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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • REVIEW

Cognitive impairment in obstructive sleep apnea syndrome: a descriptive review

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Abstract

Purpose Obstructive sleep apnea syndrome is a clinical sleep disorder defined by total or partial airflow restraint during sleep that results in fragmented sleep and hypoxemia, impacting negatively with cognitive functioning. This review was conducted on studies investigating structural brain alteration and cognitive impairment in obstructive sleep apnea syndrome.

Method We searched on PubMed databases and screening references of included studies and review articles for additional citations. From initial 190 publications, only 17 met search criteria and described the cognitive impairment in obstructive sleep apnea syndrome.

Results Findings showed that patients with this syndrome had worse performance than healthy controls in attention, memory, and executive functions, showing specific neuroanathomical features. Cognitive impairment is also related to the severity of pathology. Treatment could improve certain cognitive aspects.

Conclusions Cognitive deficits seem to be mainly attributable to decreased daytime vigilance and nocturnal hypoxemia.

Keywords Obstructive apnea · Sleep disorders · Cognitive functioning · Memory impairment · Quality of life

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent episodes of partial or complete airflow restraint during sleep [1]. OSAS with excessive daytime sleepiness occurred in 6% (range, 3–18%) of men and in 4% (range, 1–17%) of women. The prevalence increased with time and OSAS was reported in 37% of men and in 50% of women [2]. The pathophysiology of OSAS involves both anatomical factors and functional factors, such as upper airway narrowing, defective activation of upper airway dilator muscles [3]. In the diagnosis of OSAS, the number of apneas per hour of sleep (apnea index), excluding time awake, should exceed five [4]. The apnea/hypoapnea index (AHI) is acquired by an overnight polysomnography (PSG) that also consent to obtain several sleep variables, including the number of awakenings during the total sleep time and the time as well as time in each sleep stage as a percentage of total sleep time [3]. In patients with severe OSAS, the AHI may be greater than 50. A frequent symptom is the excessive daytime sleepiness, evaluating by Epworth Sleepiness Scale, a simple, self-administered questionnaire which is shown to provide a measurement of the subject's genera1 level of daytime sleepiness [5].

Continuous positive airway pressure (CPAP) [6] is typically the first-line treatment recommended for OSAS [7]. It consists of a nasal mask attached to a pneumatic pump that is able to improve oxygen saturation and reduce sleep fragmentation [8]. OSAS is associated with an increased risk of serious medical conditions, such as vascular disease (hypertension, heart disease, and stroke), but also psychiatric disorders (depression and anxiety) [9]. Indeed, OSAS patients present clinical features including snoring, sleep disruption, nocturnal hypoxemia, cardiovascular complications, irritability, and vigilance impairment that may extend from the simple inability to perform everyday tasks to a real daytime sleepiness [10]. Moreover, OSAS is associated with cognitive impairment (CI) such as deficit in attention, executive functions, and memory [11]. The onset of neuropsychological impairments

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remains unclear and controversial, maybe due to the lack of correlation between measures of a given deficit and the progressive pathogenic factors [12].

This descriptive review focused on literature studies that investigated relationship between OSAS and cognitive impairment deepening potential anathomical mechanism of this association.

Materials and methods

Search strategy

This research was conducted on the presence of cognitive impairment in OSAS patients. Studies were identified by searching on PubMed database (1991, year of the first-related published article-February 2020). The search combined the following terms: ("obstructive sleep apnea"[All Fields] OR "sleep apnea, obstructive"[MeSH Terms] OR ("sleep"[All Fields] AND "apnea"[All Fields] AND "obstructive"[All Fields]) OR "obstructive sleep apnea"[All Fields] OR ("obstructive"[All Fields] AND "sleep"[All Fields] AND "apnea"[All Fields])) AND ("cognitive dysfunction"[MeSH Terms] OR ("cognitive"[All Fields] AND "dysfunction"[All Fields]) OR "cognitive dysfunction"[All Fields] OR ("cognitive"[All Fields] AND "impairment"[All Fields]) OR "cognitive impairment"[All Fields]) AND ("adult"[MeSH Terms] OR "adult"[All Fields]). The search terms were identified as title and abstract. All articles were evaluated based on title, abstract, and text. Studies that examined the relationship between OSAS and cognitive impairment were included, after they fulfilled the following criteria:

- Published peer-reviewed research;
- The sample population included OSAS patients;
- Studies specifically assessed the relationship between OSAS and cognitive impairments;

We imposed the following additional exclusion criteria: case studies and meta-analysis;

- studies that used only screening test (Mini Mental State Examination-MMSE or Montreal Cognitive Assessment—MoCA) for the neuropsychological evaluation
- studies including children and/or adolescents defined as participants less than 18 years of age.

Results

Of 190 studies identified only 17 met the inclusion criteria (Fig. 1). All studies conducted research on 603 OSAS patients and 396 Health Controls (HCs) (Table 1). All OSAS patients were non-demented and free of other neurological and psychiatric diseases. They fulfilled diagnostic criteria for OSAS according to the Association of Sleep Disorder Centers. HCs were volunteers with no history of neurological diseases and they were matched for age, education, and sex. OSAS patients and HCs were within a range of age between 18 and 65 years and had at least 5 years of education.

The neuropsychological functions were evaluated by 34 different standardized tests (Table 2). Five tests evaluated global functioning; memory domain was assessed by seven tests; attentional domain was investigated by seven tests; 13 tests were used to estimate the executive functions; visuo-constructive abilities were evaluated by four different tests.

Seven studies used neuro-imaging instrument to explore structural and functional brain changes in OSAS patients.

Neuropsychological functions

The majority of studies investigated found neuropsychological deficits in memory, attention, executive functions, and visuo-constructive abilities. In contrast, language abilities and global cognitive functioning were spared. The cognitive

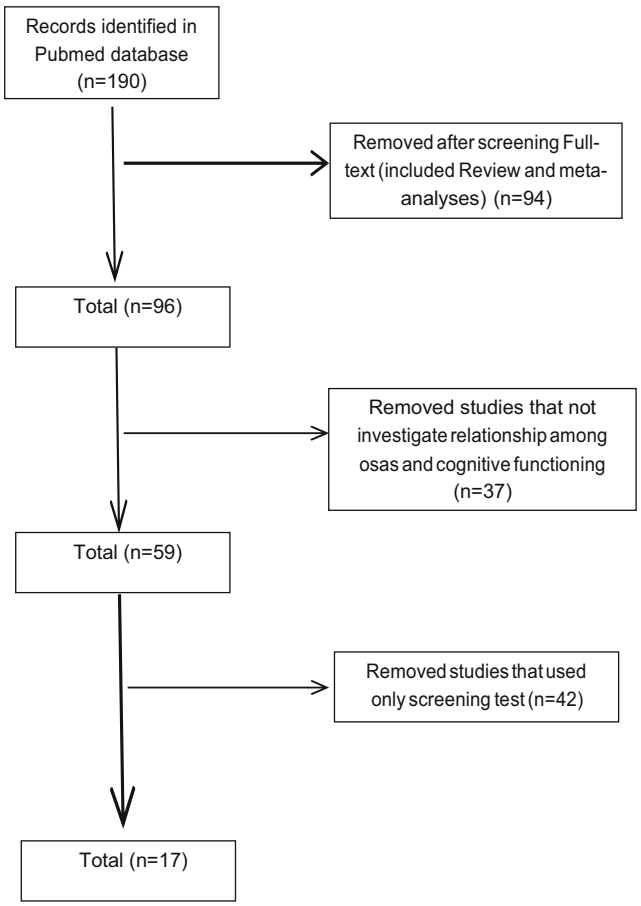

Fig. 1 Search and selection of eligible articles

Table 1 Studies assessing cognitive impairment in OSAS patients

References	Aim of the study	Sample	Neuropsychological tests	Brain investigation instruments	Results
Bédard et al. (1991)	To assess the contribution of nocturnal hypoxemia and vigilance impairment on cognitive deficits of OSAS To demonstrate a discontinuity in the appearance of cognitive deficits	10 moderate OSAS 10 severe OSAS 10 HCs	Rey-Osterreith Complex figure (copy and recall) Wechsler Adult Intelligence Scale Revised (WAIS-R) Wechsler Memory Scale Letter cancelation task Trail making Test A&B Verbal fluency test (S and C) Purdue Pegboard Hooper Visual Organization Test		OSAS patients are worse at tests than HCs Attentional and memory deficits seem related to a decrease of daytime vigilance (moderate OSAS), while later dampening of general intellectual performances and executive functions deficits were related to the nocturnal hypoxemia (severe OSAS)
Canessa et al. (2010)	To examine cognitive deficits and the corresponding brain morphology changes in OSAS To evaluate modifications after CPAP treatment	17 OSAS 15 HCs	Mini Mental State Examination (MMSE) Raven's Progressive Matrices Digit Span (forward and backward) Corsi Block-Tapping Test Rey Auditory Verbal Learning Test (learning, recall, recognition, false positive) Stroop test TMT A&B	MRI VBM	Pre-treatment, OSAS show worse performance than HCs, associated with focal reduction of gray matter volume in left hippocampus, left posterior parietal cortex and right superior frontal gyrus After treatment, improvement of memory, attention and executive functions. Paralleled increase of gray matter volume in hippocampal and frontal structures.
Chou et al. (2016)	To test if Action Monitoring is impaired in OSAS patients	25 OSAS 12 HCs	Modified Flanker Task		OSAS presented lower correct responses in both congruent and incongruent trials compared to HCs
Delhikar et al. (2019)	To determine whether individuals with untreated OSA have impaired autobiographical memory to assess the quality of autobiographical memories from three broad time points	44 OSAS 44 HCs	Autobiographical Memory Interview (AMI) Autobiographical Memory Test (AMT)		OSAS recorded a specific deficit in semantic autobiographical recall. These cognitive features seems to be related to the high incidence of depression in OSAS
Devita et al. (2017)	To evaluate if cognitive and motor response of information processing are equally impaired in OSAS	33 OSAS 30 HCs	Montreal Cognitive Assessment (MoCA) RT/S1 RT/S3 MDT/S2 MDT/S3		OSAS patients perform worse than controls at the MoCA test. As to psychomotor speed, OSAS patients show slower reaction time only for the motor component.
Edwards et al. (2014)	To study the role of cortisol on neurocognitive deficits of OSAS	55 OSAS	WAIS-R Digit symbol Digit Span Letter-Number Sequencing Test Brief Visuospatial Memory Test Revised (BVMT-R) Hopkins Verbal Learning Test Revised (HVLT-R) TMT A&B Stroop Test Digit Vigilance Test Verbal Fluency Test		OSAS performance at neurocognitive tests was poorer than HCs performance Inverse correlation between higher levels of cortisol and reduced neurocognitive functioning
Hoth et al. (2013)	To understand the contribution of hypoxemia to cognitive impairment in OSAS patients	20 OSAS with low hypoxemia 20 OSAS with high	American National Adult Reading Test (AMNART) Paced Auditory Serial Addition Task (PASAT) TMT A&B Controlled Oral Word Association Test (COWAT) Letter-Number Sequency Test HVLT		The high hypoxemia group performed significantly better on immediate recall than the low hypoxemia group. No group differences were observed on other neuropsychological measures

Table 1 (continued)

References	Aim of the study	Sample	Neuropsychological tests	Brain investigation instruments	Results
		hypox-emia	Grooved Pegboard		
Kotterba et al. (1998)	To evaluate neurocognitive profile of OSAS patients before and after CPAP treatment patients	31 OSAS 10 HCs (only for tests)	Wiener Testsystem Zimmermann Testbattery	EEG (ERPs of P300)	Before treatment, OSAS patients show worse performance in all attention parameters than HCs. P300 was prolonged. After treatment, improvement of alertness and vigilance. P300 did incongruent trials compared to HCs
Shpirer et al. (2011)	To examine the correlation between sleep apnea severity and patients' performance on the neuropsychological tests	40 OSAS	Conner's Continuous Performance Test (CPT), Trail Making Test, versions A&B (TMT-A, TMT-B), Digit Span subtest from WAIS-III, The Tower of London Test (ToL), Wisconsin Card Sorting Test (WCST), Phonological and Semantic fluency test		OSAS patients perform worse in attention. FE was not related to polysomnographic parameter.
Torelli et al. (2011)	To evaluate brain morphological changes in patients with OSA and their relationship to neuropsychological and oximetric data	16 OSAS-14 HC	neuropsychological testing	MRI (3.0 Tesla)	the significant cognitive impairment seen in patients with moderate-severe OSA is associated with brain tissue damage in regions involved in several cognitive tasks
Alchanatis et al., (2004)	To investigate brain metabolism in patients with sleep apnoea syndrome	22 OSAS 10 HC		MRI	Absolute concentrations of N-acetylaspartate and choline were also significantly reduced in the frontal white matter of patients with sleep apnoea
Park et al., (2016)	to examine the functional interactions and the complex network organization of these interactions across the whole brain in OSA, using regional functional connectivity (FC) and brain network topological properties.	69 OSAS		MRI (3.0 Tesla)	OSAS showed significantly altered FC in the cerebellar, frontal, parietal, temporal, occipital, limbic, and basal ganglia regions (FDR, $P < 0.05$)
Tulek et al. (2013)	To verify the hypothesis that attentional control is impaired in OSAS patients	24 OSAS 14 HCS	Flanker task Simon task Stroop Test MMSE		Impaired conflict adaptation in OSAS than HCs during Flanker task
Twigg et al. (2010)	To test if OSAS patients had memory impairment To explore if memory deficits were correlated with OSAS severity	60 OSAS 60 HCs	Verbal fluency Graded Naming Logical Memory (immediate and delayed recall, recognition, retention) Paired Association Rey Complex figure Topographical recognition memory test Digit Span Telephone search task Stroop test TMT A&B		Worse performance of OSAS patients in immediate and delayed recall, but not in recognition and retention of information.
Werli et al. (2016)	To evaluate residual excessive sleepiness (RES) in OSAS patients after CPAP treatment	15 RES OSAS 15 no RES OSAS	WCST Digit Span Stroop test TMT A&B RAVLT Verbal fluency Codes measures		Performances of RES OSAS in WCST, digit span and verbal fluency were worse than noRES OSAS
Yaouhi et al.		16 OSAS 14 HCs	MMSE	MRI VBM PET	

Table 1 (continued)

References	Aim of the study	Sample	Neuropsychological tests	Brain investigation instruments	Results
(2009)	To establish neuropsychological profile and brain morphology of OSAS patients		Test battery of Attentional Performance (TAP) Wechsler Memory Scale Verbal fluency Purdue Pegboard		OSAS performed more poorly than HCs in WMS and Purdue Pegboard. Loss of gray matter in the frontal and temporo–parieto–occipital cortices, the thalamus, hippocampal region, some basal ganglia and cerebellar regions, mainly in the right hemisphere. Decrease in brain metabolism in precuneus, the middle and posterior cingulate gyrus, and the parieto–occipital cortex, as well as the prefrontal cortex
Zhang et al. (2015)	To determine the presence of a disrupted disconnection between the right anterior insula and the central executive network (CEN) and the default mode network (DMN) in OSAS patients	24 OSAS 21 HCs	Digit Span	3-Tesla MRI fMRI	Significantly weakened rsFC between insula and DMN. Correlation between disconnection of insula and mPFC and severity of OSAS.
Zhang et al. (2002)	To study with event-related potentials the effect of hypoxia on cognitive profile of OSAS	12 mild OSAS 12 severe OSAS 20 HCs	Modified Sternberg Memory-Matching Paradigm	EEG (ERP N270)	In mild OSAS patients, the negative component N270 elicited in low- and high-conflict conditions was significantly reduced.

OSAS obstructive sleep apnea syndrome, *HCs* healthy controls, *MRI* magnetic resonance imaging, *fMRI* functional magnetic resonance imaging, *VBM* voxel-based morphometry, *EEG* electroencephalogram; *ERP* event-related potential, *PET* positron emission tomography, *TMS* transcranial magnetic stimulation, *FC* functional connectivity

profile of these patients changed due to the severity of the syndrome: severe OSAS patients with AHI > 30 showed worse performance in neuropsychological tests than moderate OSAS patients (AHI: 10–30) and both patients groups exhibited poorer performance than HCs. These findings demonstrate a consistent relationship between OSAS severity and cognitive impairment. In particular, attention/vigilance and global cognitive functioning seem to be more related to measure of severity [13].

We have divided studies according to the different neuropsychological functions investigated.

Memory Some studies have reported in OSAS patients deficits in verbal memory [14–17], visual episodic memory [14, 18], and semantic memory [3, 14, 17–20], suggesting deficit in learning new information.

Twigg et al. [21] investigated memory and attention in a large group of 60 OSAS patients and 60 HCs using an overnight PSG and to an extent memory battery. The results showed in OSAS patients deficit in immediate and delayed recall, but normal recognition memory and retention of information over time in the logical memory test. Working memory and attention appeared to be unaffected in OSAS patients.

Edwards et al. [22] investigated the relationship between the level of night plasma cortisol and neuropsychological deficit in 55 OSAS patients. A neuropsychological battery, assessed 7 cognitive domains, was administered to each patient. Results showed that the OSAS performance at neurocognitive tests was poorer than HCs performance. In addition, higher levels of cortisol during the nighttime were associated with neurocognitive impairment, especially regarding learning abilities, memory, and working memory. Exposure to high levels of glucocorticoids in the setting of healthy aging was associated with deficits in memory and structural changes to the hippocampus [23, 24].

In Delhikar et al. [25], a particular kind of memory was assessed in OSAS patients. Authors have hypothesized the presence of autobiographical memory deficit in population who suffered of obstructive apnea syndrome. Findings demonstrated that in OSAS patients, autobiographical memory impairments were prevalent, in

Table 2 Tests used for neuropsychological assessment

Test	Description	Neuropsychological functions evaluated
MMSE—Mini Mental State Examination [59]	30-point screening questionnaire.	Memory (immediate and delayed recall) attention and calculation, recall, language, ability to follow simple commands and orientation
MoCA—Montreal Cognitive Assessment [60]	30-point screening questionnaire.	Memory (immediate and delayed recall), attention, and calculation, language, orientation
WAIS-R—Wechsler Adult Intelligence Scale	General test of intelligence, consists of six verbal subtests and five performance subtests.	Verbal subtests: information, comprehension, arithmetic, digit span, similarities, and vocabulary. Performance subtests: picture arrangement, picture completion, block design, object assembly, and digit symbol
Raven's Standard Progressive Matrices [61]	Non-verbal group test composed of 60 items	Abstract reasoning and fluid intelligence
AMNART—American National Adult Reading Test	Read out loud correcting 50 word with varying difficulty	Premorbid verbal intelligence
COWAT—Controlled Oral Word Association Test [62]	Generation as many words as possible in 60 s to each of three letter cues	Language production
Rey-Osterreith Complex fig. [63]	Reproduce a complicated line drawing, first by copying it freehand (recognition), and then drawing from memory (recall)	Visuospatial abilities, memory, attention, planning, working memory
Clock Drawing Test [64]	To draw a clock with all numbers and lancets	Visuospatial abilities
Hooper Visual Organization Test	Patients have to identify 30 fragmented images of trait, objects or animals	Visuospatial abilities
Purdue Pegboard Test	Board with two parallel rows with 25 holes into which cylindrical metal pegs are placed by the examinee. The test involves a total of four trials. The subsets for preferred, non-preferred, and both hands require the patient to place the pins in the holes as quickly as possible.	Visuo-motor coordination
Memory		
WMS—Wechsler Memory Scale [65]	Memory test that includes seven subtests (spatial addition, symbol span, design memory, general cognitive screener, logical memory (I & II), verbal paired associates (I & II), and visual reproduction (I & II)	Auditory memory, visual memory, visual working memory, immediate memory, and delayed memory.
RAVLT—Rey Auditory Verbal Learning Test [66]	Presentation of a list of 15 words for 5 time by the examiner. Participant have to repeat all words from the list that he/she can remember. After a 20-min delay, the participant is again asked to recall as many words as possible from the first list	Verbal learning and memory (short-term and long-term both)
SRT-Selective Reminding Test [67]	Ten unrelated words were read to participants at a rate of one every 2 s. Immediately after, the participant is asked to recall the entire list. This procedure is followed for six trials, from which measures of long- and short-term memory and of total recall are obtained.	Verbal learning and memory (short-term and long-term both)
HVLT-R—Hopkins Verbal Learning Test Revised [68]	List of 12 targets with four words drawn from each of three semantic categories.	Verbal learning and memory (short-term and long-term both)
BVMT-R—Brief Visuospatial Memory Test Revised	In three learning trials, the respondent views the stimulus page for 10 s and is asked to draw as many of the figures as possible in their correct location on a page in the response booklet. A Delayed Recall Trial is administered after a 25-min delay. Last, a Recognition Trial, in which the respondent is asked to identify which of 12 figures were included among the original geometric figures, is administered	Visuospatial memory
The Autobiographical Memory Interview (AMI) [69]	It is a semi-structured interview that assessed the recall of autobiographical memories from three broad time periods: childhood (period before school, primary school, and high school years), early adult life (career, wedding, children, and meeting	Episodic and semantic autobiographical memories

Table 2 (continued)

Test	Description	Neuropsychological functions evaluated
	someone new in their twenties) and recent life (last Christmas and holiday/journey).	
The Autobiographical Memory Test (AMT) [70]	Participants were presented with a cue word, and asked to retrieve a specific memory that the word reminded them of. Cue words were five negatively valenced words (e.g., guilty, failure) and five positively valenced words (e.g., proud, happy). Memories were scored as "specific" (distinct time and place was recalled "the day I graduated"), "overgeneral" (event lasting longer than a day, encompassed many events or refers to a person or object "my mum"), or no response. For any response other than "specific," a prompt for clarification of a specific memory was given, and the clarified memory was scored accordingly. The number of overgeneral memories recalled was the primary outcome, with higher scores indicating poorer memory function	Autobiographical memory
Attention		
Single Letter Cancelation Test	Participants have to cancel a letter target between confounded stimulus	Selective attention
TMT A&B—Trail Making Test part A and part B	TMT-A: there are numbered circles from 1 to 25, and the patient should draw lines to connect the numbers in ascending order. TMT-B: circles include both numbers (1–13) and letters (A–N); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters	TMT-A: cognitive processing speed TMT-B: shifting
PASAT—Paced Auditory Serial Addition Task [71]	The subjects are given a number every 3 s and are asked to add the number they just heard with the number they heard before	Sustained attention, working memory
CPT—Conner's Continuous Performance Test	Repetitive task where the participant must maintain his focus over a period of time in order to respond to targets or inhibit response to foils. Tests may use numbers, symbols, or even sounds, but the basic task has the same concept.	Sustained and selective attention
DVT—The Digit Vigilance Test	Subjects were asked to cross as quickly as they can to a specific target number (6 or 9) that appears randomly within 59 rows of 35 single digit on two pages	Sustained attention and psychomotor speed
Digit Symbol Test	Write down a digit the corresponding symbol as fast as possible	Sustained attention
TAP—Test battery of Attentional Performance [72]	Six tests based on reaction time measurements	Alertness, divided attention, sustained attention, visual scanning, flexibility and distractibility
WT—Wiener Testsystem	Battery that evaluated different aspects of attention	Alertness, permanent attention, selective attention
ZT—Zimmermann Testbatterie	Battery that evaluated different aspects of attention	Vigilance and divided attention
Executive functions		
Verbal Fluency Test [73]	Participants have to produce as many words as possible from a category in a given time (usually 60 s). This category can be semantic, including objects such as animals or fruits, or phonemic, including words beginning with a specified letter.	Phonological version = executive function Semantic version = language
Digit Span Memory Test	Forward: to repeat a series of numbers in the same order of the examiner Backward: to repeat a series of number in the opposite order of the examiner	Verbal working memory
Letter-Number Sequencing Test	To repeat a series of numbers/letters in the same order of the examiner	Verbal working memory
Corsi Block-Tapping Test	Mimicking a researcher as he/she taps a sequence of up to nine identical spatially separated blocks	Visuospatial working memory
Sternberg Memory-Matching Paradigm [74]	To judge if the probe presented in the center of the screen is identical to or different from the items presented before	Working memory
Stroop Color-Word Test	To read three different table as fast as possible. Two of them represent the congruent conditions, in which participants have to read names of colors written in black and name different	Sustained attention, selective attention, inhibition ability

Table 2 (continued)

Test	Description	Neuropsychological functions evaluated
	color patches. The last one present the incongruent condition, in which color word are written in different colors; participants have to name the color of the ink instead of reading the word	
WCST—Wisconsin Card Sorting Test	A number of stimulus cards are presented to the participant. The participant is told to match the cards, but not how to match; however, he or she is told whether a particular match is right or wrong	Flexibility, shifting, perseveration, abstraction abilities
ToL—Tower of London	It requires the subject to move perforated balls, placed in a certain configuration on a particular structure until a new configuration is reached	Planning abilities, problem solving
Flanker Task	To indicate the direction of a central stimulus flanked by non-target stimuli in congruent or incongruent trials	Action monitoring, attentional control, error processing
Simon Task	Discriminating between two stimuli presented on the left or on the right of the screen using two different buttons	Action monitoring, attentional control, error processing

comparison to healthy controls. Specifically, OSAS participants had significantly poorer semantic recall of early adult life. These cognitive impairment is related to higher depression levels.

Attention Patients with OSAS seemed affected in a wide range of attentional processes including sustained and divided attention. Kotterba et al. [26] studied vigilance, alertness, selective attention, divided attention, and permanent attention in 31 male OSAS patients using the Wiener Testsystem (WT, to evaluate alertness, selective attention, and permanent attention) and the Zimmermann Testbatterie (ZT, to evaluate vigilance and divided attention). In addition, visual evoked-related potentials were recorded while the patients have to conduct a computer tasks and P300 component was evaluated. The results showed that vigilance parameters of OSAS patients were not significantly different from HCs; however, patient had worse scores in all attention parameters, especially regarding alertness and continuous attention. In addition, P300 component of the event-related potentials was prolonged.

In the study by Shpirer et al. [1], 40 OSAS patients were tested attention domains, working memory, and shifting with Conner's Continuous Performance Test (CPT) [27], Trail Making Test, versions A&B (TMT-A, TMT-B) [28], and Digit Span subtest from WAIS-III [29]. To estimate executive functioning were used The Tower of London Test (ToL), the Wisconsin Card Sorting Test (WCST) [30], and Phonological and Semantic fluency test. Results showed that patients' performance was significantly worse on measures of attention and executive functions compared to the HCs. Attention deficits significantly correlated with OSAS severity as determined by the AHI, the average SpO2 and the percent time spent with SpO2 < 90%.

Devita et al. [31] investigated cognitive and motor reactions time in 33 OSAS patients and 30 HCs. They used four computerized tasks to evaluate information processing speed in several difficulties and to test participant's reaction time to a moving stimulus with a congruent or incongruent motor response. Patients underwent to MoCA test to estimate global cognitive functioning. In this study, the cognitive component of RTs would correspond to the decision time and to the premotor time, while the motor component of RTs would correspond to the selection and the implementation of an appropriate motor response. OSAS patients performed worse than controls at the MoCA test, showing that this syndrome globally impairs cognitive functioning and slower reaction time only for the motor component.

In OSAS patients, motor slowdown could had a substantial impact on daily living by worsening cognitive functions.

Executive functions

OSAS patients show impairments in executive functions. Chou et al. [32] used the computerized versions of the Flanker task [33] in 25 OSAS patients and 12 HCs to evaluated executive functions. Compared with HCs, the patients with OSAS presented a significantly lower correct response rate in congruent and incongruent trials. The post-error correction rate was significantly lower in the patients with OSAS than in the controls. Action monitoring function was impaired in the patients with OSAS and that sleep fragmentation was a major determinant of impaired action monitoring in these patients.

Tulek et al. [34] also investigated executive functions in 24 OSAS patients and 14 HCs using Flanker task, Simon task [35], and Stroop task [36]. For each task, the average error rate (ER) and reaction time (RT) of correct responses were measured. Results indicated that attentional control was partially

dysfunctional in OSAS patients due to frontal lobe dysfunction.

Zhang et al. [37] investigated Working Memory (WM) in 20 HCs and 24 OSAS patients, divided into two groups according to severity degree of the syndrome (12 mild OSAS and 12 sever OSAS). Subjects underwent a modified Sternberg Paradigm, a visual S1–S2 matching paradigm when the information in the second stimulus (S2) conflicts with that of the first stimulus (S1). During this task, ERP component N270 was recorded. N270 is elicited when the probe item conflicted with the preceding memorized item, and it is encoded in WM. Results showed that for OSAS patients, the negative component N270 elicited in low- and high-conflict conditions was significantly reduced than HCs, suggesting that WM was impaired.

Neuro-imaging studies

Only three of the 17 studies have used neuro-imaging investigations, finding brain tissue damage that could explain cognitive performance in OSAS patients.

Yaouhi et al. [11] assessed functional and morphological brain's differences between 16 OSAS patients and 14 HCs using the optimized voxel-based morphometry procedure for the MRI data, resting-state 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18FDG-PET) with correction for partial volume effects (PVEs) and voxel-based analyses. Cerebral data revealed gray matter loss in the frontal and temporo–parieto–occipital cortices, the thalamus, hippocampal region, some basal ganglia, and cerebellar regions, mainly in the right hemisphere. Moreover, authors found a decrease in brain metabolism of the precuneus, the middle and posterior cingulate gyrus, and the parieto–occipital cortex and prefrontal cortex. These results could explain the impairment in memory and in motor domains that was found in these sample of OSAS patients which recorded objective daytime somnolence.

Torelli et al. [38] evaluated brain morphological changes in 16 OSAS patients compared to 14 HCs. All the participants underwent to 3.0 T brain magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) [39] to investigate white matter and voxel-based morphometry (VBM) [11, 39–41] to analyze gray matter. Brain investigations revealed that cortical gray matter, right and left hippocampus, right and left caudate, and lateral temporal regions of OSAS patients had a significant smaller volume than HCs. All subjects were also undergoing to neuropsychological tests to assess memory (Rey Auditory Verbal Learning Test, Digit span backward and forward, Visual Memory Test, Rey-Osterreith Figure recall), executive functions (Stroop color/word test, phonological fluency), attention (Stroop color/word test), language (semantic fluency), praxia (copy drawing, Rey-Osterreith Figure copy), and non-verbal learning. Results showed that patients had a significant worse performance than HCs in memory and executive functions tests. Data confirmed that CI in patients with moderate-severe OSAS were associated with brain tissue damage. Moreover, a metabolic impairment in the deep white matter seems to selectively affected in OSAS [42]; other studies demonstrated a reduction in absolute concentrations of in N-acetylaspartate (NAA) and choline (Cho) in the FWM of OSAS patients when compared to HCs that indicates axonal loss and/or dysfunction [43, 44]. Zhang et al. [45] used fMRI to estimate resting-state activity and functional disconnection of the right anterior insula in 24 OSAS patients and 21 HCs. The right anterior insula (AIns) is a critical node of the salience network (SN) that serves to switch between the central executive network (CEN) and the default mode network (DMN) through their anatomical connections, which is important for cognitive performance. Results demonstrate a functional disconnection between the right AIns and the DMN in OSAS; also, the decreased rsFCs between the right AIns and the critical nodes of the DMN were associated with OSAS severity and impaired working memory performance.

Discussion

OSAS is a respiratory disorder identified by partial or total obstruction of the airway during sleep [46]. It causes arousals, intermittent hypoxemia and hypercapnia, and excessive daytime sleepiness [47]. OSAS is also associated with poorer cognitive performances [48].

The neuropsychological profile of OSAS patients is defined by cognitive deficits [49] associated with functional and morphological brain changes, involving gray and white matter, especially in frontal regions [41]. Studies [50–53] showed altered functional connections (FC) in the whole-brain areas in OSAS subjects. The most affected FC were related to cerebellar regions, but the declines were not site specific, and appeared across whole brain regions. These authors found many brain networks with reduced connectivity such as bilateral anterior cingulate cortex (ACC), left insula, left supplementary motor area (SMA), right para-hippocampal gyrus, and right superior temporal pole. In contrast, increased FC in OSAS emerged in temporal–parietal networks. Finally, reduced FC or increased FC also appeared in temporal–occipital networks in OSAS. Lesser FC (the right inferior parietal lobule, right supramarginal gyrus, right calcarine, and left fusiform gyrus) and higher FC (the bilateral calcimine, bilateral fusiform gyrus, bilateral paracentral lobule, and left pre- and post-central gyrus) were also found in parietal–occipital areas of OSAS subjects. These findings indicated that OSAS subjects had abnormal resting-state FC in various brain regions largely related to autonomic, affective, executive, sensorimotor, and cognitive regulatory functions, areas

that appeared with structural injury in previous studies of OSAS subjects, as well as areas that appeared abnormal resting-state FC. In comparison to HCs, OSAS patients showed gray matter atrophy and para-hippocampal and frontotemporal cortex seems to be the brain region most affected [54].

Pathological basis for underlying neuropsychological comorbidities in OSAS is poorly understood.

Some authors suggested that CI are induced by nocturnal hypoxemia and oxygen deprivation in several brain areas during sleep [1, 55]; other studies associated CI to daytime vigilance impairment due to excessive sleepiness [31, 56, 57]. In this case, CI seems to be improved through the use of continuous positive airway pressure (CPAP) that is defined as the gold standard treatment for OSAS. CPAP may slow cognitive decline in patients with comorbid neurodegenerative disorders and OSAS [58]. Indeed, CPAP treatment is associated with improvements in attention and memory domains, but not in executive functions [54]. Only two of the 16 studies have compared performance before and after CPAP treatment, finding not only improvement in alertness, vigilance, and memory, but also increase of gray matter volume in hippocampal and frontal structures [26, 56].

The contribution of nocturnal hypoxemia and vigilance impairment on the CI differed between moderate and severe OSAS. In fact, progressively increasing deficits from moderate to severe include attentional tasks, immediate and delayed recall of verbal and visual materials, planning and sequential thinking. Deficits appeared only in severe OSAS were dampening of general intellectual functioning and executive functions (especially shifting and constructive abilities). These results suggested that both nocturnal hypoxemia and vigilance impairment contribute to CI in OSAS patients, but a different level. Attentional and memory deficits seem primarily related to a decrease of daytime vigilance, while dampening of general intellectual performances and executive functions deficits were related to the nocturnal hypoxemia [3].

This review focused on cognitive impairment in OSAS patients. Neuropsychological deficits include attention, memory, and executive functions.

The studies in this review involve only a limited number of participants, considering the incidence of the syndrome and the sample heterogeneity. Plus, the different tests used did not always permit a comparison between studies. Moreover, only few studies used neuro-imaging investigation; for this reason, there is still lack of correlation between neuropsychological deficits and brain changes. Future research should be conducted on the mechanisms underlying CI in OSAS in order to find preventive measure and rehabilitation for these patients. In addition, further investigations needed to clarify the relation between hypoxemia and vigilance alterations on cognitive impairment in OSAS patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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