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# A review of executive functions in obstructive sleep apnea syndrome

Saunamäki T, Jehkonen M. A review of executive functions in obstructive sleep apnea syndrome. Acta Neurol Scand 2007; 115: 1–11. © Blackwell Munksgaard 2006.

**Objectives** – To provide an update on recent research concerning obstructive sleep apnea syndrome (OSAS) and executive functions. **Methods** – A systematic review was carried out on reports drawn from MEDLINE and PSYCHLIT (January 1990–December 2005) and identified from lists of references in these reports. The selection criteria were met by 40 articles. **Results** – The sample sizes in the reviewed studies varied widely and consisted mostly of selected groups. Most patient samples were heterogeneous in terms of the severity of OSAS. Executive functions were generally assessed with standardized test methods. Half of the studies assessed executive functions using only one or two tests. The most defected domains of executive functions were working memory, phonological fluency, cognitive flexibility, and planning. Continuous positive airway pressure (CPAP) treatment improved performance times, cognitive flexibility, and planning. Deficits in working memory and phonological fluency persisted. **Conclusions** – Executive functions are the most defected cognitive domain in OSAS. Previous studies are affected by the heterogeneity of patient samples and the definitions of the domains of executive functions. Executive functions in OSAS should be assessed with a standardized neuropsychological test battery including assessments of different domains of executive functions. More research is needed on the efficiency of CPAP treatment on executive dysfunctions.

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## Introduction

According to the American Academy of Sleep Medicine (1), obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway during sleep. These conditions usually result in oxygen desaturation and arousals from sleep. Estimated prevalence of clinically important sleep apnea is up to 4% in men and 2% in women. The diagnosis of obstructive sleep apnea is based on the following: (i) the patient complains some of the following symptoms: unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, insomnia, gasping and choking, or the bed partner reports breathing interruptions, and/or loud snoring, and (ii) the polysomnographic recording shows five or more respiratory breathing events (apneas, hypopneas or respiratory effort

related arousals) per hour of sleep and evidence of respiratory effort during all or a portion of each respiratory event. The diagnostic criteria are also fulfilled when (i) polysomnographic recording shows 15 or more respiratory events per hour of sleep and evidence of respiratory effort during all or a portion of each respiratory event, and (ii) the disorder is not better explained by another current sleep disorder, medical or neurological disorder, medications, or substance use disorder. The severity of OSAS varies among the patients. The frequency of apneas and hypopneas during sleep correlates poorly with the severity of daytime symptoms. Excessive sleepiness is a major complaint and is most evident in inactive situations (e.g. watching television, reading, traveling as a passenger). In severe sleep apnea extreme sleepiness can occur during activities that require more active attention (e.g. while eating, during conversation, walking, or driving) (1).

Common symptoms of OSAS include mood disorders, reduced quality of life and cognitive problems (2). Cognitive impairment in sleep apnea has been studied since the 1980s and several authors have offered reviews of these studies (2–9). According to these reviews the most common cognitive deficits are seen in attention or concentration, vigilance, memory and learning abilities, motor performance, constructional abilities and executive functions. Both excessive daytime sleepiness and nocturnal hypoxemia contribute to cognitive deficits (3–5). Excessive daytime sleepiness has been mostly related to impairment in attention, vigilance and memory function, while hypoxemia correlates more with deficits in executive functions (2, 4). Cognitive impairment usually worsens with disease severity, but this tendency is not linear (8, 9).

Beebe and Gozal (10) recently reviewed the importance of executive dysfunction and the involvement of the frontal cortex in OSAS. Lezak et al. (11) define executive functions as a person’s ability to respond in an adaptive manner to situations and to engage successfully in independent, purposive and self-serving behavior, which is the basis for many cognitive, social and emotional skills. According to Beebe and Gozal (10) executive functions in OSAS can manifest as deficits in behavioral inhibition, set-shifting, self-regulation of affect and arousal, working memory, analysis/synthesis, and contextual memory. Although cognitive deficits can, in most cases, be improved by continuous positive airway pressure (CPAP) therapy, some deficits in executive function may remain (2, 8, 10). Persistent deficits raise the possibility of permanent brain alterations (8–10). Beebe and Gozal (10) have presented a model linking sleep disruption, hypoxemia and dysfunction of the frontal cortex. The model proposes that sleep disruption and nocturnal hypoxemia and hyper-

carbia reduce the efficacy of sleep-related restorative processes. This induces a variety of biochemical and cellular stresses and leads to disruption of the functional homeostasis and altered neuronal and glial viability within certain brain areas. The model suggests that these biochemical and cellular events are primarily manifested in dysfunction of frontal regions on the brain cortex. Furthermore, it is important to notice that executive dysfunction may also result from injury to other brain regions than the frontal cortex (11). Frontal lobes have dense connections to other cortical lobes and to subcortical brain areas. Thus, ‘frontal lobe dysfunction’ may also result from damage to these connections.

In OSAS patients executive dysfunctions are usually mild and they manifest in more demanding activities, such as social relations, traffic, and job tasks (10). Therefore, executive functions must always be assessed as a part of a neuropsychological evaluation. In OSAS patients the evaluation of executive skills is even more critical than the evaluation of basic cognitive skills (e.g. vocabulary) or skills that only partially reflect executive issues (e.g. intelligence tests) (10). Executive functions are not usually impaired across the board, but some executive functions are impaired while others are not (12). Therefore, the neuropsychological assessment must comprise several domains of executive functions so that any impairments and their nature can be detected and analyzed. Among the studies reviewed, Decary et al. (4) and Beebe and Gozal (10) have proposed recommendations on which executive functions and which tests should be included in the neuropsychological assessment of OSAS patients. An overview of these recommendations is presented in Table 1. The psychometric values (e.g. test–retest reliability, inter-item consistency and interrater reliability) of these tests as a guide to test choice are limited because these tests often measure abilities such as

**Table 1** Overview of methods recommended for the assessment of executive functions in OSAS by Decary et al. (4) and Beebe and Gozal (10)

Test method	Domain of executive function
Wisconsin Card Sorting Test (13)	Mental set shifting (4, 10) and abstract behavior (4)
Trails B of Trail Making Test (14)	Mental set shifting (4, 10) and abstract behavior (4)
Trail Making Test (14)	Conceptual and visuomotor tracking (4)
Mazes (WISC-III; 71)	Planning and foresight (4)
Stroop test (15)	Focal attention, shifting processes (4) and behavioral inhibition (4, 10)
Copy of Rey-Osterreith Complex Figure (64)	Organizational skills/analysis-synthesis on the spatial domain (4, 10)
Fluency tasks (11)	Analysis/synthesis (10)
Back digit strings (WAIS-R; 65)	Working memory (10)
Visual sequences (11)	Working memory (10)
N-back test (11)	Working memory (10)
Behavior Rating Inventory of Executive Functioning (72)	Self-regulation of affect and arousal (10)

WISC-III, Wechsler Intelligence Scale for Children – Third Edition; WAIS-R: Wechsler Adult Intelligence Scale-Revised.

response to novelty or strategy formation, which are 'one-shot' tests (12). Most of the tests also allow for retesting (Table 1), bearing in mind the impact of learning effect. Particularly high learning effects (4) have been reported in the Wisconsin Card Sorting Test (WCST) (13), the Trail Making Test (TMT) (14), and the Stroop Test (15). According to Burgess (12) the use of a wide battery of executive tests helps to overcome the problem that there is no common agreement about the aspects of executive skills that are actually measured in the most widely used neuropsychological tests or about the extent to which they are indicators of real-world impairment. The use of a wide variety of tests provides for greater coverage of many different functions. The disadvantage of this approach is that it increases the likelihood of false-positive results.

Our review offers a systematic update on recent research findings over the past 15 years (from January 1990 to December 2005) concerning executive functions in OSAS. We wanted to focus on how executive functions have been assessed in OSAS, with special emphasis on the following aspects: (i) what generalizations can be made from previous studies based on the number of subjects, the presence of a control group, severity of OSAS, and other main background variables, (ii) what tests have been used to assess executive functions, (iii) what domains of executive functions are different tests thought to measure, (iv) which executive functions are most frequently defected, and (v) what impacts does CPAP treatment have on executive functions?

### Materials and methods

#### Main terms used in the search

Obstructive sleep apnea syndrome is described in the literature by a variety of concepts: obstructive sleep apnea (OSA), OSAS, obstructive sleep apnea-hypopnea syndrome (OSAHS), sleep apnea-hypopnea syndrome (SAHS) and obstructive sleep-disordered breathing. The term that appears most frequently is 'obstructive sleep apnea', which is what we decided to use in our search. Instead of 'executive functions', we used the broader terms of 'cognitive' or 'neuropsychological' in order to identify as many studies as possible that were at least partially concerned with executive functions.

#### Selection of the articles

The first step was to search the Cochrane Library database to see whether there were any recent or

ongoing reviews on this subject, but we found none. We searched MEDLINE and PSYCHLIT for articles published between January 1990 and December 2005. The search was carried out using the terms '*obstructive sleep apnea and cognitive*' or '*obstructive sleep apnea and neuropsychological*'. We found a total of 196 articles. The exclusion criteria were: (i) non-English articles, (ii) studies of non-human, and (iii) non-adult subjects (<19 years). There now remained 107 articles. Next, we excluded case reports, reviews, experimental studies, letters, commentaries, abstracts, and chapters of edited volumes. This left us with 47 articles. The full articles of these 47 studies were reviewed. Studies that were exclusively concerned with other aspects of cognition than executive functions were excluded. All studies that reported the results of even one executive function were included. This criterion was met by 24 of the 47 articles. The lists of references of these 24 studies were searched; this yielded 16 additional articles. The total number of articles reviewed for this study was thus 40.

### Results

#### Demographic and clinical data

The number of the patients in our review ranged from 8 to 199 (median: 24). In one case (16) it was not possible to establish the number of patients, as this was a population-based study and the number of healthy controls and the number in the patient group were not differentiated. The mean age of patients ranged from 40 to 65 years (median: 49 years). Three studies (16–18) did not report the mean age for the patient group. Education in years ranged from 9 to 15 (median: 13 years). Education was not specified in 19 studies (18–36) and in five studies education was reported as a categorical variable (16, 17, 37–39). The proportion of men in the study samples ranged from 47% to 100%. In 83% of the studies the patient group consisted mainly ( $\geq 75\%$ ) of men. Two studies (20, 40) did not specify the gender of their patients. Furthermore, two studies (16, 17) reported gender only for the whole group, without specifying the gender breakdown for the patient group.

The severity of sleep apnea in the patient groups was reported in 39 studies. One study (16) reported the severity of sleep-disordered breathing only for the total group. If the severity of sleep apnea was not clearly defined, it was categorized on the basis of the range of obstructive breathing events per hour (mild: from 5 to 15 events, moderate: from 15 to 30, and severe: >30). Homogeneous patient groups with mild sleep apnea were studied in five

studies (18, 26, 31, 41, 42) and with severe sleep apnea in four studies (24, 36, 43, 44). The rest of the studies comprise heterogeneous patient groups in terms of the severity of OSAS. Patients with moderate to severe sleep apnea were studied in 14 studies (19, 20, 23, 27, 28, 30, 32, 33, 35, 45–49) and with mild to severe sleep apnea in 13 studies (17, 21, 22, 29, 37–40, 50–54). For three studies (25, 34, 55) it was not possible to establish the range of the severity of OSAS.

#### Patient selection

A selected group of patients was recruited in 29 of the 40 studies (18–20, 24, 25, 28, 30, 31, 33–38, 41–55). In nine studies the patient sample was drawn from consecutive cases (21–23, 26, 27, 29, 32, 39, 40). Two were population-based studies using consecutive samples (16, 17).

#### Description of the control groups

A control group was included in 31 studies. The OSAS patients' performance was compared with healthy controls in 15 studies (17, 23, 27, 30, 35, 36, 41–43, 45, 47, 49–52). In nine of these studies (17, 35, 41, 43, 45, 47, 49, 51, 52) the controls' healthiness was ensured by polysomnographical measurement and in six studies (23, 27, 30, 36, 42, 50) with the exclusion criteria of no evidence of sleep disorder based on an interview and/or on a physical examination and/or on sleepiness scales. In six studies the OSAS patients' performance was compared with other patient group(s): patients with multi-infarct dementia, patients with mild to moderate dementia of Alzheimer type and patients with severe chronic obstructive pulmonary disease (COPD) (40), COPD patients only (55), patients with carbon monoxide poisoning (44), heavy non-apneic snorers (46), and insomniacs (48, 54).

In 10 CPAP treatment efficiency studies, OSAS patients with effective CPAP were compared with OSAS patients receiving other treatment: placebo treatment by tablet (18, 22, 26, 28, 31), placebo treatment by ineffective CPAP (33, 34), or conservative treatment (20, 37). In one of these 10 studies the efficiency of auto-CPAP was compared with constant-CPAP (25).

#### Assessment of executive functions

The neuropsychological tests used most often for the measurement of executive functions in our review are listed in Table 2. Table 2 also describes which domains of executive functions the tests are thought to measure and how many studies repor-

ted the results of these tests. Nine studies (17, 22, 26, 28, 37, 45, 47, 51, 55) used only version B of the TMT and two studies (38, 41) used only the Digit Span backwards. Some studies also used less common tests that according to the authors are sensitive to frontal lobe and executive dysfunction: the Verbal Analogy Test (56), which measures verbal intelligence and deductive thinking (40); Generating an optimal telegram task (57), which measures the efficiency of logical reasoning (54); the Category test (11), which measures abstract thinking and mental flexibility (55); the Digit Symbol Substitution Task computerized version from the revised Wechsler Adult Intelligence Scale (58), which measures processing speed, coordination, and working memory (35); the 2-back verbal working memory task (11), which measures working memory (36); the Park and Holzman's procedure (59), which measures spatial working memory (51); and the Mental control from the Wechsler Memory Scale (60), which measures simple tracking (55). In addition, the following four tests were used without specifying any particular domain of executive function: the Temporal Rule Induction (40, 61), the D2 test (52, 62), the Five-Point Test (11, 49), and the Serial subtraction task (11, 41, 51).

Table 3 shows the number of tests measuring executive functions in each study. Twenty studies used only one or two tests to assess executive functions. Most treatment efficiency studies used the same executive tests for purposes of retesting (18, 20, 21, 22, 25, 26, 28, 31, 32, 36, 37, 39, 44). Six studies (27, 30, 33, 34, 43, 47) used partly or totally alternative or parallel versions of the tests.

OSAS patients' pre-treatment performance compared with healthy controls in the executive functions

Obstructive sleep apnea syndrome patients' pre-treatment performance was compared with healthy controls to identify the executive tests in which the patients' performance was most often defected (Table 4). Impaired test performances were found most frequently in the Digit Span forwards and backwards (23, 27, 41, 49, 52), in the Corsi's block-tapping test (23, 27), in the phonological fluency task (43, 45, 47, 50), in the copy of the Rey-Osterreith Complex Figure Test (ROCFT) (43, 45, 47, 52), in the Mazes test (45, 47, 52), and in the perseverative errors of the WCST (23, 27, 41, 51). The Double encoding task (23, 27), the 2-back test (36) and the Raven's progressive matrices (43) were rarely used, but showed significant impairment in the studies that applied these tests.

**Table 2** The most commonly used tests for assessing executive functions in OSAS patients

Test method	Domain of executive function	No. of studies using the test
Fluency tasks (11) of which:		24
(a) Phonological	Language (40, 53) Cognition (18) Planning abilities (40) Verbal cognitive speed and ability to retrieve words from lexical memory (17) Verbal fluency/production ability (22, 26, 28, 43, 45, 47) Not specified (16, 23, 27, 30, 33, 34, 38, 44, 50–52)	21
(b) Semantic	Conceptual semantic knowledge (40) Language (53) Not specified (50)	3
Trail Making Test: Trails A and B (14)	Cognitive set shifting and flexibility (43, 49) Attentional capacity (23, 27, 30) Visuomotor activity and visual search (49) Processing speed (53) General cognitive function (18, 20) Not specified (19, 21, 25, 29, 31–34, 38, 41, 44, 52, 53)	20
Digit Span forwards and backwards (65)	Short-term, immediate memory (23, 27, 30, 43, 55) Working memory (23, 30, 42, 43, 49, 51, 53) Memory efficiency (27, 30) Central executive memory (49) Attention (42, 52) Not specified (24, 33, 34, 44)	14
Wisconsin Card Sorting Test (13)	Abstract reasoning ability (39) Contextual flexibility, shifting (39, 42) Not specified (23, 27, 30, 38, 41, 50–53)	11
Stroop test (15)	Attentional capacity (18, 23, 27, 30, 46, 48) Inhibition (43, 46, 48) Not specified (23, 49)	9
Tower tests (11)	Not specified (23, 27, 30, 51, 53)	5
Copy of Rey-Osterreith Complex Figure Test (64)	Perceptual organization (42) Visuo-constructional abilities (43) Not specified (45, 47, 52)	5
Corsi's block-tapping test (11)	Short-term memory (23, 27, 30, 43) Working memory (23, 30) Memory efficiency (27) Visual attention (42)	5
Raven's progressive or colored matrices (66, 67)	Nonverbal reasoning (43) Reasoning in visuospatial modality (40, 46, 48)	4
Mazes tests (11)	Planning and problem solving (54) Not specified (45, 47, 52)	4
Double encoding task (e.g. 23)	Short-term memory (23, 27, 30) Working memory (23, 30) Memory efficiency (27, 30)	3
Twenty questions procedure (68)	Strategy formation in verbal problem-solving (23, 27, 30)	3

**Table 3** Number of neuropsychological tests assessing executive functions in the studies reviewed

No. of test(s) in each study	No. of studies
One test	13 (16, 19–21, 24, 25, 29, 31, 32, 36, 37, 39, 40)*
Two tests	7 (17, 22, 26, 28, 46, 48, 54)
Three tests	4 (18, 34, 44, 50)
Four tests	9 (33, 38, 40–42, 45, 47, 49, 55)
Five tests	0
Six tests	1 (53)
Seven tests	2 (51, 52)
Eight tests	1 (43)
Nine tests	3 (23, 27, 30)

\*Numbers in parentheses refer to the original articles reviewed.

Impact of the CPAP treatment on executive test performance

Nineteen of the 40 studies included an evaluation of treatment efficiency (18, 20, 22, 24, 25–28, 30–34, 36, 37, 39, 43, 44, 47). Most of these studies (89%) used CPAP treatment (18, 20, 22, 24, 25–28, 30–34, 36, 43, 44, 47). Both CPAP and uvulopalatopharyngopalsty surgery (UPPP) were used in one study (37). In one study (39) UPPP was used as the only method of treatment.

Minimum CPAP treatment time in the 18 studies ranged from 1 week to 12 months (median: 8 weeks). Fifteen studies (18, 20, 22, 25–28, 30–34, 36, 44, 47, 51) conducted one follow-up, and three studies (24, 37, 43) conducted two follow-ups.

**Table 4** OSAS patients' pre-treatment performance compared with the healthy control group in the tests of executive functions

Test	Naegele et al. (23)	Lee et al. (51)	Feuerstein et al. (27)	Verstraeten et al. (49)	Redline et al. (41)	Ferini-Strambi et al. (43)	Rouleau et al. (52)	Salorio et al. (50)	Laakso et al. (42)	Bedard et al. (45)	Bedard et al. (47)	Thomas et al. (36)
Digit-f	+	o	+	+	na	o	+	na	o*	na	na	na
Digit-b	+	o	+	o	+	o	+	na	o*	na	na	na
Corsi	+	na	+	na	na	o	na	na	o	na	na	na
DET	+	na	+	na	na	na	na	na	na	na	na	na
2-back	na	na	na	na	na	na	na	na	na	na	na	+
TMT-A	o	o	o	o	o	o	na	na	na	na	na	na
TMT-B	o	o	o	o	o	o	o	na	o	+	+	na
Stroop-t	+	na	+	o	na	o	na	na	na	na	na	na
Stroop-e	na	na	na	o	na	+	na	na	na	na	na	na
WCST-c	+	o	o	na	na	na	+	o	na	na	na	na
WCST-e	+	+	+	na	+	na	o	o	na	na	na	na
Tower	+	o	o	na	na	na	na	na	na	na	na	na
TQP	o	na	o	na	na	na	na	na	na	na	na	na
Fluency-p	o	na	o	na	na	+	o	+	na	+	+	na
Fluency-s	na	+	na	na	na	o	na	o	na	na	na	na
ROCFT	na	na	na	na	na	+	+	na	o	+	+	na
Raven	na	na	na	na	na	+	na	na	na	na	na	na
Mazes	na	na	na	na	na	na	+	na	na	+	+	na

Digit-f, the Digit Span forwards; Digit-b, the Digit Span backwards; Corsi, the Corsi's block-tapping test; DET, the Double encoding task; 2-back, the 2-back verbal working memory task; TMT-A, the Trail Making Test, Trails A; TMT-B, the Trail Making Test, Trails B; Stroop-t, performance time in the Stroop test; Stroop-e, errors in the Stroop test; WCST-c, categories achieved in the Wisconsin Card Sorting Test; WCST-e, perseverative errors in the Wisconsin Card Sorting Test; Tower, the Tower tests; TQP, the Twenty questions procedure; Fluency-p, the Phonological fluency tasks; Fluency-s, the Semantic fluency tasks; ROCFT, the copy of the Rey-Osterreith Complex Figure Test; Raven, the Raven's Progressive Matrices; Mazes, the Mazes Tests. '+' indicates impairment between OSAS patients and healthy control group; 'o' indicates no difference between OSAS patients and healthy control group; 'na' indicates that the cognitive domain was not assessed in the study.

\*In the studies by Laakso et al. (42) and Rouleau et al. (52) the Digit Span was reported as a sum of the Digit Span forwards and backwards.

In 12 studies (18, 20, 22, 25, 26, 28, 30–34, 43) compliance to therapy ranged from 3.2 to 6.5 h per night (median: 5.3 h). Two studies (36, 37) reported only the minimum demanded using hours per night. Four studies (24, 27, 44, 47) did not specify compliance.

Among the studies measuring CPAP treatment efficiency five (27, 30, 36, 43, 47) included a healthy control group at the baseline evaluation. In nine studies the control group consisted of OSAS patients: in seven of them (18, 22, 26, 28, 31–33) the control group used placebo treatment and in the other two (20, 37) conservative treatment. Two studies (24, 32) did not have a control group. One study (44) used a group of patients with carbon monoxide poisoning as a control group at the baseline evaluation. In one study (25) auto-CPAP was compared with constant-CPAP.

The impact of CPAP treatment on executive functions in the five studies (27, 30, 36, 43, 47) including a healthy control group is described in Table 5. CPAP treatment improved efficiently performance time in the Stroop test (27, 30), decreased perseverative errors in the WCST (27, 30) and improved performance in the Mazes test (47). Improvement was also seen in one (47) of the two studies using the copy of the ROCFT. None of these studies included a healthy control group in the follow-up phase.

**Table 5** Impact of CPAP treatment on executive test performance in studies including a healthy control group

Test	Feuerstein et al. (27)	Ferini-Strambi et al. (43)	Naegele et al. (30)	Bedard et al. (47)	Thomas et al. (36)
Digit-f	o	x	o	na	na
Digit-b	o	x	o	na	na
Corsi	o	x	o	na	na
DET	o	na	o	na	na
2-back	na	na	na	na	o
TMT-B	x	x	x	o	na
Stroop-t	+	x	+	na	na
Stroop-e	na	o	na	na	na
WCST-c	x	na	o	na	na
WCST-e	+	na	+	na	na
Fluency-p	x	o	x	o	na
ROCFT	na	o	na	+	na
Raven	na	o	na	na	na
Mazes	na	na	na	+	na

Digit-f, the Digit Span forwards; Digit-b, the Digit Span backwards; Corsi, the Corsi's block-tapping test; DET, the Double encoding task; 2-back, the 2-back verbal working memory task; TMT-B, the Trail Making Test, Trails B; Stroop-t, performance time in the Stroop test; Stroop-e, errors in the Stroop test; WCST-c, categories achieved in the Wisconsin Card Sorting Test; WCST-e, perseverative errors in the Wisconsin Card Sorting Test; Fluency-p, the Phonological fluency tasks; ROCFT, the copy of the Rey-Osterreith Complex Figure Test; Raven, the Raven's progressive matrices; Mazes, the Mazes Tests. 'x' indicates that performance in the test was not impaired pre-treatment; '+' indicates improvement with CPAP treatment; 'o' indicates no change in test performance with CPAP treatment; 'na' indicates that the cognitive domain was not assessed in the study.

In the studies (18, 20, 22, 25, 26, 28, 31, 33, 34, 37) that compared the performance of OSAS patients receiving CPAP treatment with patients receiving placebo or conservative treatment, executive functions were assessed with the Digit Span forwards and backwards, the Trails A and B, the Stroop test, and the phonological fluency task. Improvement was usually seen in executive test performance, but only three studies reported significantly better improvement with CPAP than with placebo or conservative treatment: this was in two (22, 26) of nine studies using the Trails B, and in one (18) of six studies using the phonological fluency task.

### Discussion

This review provides an update on recent research findings concerning executive functions in OSAS, with special emphasis on the following aspects: the generalizability of former studies based on patient characteristics and the presence of a control group, the methods used in assessing executive functions, the domains of executive functions that different tests are thought to measure, the executive functions that are most often defected, and the possible effect of CPAP treatment on executive functions.

The sample size in the studies reviewed ranged from 8 to 199 (median: 24). Among the 40 studies 19 had less than 24 patients. This wide variability in sample sizes very much undermines the comparability of the different studies as well as the statistical analysis of the results. The mean age of patients ranged from 40 to 65 years, representing the population of working age which is an important target group for neuropsychological assessment. Most of the studies (73%) recruited heterogeneous patient groups consisting of selected samples. Only half of the studies specified the patients' educational level, even though this is usually thought to be one of the most important background variables affecting cognitive test performance. In the studies reviewed the patient samples consisted primarily of men, but it is important to note that the estimated prevalence of OSAS in females is up to 2% (63). Twenty-five percent of the studies reviewed had homogeneous patient groups in terms of the severity of OSAS, which can significantly affect the appearance of executive dysfunction. In the studies that involved heterogeneous patient groups with patients from mild to severe OSAS, the mean number of obstructive breathing events is not informative enough as a single measure of OSAS severity. The range of obstructive breathing events and the number of patients in different severity groups

should therefore be reported in detail. To conclude, the generalizability of the studies reviewed is undermined by the variation in sample sizes, the heterogeneity of patient groups, the overrepresentation of male patients, inadequate reporting on education, and inaccuracies in defining the severity of OSAS.

A control group was used in 31 of the 40 studies: a healthy control group was used in 15 studies, other patient groups in six studies (patients with multi-infarct dementia or dementia of Alzheimer type, patients with COPD, patients with carbon monoxide poisoning, heavy non-apnetic snorers, and insomniacs), and in 10 studies OSAS patients receiving CPAP treatment were compared with OSAS patients receiving placebo or conservative treatment. As Aloia et al. (8) have pointed out, the use of a control group is scientifically more rigorous than the use of normative comparisons. In our review, we analyzed the pre-treatment executive function of OSAS patients in comparison with a healthy control group, because we wanted to evaluate the nature of executive dysfunction in OSAS patients compared with the healthy population. It is misleading to compare executive functions in OSAS patients with other patient groups as cognitive defects are common sequelae in patients suffering from dementia, COPD or carbon monoxide poisoning, for example. The healthy control group should be matched to the patient group at least according to age, gender and education, and the healthiness of the control group should be assessed by polysomnographic measurement as even asymptomatic healthy volunteers can suffer from mild obstructive breathing events. In our ongoing study a significant number of healthy controls have had to be excluded after polysomnography findings, even though they reported being asymptomatic in the screening interview.

The test methods that were used most often for evaluating executive functions in the studies reviewed were partly the same as those recommended by Decary et al. (4) and Beebe and Gozal (10): the WCST (13), the TMT (14), the Stroop test (15), the copy of the ROCFT (64), the Mazes tests (11), the fluency tasks (11), the Digit strings (Digit Span forwards and backwards; 65), and the Visual sequences (the Corsi's block-tapping test; 11). In addition, the Tower tests (11), the Raven's matrices (66, 67), the Twenty questions procedure (68), and the Double encoding task (23) were also used in the studies reviewed to assess executive functions. Some studies furthermore used less common tests to assess executive dysfunction. In some studies the authors failed to specify what particular domain of executive function they wanted to measure with a

single test, but they set about assessing executive function as a single global function. This may lead to the false conclusion that executive function *per se* is totally impaired or totally intact. Even in the most commonly used executive tests there were differing uses as to what the test was thought to measure. Some authors (18, 53) suggested that the test (e.g. the fluency tasks and the copy of the ROCFT) was an assessment of a basic cognitive skill, others (23, 42, 51) thought the same test evaluated executive functions. The Digit Spans and the Corsi's block-tapping test were in most cases thought to assess short-term and working memory, but also attention. The TMT was conducted as a method of attention, processing speed, visuomotor function and cognitive flexibility. The Stroop Test was used to measure both attention and inhibition. The ROCFT and the Raven's matrices were seen as test methods of executive function from a visual point of view while the Twenty question procedure was considered to evaluate executive function from a verbal perspective. Studies using the WCST, the Tower tests, and the Mazes tests did not normally specify the domain of executive function. Half of the studies used only one or two methods for assessing executive functions. However, this does not provide a sufficiently sound basis for drawing conclusions and it is possible that neuropsychological assessment fails to detect dysfunction in some important domains of executive functions that may still have a negative influence on the OSAS patient's daily performance. This variability in the testing of executive functions and in the domains they are thought to measure very much complicates the interpretation of the results and undermines their comparability.

Some studies concluded that neuropsychological tests are not sensitive enough to detect mild executive or other cognitive dysfunction (37, 51) and that this is most evident in patients with high general intelligence (37). According to Alchanatis et al. (69) high intelligence may have a protective effect against OSAS-related cognitive decline; cognitive reserve and a high level cognitive functioning can compensate for both hypoxic brain dysfunction and daytime somnolence. According to Verstraeten et al. (49) it is always necessary to control for attentional capacity when assessing executive function. They report that OSAS patients suffer from sleepiness-related vigilance and attention deficits, but not specific hypoxic-related executive attentional problems. They make the critical comment that many former studies have attributed attentional problems to executive deficits because they have failed to control for attentional capacity. This means that when executive function is

assessed by means of the Trails B, for example, attention capacity should always be controlled with the Trails A; and when working memory is assessed with the Digit Span backwards, memory span should first be controlled with the Digit Span forwards.

Twelve studies (23, 27, 36, 41–43, 45, 47, 49–52) compared executive functions in OSAS patients with healthy controls. All these studies used a sufficient combination of executive tests (from three to nine tests), except one study (36) which included only one executive task. The most frequently defected performances were found in the Digit Span forwards and backwards, in the Corsi's block-tapping test, in the phonological fluency tasks, in the copy of the ROCFT, in the Mazes tests, and in the WCST. The domains of executive function impaired most often were working memory, phonological fluency, cognitive flexibility, and planning (especially its non-verbal aspect).

In the five studies (27, 30, 36, 43, 47) where OSAS patients' performance was compared with healthy controls at baseline only, CPAP treatment improved cognitive flexibility and speed, and also planning in non-verbal tests. It should be noted that none of these studies used a control group at follow-up phase to control for the learning effect, although most of them (four out of five; 27, 30, 43, 47) did use an alternative or parallel version of the tests for this purpose. The studies in which learning effect was controlled with OSAS patients having placebo or conservative treatment, used only two or three tests to assess executive functions. In these studies cognitive performance generally improved, but the improvement with CPAP treatment was significantly better than with placebo or conservative treatment in only three (18, 22, 26) out of nine studies (18, 20, 22, 26, 28, 31, 33, 34, 37). In order to establish the true effects of CPAP treatment it is important to control for the learning effect of the tests. To conclude, the deficits of working memory persisted after CPAP treatment, and only one study reported an improvement in phonological fluency.

We are currently working in an ongoing study to explore the quantity and quality of executive dysfunction in OSAS patients compared with healthy controls and to assess the impact of CPAP treatment on executive functions. We use a comprehensive battery of executive tests to assess different domains of executive function, both paper-and-pencil tasks and computer-assisted tests (CANTAB; 70). Evaluations of general intellectual ability are also included. A healthy control group is included both at baseline and at the follow-up phase.

Our review and the preliminary findings of our ongoing study suggest several recommendations for further research. First, more attention should be paid to the number of subjects, to the background variables that may affect cognitive performance, and to having an adequate control group. The number of subjects in studies concerning neuropsychological deficits in OSAS should be large enough for statistical analyses, the severity of OSAS in the patient group should be reported in detail, the healthiness of healthy controls should be ensured with polysomnography, and the learning effect on executive test performance should be controlled in treatment efficiency studies either with a healthy control group both at baseline and the follow-up, or with a control group of OSAS patients receiving placebo or conservative treatment. Second, for purposes of assessing executive functions in OSAS patients it is necessary to create a comprehensive test battery using the most common executive tests (4, 10) so that different domains of executive function can be measured. In addition to neuropsychological tests, self-assessing inventories and a structured interview of patients and their relatives are needed in order that any executive dysfunctions can be detected. Third, it is essential that cognitive and especially executive function in OSAS patients is assessed when they have a reduced capacity for working or driving. Fourth, more research and discussion are needed on the impact of CPAP treatment on executive functions, as there are only a few treatment efficiency studies that control for the learning effect.

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