a p-value < .05 was considered to indicate statistical significance. P-values were adjusted using false discovery rates with the Benjamini-Hochberg method to correct for multiple testing [39]. All statistical analyses were performed using SPSS 24.0.0.0 software for Windows (IBM Corp, 2017).

3. RESULTS

3.1 Participants

Figure 1 shows the inclusion flow chart for all included patient groups. We included a total of 870 patients of whom 170 had missing questionnaires cores (CFQ and/or HADS) and 40 had missing or invalid scores on the neuropsychological tests. In our analyses we were therefore able to include 86 OSA, 166 stroke, 197 brain tumor and 204 COPD patients.

Figure 1. Flow chart of inclusion



3.2 Patient and sociodemographic characteristics

Table 2 shows the patient characteristics of the four patient groups. OSA severity ranged from mild to severe (AHI range 5.2 - 101.2) with a median of 16.2 and interquartile range of 21.5. OSA patients were significantly more often male than any of the other patients (all p's <.04). OSA patients were significantly younger than stroke and COPD patients (all p's <.001), but did not differ in age from brain tumor patients (p =.21). Furthermore, OSA patients had, on average, a significantly higher educational level than stroke (p =.01) and COPD patients (p <.001) while they did not differ on this variable from the brain tumor patients (p =.24).

3.3 Cognitive complaints

In OSA 30.2% reported significant cognitive complaints (total CFQ score of more than one standard deviation above the mean of Dutch norms (see table 2)). This percentage was significantly higher than in patients with stroke (p =.04) and with a brain tumor (p <.01), but did not differ compared to COPD patients (p =.22). OSA patients also reported a higher mean on the CFQ subscales for forgetfulness, distractibility and false triggering than stroke and brain tumor patients did (all p's <.03, see table 2). OSA and COPD patients did not differ in mean scores on any of the CFQ-subscales (all p's >.34).

3.4 Depression and anxiety symptoms

In OSA patients, 29.1% reported clinical symptoms of depression (HADS depression) and 29.1% reported clinical symptoms of anxiety (HADS anxiety). These numbers were significantly lower compared to COPD patients for both clinical symptoms of depression and anxiety (all p's <.03). OSA patients reported a higher number of clinical symptoms of depression compared to brain tumor patients (p<.001). For clinical symptoms of anxiety no differences were found between OSA and brain tumor patients (p =.08). No differences were also found between OSA and stroke for the number of patients with clinical symptoms of depression and anxiety (all p's >.21).

OSA patients had a significantly higher overall score on HADS depression and anxiety than brain tumor patients (all p's <.05), but a significantly lower overall score on HADS depression and anxiety than COPD patients (all p's <.05). Compared to stroke patients, OSA patients scored significantly higher on HADS-anxiety (p <.05), but there was no difference on HADS-depression (p =.80).

Table 2. Demographic variables, cognitive complaints, depression, anxiety and cognitive impairments in OSA, stroke, brain tumor and COPD

	Range	OSA	Stroke	p-value[1]	Brain tumor	p-value[1]	COPD	p-value[1]
		N=86	N=166		N=197		N=204	
Demographics								
Sex (% female)	0-100	21%	34%*	.04	66%***	<.001	52%	<.001
Age	>18	50.0 (10.2)	64.1 (12.6)***	<.001	52.3 (13.3)	.21	61.3 (8.6)	<.001
Education	1-7	5.3 (1.0)	4.6 (1.4)*	.01	5.0 (1.2)	.24	4.1 (1.2)	<.001
AHI	≥5	24.5 (19.7)	na	na	na	na	na	
Cognitive complaints								
CFQ Significant complaints (%)	0-100	30.2%	17.5%*	.04	13.8%**	<.01	22.7%	.22
Forgetfulness	0-32	13.3 (5.1)	11.4 (5.2)*	.01	11.1 (5.7)**	<.01	13.2 (4.4)	.83
Distractibility	0-32	11.6 (4.8)	9.4 (5.0)**	<.01	8.9 (5.1)***	<.001	11.8 (4.0)	.84
False triggering	0-32	8.3 (4.9)	6.8 (4.4)*	.03	6.8 (4.6)*	.03	8.9 (4.1)	.34
Depression and anxiety								
HADS depression score	0-21	5.3 (3.5)	5.2 (3.8)	.80	3.6 (3.1)***	<.001	7.1 (3.9)	<.001
clinical symptoms depression (%)	0-100	29.1%	30.1%	.86	9.6%***	<.001	44,1%	.03
anxiety score	0-21	5.9 (3.3)	4.7 (3.9)*	.04	4.6 (3.7)*	.02	7.3 (4.3)	.01
clinical symptoms anxiety (%)	0-100	29.1%	21.1%	.21	18.8%	.08	50.0%	<.01

Table 2. Demographic variables, cognitive complaints, depression, anxiety and cognitive impairments in OSA, stroke, brain tumor and COPD (continued)

	Range	OSA	Stroke	p-value[1]	Brain tumor	p-value[1]	COPD	p-value[1]
		N=86	N=166		N=197		N=204	
Cognitive impairments								
Verbal memory (%)	0-100	24.0%	8.7%*	.01	26.9%	.57	14.5%	.09
Cognitive flexibility (%)	0-100	30.2%	2.4%***	<.001	23.4%	.14	25.4%	.23
Processing speed (%)	0-100	8.2%	19.3%	.06	17.8%	.10	26.4%	.01

AHI = Apnea-Hypopnea Index, CFQ = Cognitive Failure Questionnaire, HADS = Hospital Anxiety Depression Scale, na = not applicable, [1] compared to OSA, * = p <.05, ** = p <.01, *** = p <.001

3.5 Cognitive impairments

In OSA patients, 24% had an impairment in verbal memory, 30% in cognitive flexibility and 8% in processing speed (see table 2). A significantly higher proportion of OSA patients had an impairment in verbal memory and cognitive flexibility (all p's <.05) compared to stroke patients, but there was no significant difference for processing speed (p = .06). A significantly lower number of OSA patients had a cognitive impairment in processing speed compared to COPD (p < .05), with no significant differences for verbal memory and cognitive flexibility (all p's >.09). OSA patients also did not significantly differ in the proportions of cognitive impairments on any domain compared to brain tumor patients (all p's >.10).

3.6 Risk factors for cognitive complaints

For all three subscales of the CFQ we performed separate multivariate regression analyses (see table 3). We entered age, sex, education, HADS depression score, HADS anxiety score and cognitive impairments in verbal memory, cognitive flexibility and processing speed as candidate predictors. All three models were significant (CFQ forgetfulness: $F(8,651) = 13.5$, $p<.001$, CFQ distractibility: $F(8,651) = 19.6$, $p<.001$, CFQ false triggering: $F(8,651) = 14.5$, $p<.001$), with R^2's of .14 for CFQ forgetfulness,.20 for CFQ distractibility and.15 for CFQ false triggering.

For our combined sample of all patient groups we found that a higher score on CFQ forgetfulness (i.e. more severe complaints of forgetfulness) was associated with a higher score on HADS depression (ß=.25) and a higher score on HADS anxiety (ß=.16).

A higher score on CFQ distractibility (i.e. more severe complaints of distractibility) was associated with a higher score on HADS depression (ß=.20) and HADS anxiety (ß=.26). A lower score on CFQ distractibility (i.e. less severe complaints of distractibility) was associated with female sex (ß=-.09), a younger age (ß=-.09) and an impairment in processing speed (ß=-.09).

A higher score on CFQ false triggering (i.e. more severe complaints of false triggering) was associated with a higher score on HADS depression (ß=.18), a higher score on HADS anxiety (ß=.21) and female sex (ß=.12).

Table 3. Multilinear regression analyses for all three CFQ subscales in the total sample

	CFQ forgetfulness N=652		CFQ distractibility N=652		CFQ false triggering N=652	
Variables	Stand. ß	p-value	Stand. ß	p-value	Stand. ß	p-value
Sex	.06	.21	-.09*	<.05	.12**	.001
Age	.00	.96	-.09*	<.05	.00	.96
Education	.04	.42	-.08	.10	-.01	.83
HADS depression score	.25***	<.001	.20***	<.001	.18***	<.001
HADS anxiety score	.16**	.001	.26***	<.001	.21***	<.001
Verbal memory impairment	.07	.13	.06	.21	.08	.09
Cognitive flexibility impairment	-.06	.21	-.05	.28	-.03	.46
Processing speed impairment	-.04	.42	-.09*	<.05	-.05	.28

CFQ = Cognitive Failure Questionnaire, HADS = Hospital Anxiety and Depression Scale, OSA = Obstructive Sleep Apnea, * = p <.05, ** = p <.01, *** = p <.001

4. DISCUSSION

To our knowledge, this is the first study comparing cognitive complaints in patients with untreated OSA to such complaints of patients with neurological or respiratory diseases. A high rate of our OSA sample reported clinically significant cognitive complaints (30.2%). Previous studies have shown that cognitive complaints are more prevalent in OSA compared to healthy controls [40, 41]. Our prevalence numbers are somewhat lower than what has been reported in previous studies (59% for memory complaints [41]and 69% for concentration complaints [42]). However, these studies used a single yes/no question to assess cognitive complaints. We do not know the percentages with similar reports of memory or concentration complaints in the healthy population. Because we used a validated questionnaire with norm-referenced cut-off scores, our prevalence numbers only include clinically significant cognitive complaints, not just any cognitive complaint also prevalent in the general population. This may explain why previous studies have found a higher prevalence of cognitive complaints in OSA.

The prevalence and severity of cognitive complaints in OSA were at least comparable to our sample of patients with other neurological and respiratory

diseases. Cognitive complaints in OSA were even more prevalent and severe compared to our sample of neurological patients (stroke, brain tumor). We did not expect this last finding. There are four possible explanations for this. Firstly, patients with communication difficulties were excluded from the stroke group, likely excluding stroke patients with more severe cognitive complaints. Secondly, the datasets we used for stroke and brain tumors assessed patients three months after an acute neurological event (stroke, brain surgery). Patients at this stage of their disease may have not yet been confronted enough with cognitive failures to adequately report them [21]. Thirdly, after an acute medical event (such as stroke or brain tumor) patients may shift their evaluation of their health standards. Gratitude about their health may overshadow cognitive complaints [43]. Fourthly, we included OSA patients in the diagnostic phase at a sleep center. This sample probably has a bigger focus on and incentive to report cognitive complaints, compared to OSA patients that did not seek for help at a sleep center. Therefore the finding that OSA patients report more cognitive complaints than neurological patients need to be interpreted with caution. Current findings can only be generalized to OSA patients attending a sleep clinic and the prevalence and severity of cognitive complaints in our neurological sample might be an underestimation compared to the overall population of stroke and brain tumor patients.

For the combined sample (OSA, stroke, brain tumor and COPD together) cognitive complaints were most strongly associated with symptoms of depression and anxiety. This corresponds to results of previous cross-sectional studies in stroke [15] ,glioma [11], meningioma[10] and various other diseases [44]. Because our data is also cross-sectional the nature of this relation is unclear: cognitive complaints may be a sign of anxiety or depression, cognitive complaints may cause anxiety of depression or an unknown disease factor (such as fatigue or pain) may cause all three. Studies do show, however, that treating a depressive disorder reduces cognitive complaints [45]. This, together with our findings, implies that patients with cognitive complaints need to be screened for anxiety and depression. And if patients fit the criteria of a depressive disorder treatment for it will likely improve cognitive complaints.

A limitation of our study is that the medical diseases we included may share comorbidities, and there may be overlap between patient groups in the possible causes for cognitive complaints. For instance, OSA is also prevalent in stroke [46] and COPD [47] and OSA increases the risk for a primary brain tumor [48]. All included patient groups share comorbidities such as hypertension and diabetes mellitus. Unfortunately, the stroke, COPD and brain tumor patients we included were not screened for OSA. Also, data on comorbidities such as hypertension or diabetes mellitus was not available for all patient groups. However, for all patient groups we did exclude patients with psychiatric disorders, (other) neurological disorders and use of medication

or substances that impact cognition. Therefore, we believe that the included patient groups are a good representation of patients in clinical practice with common comorbidities, but excluding comorbidities that have a large impact on cognition.

We were able to compare cognitive complaints in patients with untreated OSA to patients with other diseases using a well-validated questionnaire (CFQ). We also used well-established instruments to assess cognitive impairments. Almost all test scores were adjusted using age, sex and education corrected norms. This was done so we could compare across diseases, who inherently differ in age, sex and educational level. Although neuropsychological tests were often comparable across patient groups (e.g. a computerized adaptation versus a paper-and-pencil version of a test), it was not possible to use exactly the same tests (and norm scores) for all patient groups. We should therefore be careful when making comparisons between OSA and the other patient groups on cognitive impairments. This is most notable for stroke patients. For stroke patients a relatively easier and less sensitive verbal memory test was used compared to the patients with untreated OSA (WMS-PA-DR for stroke versus RAVLT-DR for OSA). WMS-PA-DR is less likely to pick up a verbal memory impairment than RAVLT-DR [49].

5. CONCLUSIONS

Cognitive complaints are as prevalent and severe in patients with OSA as in patients with neurological diseases (stroke, primary brain tumors) and respiratory diseases (COPD). For all patient groups combined (OSA, stroke, brain tumor and COPD) symptoms of anxiety and depression were important risk factors for cognitive complaints. Our results underscore the importance of screening for symptoms of anxiety and depression in patients who express cognitive complaints. Future studies in OSA should examine the relation between cognitive complaints, anxiety, depression and cognitive impairments to assess which OSA patients are at risk for cognitive complaints.

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CHAPTER 4

Cognitive Complaints In Patients With Suspected Obstructive Sleep Apnea Are Associated With Sleepiness, Fatigue, And Anxiety, Not With Final Diagnosis Or Objective Cognitive Impairment

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ABSTRACT

This study examined the nature, severity, and predictors of cognitive complaints in patients referred for suspected obstructive sleep apnea (OSA). The sample included 127 patients classified as no OSA (AHI, apnea-hypopnea index <5, N = 32), mild OSA (AHI 5–15, N = 46), moderate OSA (AHI 15–30, N = 25), or severe OSA (AHI≥30, N = 24), and 53 healthy controls (HCs), matched for age, sex, education, and IQ. Cognitive complaints were assessed using the Cognitive Failure Questionnaire (CFQ) and the Behavioral Rating Inventory of Executive Functioning Adult Version (BRIEF-A). Regression analyses examined predictors of cognitive complaints including AHI, sleepiness, anxiety, depression, fatigue, and neuropsychological performance. Compared to HCs, those with mild OSA reported more forgetfulness, distractibility, and working memory issues, while those with severe OSA reported more difficulties with initiative, both with large effect sizes. Cognitive complaints were linked to sleepiness, anxiety, and fatigue (*ß's 0.29–0.37)*, but not AHI or cognitive performance. Cognitive complaints were not specific to subjects with OSA but were also common among individuals with sleep complaints suspected for OSA. In conclusion, cognitive complaints were associated with anxiety, fatigue, and sleepiness rather than objective cognitive performance or impairment.

1. INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder affecting millions worldwide[1], and is linked to cardiovascular and metabolic complications[2]. OSA is also associated with cognitive deficits[3], particularly in attention, memory, and executive functioning. Patients with OSA commonly exhibit mild cognitive impairment[4] and perform worse on neuropsychological tests[5]. Interestingly, research has shown that these cognitive impairments do not always align with cognitive complaints—defined as individuals' subjective concerns about their everyday cognitive abilities[6-8]. Cognitive complaints are self-reported problems or concerns with memory, attention, or executive functioning, assessed through open questions in interviews or via questionnaires. While some OSA patients under-report these complaints[9,10], they remain clinically significant due to their strong association with reduced quality of life[8-11] and increased healthcare utilization[12]. Studies suggest that cognitive complaints, rather than objective impairments, are more closely tied to quality of life in various medical conditions[11].

Research on cognitive complaints in OSA remains limited, however. Studies suggest that OSA patients report more cognitive complaints than healthy controls[13,14], particularly related to attention and memory[15]. However, findings on executive functioning complaints remain inconsistent[6]. Moreover, cognitive complaints do not appear to correlate with severity of OSA, as measured by the apnea–hypopnea index (AHI)[13], suggesting other contributing factors.

Potential influences on cognitive complaints in OSA remain unclear as well. Subjective sleepiness, measured by tools such as the Epworth Sleepiness Scale (ESS), has been proposed as a contributing factor[6], but other aspects such as fatigue[16], anxiety[17], and depression[18] have received less attention. They may contribute to actual cognitive difficulties or heighten patients' awareness of cognitive lapses[19]. Given that fatigue, anxiety, and depression are prevalent in OSA[20], their role in cognitive complaints warrants further investigation. Understanding these relationships may help clinicians better address patient concerns and improve treatment strategies.

This study examined cognitive complaints in individuals referred to a sleep clinic for suspected OSA. We used validated questionnaires (Cognitive Failure Questionnaire, CFQ, and Behavior Rating Inventory for Executive Functioning Adult Version, BRIEF-A) to assess cognitive complaints and their potential correlates. Patients underwent overnight polysomnography (PSG) at a sleep laboratory to determine OSA diagnosis and severity (no OSA, mild, moderate, or severe), and their cognitive complaints were compared to a healthy control group recruited through hospital staff. Additional assessments included sleepiness (Epworth Sleepiness Scale, ESS), fatigue (Fatigue Assessment Scale, FAS), anxiety and depression (Hospital Anxiety and Depression

Scale, HADS), and objective cognitive performance (paper-and-pencil and computerized tests from Central Nervous System Vital Sign, CNS-VS). We compared cognitive complaints between patients with and without an OSA diagnosis, as well as between cognitively impaired and unimpaired patients across OSA severity levels.

We hypothesized that patients referred for suspected OSA would report more cognitive complaints than healthy controls, regardless of OSA severity[15]. Based on previous research, we expected cognitive complaints to correlate with sleepiness[6], fatigue[16], anxiety[17], and depression[18] but not with objective cognitive performance[6-8]. Additionally, we predicted that cognitive complaints would not differ significantly between patients with and without a confirmed OSA diagnosis, as symptoms like sleepiness, fatigue, and anxiety can occur in those without OSA[21]. Lastly, we anticipated that cognitive complaints would not be linked to cognitive impairments across OSA severity levels[7].

2. MATERIALS AND METHODS

2.1 Participants

2.1.1 Patients with Suspected OSA

Participants were referred by their general practitioner to sleep units at VieCuri Medical Center (Venlo) and Reinier de Graaf Hospital (Delft) for suspected OSA. Referral was based on self-reported symptoms such as snoring and observed apneas. Patients were recruited before undergoing overnight PSG. Based on the AHI, they were categorized as follows: no OSA (AHI < 5), mild OSA (AHI 5–15), moderate OSA (15–30), and severe OSA (AHI ≥ 30). Final OSA diagnosis followed the American Academy of Sleep Medicine guidelines[35]: AHI of ≥15 or AHI of ≥5 with significant daytime symptoms, such as an elevated Epworth Sleepiness Scale (ESS) score, requiring treatment. Inclusion criteria were as follows: 1. native Dutch speaker; 2. age 18–70 years old; 3. no substance or alcohol abuse (max. three units/day for males, two for females); 4. no psychiatric diagnoses; 5. no cognition-affecting medication; 6. no neurological diseases, diabetes mellitus, thyroid disease, or pulmonary disease. Screening was based on verbal report and medical records.

2.1.2 Healthy Controls

Healthy controls were recruited from hospital personnel and their relatives. Inclusion criteria ensured a low risk of sleep disorders: 1. no snoring or apneas (confirmed by a partner); 2. PSQI score ≤7[36]; and 3. ≥80% sleep efficiency based on a two-week sleep diary. The same six inclusion criteria as for suspected OSA patients were applied[37-39]. Controls did not undergo PSG.

The study followed the Declaration of Helsinki and was approved in March 2012 by a national ethics committee (NL37795.068.11, data collected from June 2012 until April 2018). Written informed consent was obtained.

2.2 Measures

2.2.1 Demographic Characteristics

Data on age, sex, and education were collected. Educational level was rated on the Dutch Verhage scale[40] (comparable to the International Standard Classification of Education) [41]. Premorbid verbal intelligence quotient (IQ) was estimated using a Dutch reading test [42].

2.2.2 Sleep Measures

Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI)[36], a validated and reliable self-report questionnaire consisting of 19 items and resulting in a total score ranging from 0 to 21. Higher scores indicate worse sleep quality[44-45]. Subjective sleepiness was measured with the Epworth Sleepiness Scale (ESS), where scores above >10 indicate excessive daytime sleepiness [43]. OSA severity was determined by the AHI and lowest nighttime oxygen saturation (SaO_2lowest) from PSG.

2.2.3 Cognitive Complaints

Cognitive complaints were assessed with the Cognitive Failure Questionnaire (CFQ) and the Behavior Rating Inventory of Executive Function-Adult (BRIEF-A). The CFQ measures cognitive lapses over three months (25 items, score range 25–125). Subscales assess forgetfulness, distractibility, and false triggering. BRIEF-A evaluates executive function complaints over the past month (75 items, score range 75–225) across nine subscales. Higher scores indicate greater impairment. For an explanation of the content of the subscales, see Table 1. As for missing data, if one item was missing on a subscale, it was replaced with the mean subscale score. If multiple items were missing, the subscale was excluded.

Table 1. Content of subscales of CFQ and BRIEF-A.

Subscale	Content
CFQ	
Forgetfulness	Memory slips
Distractibility	Attentional misses, such as absentmindedness
False triggering	Blunders or slips in thinking or motor actions
BRIEF-A	
Inhibit	Problems with controlling impulses
Shift	Problems with thinking flexibly
Emotional control	Problems modulating appropriate emotional responses
Self-monitor	Problems recognizing the effect of one's behavior on others
Initiate	Problems independently generating ideas
Working memory	Problems holding information in mind to complete a task
Plan/organize	Problems carrying out tasks systematically
Task monitor	Problems assessing mistakes in one's performance
Organization of materials	Problems keeping one's workspace in an orderly manner

2.2.4 Depression, Anxiety, and Fatigue

Mood symptoms were assessed with the Hospital Anxiety and Depression Scale (HADS), including anxiety (0–21) and depression (0–21) subscales. Fatigue was measured with the Fatigue Assessment Scale (FAS, 10 items, range 10–50). Missing data were handled as described for cognitive complaints.

2.2.5 Neuropsychological Tests

A combination of paper-based and computerized tests assessed cognitive function.

Paper-and-Pencil Tests:

- Working memory: WAIS-III Digit Span total score[44].
- Episodic verbal memory: Rey Auditory Verbal Learning Test (immediate recall)[45].
- Divided attention: Trail Making Test AB index[46].
- Verbal fluency: Total correct responses in Animal Fluency[47].
- Except for Digit Span, scores were standardized (Z-scores) for age, sex, and education.

Computerized Tests:

- CNS Vital Signs battery[48]: Symbol Digit Coding (processing speed), Stroop Test (reaction time), Shifting Attention Test (cognitive flexibility), Continuous Performance Test (complex attention).
- CNS-VS domain scores were calculated and standardized for age, sex, and education[49].

Cognitive impairment was classified using the Cognitive Impairment Non-Dementia (CIND) criteria[22]. A test score below −1.65 SD was considered impaired. Patients were classified as cognitively impaired if they had ≥2 impaired scores.

2.3 Statistics

A power analysis for multilevel analysis was performed following the method described by Twisk[50]. Assuming a high reliability of 0.70 [51,52], a significance level (alpha) of 0.05, and a power of 0.80, it was determined that 64 participants were needed in each group (OSA and HC) to detect a medium effect size (at least 0.5 standard deviation) on the total scores of the CFQ and BRIEF-A.

All OSA groups and healthy controls were matched at group level on age, sex, educational level, and estimated IQ using one-way analysis of variance (ANOVA) for continuous variables and Chi-square tests for categorical variables. Healthy controls that differed significantly from the OSA groups were excluded one-by-one until subjects matched across all groups. Demographic characteristics, sleep measures, cognitive complaints, anxiety, depression, fatigue, and performance on neuropsychological tests were compared between all groups using one-way analysis of variance (ANOVA) for continuous variables. If significant, post hoc independent t-tests were conducted. Chi-square tests were used for categorical variables. *p*-values were adjusted using the Benjamini–Hochberg method [63].

For all patients suspected of OSA, regression analyses were conducted to identify predictors of cognitive complaints (CFQ and BRIEF-A subscales). Predictors included OSA severity (AHI), sleepiness (ESS), anxiety (HADS), depression (HADS), fatigue (FAS), and the performance on each neuropsychological test.

We also compared healthy controls, patients with an OSA diagnosis, and patients without an OSA diagnosis using ANOVAs on the total scores of the CFQ and the BRIEF-A. If significant, post hoc *t*-tests were performed.

Within each OSA severity category, cognitively impaired and unimpaired patients were compared using independent t-tests on total CFQ and BRIEF-A scores.

Two sided *p*-values are reported and a p-value < 0.05 was considered statistically significant. *p*-values for the regression analysis were adjusted

with the Benjamini–Hochberg method to correct for multiple testing[53]. Only corrected *p*-values are reported. All statistical analyses were performed using SPSS 24.0.0.0 for Windows.

3. RESULTS

3.1 Participants

Figure 1 shows the flow chart for inclusion of patients suspected of OSA and healthy controls. We initially included 147 patients, but 20 had missing values on one or more measures. Those who dropped out were more likely to be female ($p < 0.001$); no differences were observed in AHI, age, education, or estimated IQ (all p's > 0.29). The remaining 127 were categorized as having no OSA (AHI < 5, N = 32), mild OSA (AHI 5–15, N = 46), moderate OSA (AHI 15–30, N = 25) and severe OSA (AHI ≥ 30, N = 24). Among those without OSA, two were diagnosed with restless legs syndrome, one with periodic limb movement disorder, and one with both snoring and insomnia. Four had a history of a burn-out, one had panic attacks, and one had a leaky heart valve. The remaining 24 had no significant medical or psychiatric history. We recruited 53 healthy controls, excluding 5 to match the OSA groups on age, sex, education, and estimated IQ at group level.

3.2 Demographic Characteristics and Sleep Measures

Table 2 summarizes the demographic and sleep measures of the included groups. Patients and controls did not differ with respect to age, sex, education, and estimated IQ (all p's >0.10). All patient groups displayed higher Pittsburgh Sleep Quality Index (PSQI) scores than controls (all p's < 0.001). Patients without OSA (AHI < 5) more often exceeded the PSQI clinical cut-off than other OSA groups and controls (all p's < 0.01). Mild (AHI 5–15) and severe OSA (AHI ≥ 30) patients scored higher on the ESS than controls (all p's <0.05). The prevalence of excessive sleepiness did not differ across OSA severity and from healthy controls, however (all p's > 0.51).

3.3 Cognitive Complaints

Cognitive complaints were assessed using the CFQ and the BRIEF-A. The subscales of both questionnaires cover various complaints regarding attention, memory, and executive functioning. Table 3 presents CFQ and BRIEF-A subscale scores across OSA groups and controls. Patients with mild OSA (AHI 5–15) reported more complaints about forgetfulness, distractibility, and working memory than controls (all p's < 0.03) with large effect sizes (all Cohen's ds > 0.8). Patients with severe OSA reported more initiative problems ($p < 0.001$) with a large effect size (Cohen's d = 1.1). Patients with no OSA (AHI < 5) or moderate OSA (AHI 15–30) did not differ from controls on any of the CFQ and BRIEF-A subscales (all p's > 0.06).

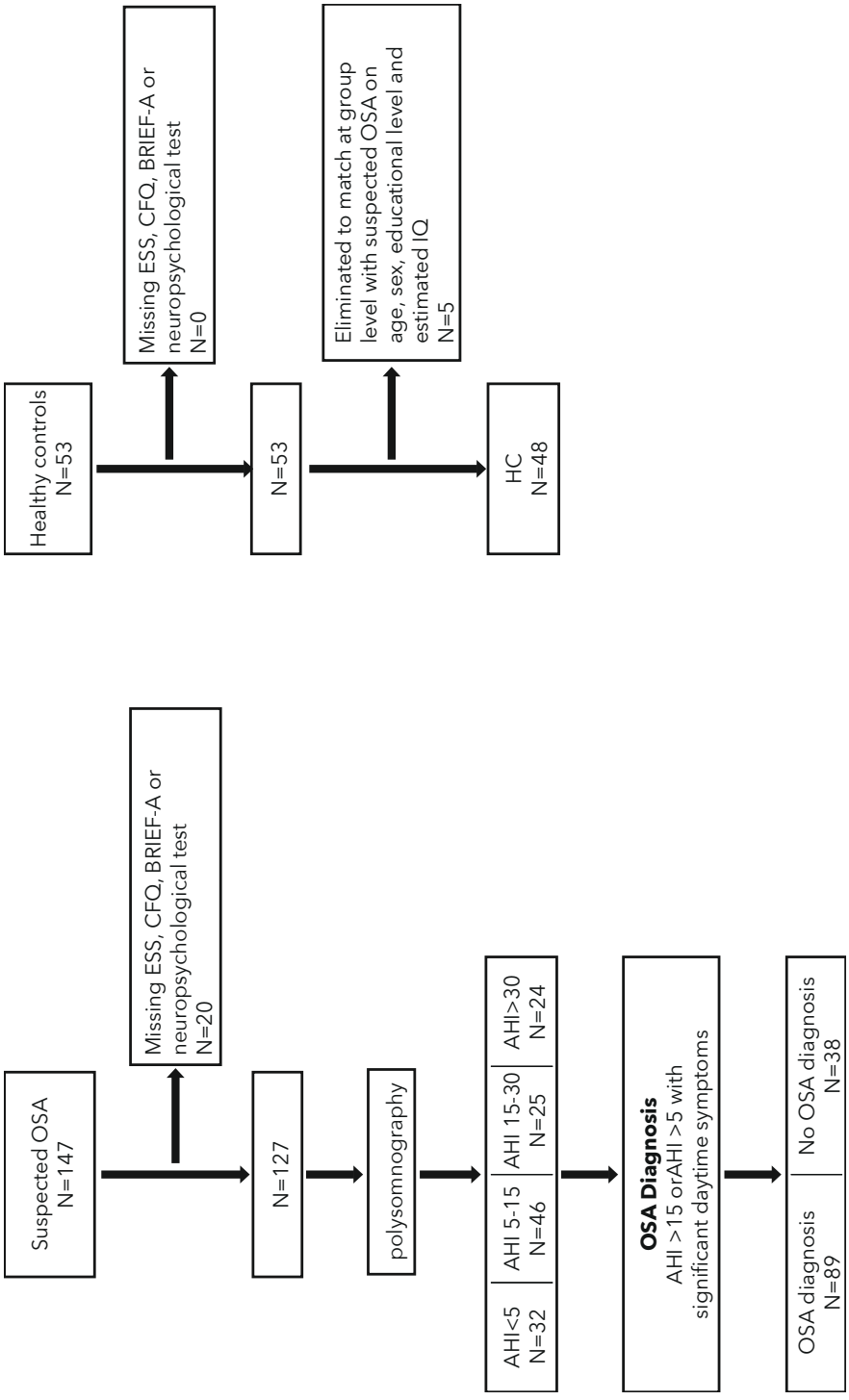

Figure 1. Flow chart suspected OSA and healthy controls.

Table 2. Demographic and sleep variables in patients with suspected OSA and healthy controls (HC).

	Range	HC N=48	AHI<5 N=32	AHI 5-15 N=46	AHI 15-30 N=25	AHI≥30 N=24	ANOVA/χ^2			
							df	F	χ^2	p
Demographics										
Sex (% male)	0–100	69%	72%	78%	80%	83%	4	-	2.66	0.62
Age	>18	52.9 (8.8)	46.8 (11.8)	49.4 (10.7)	53.3 (10.1)	49.8 (11.4)	4;170	2.31	-	0.10
Educational level	1–7	5.3 (0.7)	5.1 (0.8)	5.5 (1.0)	5.2 (1.2)	5.2 (1.2)	20	-	26.60	0.21
Estimated IQ	M=100/ SD=15	97.6 (12.1)	91.9 (14.0)	94.9 (16.6)	98.0 (17.1)	94.5 (15.0)	4;170	0.94	-	0.55
Sleep variables										
PSQI	0–21	3.0 (1.6)	7.4 (3.4)***	6.3 (2.8)***	6.7 (3.6)***	7.1 (3.7)***	4;170	14.79	-	<0.001
PSQI > 8	0–100	0%	42%***	30%	28%	36%	4	-	23.44	<0.001
ESS total score	0–24	4.5 (3.4)	7.1 (4.0)	6.9 (3.9)*	6.4 (4.0)	7.8 (3.9)**	4;170	4.11	-	<0.01
ESS > 10	0–100	8%	16%	12%	12%	21%	4	-	0.51	0.51
AHI	>0	na	2.5 (1.3)***	8.8 (2.7)***	21.7 (5.3)***	50.4 (17.8)***	3;123	182.68	-	<0.001
SaO_2lowest	<100%	na	89.8 (2.0)***	85.7 (4.2)***	80.8 (6.6)***	76.8 (7.1)***	3;123	35.70	-	<0.001

AHI = apnea-hypopnea index on overnight polysomnography, df = degrees of freedom between groups for χ^2 between groups and within groups for ANOVA, ESS = Epworth Sleepiness Scale; HC = healthy controls, IQ = intelligence quotient, na = not applicable, OSA = obstructive sleep apnea, PSQI = Pittsburgh Sleep Quality Index, SaO_2lowest = lowest oxygen saturation on polysomnography, * = p<0.05, **= p<0.01, *** = p<0.001 is significantly different compared to HC based on post-hoc analyses, for AHI and SaO_2lowest, all groups significantly different from each other

Table 3. Cognitive complaints in healthy controls (HC) and patients with suspected OSA.

	Range	HC N=48	AHI<5 N=32	AHI 5-15 N=46	AHI 15-30 N=25	AHI≥ 30 N=24	ANOVA		
							df	F	p
CFQ									
Forgetfulness	8–40	18.3 (4.2)	21.9 (5.0)	22.1 (4.4)*	19.8 (5.2)	20.5 (5.2)	4;170	4.97	<0.01
Distractibility	8–40	16.9 (4.0)	20.0 (4.9)	20.4 (4.7)*	18.4 (5.3)	19.4 (4.4)	4;170	4.00	0.01
False triggering	8–40	14.1 (3.0)	16.9 (4.6)	16.3 (4.3)	15.2 (2.)	15.9 (5.1)	4;170	2.73	0.06
BRIEF-A									
Inhibit	8–24	11.8 (2.5)	12.4 (2.7)	12.3 (2.4)	13.0 (3.0)	12.7 (2.4)	4;169	1.30	0.27
Shift	8–24	8.8 (2.3)	9.6 (2.3)	9.7 (2.6)	9.5 (2.6)	10.1 (2.6)	4;169	1.38	0.27
Emotional control	8–24	14.0 (3.9)	15.9 (4.0)	16.5 (3.5)	15.2 (3.6)	16.2 (4.3)	4;169	2.89	0.06
Self-monitor	8–24	8.4 (2.0)	8.7 (2.1)	8.7 (2.3)	9.5 (2.7)	9.3 (1.8)	4;169	1.40	0.27
Initiate	8–24	10.8 (2.4)	11.8 (2.8)	12.8 (2.9)	12.3 (3.6)	14.1 (3.5)***	4;169	5.93	<0.001
Working memory	8–24	11.3 (2.4)	13.4 (3.4)	14.3 (3.3)***	13.0 (3.8)	13.9 (3.3)	4;169	6.10	<0.001
Plan/organize	8–24	9.0 (2.1)	14.3 (3.4)	15.3 (3.4)	14.6 (3.3)	15.9 (3.6)	4;169	2.46	0.07
Task monitor	8–24	9.7 (2.3)	9.4 (2.0)	10.1 (2.1)	10.0 (2.4)	10.2 (2.6)	4;169	1.96	0.14
Organization materials	8–24	11.2 (2.7)	12.4 (3.3)	12.5 (3.2)	13.4 (3.7)	13.1 (3.2)	4;169	2.58	0.07

AHI = apnea-hypopnea index; BRIEF-A = Behavior Rating Inventory of Executive Function Adult version; CFQ = Cognitive Failure Questionnaire; df = degrees of freedom between groups and within groups; OSA = obstructive sleep apnea patients; * = $p<0.05$; *** = $p<0.001$ is significantly different compared to HC based on post-hoc analyses.

3.4 Anxiety, Depression and Fatigue

Anxiety and depression were measured using the HADS anxiety and depression scales and fatigue was measured using the FAS scale, with results shown in Table 4. Patients with no or mild OSA reported more severe anxiety and depression symptoms than controls (all p's < 0.04). All OSA groups reported more fatigue than controls (all p's < 0.001). Anxiety, depression, and fatigue levels did not differ among OSA groups (all p's > 0.11).

3.5 Neuropsychological Tests

Patients and controls underwent a neuropsychological assessment that covered the domains of attention, memory, and executive functioning. Table 4 presents norm-corrected Z-scores for neuropsychological tests for all groups. Patients without OSA performed worse on episodic memory (RAVLT immediate recall) compared to controls (p < 0.01). No other significant differences were found across groups (all p's > 0.09).

3.6 Predictors of Cognitive Complaints in Suspected OSA

We performed multivariate regression analyses for all CFQ and BRIEF-A subscales (see Table 5 and 6). Models were significant (p < 0.04), except for BRIEF-A inhibit (p = 0.19) and BRIEF-A self-monitor (p = 0.67), with R^2 values ranging from 0.23 to 0.42. Higher ESS scores predicted forgetfulness (ß = 0.32, p < 0.001), distractibility (ß = 0.31, p = 0.01), and false triggering (ß = 0.34, p < 0.001). Higher HADS anxiety scores predicted more issues with shifting (ß = 0.40, p < 0.001), emotional control (ß = 0.35, p = 0.01), and planning/organizing (ß = 0.29, p = 0.03). Higher FAS scores were linked to more forgetfulness (ß = 0.32, p = 0.01), problems with initiation (ß = 0.35, p < 0.001), working memory issues, (ß = 0.37, p < 0.001), and planning/organizing difficulties (ß = 0.29, p = 0.03).

Table 4. Anxiety, depression, fatigue and performance on neuropsychological tests (norm-corrected Z-scores) in patients with suspected OSA and healthy controls (HC).

	Range	HC N=48	AHI<5 N=32	AHI 5-15 N=46	AHI 15-30 N=25	AHI≥ 30 N=24	ANOVA		
							df	F	p
HADS anxiety	0–21	3.8 (2.6)**	6.4 (2.8)**	6.3 (3.5)**	6.1 (3.5)	5.2 (2.5)	4;169	5.42	<0.001
HADS depression	0–21	3.4 (2.4)**	5.9 (3.7)**	5.9 (3.4)**	5.3 (3.7)	5.2 (3.3)	4;169	4.50	<0.01
FAS fatigue	10–50	20.7 (3.0)***	26.4 (4.6)***	26.8 (5.3)***	25.4 (5.1)**	26.9 (5.2)***	4;170	13.88	<0.001
Neuropsychological tests	Z-scores								
Digit span	M=0/SD=1	0.0 (.9)	0.0 (.8)	0.0 (1.2)	0.5 (.9)	0.0 (.9)	4;170	1.44	0.27
TMT AB-index	M=0/SD=1	0.2 (.8)	0.2 (.7)	-0.1 (.9)	0.1 (.9)	0.1 (1.0)	4;170	1.10	0.40
RAVLT immediate recall	M=0/SD=1	-0.2 (1.2)**	-1.2 (0.8)**	-0.6 (1.1)	-0.8 (1.1)	-0.5 (1.1)	4;170	4.50	<0.01
Verbal fluency	M=0/SD=1	0.6 (1.1)	0.1 (1.0)	0.1 (1.2)	0.1 (1.2)	-0.1 (0.9)	4;170	2.09	0.13
CNS-VS Reaction time	M=0/SD=1	-0.6 (1.1)	-0.9 (1.1)	-1.4 (1.6)	-0.8 (1.6)	-1.3 (1.8)	4;170	2.57	0.09
CNS-VS Processing speed	M=0/SD=1	-0.3 (0,9)	-0.6 (0.8)	-0.4 (0.8)	-0,3 (1,1)	-0,3 (0,9)	4;170	0.77	0.55
CNS-VS Complex attention	M=0/SD=1	-0.1 (1.2)	-0.4 (1.5)	-0.5 (1.4)	-1.1 (2.1)	-0.8 (1.2)	4;170	2.10	0.13
CNS-VS Cognitive flexibility	M=0/SD=1	-0.5 (1,0)	-0.7 (1.2)	-1.0 (1.3)	-1.3 (1.8)	-1.2 (1.2)	4;170	2.01	0.13

CNS-VSs = central nervous system vital signs; df = degrees of freedom between groups and within groups; FAS = Fatigue Assessment Scale; HADS = Hospital Anxiety and Depression Scale; HC = healthy controls; OSA = obstructive sleep apnea; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; **= p<0.01, *** = p<0.001 are significantly different from HC based on post-hoc analyses.

Table 5. Complaint-specific analyses of predictors for cognitive complaints in patients with suspected OSA using subscales of the CFQ.

	CFQ forgetfulness N=125 R^2=.36		CFQ distractibility N=125 R^2=.30		CFQ false triggering N=125 R^2=.25	
	Stand.ß	p-value	Stand. ß	P-value	Stand. ß	p-value
AHI	-.16	0.29	-.06	0.81	-.12	0.53
ESS, sleepiness	.32	<0.001***	.31	0.01*	.34	<.001***
HADS anxiety	.03	0.86	.21	0.22	-.05	0.86
HADS depression	.05	0.91	.07	0.86	.03	0.90
FAS, fatigue	.32	0.01*	.17	0.39	.22	0.63
Digit Span	.05	0.86	-.01	0.95	.00	0.97
TMT AB-index	.01	0.95	.05	0.86	.09	0.71
RAVLT immediate recall	.01	0.94	.08	0.71	.00	0.97
Verbal fluency	-.13	0.50	.00	0.95	-.14	0.50
CNS-VS Reaction time	.03	0.93	-.01	0.95	.06	0.86
CNS-VS Processing speed	.02	0.93	-.03	0.91	.03	0.90
CNS-VS Complex attention	.16	0.76	.16	0.78	.23	0.65
CNS-VS Cognitive flexibility	-.09	0.86	.10	0.86	-.19	0.76

AHI = Apnea-Hypopnea Index; CFQ = Cognitive Failure Questionnaire; CNS-VS = Central Nervous System – Vital Signs; ESS = Epworth Sleepiness Scale; FAS = Fatigue Assessment Scale; HADS = Hospital Anxiety and Depression Scale; RAVLT =Rey Auditory Verbal Learning Test; TMT = Trailmaking Test; * = $p<0.05$, *** = $p<0.001$.

Table 6. Complaint-specific analyses of predictors for cognitive complaints in patients with suspected OSA using subscales of the BRIEF-A.

	BRIEF-A shift N=124 R^2=.30		BRIEF-A emotional control N=124 R^2=.25		BRIEF-A initiate N=124 R^2=.42		BRIEF-A working memory N=124 R^2=.35		BRIEF-A plan/ organize N=124 R^2=.31		BRIEF-A task monitor N=124 R^2=.23		BRIEF-A organize materials N=124 R^2=.24	
	Stand. ß	p-value	Stand. ß	p-value	Stand.ß	p-value	Stand.ß	p-value	Stand.ß	p-value	Stand.ß	p-value	Stand.ß	p-value
AHI	.12	0.53	-.02	0.93	.21	0.07	.00	0.98	.15	0.35	.11	0.64	.12	0.56
ESS, sleepiness	.04	0.86	0.10	0.69	.11	0.58	.16	0.35	.08	0.75	.08	0.76	.20	0.24
HADS anxiety	.40	<0.001***	.35	0.01*	.08	0.76	.13	0.56	.29	0.03*	.18	0.36	.14	0.59
HADS depression	.07	0.85	-.13	0.65	.27	0.04	.13	0.59	.03	0.93	.06	0.86	.12	0.68
FAS, fatigue	.04	0.86	.23	0.19	.35	<.001***	.37	<0.001***	.29	0.03*	.21	0.26	.16	0.47
Digit Span	-.08	0.76	.05	0.86	.03	0.86	.09	0.69	-.04	0.86	.06	0.86	.06	0.86
TMT AB-index	.03	0.89	-.07	0.81	.09	0.69	.02	0.93	.04	0.86	-.04	0.87	-.08	0.78
RAVLT immediate recall	.13	0.50	.10	0.64	.09	0.66	.05	0.86	.08	0.75	.11	0.64	-.03	0.90
Verbal fluency	-.15	0.41	-.11	0.64	-.02	0.93	-.06	0.86	.02	0.94	.05	0.86	.01	0.95
CNS-VS Reaction time	-.01	0.96	.07	0.86	.06	0.86	-.03	0.90	-.02	0.95	.08	0.81	.08	0.81
CNS-VS Processing speed	-.14	0.50	.02	0.94	.08	0.76	.02	0.94	-.07	0.81	.05	0.86	.80	0.78
CNS-VS Complex attention	.08	0.87	.11	0.86	.28	0.49	.25	0.59	.09	0.86	.48	0.15	.37	0.35
CNS-VS Cognitive flexibility	.08	0.90	-.11	0.86	-.24	0.64	-.24	0.65	.04	0.94	-.45	0.28	-.29	0.59

AHI = Apnea-Hypopnea Index; BRIEF-A = Behavioral Rating Inventory for Executive Function Adult version; CNS-VSs = Central Nervous System Vital Signs; ESS = Epworth Sleepiness Scale; FAS = Fatigue Assessment Scale; HADS = Hospital Anxiety and Depression Scale; RAVLT =Rey Auditory Verbal Learning Test; TMT = Trail Making Test; * = p<0.05; *** = p<0.001; models for BRIEF-inhibit, BRIEF-A self-monitor are not listed because they were not significant (all p's >0.05).

3.7 Cognitive Complaints and OSA Diagnosis

Not only did we categorize patients in different groups based on the AHI, we also split patients into those who received an OSA diagnosis based on clinical criteria (see Section 2.1.1.) and those who did not meet clinical criteria for OSA. Of the 127 patients suspected of OSA, 89 (70%) received an OSA diagnosis based on clinical criteria. Table 7 presents total CFQ and BRIEF-A scores for patients with and without a clinical OSA diagnosis, and healthy controls. Patients without OSA reported more cognitive complaints on the CFQ than controls (p = 0.04). Those with an OSA diagnosis reported more complaints on the BRIEF-A than controls (p = 0.02). However, cognitive complaints did not significantly differ between patients with and without an OSA diagnosis (all p's > 0.06).

Table 7. Total scores on the CFQ and BRIEF-A for healthy controls and patients suspected of OSA with and without final OSA diagnosis.

	Range	healthy controls	suspected OSA				
		N=48	no OSA diagnosis N=38	OSA diagnosis N=88	ANOVA		
					df	F	p
CFQ	25–125	52.5 (10.4)	60.8 (12.9)**	59.0 (14.7)	2;171	5.03	<0.01
BRIEF-A	75–225	106.6 (19.0)	117.1 (19.7)	120.7 (23.7)**	2;169	6.63	<0.01

BRIEF-A = Behavioral Rating Inventory for Executive Function Adult version; CFQ = Cognitive Failure Questionnaire; df = degrees of freedom between groups and within groups, OSA = obstructive sleep apnea; **= p<0.01 is significantly different compared to HC based on post-hoc analyses.

3.8 Cognitive Complaints and Cognitive Impairments

Patients were categorized as cognitively impaired if the score of two or more neuropsychological tests fell below international criteria for cognitive impairments[22]. Cognitive impairment was identified in 34% of the subjects with no OSA, 53% of those with mild OSA, 56% of those with moderate OSA, and 25% of those with severe OSA. Table 8 shows the CFQ and BRIEF-A scores for cognitively impaired and unimpaired patients across severity levels. Within each OSA severity group, cognitive complaints did not differ between impaired and unimpaired patients (all p's > 0.16).

Table 8. Total scores on the CFQ and BRIEF-A for patients with and without cognitive impairments across various OSA severities.

OSA severity	Cognitive impairment	N	CFQ	p-value	BRIEF-A	p-value
AHI <5	yes	11	59.2 (15.8)	0.89	118.2 (24.5)	0.89
	no	21	62.2 (12.8)		116.1 (16.5)	
AHI 5-15	yes	16	62.1 (10.7)	0.90	120.4 (19.7)	0.89
	no	30	61.6 (12.9)		117.3 (27.9)	
AHI 15-30	yes	14	51.4 (16.1)	0.89	113.8 (23.2)	0.59
	no	11	55.5 (20.8)		125.9 (24.1)	
AHI ≥30	yes	6	48.0 (7.0)	0.16	114.2 (10.6)	0.59
	no	18	62.2 (13.2)		127.7 (23.0)	

BRIEF-A = Behavioral Rating Inventory for Executive Function Adult version; CFQ = Cognitive Failure Questionnaire; OSA = obstructive sleep apnea.

4. DISCUSSION

This study examined cognitive complaints in patients referred to a sleep clinic with suspected OSA. Compared to a healthy control group, patients with mild OSA (AHI 5–15) reported more frequent complaints related to forgetfulness, distractibility, and working memory, with large effect sizes. Patients with severe OSA (AHI ≥ 30) reported greater difficulties with taking initiative, also with a large effect size. These findings expand the existing literature by highlighting that OSA patients not only report memory and attention-related issues but also complaints associated with executive functioning[6]. Furthermore, our results suggest that the nature of cognitive complaints may vary with OSA severity. Interestingly, cognitive complaints were also prevalent in individuals referred to the sleep clinic under suspicion of OSA, regardless of whether they received an OSA diagnosis. This suggests that cognitive complaints are not specific to OSA, but common among individuals with sleep complaints suspected of OSA.

Our findings indicate that subjective sleepiness, anxiety, and fatigue were the strongest predictors of cognitive complaints, independent of OSA severity. This aligns with previous research demonstrating a link between subjective sleepiness and cognitive complaints[6], as well as studies in other medical conditions that have highlighted the role of fatigue and anxiety in self-reported cognitive difficulties[16-17]. The cross-sectional design of our study limits causal conclusions, but bidirectional relationships may exist. Anxiety, fatigue, and sleep problems may contribute to cognitive complaints

by impairing focus and increasing distractibility[23]. Anxiety also increases vigilance, leading to catastrophizing and over-reporting minor cognitive lapses[19,24]. Similarly, fatigue and sleep disturbances can exacerbate cognitive complaints by impairing working memory and attention[25,26]. Conversely, cognitive complaints may themselves contribute to increased stress, worry, and fatigue[27], perpetuating poor sleep and daytime dysfunction. Future longitudinal studies are needed to clarify these relationships.

Our results also showed that cognitive complaints in OSA are not directly related to cognitive performance or underlying cognitive impairments. Despite 25–53% of our patients being classified as cognitively impaired, these individuals were not more likely to report cognitive complaints. This finding is consistent with prior studies in OSA[6] and underscores the complexity of cognitive complaints. Clinicians should be aware that cognitively impaired patients may not report difficulties due to lack of insight, denial, or reduced awareness of deficits. Moreover, standard neuropsychological tests may not adequately capture daytime vigilance impairments, which are commonly observed in sleep disorders like OSA[28]. Traditional tests assess cognitive abilities under optimal conditions, potentially overlooking fluctuations in alertness and attention deficits caused by sleep disruption[28,29].

A key strength of this study is the use of validated questionnaires to assess cognitive complaints across multiple domains, along with the inclusion of patients across the full spectrum of OSA severity. By comparing OSA patients with both healthy controls and sleep center patients without OSA, we gained two important insights. First, cognitive complaints can be present even in mild OSA and in individuals without a formal OSA diagnosis. Second, non-OSA-specific factors, such as fatigue, anxiety, and subjective sleepiness, play a significant role in cognitive complaints, emphasizing the need to assess these symptoms alongside OSA severity.

This study has limitations as well. First, we only assessed AHI as a measure of OSA severity. Emerging research suggests that OSA is a heterogeneous condition with phenotypic subtypes, characterized by varying degrees of symptoms such as sleep fragmentation, hypoxemia, and daytime sleepiness[29]. These phenotypes may be linked to different patterns of cognitive dysfunction[30]. While prior studies have explored phenotypic differences in objective cognitive impairment[31], no research has yet investigated whether subjective cognitive complaints differ between OSA phenotypes. Understanding these differences could provide insight into why some patients experience pronounced cognitive complaints despite minimal objective deficits, whereas others with cognitive impairments report few complaints. Large cohort studies are needed to explore these associations, as our sample size was too small for such an analysis. Future research should examine whether distinct OSA phenotypes are associated with specific patterns of

cognitive complaints and whether this could inform personalized treatment approaches.

Second, dropout analyses revealed that women were more likely to discontinue participation, potentially limiting the generalizability of our findings to female patients. There is evidence suggesting that women with medical diseases may be more prone to cognitive complaints than men[16], making gender-specific analyses an important area for future research. Additionally, our sample was predominantly white European, limiting the applicability of findings to more diverse populations. Prior research has indicated that predictors of cognitive complaints may vary across racial and ethnic groups, highlighting the need for studies with more diverse participant samples and limiting the generalizability of findings. Prior research has indicated that predictors of cognitive complaints may vary across racial and ethnic groups[32].

This study has important clinical implications. At sleep clinics, clinicians should be cautious when attributing cognitive complaints solely to OSA or to cognitive impairments, especially in patients without neurological or psychiatric comorbidities. Our findings suggest that cognitive complaints in this population are more strongly linked to symptoms such as fatigue, anxiety, or other sleep problems rather than OSA itself. When patients report cognitive complaints, additional evaluations for coexisting sleep problems (e.g., insomnia), anxiety, or fatigue-related conditions should be considered. Treatment strategies targeting these symptoms, such as cognitive behavioral therapy for insomnia or psychological interventions for anxiety and fatigue, may be beneficial.

Future studies should focus on the generalizability of the findings by including more women and participants from diverse racial and ethnic backgrounds. Moreover, studies should focus on OSA patients outside sleep centers, such as those identified through general community screening, or those with neurological or psychiatric comorbidities, to test the generalizability of our findings. Another crucial area of future research is to investigate the effect of OSA treatment on cognitive complaints. While OSA treatments, such as CPAP or mandibular advancement devices, are known to improve sleepiness[33] and mood symptoms[34], their impact on cognitive complaints remains poorly understood. Given the links between cognitive complaints, sleepiness, and mood disturbances, it is plausible that OSA treatment could alleviate cognitive complaints as well. Randomized controlled trials (RCTs) assessing the effects of OSA treatment on cognitive complaints, particularly in relation to subjective sleepiness and mood symptoms, are needed to clarify these potential benefits.

5. CONCLUSIONS

Cognitive complaints are common among patients seeking evaluation for suspected OSA, regardless of the final diagnosis. In OSA patients, cognitive complaints were linked to subjective sleepiness, anxiety, and fatigue. However, the complaints did not reflect objective cognitive impairments. Patients can be reassured that their cognitive concerns are unlikely to indicate true cognitive deficits. When complaints persist, further evaluation and treatment of sleep disturbances, anxiety, and fatigue should be considered.

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CHAPTER 5

Cognitive Complaints In Obstructive Sleep Apnea: The Overlooked Role Of Coping Styles

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ABSTRACT

Objective: Cognitive complaints are common in obstructive sleep apnea (OSA) but do not correlate with objective cognitive impairments, leaving their underlying cause unclear. The present study aims to (1) compare coping styles between OSA patients and healthy controls, and (2) investigate the relationship between cognitive complaints and various coping styles in OSA patients.

Methods: In a cross-sectional design, cognitive complaints and coping styles were compared between OSA patients (n=24) and healthy controls (n=15). Validated questionnaires were used to assess cognitive complaints (Cognitive Failure Questionnaire, CFQ; Behavior Rating Inventory of Executive Function for adults, BRIEF-A) and coping styles (Utrecht Coping List, UCL). Additional variables included demographics, indicators of OSA severity, sleep quality, subjective sleepiness, anxiety, depression, and cognitive impairments. Pearson correlations were used to identify variables associated with cognitive complaints. These variables were then included as controls in hierarchical regression analyses to determine the unique contribution of coping styles to explaining cognitive complaints.

Results: Compared to healthy controls, OSA patients reported more cognitive complaints on the CFQ and reported a more passive coping style. In OSA patients, reduced active problem-solving on the UCL was independently associated with higher CFQ scores ($\beta = -0.43$), regardless of AHI, anxiety or depression symptoms. Avoidant ($\beta = 0.49$) coping styles were independently linked to higher BRIEF-A scores. Coping styles accounted for 51% to 59% of the variance in cognitive complaints among OSA patients.

Conclusions: Psychological mechanisms, specifically avoidant and less pro-active coping styles, significantly contribute to cognitive complaints in OSA, independent of OSA severity and symptoms of anxiety and depression. Psychological interventions improving coping skills may benefit OSA patients experiencing cognitive complaints.

1. INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent disorder, affecting 9-38% of the general population[1], and is characterized by repeated upper airway obstruction during sleep, leading to intermittent hypoxemia and sleep fragmentation. Cognitive complaints are subjective and self-reported difficulties in cognitive functioning as assessed by questionnaires or interviews [2]. They are common in OSA, with 59% of patients reporting memory difficulties and 69% reporting problems with concentration [3]. These issues are most frequent in untreated OSA[3], but may also persist following treatment, e.g. with continuous positive airway pressure (CPAP)[4]. The causes behind cognitive complaints are still poorly understood. While extensive literature shows that OSA patients tend to exhibit cognitive impairments[5,6] on standard neuropsychological tests, there is no clear evidence linking cognitive complaints directly to these impairments[7]. Interestingly, recent studies suggest that OSA patients with cognitive impairments are less likely to report cognitive complaints than those without impairments [8,9]. One study highlighted that cognitive complaints are more closely associated with subjective sleepiness[7], indicating in OSA they may be more connected to poor sleep quality.

Cognitive complaints have also been examined in other neurological or respiratory conditions, as well as in the general population. In various disorders these complaints have been correlated with symptoms of anxiety, depression and fatigue[10,11], symptoms commonly associated with stress[12]. In the general population, cognitive complaints have been linked to personality traits such as neuroticism[13], where individuals high in neuroticism are more prone to experiencing negative emotions and greater difficulty in stress regulation. In healthy elderly individuals, an avoidant coping with stress, as measured by self-report, has been associated with cognitive complaints, regardless of underlying cognitive impairment.[14]. These findings suggest that cognitive complaints in both the general population and in disease contexts may be related to inadequate coping mechanisms[15]. Despite the recognized elevation of stress in OSA patients[12], no study to date has explored the relationship between cognitive complaints and coping strategies in OSA.

The present study is part of a broader investigation into cognitive complaints in OSA. Questionnaires assessing coping styles were added in an exploratory phase to investigate whether psychological coping mechanisms might help explain why some OSA patients experience persistent cognitive complaints. Specifically, we aimed to (1) compare coping styles between OSA patients and healthy controls, and (2) explore whether particular coping styles are associated with cognitive complaints in OSA patients, while controlling for sleep quality, subjective sleepiness, anxiety, depression, and cognitive impairments.

2. METHODS

2.1 Design and procedure

Data came from a cross-sectional study on cognitive complaints in OSA that was conducted at VieCuri Medical Center and Reinier de Graaf Hospital in the Netherlands. The study adhered to the Declaration of Helsinki and received approval from a nationally certified medical ethical committee (NL37795.068.11, data collected from June 2012 till April 2018). Written informed consent was obtained from all participants.

Patients suspected of OSA (identified through reports of snoring and apneas by partners or family) from the sleep units of both hospitals participated the day before their overnight diagnostic polysomnography (PSG). They completed questionnaires on cognitive complaints, anxiety and depression and sleep quality and underwent an extensive neuropsychological assessment. Healthy controls followed the same protocol, except they filled in a two-week sleep diary instead of undergoing a PSG.

2.2 Participants

2.2.1 OSA patients

Patients with an apnea-hypopnea index (AHI) greater than 5 and aged 18 years or older were eligible. Exclusion criteria included: (1) non-native Dutch speakers, (2) substance or alcohol abuse (more than three units of alcohol per day for males and more than two units per day for females, as verified by verbal report and medical records), (3) diagnosis of a psychiatric disorder, (4) use of cognition-affecting medication according to the Dutch Medicine Authority, including benzodiazepines, antipsychotics, antidepressants, antiepileptics, mood stabilisers, opioids and psychostimulants (as checked by verbal report and medical records), (5) neurological diseases, diabetes mellitus, hypo- or hyperthyroidism, or pulmonary diseases (as verified by verbal report and medical records).

2.2.2 Healthy controls

Healthy controls were recruited from the family members of personnel from other units (unrelated to the sleep units) of the participating hospitals. Participants were also recruited through family members of hospital staff. Inclusion criteria required a low suspicion of a sleep disorder based on: (1) no reports of snoring or apneas (as verified by verbal report of the participant's partner), (2) a score of 7 or lower on the Pittsburgh Sleep Quality Index (PSQI)[16], (3) an average sleep efficiency of 80% or higher on a two-week sleep diary. The same exclusion criteria 1 to 5 as listed for OSA patients were applied.

2.3 Materials

2.3.1 Demographic characteristics, OSA severity, subjective sleepiness, anxiety and depression

Data on age, sex, and educational level were collected for all participants. Educational level was rated according to the Dutch Verhage system, a 7-point scale similar to the International Standard Classification of Education[17] but adapted to the Dutch educational system. For OSA patients, both AHI and the lowest nighttime oxygen saturation (SaO_2lowest) from the overnight PSG were used as measures of OSA severity. In both OSA patients and healthy controls, sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI)[16], a validated and reliable self-report questionnaire consisting of 19 items that result in a total score ranging from 0 to 21. A higher score indicates poorer sleep quality, with a total score above 8 indicating significant sleep disturbances[18,19]. Subjective sleepiness was measured using the Epworth Sleepiness Scale (ESS), a widely accepted standard questionnaire [20]. Higher scores indicate more severe sleepiness, with scores above 10 indicating excessive daytime sleepiness [20]. Depression and anxiety symptoms were measured using the anxiety and depression scale of the Hospital Anxiety and Depression Scale (HADS) [21]. A higher score on both subscales indicates more severe symptoms of anxiety or depression.

2.3.2 Cognitive complaints

Cognitive complaints were assessed using the total scores of the Cognitive Failure Questionnaire (CFQ)[22] and the Behavior Rating Inventory of Executive Function for adults (BRIEF-A)[23]. The CFQ is a validated and reliable instrument that assesses the severity of everyday cognitive complaints in the last three months and consists of 25 items. Every item is rated on a 5-point Likert-scale (ranging from "never" to "very often"). Higher scores indicate a higher severity of everyday cognitive complaints. The total score is a sum of 25 items (range 25-125). The BRIEF-A is a validated and reliable questionnaire assessing the severity of complaints related to executive functioning in the last month and consists of 75 items. Every item is rated on a 3-point Likert-scale ("never", "sometimes" and "often"). Higher scores indicate more severe complaints related to executive functioning. The total score is a sum of 75 items (75-225). If one item was missing on the CFQ or BRIEF-A, it was replaced by the average score of the same questionnaire. If more than one item was missing the questionnaire was labeled as missing

2.3.3 Coping styles

Three subscales of the Utrecht Coping List (UCL) were used to evaluate coping style[24]: (1) active problem solving, which reflects a constructive and goal-

oriented approach to resolving difficulties; (2) passive coping, which involves withdrawal, rumination, and feelings of helplessness in response to stress; (3) avoidance, characterized by distraction or evasion rather than addressing problems directly. Each item is rated on a 4-point rating scale ranging from 1 (never) to 4 (very often). Total scores are computed for each subscale with higher scores indicating a preference for a specific coping style. The UCL has moderate to good internal consistency and test–retest reliability[25]. If one item was missing on any of the subscales, it was replaced by the average score of the same subscale. If more than one item was missing the subscale was labeled as missing.

2.4 Cognitive impairment

Neuropsychological tests included assessments for working memory (WAIS-III digit span)[26], episodic verbal memory (immediate recall Rey Auditory Verbal Learning Test) [27] and divided attention (AB-index of Trailmaking Test) [28]. The computerized test battery Central Nervous System-Vital Signs (CNS-VS) provided domain scores for reaction time, processing speed, complex attention, and cognitive flexibility[29]. All scores were norm-corrected into Z-scores adjusted for age, sex, and educational level, except for WAIS-III digit span, which used only age-corrected norms. According to the Cognitive Impairment Non-Dementia (CIND) criteria, a test score is impaired if the norm-corrected Z-score is below -1.65. OSA patients were categorized as having cognitive impairment if two or more neuropsychological test scores were impaired.

2.5 Statistics

Data are presented as mean ± standard deviation (SD) or percentages. OSA patients and healthy controls were compared on demographic variables (age, sex, education), sleep quality (PSQI), anxiety, depression (HADS), cognitive impairments, subjective sleepiness (ESS), cognitive complaints (CFQ, BRIEF-A), and UCL scales for active problem solving, passive coping, and avoidance. The associations between demographic variables, OSA severity, sleep quality, subjective sleepiness, anxiety, depression, cognitive impairments, coping styles, and cognitive complaints were determined using Pearson product-moment correlations (r) (unadjusted model). Multiple linear hierarchical regression analysis was used to determine which coping styles were independently associated with cognitive complaints. Only variables that showed a significant or near-significant association ($p < .10$) in the unadjusted model were included in the regression models. These variables were entered in the first block, with the added predictive value of all three coping styles examined in the second block (adjusted model). Regression coefficients (standardized β) indicate the strengths of the associations for each variable,

and R^2 describes the amount of variance explained by the model. Two-sided p-values <.05 were considered statistically significant. All statistical analyses were performed using SPSS 26.0.0.0 for Windows.

3. RESULTS

3.1 Participants

Demographic and sleep characteristics are presented in Table 1. Two healthy controls (HC) were excluded to ensure matching with the OSA group in terms of age, sex, and educational level (all p's >.13). OSA severity varied from mild to severe (AHI range: 5.7–65.7; median: 15.6; interquartile range: 25.8). Cognitive impairments were present in 56% of OSA patients compared to 13% of HCs ($p < .01$). No significant differences were observed between OSA and HCs in subjective sleepiness (ESS), anxiety, depression or in the proportion reporting severe sleepiness (all p's >.15). However, OSA patients reported more severe sleep disturbances (PSQI) compared to HCs and were more likely to experience significant sleep problems (all p's < .01).

Table 1. Demographic characteristics and sleep measures for OSA and healthy controls

		OSA	Healthy Controls	
Characteristics	Range	N=25	N=15	p-value
Age	>18	48.3 (10.8)	53.3 (7.2)	.13
Sex (%male)	0-100	72%	56%	.43
Educational level	1-7	5.7 (1.1)	5.7 (0.9)	.19
HADS anxiety	0-21	6.3 (3.2)	5.2 (2.5)	.33
HADS depression	0-21	5.5 (2.6)	4.1 (3.4)	.15
Cognitive impairment %	0-100	56%**	13%	<.01
AHI	≥5	22.9 (19.8)	-	
Lowest SAO_2	<100%	83.0 (6.2)	-	
ESS	0-24	7.7 (4.4)	6.4 (5.1)	.39
ESS >10	0-100	28%	33%	.72
PSQI	0-21	7.6 (3.5)***	3.7 (1.9)	<.001
PSQI>8	0-100	42%**	0%	<.01

AHI = Apnea-Hypopnea Index, ESS = Epworth sleepiness scale, PSQI = Pittsburgh sleep quality index, SAO_2 = Oxygen Desaturation. * = p<.05, **= p<.01, *** = p<.001.

3.2 Cognitive complaints and coping styles

Table 2 displays the mean scores for cognitive complaints (CFQ, BRIEF-A) and coping styles (UCL-active problem solving, passive coping, avoidance) for both OSA patients and HCs. OSA patients reported a higher frequency of cognitive complaints on the CFQ compared to HCs (p = .02), though no significant difference was found for the BRIEF-A (p = .09). OSA patients were also more likely to report an avoidant and passive coping styles compared to HCs (p < .02). No significant differences were observed in reported active problem-solving strategies between the two groups (p =.27).

Table 2. Cognitive complaints and coping styles in OSA and healthy controls

		OSA	Healthy Controls	
	Range	N=25	N=16	p-value
CFQ	25-125	64.0 (10.5)*	55.1 (12.9)	.02
BRIEF-A	25-225	127.0 (20.0)	114.7 (22.8)	.09
UCL-active problem solving	7-28	17.9 (3.7)	19.2 (3.3)	.27
UCL-passive coping	7-28	12.9 (2.8)*	10.5 (2.7)	.01
UCL-avoidance	8-32	17.0 (2.8)*	14.7 (3.1)	.02

CFQ = Cognitive Failure Questionnaire, BRIEF-A = Behavior Rating Inventory of Executive Function for Adults, ESS = Epworth Sleepiness Scale, UCL = Utrecht Coping List, * = p<.05

3.3 The role of coping styles in cognitive complaints

3.3.1 Unadjusted models

Correlations between demographic variables (age, sex, education), OSA severity (AHI, lowest SaO_2), sleep quality (PSQI), subjective sleepiness (ESS), anxiety and depression (HADS), cognitive impairments, coping styles and cognitive complaints are provided in Table 3. In the unadjusted model, cognitive complaints were negatively correlated to active coping styles (r =.-45) and positively correlated to avoidant coping styles (r = .50) for CFQ (both p's < .02). For BRIEF-A passive (r = .58) and avoidant (r = .68) coping styles were positively correlated to cognitive complaints (both p's < .01). There was a trend for cognitive complaints to be correlated to AHI (r = -.36, p= .08) and anxiety (r = .37, p= .08) for CFQ and for BRIEF-A there was a trend for a correlation with depression (r = .36, p= .09). Cognitive complaints were unrelated to demographic variables, PSQI, ESS and cognitive impairments (all p's >.13).

Table 3. Unadjusted model: correlations between cognitive complaints, demographic variables, sleep measures, anxiety, depression, cognitive impairments and coping styles.

	CFQ N=25		BRIEF-A N=23	
	Pearson's r	p-value	Pearson's r	p-value
Age	.09	.67	.16	.48
Sex (%male)	-.07	.75	.20	.37
Educational level	.08	.70	.04	.84
AHI	-.36	.08*	-.16	.48
Lowest SAO_2	.00	.98	.17	.44
ESS	.09	.66	-.07	.77
PSQI	.05	.84	.12	.58
HADS anxiety	.37	.08*	.32	.13
HADS depression	.18	.40	.36	.09*
Cognitive impairment	-.08	.84	.22	.58
UCL active problem solving	-.45	.02**	-.09	.68
UCL passive coping	.39	.58	.58	<.01***
UCL avoidance	.50	.01**	.68	<.001****

AHI = Apnea-Hypopnea Index, ESS = Epworth sleepiness scale, HADS = Hospital Anxiety and Depression Scale, PSQI = Pittsburgh sleep quality index, SAO_2 = Oxygen Desaturation, * = p<.10, **= p<.05, ***=p<.02, ****=p<.001

3.3.2 Adjusted models

Regression analyses are summarized in Table 4. In the first step, variables that were associated with cognitive complaints in the unadjusted models were included (AHI, anxiety, depression). These variables did not significantly predict either CFQ or BRIEF-A scores (both p's >.22). However, after adding coping styles to the models, the predictive power significantly increased for both the CFQ ($F(6,23) = 2.99$, $p = .04$) and the BRIEF-A ($F(6,21) = 3.77$, $p = .02$). The inclusion of coping styles raised the explained variance from 19% to 51% for the CFQ and from 19% to 59% for the BRIEF-A. Active problem-solving (UCL) was independently and negatively associated with CFQ scores ($\beta = -.43$, $p = .03$) but not with BRIEF-A scores ($p = .93$). Avoidant coping (UCL) was independently associated with BRIEF-A scores ($\beta = .49$, $p = .02$). Passive coping was not significantly associated with either CFQ or BRIEF-A scores (both p's > .10).

Table 4. Hierarchical regressions between cognitive complaints, OSA severity, anxiety, depression and coping styles

	CFQ N=25	BRIEF-A N=23
	R^2=.51	R^2=.59
	Stand. β (p-value)	Stand. β (p-value)
AHI	-.33 (.10)	.02 (.91)
HADS		
anxiety	.04 (.84)	.05 (.81)
depression	-.07 (.72)	.12 (.53)
UCL		
active problem solving	-.43 (.03)*	-.01 (.93)
passive coping	.19 (.37)	.34 (.10)
avoidance	.29 (.16)	.49 (.02)*

AHI = Apnea-Hypopnea Index CFQ = cognitive failure questionnaire, BRIEF-A = behavior rating inventory of executive function for adults, HADS = Hospital Anxiety and Depression Scale, UCL = utrecht coping list, * = p<.05.

4. DISCUSSION

This study is the first to explore how coping styles relate to cognitive complaints in OSA patients. Our findings show that greater use of avoidant coping –characterized by distraction or evasion rather than directly addressing problems– and lower levels of active problem-solving –reflecting constructive and goal-oriented responses to stress– are both significantly associated with higher levels of cognitive complaints in newly diagnosed OSA patients. These associations remained significant even after controlling for AHI, symptoms of anxiety and depression, subjective sleepiness, and objective cognitive impairments. This suggests that individuals who rely more on maladaptive coping strategies may be more vulnerable to experiencing cognitive difficulties in daily life, regardless of the severity of their sleep apnea or emotional and cognitive status. These results highlight the potential role of psychological mechanism in shaping the subjective experience of cognitive dysfunction in OSA.

These findings align with previous research in other clinical populations showing that avoidant coping styles [15,30,31] are related to higher levels of cognitive complaints, regardless of objective cognitive impairments. Importantly, in our study, coping styles remained significantly associated

with cognitive complaints even after controlling for symptoms of anxiety and depression, suggesting that the impact of coping is not merely a reflection of emotional distress. This is particularly relevant given that psychological symptoms are common in OSA: approximately 15–29% of patients experience clinically significant symptoms of anxiety and depression [32], and up to 38% report pathological fatigue [32]. Coping styles may influence how individuals perceive and respond to cognitive difficulties. They promote attentional bias [33], and foster negative interpretations [34] of minor cognitive lapses, thereby amplifying their perceived severity. In contrast, proactive coping has been shown to protect against such complaints [15,35], possibly by promoting adaptive responses to stress and enhancing a sense of control. Our findings emphasize the importance of exploring psychological mechanisms such as coping in the broader context of OSA-related cognitive complaints, especially given the limited effectiveness of standard OSA treatments (e.g., CPAP) in alleviating subjective cognitive complaints [4].

Previous studies have primarily focused on the roles of cognitive impairments and sleepiness in cognitive complaints. Consistent with the literature, we found no association between cognitive complaints and cognitive impairments [7,9,42,43]. This underscores that cognitive complaints are not reliable indicators of cognitive impairments and that OSA patients with cognitive impairments may not always report such complaints. The lack of a strong relationship between cognitive complaints and cognitive impairments may stem from a dual phenomenon: 1) underreporting by patients with actual impairments [8,44], due to lack of insight, denial, or downplaying, and 2) overreporting by those without impairments, often driven by heightened sensitivity to cognitive lapses [45]. This discrepancy reflects a psychological mechanism where patients with impairments may fail to recognize or acknowledge their deficits, while those without impairments may interpret normal lapses as evidence of significant dysfunction. In addition, methodological factors may also contribute to the often low correlations between cognitive complaints and cognitive impairments. Many studies in the OSA field are cross-sectional and vary widely in how they conceptualize and measure cognitive complaints and cognitive impairment [46]. This heterogeneity—both in assessment tools and in the cognitive domains evaluated—limits comparability across studies and may obscure potential associations. Contrary to the literature, we did not find a relationship between subjective sleepiness and cognitive complaints [7,9,47,48], which could be attributed to the low levels of sleepiness in our OSA sample. Typically, OSA is associated with high levels of sleepiness[49], but the OSA patients in our study did not differ from healthy controls in terms of sleepiness, indicating a relatively mild impact on daily functioning. Nevertheless, our findings highlight that even in the absence of cognitive impairments or excessive sleepiness, OSA patients may report cognitive complaints, with psychological mechanisms playing a role in this phenomenon.

4.1 Strengths and limitations

A strength of this study is the use of two validated questionnaires for assessing cognitive complaints (CFQ, BRIEF-A). Although the sample size was relatively small, we found strong effects of coping styles, with these variables explaining 51% to 59% of the variance in cognitive complaints. This suggests a meaningful relationship between coping and cognitive complaints in OSA that warrants further investigation. To minimize the risk of overfitting, only variables showing significant or near-significant associations in preliminary analyses were included in the regression models. Nonetheless, the findings should be interpreted with caution and replicated with larger samples, also differentiating between different OSA severities. Some other limitations should be mentioned. A limitation is that healthy controls did not undergo a PSG, so the presence of undiagnosed sleep disorders cannot be entirely ruled out. However, strict exclusion criteria were applied, including a validated sleep questionnaire (PSQI) and a two-week sleep diary, and the main regression analyses were limited to OSA patients. The cross-sectional design precludes causal conclusions; thus, we cannot determine whether inadequate coping causes cognitive complaints or whether cognitive complaints lead to a more cautious approach to problems and passive coping style. Additionally, disrupted sleep in OSA may lower tolerance for stress[50] and cognitive mishaps. Since cognitive complaints can persist after CPAP treatment[4], future prospective studies should explore whether patients with residual cognitive complaints would benefit from psychological interventions. Such research could further elucidate the relationship between coping styles and cognitive complaints. Moreover, our results may not generalize to all OSA patients, as our sample had relatively low subjective sleepiness. Previous studies have linked sleepiness to cognitive complaints[7], so follow up studies may show to what extent these findings apply to patients with higher levels of sleepiness.

5. CONCLUSIONS

Cognitive complaints are common in OSA but are poorly understood, as they have so far not been linked to cognitive impairments. Our study demonstrates that psychological mechanisms, particularly passive and avoidant coping and low active problem-solving, are related to cognitive complaints. This relationship is independent of AHI, anxiety and depression. To better understand the connection between coping styles and cognitive complaints, future research should replicate our findings in larger samples and investigate psychological interventions aimed at improving coping styles in OSA patients who continue to experience cognitive complaints after successful treatment of OSA.

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CHAPTER 6

Treating Obstructive Sleep Apnea May Ease Cognitive Complaints

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ABSTRACT

Purpose: Cognitive complaints are common in obstructive sleep apnea (OSA) and affect quality of life, yet they are not linked to objective cognitive impairments. OSA treatment in the form of continuous positive airway pressure (CPAP) or mandibular advancement devices (MAD) may improve cognitive impairments, but their effects on cognitive complaints remain unclear.

Methods: This study compared 31 newly diagnosed OSA patients with 36 healthy controls (HC). Both groups completed the Cognitive Failure Questionnaire (CFQ) and Behavioral Rating Inventory for Executive Function-Adult Version (BRIEF-A) at baseline and after 6 months follow up, for the patients under CPAP (n=22) or MAD (n=9) treatment. A 2-way mixed ANOVA was used to examine group (OSA vs. HC) and time (baseline vs. follow-up) effects on CFQ and BRIEF-A subscales. Reliable change indices assessed individual changes. Pearson's correlations analysed associations between changes in cognitive complaints, apnea-hypopnea index (AHI), and Epworth sleepiness scale (ESS).

Results: OSA patients showed significant reductions in CFQ "forgetfulness" and BRIEF-A "working memory" at 6 months follow-up, while HC did not. Reliable change indices indicated greater individual improvements in CFQ "forgetfulness" in the OSA group compared to HC. Changes in cognitive complaints were not correlated with reduction in the apnea-hypopnea index but were significantly related to improvements in ESS for CFQ "false triggering" and BRIEF-A "task monitoring" and "organization of materials".

Conclusion: OSA treatment may reduce cognitive complaints, particularly regarding forgetfulness and working memory. Improvements in cognitive complaints were related to reduced daytime sleepiness, not to apnea-hypopnea index.

1. INTRODUCTION

In obstructive sleep apnea (OSA), the upper airway (partially) collapses in recurrent episodes during sleep obstructing air flow into the lungs, causing oxygen desaturations, and sleep disruption in the form of arousals and fragmented sleep[1]. Daytime symptoms of OSA include excessive sleepiness and fatigue[2]. OSA is also linked to both impaired (objective) cognitive performance[3,4] and the report of (subjective) cognitive complaints[5,6]. Cognitive complaints in OSA are unrelated to impaired cognitive performance[10]. On one hand, it appears OSA patients with cognitive impairments are less aware of their impairments and underreport cognitive complaints [5,10]. Other studies suggest OSA patients without cognitive impairments may overreport cognitive complaints[11]. Cognitive complaints are related to health care utilization and a higher incidence of sick leave and therefore it is important to understand how to best treat cognitive complaints in OSA, regardless of underlying objective cognitive impairments.

The current reference treatment for OSA is continuous positive airway pressure (CPAP)[12]. CPAP is effective in reducing the number of hourly nighttime respiratory events (apnea-hypopnea index, AHI)[14], subjective sleepiness[14], fatigue[15] and symptoms of depression and anxiety[16]. An often used alternative treatment uses a mandibular advancement device (MAD), which mechanically moves the jaw and tongue forward to make space in the upper airway during sleep [17]. Though CPAP appears slightly more effective than MAD in reducing AHI[18,19], both treatments perform equally on outcome measures such as subjective sleepiness[17].

Studies on the effect of CPAP or MAD on cognition have primarily focused on (objective) cognitive performance and much less on (subjective) cognitive complaints. The effects of CPAP on cognitive performance are small[20] and cognitive impairments may persist even after successful treatment with CPAP[21,22]. There are even fewer studies on MAD and cognitive performance, but results appear comparable to CPAP [18]. Cognitive complaints have rarely been used as an outcome measure for CPAP or MAD trials. The limited CPAP studies suggest a potential positive effect[23], although cognitive complaints may persist after successful CPAP treatment [24]. None of the studies used validated questionnaires potentially underestimating the effect of treatment. As a result, it remains unclear whether CPAP or MAD are an effective treatment for cognitive complaints in OSA.

Here, we examine the effect of CPAP or MAD on cognitive complaints. In OSA cognitive complaints are related to subjective sleepiness[10,11] and symptoms of anxiety and depression[11]. Because these daytime symptoms improve with CPAP or MAD[14,16] we expect cognitive complaints to improve with CPAP and MAD as well. To test this, we assessed cognitive complaints

using validated questionnaires in newly diagnosed OSA patients and healthy controls and re-assessed OSA patients after 6 months of CPAP or MAD treatment and healthy controls, matched on age, sex and educational level, at a 6 months follow-up. We assessed both AHI and subjective sleepiness at baseline and follow-up to check if any improvement in cognitive complaints was related to decline in nighttime apneas or improvement in daytime sleepiness. We expect a decline in cognitive complaints to be related to a decline in subjective sleepiness, not AHI, because past studies showed a strong relationship between cognitive complaints and subjective sleepiness[25], not AHI[26].

2. METHODS

2.1 Participants

OSA patients were recruited from the sleep units of two general hospitals in the Netherlands (VieCuri Medical Center, Venlo; and Reinier de Graaf Hospital, Delft). Patients were eligible if they had an apnea-hypopnea index (AHI) of 5 or more on an overnight polysomnography (PSG) and were advised to start CPAP or MAD treatment. Cognitive complaints were assessed before the start of treatment and at follow-up: 6 months after starting treatment. The period of 6 months was chosen to minimize placebo effects that have been reported in past studies on the treatment of OSA[27–29] specifically in the first two months of treatment ("CPAP honeymoon")[30]. The following inclusion criteria also applied: 1. native Dutch speaker, 2. aged between 18 and 70 years old, 3. no substance or alcohol abuse (e.g. no more than three units of alcohol per day for males and no more than two units of alcohol per day for females, as checked by verbal report and medical records), 4. no diagnosis of a psychiatric disorder, 5. no use of medication effecting cognition, 6. no neurological disease, diabetes mellitus, hypo- or hyperthyroidisme or lung disease (as checked by verbal report and medical records).

Healthy controls (HC) were volunteers recruited through pamphlets among staff of the general hospitals participating in the study or recruited through family and friends of involved research staff. HC did not undergo an overnight PSG. They were eligible if there was a low suspicion for a sleep disorder based on, 1. no report of snoring or apneas by partner, 2. a score of ≤7 on the Pittsburgh Sleep Quality Index (PSQI[31]), 3. an average sleep efficiency of ≥80% on a two week sleep diary. For HC their assessment was repeated 6 months after the baseline assessment. Also, the same inclusion criteria 1 to 6 as listed under OSA patients applied.

The study was conducted in accordance with the declaration of Helsinki and approved in march 2012 by a nationally certified medical ethical committee

(NL37795.068.11, data collected from June 2012 till April 2018). Informed consent was obtained for all participants.

2.2 Measures

2.2.1 Sociodemographic characteristics

Data on age, sex and educational level were collected for OSA and HC. Educational level was rated according to the Dutch Verhage system: a 7-point scale similar to the International Standard Classification of Education [32], but adapted to the Dutch educational system.

2.2.2 Clinical Characteristics

OSA severity before treatment was measured by AHI assessed at an overnight PSG. At 6 months follow-up AHI was collected from medical records based on PSG, polygraphy (PG) or reading from a CPAP machine, depending on availability. Subjective sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI, [31]),a validated and reliable self-report questionnaire consisting of 19 items that result in a total score ranging from 0 to 21. A higher score indicates poor sleep quality. A total score above 8 has previously been found to indicate significant sleep disturbances [33,34]. Subjective sleepiness was measured using the Epworth sleepiness scale (ESS) a widely accepted golden standard [35]. A higher score indicates more severe sleepiness and a score above >10 indicates excessive daytime sleepiness [35].

2.2.3 Cognitive complaints

Cognitive complaints were assessed using the Cognitive Failure Questionnaire (CFQ)[36], and the Behavior Rating Inventory of Executive Function for adults (BRIEF-A)[37]. The CFQ is a validated and reliable instrument that assesses the severity of everyday cognitive complaints in the last three months and consists of 25 items. Every item is rated on a 5-point Likert-scale (ranging from "never" to "very often"). Higher scores indicate a higher severity of everyday cognitive complaints. Rast and colleagues[38] found a stable factor structure of the CFQ across different ages in a Dutch population consisting of three subscales: "forgetfulness" (sum of 8 items, score range 8-40), "distractibility" (sum of 8 items, score range 8-40) and "false-triggering" (sum of 8 items, score range 8-40). The scale "forgetfulness" measures memory slips, the scale "distractibility" measures attentional misses, such as absentmindedness and the scale "false triggering" measure blunders or slips in thinking or motor actions. The BRIEF-A is a validated and reliable questionnaire assessing the severity of complaints related to executive functioning in the last month and consists of 75 items. Every item is rated on a 3-point Likert-scale ("never", "sometimes" and "often"). Higher scores indicate more severe complaints

related to executive functioning. The BRIEF-A consists of 9 subscales: "inhibit" (sum of 8 items, score range 8-24), "shift" (sum of 6 items, score range 6-18), "emotional control" (sum of 10 items, score range 10-30), "self-monitor" (sum of 6 items, score range 6-24), "initiate" (sum of 8 items, score range 8-24), "working memory" (sum of 8 items, score range 8-24), "plan/organize" (sum of 10 items, score range 10-30), "task monitor" (sum of 6 items, score range 6-18), "organization of materials" (sum of 8 items, score range 8-24). The scale "inhibit" measures problems with controlling impulses, "shift" problems with thinking flexibly, "emotional control" problems modulating appropriate emotional responses, "self-monitor" problems recognizing the effect of one's behavior on others, "initiate" problems independently generating ideas, "working memory" problems holding information in mind to complete a task, "plan/organize" problems carrying out tasks systematically, "task monitor" problems assessing mistakes in one's performance and "organization of materials" measures problems keeping one's workspace in an orderly manner.

If one item was missing on any of the CFQ or BRIEF-A subscales of a participant, it was replaced by the average score of the same subscale. If more than one item was missing on any of the subscales that subscale was labeled as missing.

2.3 Statistical analysis

OSA and HC were compared on sociodemographic (age, sex, educational level, estimated verbal IQ) and available clinical variables (PSQI, ESS). To test if OSA patients that dropped out at follow-up were different from OSA included at follow-up, we compared both groups at baseline on demographic (age, sex, educational level, estimated verbal IQ) and clinical variables (PSQI, ESS, AHI, SAO_2) and all subscales of CFQ and BRIEF-A. For all comparisons we used 2-sided independent t-tests and Chi-square tests of independence.

Effects of group (OSA vs. HC) and time (baseline to 6 months follow-up) were examined using a series of 2-way mixed ANOVAs for each subscale of the CFQ and BRIEF-A. In the case of statistically significant interaction between group and time, simple main effects for group (independent t-tests) and time (paired-samples t-tests) were performed to assess which group contributed to the significant effect. Main group and time effects were also assessed using the ANOVAs. Partial eta-square was considered as a measure of effect size (ES), with values of 0.02 representing small effects; 0.13, medium effects; and 0.26, a large ES.

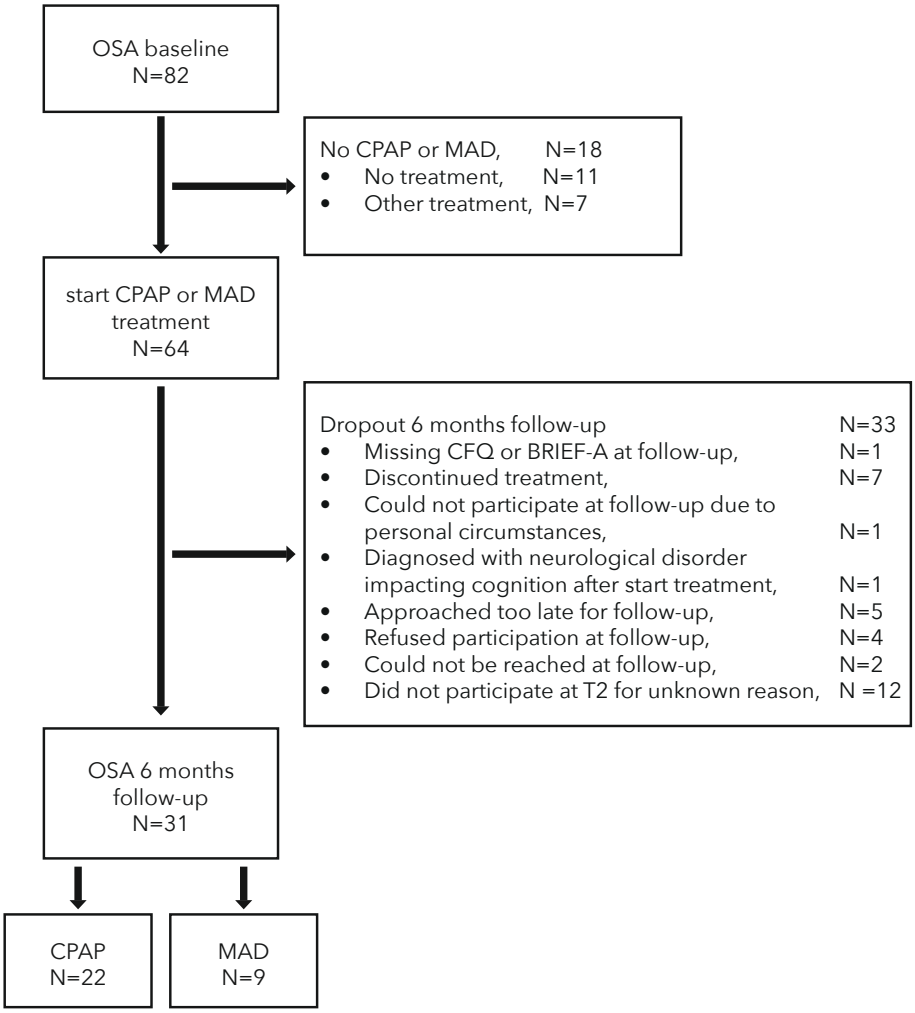
Reliable change indices (RCIs) were calculated for individual patients for each subscale of the CFQ and BRIEF-A to determine whether observed changes in scores reliably reflect true changes, while taking into account methodological confounders such as natural progression or retest effects[39]. The RCI was derived from the standard error of measurement of each subscale

of the CFQ and BRIEF-A using scores of HC. RCI formulae used are based on the repeated assessments in our HC group. Based on a 95% confidence interval, the difference in test score from baseline to follow-up, that would be expected if no real change occurred, can be calculated as follows: $RCI = 1.64(SE_{diff})$, where $SEdiff=[2(SEM)^2]^{1/2}$ and $SEM=SD_1(1-r_{12})^{1/2}$ where SD is the standard deviation of the baseline assessment, SEM is the standard error of measurement, and r is the test–retest reliability from baseline to follow-up. All RCI thresholds were rounded to the nearest whole number. After adjusting for the mean practice effect, changes that did not meet the RCI threshold for improvement were categorized as non-improved (i.e., stable or declined) performance. Subsequently, the statistical significance of the proportion of patients with cognitive improvement was determined with a binomial test. Change was defined as RCI values exceeding ± 1.96, which equates to the 95% confidence interval, with positive values representing improvement and negative values representing a decline in complaints. The number and percentages of patients with improved, stable, or a decline in performance were counted for each subscale of the CFQ and BRIEF-A for OSA and HC, and then compared using Chi-square tests of independence.

To determine if change in cognitive complaints in OSA patients was related to treatment effect, Pearson's correlations were calculated between change on CFQ or BRIEF-A subscales over time and change on ESS and in AHI over time (baseline to 6 months follow-up).

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM Corp.). To reduce the false discovery rate due to multiple statistical testing, p-values were corrected using the Benjamini-Hochberg (BH) procedure[40].

Figure 1. Flow chart OSA patients from baseline to six months follow-up.



3. RESULTS

3.1 Patient characteristics

Figure 1 shows the flow of OSA patients in our study. At baseline 82 OSA were included, of which 64 started CPAP or MAD treatment and 31 completed both the baseline and follow-up assessment. See figure 1 for a breakdown of reasons OSA patients failed to complete the follow-up. There were no significant differences between OSA who completed the follow-up and OSA who dropped out before the follow-up on age, sex, educational level, estimated verbal IQ, AHI, sleep quality, subjective sleepiness and lowest oxygen desaturation (all p's >.28, see table 1.).

Table 1. Differences at baseline between OSA patients, healthy controls and OSA dropout.

	OSA	HC	p-value	OSA dropout	p-value
	N=31	N=36		N=33	
Demographic variables					
Age	52.1 (9.7)	53.3 (8.6)	.78	50.5 (10.2)	.74
Sex (%male)	84%	67%	.28	82%	.90
Educational level	5.4 (1.0)	5.3 (0.8)	.66	5.1 (1.1)	.39
Estimated verbal IQ	94.7 (16.8)	98.9 (13.3)	.48	94.1 (16.5)	.92
Clinical variables					
PSQI	6.4 (2.8)	3.1 (1.4)	<.01**	7.1 (3.9)	.64
ESS	6.5 (2.9)	4.3 (3.1)	<.01**	7.8 (3.8)	.28
AHI	27.7 (21.7)	Na	na	27.2 (19.0)	.92
SAO_2	81.5 (5.8)	na	na	80.4 (8.1)	.75

AHI = Apnea-Hypopnea Index on overnight polysomnography, ESS = Epworth Sleepiness Scale, HC = Healthy Controls, IQ = Intelligence Quotient, OSA = Obstructive Sleep Apnea, PSQI = Pittsburgh Sleep Quality Index, SaO_2lowest = lowest Oxygen Saturation on overnight polysomnography, * = p<.05, **= p<.01, *** = p<.001.

OSA who did not complete the follow-up assessment reported significantly more frequent complaints for initiative (p< .01) and planning and organizing (p< .01) compared to OSA that completed the follow-up assessment (see table 2.). No other differences were found on any of the other subscales of the CFQ or BRIEF-A between OSA who completed and did not complete the follow-up assessment (all p's> .09).

Table 2. Differences in cognitive complaints at baseline between OSA patients included at follow-up and OSA patients who dropped out at follow-up.

	OSA	OSA dropout	p-value
	N=31	N=33	
CFQ			
Forgetfulness	20.5 (5.4)	21.5 (5.1)	.65
Distractibility	18.6 (5.0)	20.5 (4.4)	.28
False Triggering	15.6 (5.0)	16.9 (5.2)	.54
BRIEF-A			
Inhibit	12.2 (2.4)	13.3 (2.7)	.25
Shift	8.9 (2.2)	10.4 (2.5)	.09
Emotional control	15.9 (3.8)	16.1 (3.8)	.92
Self-monitor	9.0 (2.5)	9.8 (2.1)	.38
Initiate	11.9 (2.7)	14.0 (3.1)	<.01**
Working memory	13.6 (3.8)	14.2 (3.3)	.66
Plan/organize	13.9 (3.2)	16.1 (3.0)	<.01**
Task monitor	9.6 (2.2)	10.6 (2.3)	.18
Organization of materials	12,7 (3.0)	14.1 (3.4)	.25

BRIEF-A = Behavior Rating Inventory of Executive Function adult version, CFQ = Cognitive Failure Questionnaire, HC = healthy controls, OSA = Obstructive Sleep Apnea, * = p<.05, **= p<.01, *** = p<.001.

Of the 31 OSA who completed both assessments, OSA severity at baseline ranged from mild to severe (AHI range 5.4 - 101.2) with a median of 26.8 and interquartile range of 21.7 (see table 1.). OSA patients did not differ from HC in age, sex, educational level or estimated verbal IQ (all p's > .28). At baseline OSA reported poorer sleep quality (PSQI, P<.01) and more subjective sleepiness (ESS, p <. 01) than HC.

3.2 Group and time differences in cognitive complaints

We found a significant interaction effect between group (OSA vs HC) and time (baseline vs 6 months follow-up) for CFQ forgetfulness (p=.02) with medium-effect (η2=.16) and BRIEF-A working memory (p=.02) with medium effect (η2=.14, see Table 3 and Fig. 2). Post-hoc analyses revealed that OSA significantly improved on CFQ forgetfulness (p<.01) and BRIEF-A working memory (p=.02) over time, but HC did not (both p's>.80). No differences were found between OSA and HC on both scales at baseline and 6 months follow-

up (both p's >.16). No significant interaction effects were found on any of the other subscales (all p's>.09). We found a significant main effect for time for BRIEF-A inhibit (p=.04) with small effect (η2=.11), meaning OSA and HC both improved over time. We did not find a significant main effect for time or any of the other CFQ or BRIEF-A subscales (p>.06) nor did we find a significant main effect for group on any of the CFQ or BRIEF-A subscales.

Table 3. Cognitive complaints of OSA and healthy controls: group effects, effects over time and interaction (group x time).

	Group effects (OSA vs HC)			Effects over time (baseline – 6 months follow up)			Interaction (group x time)		
Cognitive complaints	F	p-value	Partial η2†	F	p-value	Partial η2†	F	p-value	Partial η2†
CFQ									
Forgetfulness	.75	.62	.01	8.86	.04*	.12	12.22	.02*	.16
Distractibility	.24	.79	.00	4.05	.16	.06	17.64	.31	.04
False Triggering	.40	.74	.01	4.58	.14	.07	5.57	.09	.08
BRIEF-A									
Inhibit	.34	.76	.01	8.31	.04*	.11	1.14	.52	.02
Shift	.37	.75	.01	.70	.64	.01	.02	.92	.00
Emotional control	.11	.85	.00	6.87	.06	.10	5.56	.09	.079
Self-monitor	.05	.90	.00	4.69	.14	.07	2.70	.28	.04
Initiate	.06	.89	.00	.93	.56	.01	5.12	.11	.073
Working memory	1.25	.50	.02	9.91	.02*	.13	10.44	.02*	.14
Plan/organize	2.21	.34	.03	1.36	.48	.02	2.24	.34	.03
Task monitor	.09	.86	.00	1.55	.14	.02	2.61	.28	.04
Organization of materials	.48	.70	.01	7.53	.06	.10	1.83	.39	.03

BRIEF-A = Behavior Rating Inventory of Executive Function adult version, CFQ = Cognitive Failure Questionnaire, HC = Healthy Controls, OSA = Obstructive Sleep Apnea, * = p<.05, **= p<.01, *** = p<.001, † Partial eta-square ES values of 0.02 represent small effects; 0.13, medium effects; and 0.26, large effects (Cohen).

Figure 2. Scores on all subscales of the CFQ and BRIEF-A for OSA and HC from baseline to 6 months follow-up.

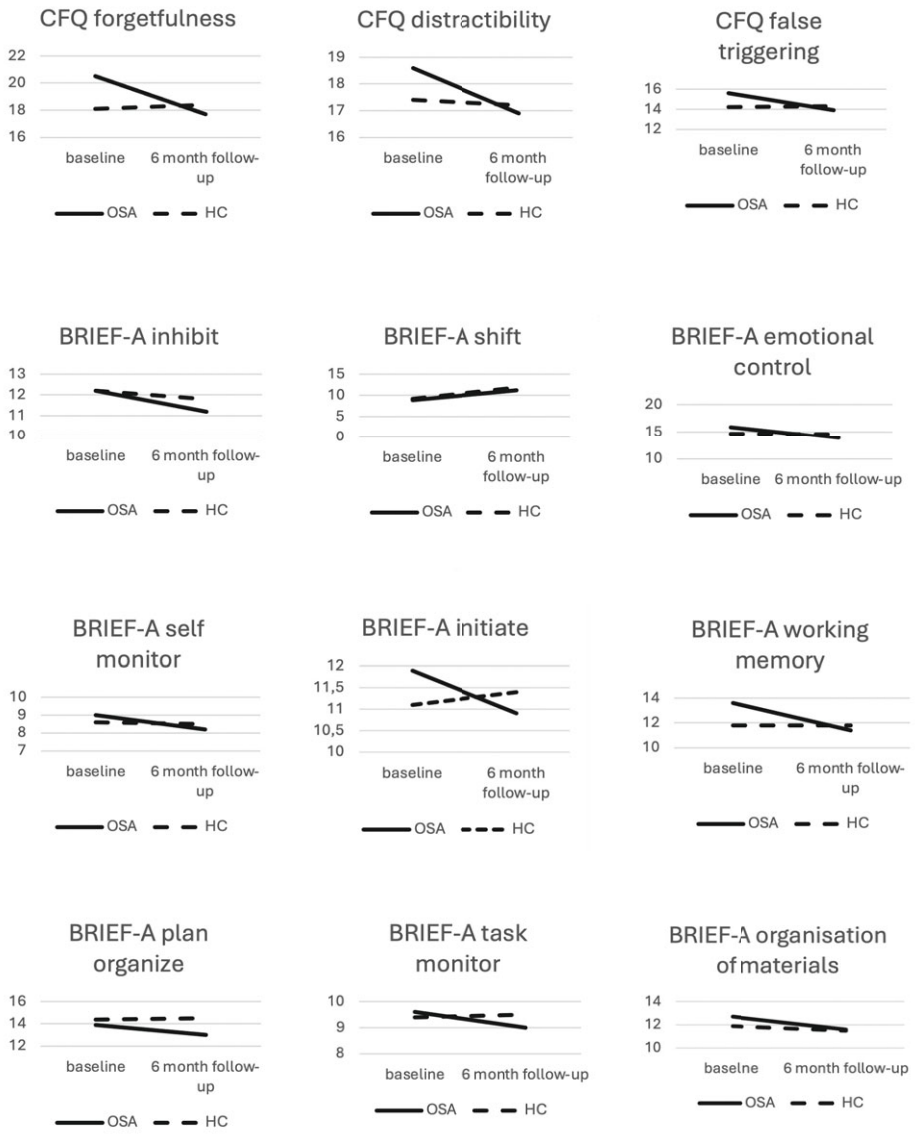


Table 4. Change in cognitive complaints at 6 months follow-up for OSA and healthy controls

		Declined %	Stable %	Increased %	p-value
CFQ					
Forgetfulness	OSA	26	71	3	.02*
	HC	0	100	0	
Distractibility	OSA	16	74	10	.16
	HC	6	94	0	
False Triggering	OSA	19	81	0	.18
	HC	3	94	3	
BRIEF-A					
Inhibit	OSA	3	97	0	.79
	HC	6	94	0	
Shift	OSA	0	97	3	.59
	HC	3	97	0	
Emotional control	OSA	16	84	0	.37
	HC	6	94	0	
Self-monitor	OSA	10	90	0	.44
	HC	3	92	6	
Initiate	OSA	10	87	3	.66
	HC	3	92	6	
Working memory	OSA	19	81	0	.08
	HC	0	97	3	
Plan/organize	OSA	10	90	0	.56
	HC	3	94	3	
Task monitor	OSA	7	93	0	.92
	HC	6	94	0	
Organization of materials	OSA	19	81	0	.18
	HC	3	94	3	

BRIEF-A = behavior rating inventory of executive function adult version, CFQ = cognitive failure questionnaire,HC = healthy controls, OSA = obstructive sleep apnea. * = p< .05

3.3 Individual changes in cognitive complaints over time

Table 4 shows the percentage of change (declined, stable, increased) for all subscales of the CFQ and BRIEF-A for OSA and HC. We found a decline in cognitive complaints in 0-26% of the OSA patients and 0-6% of HC. An increase of cognitive complaints was found for 0-10% of OSA and 0-6% for HC. Seventy-one to 97% of OSA and 92-100% of HC remained stable. For CFQ forgetfulness we found a significant difference between OSA and HC in proportions who remained stable, increased and declined in cognitive complaints (p=.02). For all other CFQ and BRIEF-A subscales we did not find a difference in proportions who remained stable, increased or declined (all p's >.16).

3.4 Treatment effect and cognitive complaints

For 21 OSA patients AHI was available at 6 months follow-up. The average AHI at baseline was 26.7±11.0 and after 6 months treatment 4.8±6.7. Change in AHI from baseline to follow-up did not significantly correlate with change over time on any of the CFQ or BRIEF-A subscales (all p's >.06). For 31 OSA data was available for ESS at 6 months follow-up. For those 31 OSA the average ESS dropped from 6.5±2.9 to 4.1±3.2. Improvement on ESS over time significantly correlated with improved over time on CFQ false triggering, BRIEF-A task monitoring and organization of materials (all p's <.04 , all ρ's ranging from .49 to .55, see table 5.). No significant correlations were found between change over time on ESS and BRIEF-A on any of the other subscales of the CFQ or BRIEF-A (all p's > .06).

Table 5. Correlations in OSA between change (Δ) in cognitive complaints, AHI and ESS from baseline to 6 months follow-up.

	ΔAHI N=21		ΔESS N=31	
	ρ	p-value	ρ	p-value
ΔCFQ				
Forgetfulness	.26	.46	.46	.06
Distractibility	.29	.42	.47	.06
False Triggering	.20	,59	.49	.04*
ΔBRIEF-A				
Inhibit	.17	.64	.37	.16
Shift	.15	.67	.33	.29
Emotional control	.37	.27	.56	.02
Self-monitor	.30	.39	.09	.79
Initiate	.41	.20	.47	.06
Working memory	.24	.50	.44	.07
Plan/organize	.17	.64	.34	.18
Task monitor	.06	.89	.54	.02*
Organization of materials	.31	.38	.55	.02*

Δ = change from baseline to 6 months follow-up, AHI = apnea-hypopnea index, BRIEF-A = behavior rating inventory of executive function adult version, CFQ = cognitive failure questionnaire, ESS = Epworth Sleepiness Scale, HC = healthy controls, OSA = obstructive sleep apnea. * = p<.05

4. DISCUSSION

To our knowledge, this is the first study comparing cognitive complaints in OSA patients to healthy controls after six months of treatment with CPAP or MAD, using well-validated questionnaires. Our study shows that both CPAP and MAD can improve cognitive complaints, particularly related to forgetfulness and working memory. These improvements were related to reductions in post-treatment subjective sleepiness but not to changes in nighttime OSA severity as indicated by the AHI.

On a group level, both CPAP and MAD were effective in reducing nighttime respiratory events in our study (AHI decreased from 26.7 to 4.8 on average). However, this reduction did not correlate with a decrease in cognitive complaints. This suggests that reducing apneas may not be a prerequisite for subjective improvements in cognition. Previous studies of untreated OSA

patients have also failed to show a relationship between cognitive complaints and AHI[26]. Our study finds that cognitive complaints are associated with reductions in subjective sleepiness following treatment. In untreated OSA, cognitive complaints are also linked to subjective sleepiness[25], and even after CPAP treatment, residual sleepiness is associated with continued cognitive complaints[24]. Our findings underscore the importance of treating OSA patients with sleepiness using CPAP or MAD, as this can lead to improvements in cognitive complaints.

Strengths of this study include the use of validated questionnaires to assess cognitive complaints as an outcome measure in a treatment study involving both CPAP and MAD, as well as the inclusion of a healthy control group. However, there are limitations. The OSA patients in our study, reported relatively few cognitive complaints at baseline compared to some previous studies [25,41,42]. Before treatment, we found no difference in cognitive complaints between OSA patients and healthy controls. However, dropout analysis revealed that patients with more pronounced cognitive (especially executive) complaints were less likely to participate in the follow-up assessment, for various reasons. Consequently, patients experiencing more significant cognitive complaints were underrepresented in our sample.

This has two main implications. First, it limits the generalizability of our results. Based on this study, we cannot make definitive conclusions about the effect of CPAP or MAD on more extensive cognitive complaints. Previous research by Vernet et al.[24] indicated that some patients continue to experience cognitive complaints even after CPAP treatment. However, our current study suggests that patients with mild cognitive complaints can still expect some improvement following CPAP or MAD.

Second, we do not know if CPAP or MAD can effectively address complaints beyond memory, such as those related to attention or executive function[6]. While patients with executive complaints were more likely to drop out of our study, we did observe that improvements in sleepiness were associated with reductions in executive complaints. Given that CPAP and MAD have been shown to improve subjective sleepiness[14,17], it is reasonable to expect that executive complaints, if present, may also improve with treatment. Future studies should include patients with significant memory, attention, and executive function complaints, clearly deviating from a healthy control group, preferably in a randomized controlled trial.

5. CONCLUSIONS

Our study provides first evidence that CPAP or MAD can improve memory complaints in OSA patients with mild cognitive symptoms. Improvements in cognitive complaints following treatment were not associated with reductions

in AHI, but were instead related to reductions in subjective sleepiness. Future research should investigate whether CPAP and MAD are also effective in addressing attention and executive function complaints, and these findings should be replicated in randomized controlled trials (RCTs).

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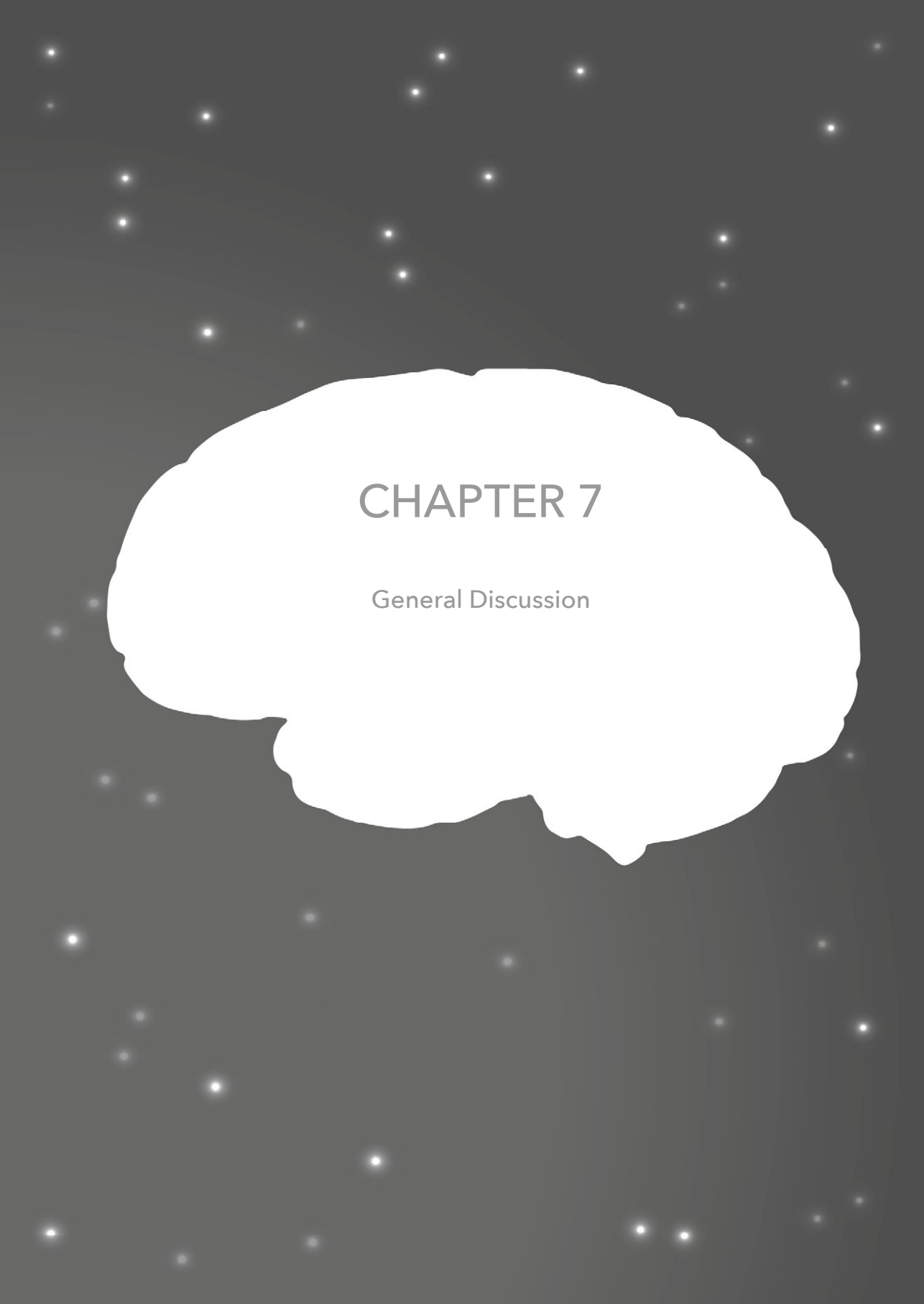

CHAPTER 7

General Discussion

SUMMARY OF FINDINGS

This dissertation focuses on cognitive complaints in obstructive sleep apnea (OSA), with the aim of exploring their nature, prevalence, contributing factors, and the effects of treatment. The research presented examined cognitive complaints and their relationships with objective cognitive impairments, sleepiness, anxiety, depression, fatigue, and coping styles. Furthermore, the studies investigated whether treatment for OSA can alleviate cognitive complaints. The following sections summarize the key findings from each chapter.

Chapter 1 provided a general introduction and discussed the definition of obstructive sleep apnea, its prevalence, risk factors and treatment options. The relationship between OSA and cognition is outlined as background for the aims of the thesis.

In Chapter 2, an expansive review of the literature showed that while cognitive complaints are commonly reported by OSA patients, research on this topic remains limited compared to studies on objective cognitive impairments. The review reveals that complaints about concentration are consistently found to be more prevalent and severe in OSA patients than in healthy controls or snorers without OSA. Findings regarding memory complaints and subjective executive dysfunction are less conclusive, likely due to methodological differences across studies, including varied outcome measures, small sample sizes, and inconsistent control groups. Cognitive complaints in OSA appear to be associated with subjective sleepiness but are not necessarily indicative of objective cognitive impairments, emphasizing the importance of distinguishing between subjective and objective measures of cognition. The review identified only one study that reported an improvement in cognitive complaints following CPAP treatment, though its findings were limited by a high dropout rate and the absence of a control group. Another study suggested that cognitive complaints may persist even after successful CPAP therapy, underscoring the need for a better understanding of the relationship between OSA treatments and cognitive complaints.

Chapter 3 deepened the understanding of cognitive complaints by examining their prevalence and severity across various patient groups, including those with OSA, neurological conditions (stroke, brain tumors), and chronic pulmonary disease (COPD). The study revealed that cognitive complaints were prevalent and significant in OSA, with 30.2% of the sample reporting clinically meaningful complaints. Notably, the prevalence and severity of complaints in OSA were at least comparable to those in COPD and exceeded those in stroke and brain tumor patients. The higher levels of reported complaints in OSA patients compared to neurological patients may be explained by several factors. Neurological patients were assessed

shortly after acute medical events, a time when cognitive issues may be less prominent in their awareness. In contrast, OSA patients were undergoing evaluation for symptoms that often include cognitive concerns, potentially making them more attuned to—or focused on—these issues. Consequently, the results should be interpreted cautiously, as they may not be generalizable to all patients with OSA or neurological conditions. Across all patient groups, symptoms of anxiety and depression emerged as the strongest predictors of cognitive complaints. This aligns with prior cross-sectional research [1-3], which suggests that such complaints may not necessarily indicate objective cognitive deficits but instead reflect psychological distress. While the causal direction of these relationships remains uncertain, evidence indicates that treating depressive symptoms can reduce these complaints. This highlights the importance of screening for and addressing anxiety and depression in medical patients who report cognitive difficulties.

Chapter 4 explored cognitive complaints in patients referred to a sleep clinic with suspected OSA compared to healthy controls. It examined the nature and severity of cognitive complaints across the full spectrum of OSA severity and evaluated associations with subjective sleepiness, fatigue, anxiety, depression, and objective cognitive impairment. Patients with mild OSA reported more frequent issues with memory and attention, while those with severe OSA more often reported difficulties with initiative, suggesting that the nature of complaints may vary with OSA severity. However, cognitive complaints were also common among individuals who did not receive an OSA diagnosis, indicating these complaints are not specific to OSA but are prevalent among those with sleep-related symptoms. The strongest predictors of cognitive complaints were subjective sleepiness, anxiety, and fatigue, independent of OSA severity. Cognitive complaints were not related to objective cognitive impairments, underscoring the need for clinicians to consider co-occurring symptoms such as insomnia, anxiety, or fatigue when addressing cognitive complaints in OSA.

In Chapter 5, the role of coping styles among newly diagnosed OSA patients was explored, revealing significant associations between passive and avoidant coping strategies, low active problem-solving, and reported cognitive difficulties. These associations were independent of subjective sleepiness and cognitive impairments, highlighting the importance of psychological mechanisms in shaping these perceptions. The findings align with previous research in other populations, where poor coping strategies, perceived stress, and neuroticism exacerbate cognitive concerns, while proactive coping offers protection [4–7]. These results suggest that such difficulties may reflect psychological rather than neurocognitive dysfunction. Clinically, the findings emphasize the need to consider coping strategies

when managing OSA patients who report these issues, particularly those unresponsive to CPAP or MAD treatment.

Chapter 6 described the first study to compare cognitive complaints in OSA patients and healthy controls after six months of treatment, using validated questionnaires. The findings demonstrate that OSA treatment (in the study in the form of CPAP or MAD) can improve cognitive complaints, particularly related to forgetfulness and working memory. These improvements were associated with reductions in subjective sleepiness rather than changes in AHI, suggesting that alleviating sleepiness may drive the perceived cognitive benefits of OSA treatment. While CPAP and MAD effectively reduced AHI at the group level, cognitive complaints at baseline were mild, and there were no significant differences between OSA patients and healthy controls. Patients with more pronounced executive complaints were underrepresented at follow-up, limiting the generalizability of findings. Nonetheless, reductions in subjective sleepiness appeared to correlate with improvements in executive complaints, implying treatment may improve cognitive complaints beyond the domain of memory. These results underscore the importance of treating sleepiness in OSA patients to address cognitive complaints.

GENERAL DISCUSSION

This dissertation investigated cognitive complaints in OSA, exploring their prevalence, underlying mechanisms, and response to treatment. Across studies, several consistent findings emerged that contribute to a more nuanced understanding of cognitive complaints in OSA.

Prevalence and Nature of Cognitive Complaints

Cognitive complaints are a common yet multifaceted symptom in OSA. While the literature review in Chapter 2 highlighted increased issues with concentration and potential subjective executive dysfunction, Chapters 3 and 4 demonstrated that these subjective difficulties are as prevalent in OSA patients as in individuals with neurological conditions (e.g., stroke, brain tumors) and chronic pulmonary diseases like COPD. This suggests that such complaints are not uniquely characteristic of OSA but are shaped by factors shared across medical populations. The types of reported difficulties extend beyond attention problems to include challenges with forgetfulness, working memory and initiative (Chapter 4).

The lack of a strong relationship between subjective complaints and objective cognitive performance, as observed in Chapters 4 and 5, is consistent with cross-sectional studies in other medical populations[1–3]. Research frequently shows no or only weak correlations between subjective perceptions of cognitive issues and measured impairments, particularly when

different cognitive domains are evaluated [8,9]. This finding highlights that self-reported difficulties may not reliably reflect actual cognitive dysfunction in OSA. Instead, they are likely influenced by psychological and emotional factors, such as anxiety, fatigue, and maladaptive coping strategies.

Psychological and Emotional Influences

Psychological factors such as anxiety, depression, and coping mechanisms emerge as critical influences on cognitive complaints in OSA patients, as shown in Chapters 3, 4, and 5. The lack of a strong relationship between cognitive complaints and cognitive impairments may stem from a dual phenomenon: 1) underreporting by patients with actual impairments [8,10], due to lack of insight, denial, or downplaying, and 2) overreporting by those without impairments, often driven by heightened sensitivity to cognitive lapses [11]. This discrepancy reflects a psychological mechanism where patients with impairments may fail to recognize or acknowledge their deficits, while those without impairments may interpret normal lapses as evidence of significant dysfunction. The cognitive-behavioral framework [11] highlights how hypervigilance, catastrophizing, and avoidance can amplify perceptions of dysfunction. Patients' heightened awareness and misinterpretation of everyday memory or concentration lapses reinforce this cycle, leading to increased emotional distress and cognitive complaints.

Anxiety and depression significantly overlap with cognitive complaints, partly because the questionnaires used to measure these constructs often include similar items. For instance, items related to concentration difficulties, fatigue, and irritability appear across scales assessing cognitive complaints, anxiety, and depression, contributing to a shared variance. This overlap complicates the interpretation of results and highlights the interconnectedness of these factors. Depressed individuals are more likely to focus on their cognitive lapses and interpret them as indicative of broader dysfunction, intensifying the distress associated with these lapses[12].

Treating cognitive complaints remains highly relevant, even in the absence of measurable cognitive impairments, because these complaints affect patients' quality of life [13], mental health [14], and functional outcomes [15]. Persistent complaints can lead to increased emotional burden, reduced self-efficacy [16], and impaired social and occupational functioning [17]. Interventions targeting the psychological mechanisms underlying cognitive complaints can help patients reframe their perceptions of lapses, reduce emotional distress, and enhance their overall well-being. Such interventions include psychoeducation, cognitive-behavioral therapy (CBT), and coping-skills training. Encouraging proactive and problem-focused coping styles may also mitigate the negative impact of these perceptions and empower patients to manage their symptoms more effectively. Future research should assess the

effectiveness of these approaches in reducing cognitive complaints in OSA populations and improving functional outcomes.

Effects of OSA Treatment

Chapter 6 provided promising evidence that cognitive complaints, particularly those related to memory and working memory, can improve following OSA treatment. However, these improvements were not linked to reductions in AHI, further supporting the notion that the resolution of cognitive complaints is more closely tied to reductions in subjective sleepiness. Despite these improvements, the study highlighted important gaps: patients with more pronounced cognitive complaints, especially executive complaints, were underrepresented at follow-up, limiting the generalizability of the findings. Nonetheless, the results suggest that addressing sleepiness through treatment may have broader implications for cognitive well-being, even in patients with mild complaints.

METHODOLOGICAL CONSIDERATIONS

Cross-Sectional Design

Most studies (Chapters 3, 4, and 5) employed cross-sectional designs, limiting the ability to draw causal inferences about the relationships between cognitive complaints, psychological factors, and coping styles. For instance, while passive and avoidant coping were associated with cognitive complaints, the directionality of this relationship remains unclear. Longitudinal studies are necessary to establish causality and understand how these relationships evolve over time.

Sample Representativeness and Size

In some chapters, relatively small or selective samples may have introduced bias. For example, Chapter 6 noted that patients with more severe cognitive complaints, particularly executive complaints, were less likely to participate in the follow-up assessment. This limits the generalizability of findings to OSA patients with more pronounced cognitive difficulties. Similarly, the relatively mild levels of sleepiness in some study samples (e.g., Chapters 4 and 6) may not fully represent the broader OSA population, where sleepiness often plays a central role.

Focus on Cognitive Complaints vs. Objective Impairments

Across the studies, a disconnect was highlighted between subjective cognitive complaints and objective cognitive performance in OSA. Cognitive complaints often do not correspond to actual cognitive impairments, as evidenced in Chapter 4, where no association was found between self-reported complaints

and objective cognitive deficits. This lack of correlation underscores a critical issue: patients with measurable cognitive impairments may not report subjective complaints [10,18], and conversely, those with complaints may not show detectable cognitive deficits. The findings suggest that cognitive complaints alone are insufficient to identify cognitive impairments in OSA. Psychological factors, such as anxiety, depression, and coping styles, appear to influence complaints more strongly than objective impairments. This highlights the need for a dual approach in clinical assessment—evaluating both cognitive complaints and objective cognitive functioning. Failing to assess cognitive impairments directly could lead to underdiagnosis of subtle but clinically significant cognitive deficits in patients who do not perceive or report them. Future studies should focus on refining methods to simultaneously evaluate subjective and objective cognitive outcomes in OSA. This could involve exploring how subjective complaints relate to specific cognitive domains or testing whether tailored neuropsychological assessments can detect impairments in patients who do not report complaints. Such efforts would enhance our ability to accurately identify and address cognitive issues in OSA, ensuring comprehensive patient care. Improving cognitive complaints can have an impact on the quality of life [19] for patients with OSA.

Potential Bias in Treatment Studies

The dropout of participants in Chapter 6, particularly those with more severe cognitive complaints, may have introduced a bias that affected the observed outcomes of (CPAP and MAD) treatment. Patients with significant complaints are often the ones who stand to gain the most from interventions, yet their absence from the study limits our ability to assess the full range of treatment effects. This omission could result in an underestimation of the efficacy of CPAP or MAD in more pronounced cognitive complaints.

Furthermore, the study did not directly measure adherence to these treatments, a factor that can substantially influence both subjective [20] and objective outcomes [21]. Incorporating adherence monitoring would provide a more accurate understanding of how treatment engagement influences cognitive outcomes.

Overreliance on AHI as an OSA Marker

Although the apnea-hypopnea index (AHI) was used as a primary marker of OSA severity and treatment efficacy, the findings across chapters suggest that AHI is not strongly linked to cognitive complaints. Future research should incorporate additional markers of OSA severity (e.g., nocturnal oxygen desaturation markers, and metrics assessing sleep fragmentation) to gain a more comprehensive understanding of its relationship with cognitive and psychological outcomes.

To address these limitations, future studies should:

- Employ longitudinal designs to explore causality between cognitive complaints, coping mechanisms, and treatment outcomes.
- Include larger and more representative samples, particularly patients with moderate-to-severe cognitive complaints or higher levels of sleepiness.
- Investigate both subjective complaints and objective cognitive performance to clarify their interrelationship.
- Use randomized controlled trials (RCTs) to evaluate the efficacy of CPAP, MAD, and psychological interventions in addressing cognitive complaints.
- Incorporate diverse OSA populations, including patients with comorbidities or those identified through community screening, to enhance generalizability.

CLINICAL IMPLICATIONS

The findings from this dissertation have several implications for clinical practice. Cognitive complaints in OSA are multifactorial and often unrelated to objective cognitive impairments. Clinicians should avoid attributing these complaints solely to OSA or cognitive dysfunction and instead consider other contributing factors, such as sleepiness, anxiety, and coping strategies. Comprehensive assessment and personalized treatment plans are essential, potentially including interventions for anxiety and fatigue or psychological therapies to address maladaptive coping.

Additionally, while OSA treatment in the form of CPAP or MAD appear beneficial for reducing cognitive complaints, particularly when linked to sleepiness, their effects on more severe complaints and other cognitive domains remain uncertain. Clinicians should educate patients on the multifactorial nature of cognitive complaints and the realistic benefits of OSA treatments, emphasizing the potential for gradual improvements in sleepiness-related complaints.

CONCLUSION

In summary, this dissertation advances our understanding of cognitive complaints in OSA, emphasizing their psychological underpinnings, limited association with objective cognitive impairments, and potential for improvement with treatment. By adopting a multidimensional approach to assessment and intervention, we can better address these pervasive and impactful complaints in OSA patients.

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APPENDIX

APPENDIX A. QUESTIONNAIRES

This Appendix contains the Dutch items of the questionnaires used in this dissertation. For instruments that are subject to copyright restrictions (BRIEF-A, UCL), only descriptions and references are provided (see Appendix B).

Cognitive Failures Questionnaire[1] (CFQ – Dutch version[2])
De volgende vragen gaan over kleine alledaagse vergissingen die iedereen van tijd tot tijd maakt. Geeft u bij iedere vraag aan hoe vaak het bij u de afgelopen 3 maanden is voorgekomen.

Nooit – Zelden – Af en toe – Vaak – Zeer vaak

1. Iets lezen en vlak daarna niet meer weten wat u gelezen hebt, zodat u het moet overlezen.
2. Vergeten waarom u naar een bepaald gedeelte van uw huis bent gelopen.
3. Wegwijzers over het hoofd zien.
4. Links en rechts verwarren bij het beschrijven van een route.
5. Per ongeluk tegen mensen opbotsen.
6. Niet meer weten of u het licht of het gas hebt uitgedaan, of de deur hebt afgesloten.
7. Niet luisteren naar de naam van een persoon op het moment dat deze zich aan u voorstelt.
8. Iets er uitflappen en achteraf bedenken dat dit wel eens beledigend voor iemand zou kunnen zijn.
9. Niet merken dat iemand iets tegen u zegt als u met iets anders bezig bent.
10. Boos worden en daar later spijt van hebben.
11. Belangrijke brieven dagenlang onbeantwoord laten.
12. Vergeten welke straat u moet inslaan als u een route kiest die u goed kent, maar zelden gebruikt.
13. In een supermarkt niet kunnen vinden wat u zoekt terwijl het er wel is.
14. U plotseling afvragen of u een woord op de juiste manier gebruikt.
15. Moeite hebben met het nemen van een beslissing.
16. Afspraken vergeten.
17. Vergeten waar u iets heeft neergelegd, zoals een boek of een krant.
18. Per ongeluk iets weggooien wat u nodig hebt en bewaren wat u weg wilde gooien.
19. Dagdromen terwijl u eigenlijk naar iets of iemand zou moeten luisteren.
20. Namen van mensen vergeten.
21. Beginnen met iets maar het niet afmaken, omdat u ongemerkt met iets anders begonnen bent.
22. Niet op een woord kunnen komen terwijl het 'op het puntje van uw tong' ligt.
23. In een winkel vergeten wat u kwam kopen.

24. Dingen uit uw handen laten vallen.
25. In een gesprek niets meer weten om over te praten.

Hospital Anxiety and Depression Scale[3] (HADS – Dutch version[4])
Deze lijst gaat over uw stemming. Kies het antwoord dat het beste weergeeft hoe u zich de afgelopen week, met vandaag erbij, heeft gevoeld.

1. Ik voel me gespannen:
   Meestal/Vaak/Af en toe/Helemaal niet
2. Ik geniet nog steeds van de dingen waar ik vroeger van genoot:
   Zeker zo veel/Wel wat minder/Duidelijk minder/Eigenlijk nauwelijks nog
3. Ik heb een soort angstgevoel alsof er iets vreselijks zal gebeuren:
   Jazeker, en vrij erg/Ja, maar niet zo erg/Een beetje, maar het hindert me niet/Helemaal niet
4. Ik kan best lachen en de dingen van de vrolijke kant zien:
   Net zoveel als vroeger/Nu wel wat minder/Duidelijk minder/Helemaal niet
5. Ik maak me ongerust:
   Heel erg vaak/Vaak/Af en toe, maar niet zo vaak/Heel soms
6. Ik voel me opgewekt:
   Helemaal niet/Heel af en toe/Soms/Meestal
7. Ik kan best rustig zitten en me ontspannen:
   Jazeker/Meestal/Af en toe/Helemaal niet
8. Ik heb het gevoel dat alles moeizamer gaat:
   Bijna altijd/Heel vaak/Soms/Helemaal niet
9. Ik heb een soort angstig, gespannen gevoel in mijn buik:
   Helemaal niet/Soms/Vrij vaak/Heel vaak
10. Het interesseert me niet meer hoe ik eruit zie:
    Inderdaad, helemaal niet meer/Niet meer zoveel als eigenlijk zou moeten/Het interesseert me wel, maar iets minder dan vroeger/Het interesseert me nog net zoveel als vroeger
11. Ik ben onrustig en voel dat ik iets te doen moet hebben:
    Inderdaad, heel duidelijk/Duidelijk/Enigszins/Helemaal niet
12. Ik verheug me van tevoren op dingen die komen gaan:
    Net zoveel als vroeger/Een beetje minder dan vroeger/Veel minder dan vroeger/Bijna nooit
13. Ik raak plotseling in paniek:
    Inderdaad, zeer vaak/Tamelijk vaak/Soms/Helemaal nooit
14. Ik kan van een goed boek genieten, of van zoiets als een radio- of televisieprogramma:
    Vaak/Tamelijk vaak/Af en toe/ Heel zelden

Epworth Sleepiness Scale[5] (ESS – Dutch version)
Hoe vaak zou u indutten in de volgende situaties?

Nooit – Af en toe – Vrij vaak – Altijd
1. Tijdens een gesprek met iemand anders
2. Tijdens een bezoek aan familie of vrienden
3. Tijdens een passieve ontspanning (lezen, tv kijken)
4. Tijdens een actieve ontspanning (klusjes, handwerken)
5. Als medereiziger tijdens een auto- of treinrit van 1 uur
6. In de auto wanneer u 5 minuten moet wachten (stoplicht, file)
7. 's Middags of 's avonds na het eten
8. Tijdens werktijd

Fatigue Assessment Scale (FAS – Dutch version[6])
De volgende vragen gaan over hoe u zich normaal gesproken voelt.

Nooit – Soms – Regelmatig – Vaak - Altijd
1. Ik voel mij vermoeid.
2. Ik heb moeite om dingen te beginnen.
3. Ik heb last van concentratieproblemen.
4. Ik voel mij energiek.
5. Ik heb moeite om dingen vol te houden.
6. Fysieke inspanning valt mij zwaar.
7. Ik voel mij uitgerust.
8. Ik heb moeite om helder te denken.
9. Ik voel mij lichamelijk uitgeput.
10. Ik heb moeite met focussen op mijn bezigheden.

Pittsburgh Sleep Quality Index[7] (PSQI – Dutch version)
De volgende vragen hebben betrekking op uw slaap van de afgelopen maand. Uw antwoorden moeten een zo nauwkeurig mogelijke weergave zijn van de meerderheid van de dagen en nachten tijdens deze maand. Als u slaapmiddelen gebruikte, gaat het erom hoe u mét deze middelen sliep.

Vragen:
1. Hoe laat ging u 's avonds meestal naar bed gedurende de afgelopen maand?
   Gebruikelijke bedtijd: ……
2. Hoeveel minuten duurde het gewoonlijk voordat u in slaap viel 's avonds?
   Aantal minuten: ……

3. Hoe laat stond u de afgelopen maand meestal op?
   Gebruikelijk tijdstip: ……
4. Aan hoeveel uren daadwerkelijke slaap kwam u gemiddeld per nacht tijdens de afgelopen maand?
   Aantal uren slaap per nacht: ……
5. Hoe vaak had u gedurende de afgelopen maand problemen met slapen, omdat u:

Situatie	Niet	Minder dan 1x per week	1–2x per week	3x per week of vaker
5a. Niet in slaap kon vallen binnen 30 minuten	☐	☐	☐	☐
5b. 's Nachts of in de vroege ochtend wakker werd	☐	☐	☐	☐
5c. Naar het toilet moest gaan	☐	☐	☐	☐
5d. Niet makkelijk kon ademhalen	☐	☐	☐	☐
5e. Luid hoestte of snurkte	☐	☐	☐	☐
5f. Het te koud had	☐	☐	☐	☐
5g. Het te warm had	☐	☐	☐	☐
5h. Nachtmerries had	☐	☐	☐	☐
5i. Pijn had	☐	☐	☐	☐
5j. Een andere reden (omschrijving)		☐	☐	☐

6. Hoe zou u uw slaapkwaliteit in de afgelopen maand beoordelen?
- Zeer goed
- Redelijk goed
- Vrij slecht
- Zeer slecht

7. Hoe vaak nam u de afgelopen maand medicijnen in als hulp bij het slapen (al dan niet door een arts voorgeschreven)?
- Niet
- Minder dan één keer per week
- Eén of twee keer per week
- Drie keer per week of vaker

8. Hoe vaak had u de afgelopen maand moeite om wakker te blijven tijdens autorijden, eten of deelname aan sociale activiteiten?
- Niet
- Minder dan één keer per week
- Eén of twee keer per week
- Drie keer per week of vaker

9. In hoeverre was het de afgelopen maand voor u een probleem om met voldoende enthousiasme uw dagelijkse activiteiten uit te voeren?
- Geen enkel probleem
- Slechts een klein probleem
- Enigszins een probleem
- Een heel groot probleem

10. Heeft u een bedpartner of kamergenoot?
- Nee (sla vraag 11 over)
- Partner in een andere kamer
- Partner in dezelfde kamer, maar niet in hetzelfde bed
- Partner in hetzelfde bed

11. Als u een bedpartner of kamergenoot heeft, vraagt u dan aan hem/haar hoe vaak u in de afgelopen maand tijdens uw slaap:

Situatie	Niet	Minder dan 1x per week	1–2x per week	3x per week of vaker
Luid snurkte	☐	☐	☐	☐
Lange adempauzes had	☐	☐	☐	☐
Trekkende of schoppende bewegingen met uw benen maakte	☐	☐	☐	☐
Periodes van verwardheid had	☐	☐	☐	☐
Een andere 'rusteloosheid' had (omschrijving)		☐	☐	☐

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APPENDIX B. COPYRIGHTED QUESTIONNAIRES

For the following questionnaires, reproduction of full items is not permitted due to copyright restrictions. Therefore, only a short description and reference are provided.

Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A – Dutch version)

The BRIEF-A consists of 75 items assessing executive functioning in daily life across nine clinical scales (e.g., Inhibit, Shift, Working Memory). Due to copyright, the full items cannot be reproduced here. For details, see the official manual:

- Roth, R. M., Isquith, P. K., & Gioia, G. A. (2005). Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A). Lutz, FL: Psychological Assessment Resources.
- Scholte, E., & Noens, I. (2012). BRIEF-A: Vragenlijst voor executieve functies bij volwassenen – Handleiding. Hogrefe Uitgevers.

Utrechtse Coping Lijst (UCL)

The UCL contains 47 items assessing coping styles across seven dimensions (e.g., active problem solving, avoidance, seeking social support). Due to copyright, the full items cannot be reproduced here. For details, see the official manual:

- Schreurs, P. J. G., van de Willige, G., Brosschot, J. F., Tellegen, B., & Graus, G. M. H. (1993). De Utrechtse Coping Lijst: UCL-handleiding. Lisse: Swets & Zeitlinger.

ADDENDUM

SUMMARY

Introduction and Aim

Obstructive Sleep Apnea (OSA) is a common sleep disorder in which breathing repeatedly stops or becomes shallow during sleep due to a blocked airway. These breathing pauses disrupt the sleep cycle and reduce oxygen levels in the blood, leading to poor, non-restorative sleep. As a result, people with OSA often feel sleepy and tired during the day and may experience a range of symptoms—from snoring and morning headaches to mood changes like anxiety and depression.

One area that has received growing attention is the impact of OSA on thinking and memory. Many patients report difficulties with concentration, forgetfulness, or decision-making. These are known as cognitive complaints. Importantly, these complaints do not always match up with what is found in standard neuropsychological testing—some people feel their thinking is impaired even when tests show normal results, while others may have measurable impairments but don't notice them.

Despite being a major concern for many patients, cognitive complaints have received far less scientific attention than objective cognitive impairments. Moreover, it remains unclear what causes these complaints, how they relate to fatigue and sleepiness and psychological symptoms like anxiety, depression, and whether they improve with OSA treatment.

The goal of this dissertation is to better understand cognitive complaints in OSA: how common and severe they are, what factors contribute to them, and how they respond to treatments such as CPAP (a breathing machine used at night) or MAD (a mouthpiece that keeps the airway open during sleep). The research aims to support clinicians in recognizing and treating these often-overlooked symptoms.

Main Findings

1. Literature Review (Chapter 2):

A broad overview of existing research revealed that cognitive complaints—especially problems with concentration—are more common in OSA patients than in healthy individuals. However, findings on memory and executive functioning are mixed. One key insight is that these complaints are linked more to how sleepy someone feels than actual cognitive performance. Surprisingly, only one previous study had explored whether treatment reduces cognitive complaints, and that study had major limitations.

2. OSA Compared to Other Medical Conditions (Chapter 3):
This study compared OSA patients to people with conditions like stroke, brain tumors, and chronic lung disease (COPD). It found that cognitive complaints are just as common, and sometimes more common, in OSA patients than in those with clear brain damage. Across all groups, the strongest predictors of complaints were anxiety and depression, not the illness itself or test-measured cognitive impairments. This suggests psychological distress plays a major role in how people experience their thinking abilities across medical conditions.

3. Complaints Among Patients Referred for OSA Testing (Chapter 4):
This study looked at people referred to a sleep clinic, some of whom were later diagnosed with OSA and others not. All groups, regardless of diagnosis, reported cognitive complaints—suggesting that the complaints may not be specific to OSA itself. Instead, they were more closely related to fatigue, anxiety, and how sleepy people felt during the day. Again, there was no link between cognitive complaints and actual cognitive test scores.

4. Coping Styles and Complaints (Chapter 5):
This chapter focused on how people deal with stress and challenges. Patients who used avoidant or passive coping styles—such as ignoring problems or feeling helpless—were more likely to report cognitive complaints. This was true even when they weren't particularly sleepy or didn't have measurable cognitive impairments. On the other hand, active problem-solving seemed protective. These findings support the idea that psychological habits and coping play an important role in how people perceive their cognitive functioning.

5. Effects of Treatment (Chapter 6):
The final study looked at whether OSA treatment (CPAP or MAD) helped improve cognitive complaints. After six months of treatment, many patients reported feeling less forgetful and more mentally clear, especially if their daytime sleepiness improved. However, improvements were not related to how much their sleep apnea actually improved. This suggests that the benefit for cognitive complaints may come from feeling more rested, rather than from fewer breathing disruptions per se.

Conclusion
This dissertation highlights that cognitive complaints in OSA are real, common, and meaningful, even though they often don't reflect measurable cognitive impairments. Instead, these complaints seem to arise mainly from psychological factors like anxiety, fatigue, and unhelpful coping styles. Sleepiness plays a central role—people who feel more rested tend to feel mentally sharper.

Importantly, the research shows that we should not assume cognitive complaints mean there is brain damage, nor should we dismiss these complaints if tests look normal. Instead, healthcare providers should assess cognitive complaints alongside sleepiness, mood symptoms, and coping patterns. Doing so will help offer more personalized care, which may include psychological support in addition to standard OSA treatment.

The studies also reveal that treatment can help. CPAP and MAD appear to reduce cognitive complaints—especially memory-related ones—by improving how well-rested patients feel. However, those with more severe complaints were underrepresented in the treatment follow-up, so we don't yet know how well treatment works for them. More research is needed to evaluate long-term effects, include more diverse patient groups, and test whether psychological therapies can improve cognitive complaints even further.

Ultimately, this dissertation encourages a more nuanced and patient-centered approach to OSA. By recognizing cognitive complaints as valid and treatable symptoms—shaped by emotional, behavioral, and sleep-related factors—we can better address patients' concerns and improve their quality of life.

NEDERLANDSE SAMENVATTING

Introductie en doel van het proefschrift

Obstructieve Slaapapneu (OSA) is een veelvoorkomende slaapstoornis waarbij de ademhaling tijdens de slaap herhaaldelijk stopt of oppervlakkig wordt door een blokkade in de luchtweg. Deze ademstops verstoren de slaapcyclus en verlagen het zuurstofgehalte in het bloed, wat leidt tot een slechte, niet-herstellende slaap. Mensen met OSA voelen zich hierdoor overdag vaak slaperig en moe, en kunnen uiteenlopende klachten ervaren van snurken en ochtendhoofdpijn tot stemmingsveranderingen zoals angst en depressie.

Een onderwerp dat steeds meer aandacht krijgt, is het effect van OSA op het denken en geheugen. Veel patiënten melden moeite met concentratie, vergeetachtigheid of besluitvorming. Dit worden cognitieve klachten genoemd. Belangrijk is dat deze klachten niet altijd overeenkomen met wat uit neuropsychologisch onderzoek blijkt—sommige mensen voelen zich cognitief beperkt terwijl testen normale resultaten laten zien, terwijl anderen meetbare beperkingen hebben maar daar zelf weinig van merken.

Ondanks dat deze klachten veel voorkomen en grote impact kunnen hebben, is er in de wetenschap tot nu toe veel meer aandacht geweest voor objectieve cognitieve stoornissen dan voor subjectieve klachten. Het is bovendien nog onduidelijk wat deze klachten veroorzaakt, hoe ze samenhangen met vermoeidheid, slaperigheid en psychologische klachten zoals angst en depressie, en of ze verbeteren met behandeling van OSA.

Het doel van dit proefschrift is om cognitieve klachten bij OSA beter te begrijpen: hoe vaak ze voorkomen, hoe ernstig ze zijn, welke factoren eraan bijdragen, en of ze verbeteren na behandeling met bijvoorbeeld CPAP (een ademhalingsapparaat voor 's nachts) of een MRA (een beugel die de luchtweg openhoudt tijdens de slaap). Het onderzoek beoogt zorgverleners te ondersteunen bij het herkennen en behandelen van deze vaak onderbelichte klachten.

Belangrijkste bevindingen

1. Literatuuronderzoek (Hoofdstuk 2):

Een overzicht van bestaande studies laat zien dat cognitieve klachten—vooral concentratieproblemen—vaker voorkomen bij OSA-patiënten dan bij gezonde mensen. De bevindingen over geheugen en uitvoerende functies zijn minder eenduidig. Een belangrijk inzicht is dat deze klachten vaker samenhangen met hoe slaperig iemand zich voelt dan met de resultaten van cognitieve tests. Slechts één eerdere studie onderzocht of behandeling cognitieve klachten vermindert, en die studie had aanzienlijke beperkingen.

2. Vergelijking met Andere Medische Aandoeningen (Hoofdstuk 3):
In dit onderzoek werden OSA-patiënten vergeleken met mensen met aandoeningen zoals een beroerte, hersentumor of chronische longziekte (COPD). Cognitieve klachten bleken net zo vaak, en soms vaker, voor te komen bij OSA-patiënten als bij mensen met zichtbare hersenschade. In alle groepen waren angst en depressie de sterkste voorspellers van cognitieve klachten, niet de ziekte zelf of de resultaten van cognitieve tests. Dit wijst op een belangrijke rol van psychisch onwelbevinden in hoe mensen hun denkvermogen ervaren.

3. Cognitieve Klachten bij Verwijzingen naar een Slaapkliniek (Hoofdstuk 4):
In dit onderzoek werden mensen onderzocht die verwezen waren naar een slaapkliniek, van wie sommigen later een OSA-diagnose kregen en anderen niet. Alle groepen—ongeacht diagnose—gaven aan cognitieve klachten te ervaren. Dit suggereert dat deze klachten niet specifiek zijn voor OSA. Ze hingen sterker samen met vermoeidheid, angst en slaperigheid dan met OSA zelf. Er was opnieuw geen verband tussen cognitieve klachten en prestaties op cognitieve tests.

4. Copingstijlen en Cognitieve Klachten (Hoofdstuk 5):
Dit hoofdstuk onderzocht hoe mensen omgaan met stress en problemen. Patiënten die vermijdende of passieve copingstijlen gebruikten—zoals het negeren van problemen of zich hulpeloos voelen—rapporteerden vaker cognitieve klachten. Dit gold zelfs wanneer ze niet bijzonder slaperig waren of geen meetbare cognitieve beperkingen hadden. Actieve probleemoplossing leek daarentegen beschermend. Deze bevindingen onderstrepen het belang van psychologische factoren en coping in hoe mensen hun cognitief functioneren beleven.

5. Effect van Behandeling (Hoofdstuk 6):
Het laatste onderzoek keek of OSA-behandeling (CPAP of MRA) cognitieve klachten verminderde. Na zes maanden behandeling gaven veel patiënten aan zich minder vergeetachtig en mentaal helderder te voelen, vooral als hun slaperigheid overdag afnam. Deze verbetering was echter niet gerelateerd aan hoeveel hun slaapapneu technisch gezien verbeterde. Dit suggereert dat het gunstige effect op cognitieve klachten vooral komt door het zich uitgeruster voelen, niet per se door een afname van ademstops.

Conclusie

Dit proefschrift laat zien dat cognitieve klachten bij OSA echt, veelvoorkomend en betekenisvol zijn, ook al weerspiegelen ze vaak geen meetbare cognitieve stoornissen. In plaats daarvan lijken deze klachten vooral voort te komen uit psychologische factoren zoals angst, vermoeidheid en ineffectieve coping. Slaperigheid speelt hierbij een centrale rol—mensen die zich uitgeruster voelen, ervaren vaak ook minder cognitieve problemen.

Belangrijk is dat zorgverleners cognitieve klachten niet automatisch moeten zien als teken van hersenschade, maar ze ook niet moeten negeren als testresultaten normaal zijn. Een bredere beoordeling—die ook slaperigheid, stemming en copingstijlen meeneemt—biedt ruimte voor een persoonlijkere behandeling, mogelijk met psychologische ondersteuning naast de standaard OSA-zorg.

De studies laten ook zien dat behandeling kan helpen. CPAP en MRA lijken cognitieve klachten—vooral geheugenproblemen—te kunnen verminderen door de slaapkwaliteit te verbeteren. Wel waren patiënten met ernstigere klachten ondervertegenwoordigd in het vervolgonderzoek, waardoor het nog onduidelijk is hoe goed behandeling voor hen werkt. Toekomstig onderzoek moet zich richten op langere termijn effecten, bredere patiëntgroepen, en ook psychologische interventies als mogelijke behandelmethode voor cognitieve klachten.

Samengevat pleit dit proefschrift voor een meer genuanceerde en patiëntgerichte benadering van OSA. Door cognitieve klachten te erkennen als legitieme en behandelbare symptomen—die beïnvloed worden door emotionele, gedragsmatige en slaapgerelateerde factoren—kunnen we de zorg verbeteren en bijdragen aan een betere kwaliteit van leven voor mensen met OSA.

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Mijn **vader** kan helaas niet aanwezig zijn bij de verdediging, omdat hij er niet meer is. "Intelligentie is aangeleerd," zei hij altijd. Hij zette zich onvermoeibaar in om ons de beste schoolresultaten te bezorgen en wilde dat wij alle opleidingskansen optimaal benutten. Deze opvoeding heeft zeker bijgedragen aan mijn keuze voor een promotietraject. Ik weet zeker dat ik met dit proefschrift zijn ambitie en verwachtingen ruimschoots heb overtroffen.

Mam, je zei vroeger al: "Al moet Tim door een muur lopen." Die vasthoudendheid heb ik niet van een vreemde. Zonder jouw strijdlust had ik niet leren doorzetten. Ik hoop dat je trots bent, niet alleen op mij, maar ook op wat jij zelf hebt bereikt. Jij hebt gevochten, en daardoor kon ik dit bereiken. Zonder jouw kracht was ik nooit zo ver gekomen.

Last but not least, my paranimfen **Remi** and **Nate**. The last 15 years of my life have been quite the rollercoaster with many lows and some highs (excellent title for my memoir!). We bonded through similarities in our histories and were able to support each other in a way that respected our boundaries. As a wise man once said: *"You know, we as gay people, we get to choose our family. We get to choose the people we're around."* I am so fortunate to have you guys by my side at the defense of my PhD and in life. There were times I almost lost everything. You kept me safe and most importantly never lost faith in me. With that, you saved my life, and I will be eternally grateful.

CURRICULUM VITAE

Tim Vaessen werd in 1982 geboren in Heerlen. Na het cum laude afronden van het gymnasium (2000) behaalde hij cum laude zijn doctoraal Klinische Psychologie (2006). Hoewel hij altijd al een sterke interesse had in wetenschappelijk onderzoek, koos hij ervoor zijn loopbaan te beginnen in de klinische praktijk door de opleiding tot gezondheidszorgpsycholoog (GZ-psycholoog) te volgen in het Kennemer Gasthuis in Haarlem (2008-2010).

Tijdens deze opleiding raakte hij gefascineerd door patiënten met cognitieve stoornissen, wat hem motiveerde om de vervolgopleiding tot klinisch neuropsycholoog te volgen in het VieCuri Medisch Centrum in Venlo en Venray (2010-2014). Gedurende deze periode pakte hij wetenschappelijk onderzoek op, wat uiteindelijk leidde tot het huidige proefschrift.

Na zijn opleiding werkte hij in verschillende ziekenhuizen, waaronder het Reinier de Graaf Gasthuis in Delft (2014-2017), het OLVG in Amsterdam (2017-2019) en het Spaarne Gasthuis in Haarlem en Hoofddorp (2019 – huidig). Zijn werk richt zich vooral op diagnostiek en behandeling van patiënten met cognitieve stoornissen, zoals dementie en niet-aangeboren hersenletsel.

Tijdens zijn promotietraject heeft Tim zich naast zijn onderzoek en klinisch werk ook op diverse andere manieren ingezet voor de ontwikkeling van zijn vakgebied. Zo werd hij erkend gedragstherapeut (VGCT, 2017), was hij praktijkopleider voor de opleiding tot klinisch neuropsycholoog (2017-2019), trad hij meerdere keren op als waarnemend vakgroepvoorzitter medische psychologie (2016-2017 en 2022-2023) en deed hij commissiewerk voor de Landelijke Vereniging Medische Psychologie (LVMP, 2015-2018) en het Nederlands Geheugenpoli Netwerk (NGN, 2021-2024). Nu is hij praktijkopleider voor de opleiding tot GZ-psycholoog, verzorgt hij webinars over neuropsychologie voor Psyflix en is hij medeoprichter van het Geheugencentrum van het Spaarne Gasthuis.

In de toekomst wil hij zich blijven inzetten voor wetenschappelijk onderzoek en zorginnovatie, in het bijzonder voor patiënten met dementie op jonge leeftijd en cultuursensitieve zorg.