A review of executive functions in obstructive sleep apnea syndrome (OSAS)

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Abstract

Objectives: This review provides 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.

Key words: executive functions, neuropsychological assessment, obstructive sleep apnea

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: 1) 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 2) 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 fullfilled when 1) polysomnographic recording shows fifteen or more respiratory events per hour of sleep and evidence of respiratory effort during all or a portion of each respiratory event, and 2) 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, travelling 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 (2,3-9). 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 (11) defines 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 behaviour, 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 behavioural 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 hypercarbia 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 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 (16). According to Burgess (13) 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 in creases 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: 1) 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,

2) what tests have been used to assess executive functions, 3) what domains of executive functions are different tests thought to measure, 4) which executive functions are most frequently defected, and 5) what impacts does CPAP treatment have on executive functions?

Materials and methods

Main terms used in the search

Obstructive sleep apnea syndrome (OSAS) is described in the literature by a variety of concepts: obstructive sleep apnea (OSA), obstructive sleep apnea syndrome (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: 1) non-English articles, 2) studies of non-human, and 3) 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 (20) it was not possible to establish the number of patients, since this was a population-based study and the number of healthy controls and the patient group were not differentiated. The mean age of patients ranged from 40 to 65 years (median: 49 years). Three studies (20-22) 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 (22-40) and in five studies education was reported as a categorical variable (20,21,41-43). The proportion of men in the study samples ranged from 47% to 100%. In 83% of the studies the patient group consisted mainly (≥ 75%) of men. Two studies (24,44) did not specify the gender of their patients. Furthermore, two studies (20,21) 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 (20) 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 (22,30,35,45,46) and with severe sleep apnea in four studies (28,40,47,48). 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 (23,24,27,31,32,34,36,37,39,49-53) and with mild to severe sleep apnea in 13 studies

(21,25,26,33,41-44,54,55-58). For three studies (29,38,59) 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 (22-24,28,29,32,34,35,37-42,45-49,50-59). In nine studies the patient sample was drawn from consecutive cases (25,26,27,30,31,33,36,43,44). Two were population-based studies using consecutive samples (20,21).

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 (21,27,31,34,39,40,45-47,49,51,53-56). In nine of these studies (21,39,45,47,49,51,53,55,56) the controls' healthiness was ensured by polysomnographical measurement and in six studies (27,31,34,40,46,54) 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) (44), COPD patients only (59), patients with carbon monoxide poisoning (48), heavy non-apnetic snorers (50), and insomniacs (52,58).

In ten CPAP treatment efficiency studies, OSAS patients with effective CPAP were compared with OSAS patients receiving other treatment: placebo treatment by tablet (22,26,30,32,35), placebo treatment by ineffective CPAP (37,38) or conservative treatment (24,41). In one of these ten studies the efficiency of auto-CPAP was compared with constant-CPAP (29).

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 reported the results of these tests. Nine studies (21,26,30,32,41,49,51,55,59) used only version B of the TMT and two studies (42,45) 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 (63), which measures verbal intelligence and deductive thinking (44); Generating an optimal telegram task (64), which measures the efficiency of logical reasoning (58); the Category test (11), which measures abstract thinking and mental flexibility (59); the Digit Symbol Substitution Task computerized version from the revised Wechsler Adult Intelligence Scale (65), which measures processing speed, coordination, and working memory (39); the 2-back verbal working memory task (11), which measures working memory (40); the Park and Holzman's procedure (66), which measures spatial working memory (55); and the Mental control from the Wechsler Memory Scale (67), which measures simple tracking (59). In addition, the following four tests were used without specifying any particular domain of executive function: the Temporal Rule Induction (68) (44), the D2 test (69) (56), the Five-Point Test (11) (53), and the Serial subtraction task (11) (45,55).

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 (22,24,26,28-30,32,35,36,40,41,43,48). Six studies (31,34,37,38,47,51) used partly or totally alternative or parallel versions of the tests.

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

OSAS 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 (27,31,45,53,56), in the Corsi's block-tapping test (27,31), in the phonological fluency task (47,49,51,54), in the copy of the Rey-Osterreith Complex Figure Test (ROCFT) (47,49,51,56), in the Mazes test (49,51,56), and in the perseverative errors of the WCST (27,31,45,55). The Double encoding task (27,31), the 2-back test (40) and the Raven's progressive matrices (47) were rarely used, but showed significant impairment in the studies that applied these tests.

Impact of the CPAP treatment on executive test performance

Nineteen of the 40 studies included an evaluation of treatment efficiency (22,24,26,28-32,34-38,40,41,43,47,48,51). Most of these studies (89%) used CPAP treatment (22,24,26,28-32,34-38,40,47,48,51). Both CPAP and uvulopalatopharyngopalsty surgery (UPPP) were used in one study (41). In one study (43) UPPP was used as a the only method of treatment.

Minimum CPAP treatment time in the 18 studies ranged from one week to twelve months (median: eight weeks). Fifteen studies (22,24,26,29-32,34-38,40,48,51,55) conducted one follow-up, and three studies (28,41,47) conducted two follow-ups. In 12 studies (22,24,26,29,30,32,34-38,47) compliance to therapy ranged from 3.2 to 6.5 hours per night (median: 5.3 hours). Two studies (40,41) reported only the minimum demanded using hours per night. Four studies (28,31,48,51) did not specify compliance.

Among the studies measuring CPAP treatment efficiency five (31,34,40,47,51) included a healthy control group at the baseline evaluation. In nine studies the control group consisted of OSAS patients: in seven of them (22,26,30,32,35-37) the control group used placebo treatment and in the

other two (24,41) conservative treatment. Two studies (28,36) did not have a control group. One study (48) used a group of patients with carbon monoxide poisoning as a control group at the baseline evaluation. In one study (29) auto-CPAP was compared with constant-CPAP.

The impact of CPAP treatment on executive functions in the five studies (31,34,40,47,51) including a healthy control group is described in Table 5. CPAP treatment improved efficiently performance time in the Stroop test (31,34), decreased perseverative errors in the WCST (31,34) and improved performance in the Mazes test (51). Improvement was also seen in one (51) of the two studies using the copy of the ROCFT. None of these studies included a healthy control group in the follow-up phase.

In the studies (22,24,26,29,30,32,35,37,38,41) 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 (26,30) of nine studies using the Trails B, and in one (22) 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% (70). 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, in adequate 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 ten 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 since 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 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 (16), the copy of the ROCFT (17), the Mazes tests (11), the fluency tasks (11), the Digit strings (Digit Span forwards and backwards; 18), and the Visual sequences (the Corsi's block-tapping test; 11). In addition, the Tower tests (11), the Raven's matrices (60, 61), the Twenty questions procedure (62), and the Double encoding task (27) 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 the particular domain of executive function that 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 use as to what the test was thought to measure. Some authors (22,57) suggested that the test (e.g. the fluency tasks and the copy of the ROCFT) was an assessment of a basic cognitive skill, others (27,46,55) 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 from 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 (41,55) and that this is most evident in patients with high general intelligence (41). According to Alchanatis et al. (71) 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 Verstaraeten et al. (53) 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 hypoxemic-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 (27,31,40,45-47,49,51,53-56) 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 (40) 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 (31,34,40,47,51) 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; 31,34,47,51) 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 (22,26,30) out of nine studies (22,24,26,30,32,35,37,38,41). 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; 72). 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 of executive functions in OSAS patients it is necessary to create a comprehensive test battery using the most common executive tests (4,10) so that the 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 reduced capacity for working or driving. Fourth, more research and discussion is needed about the impact of CPAP treatment on executive functions, since there are only a few treatment efficiency studies that control for the learning effect.

References

1. American Academy of Sleep Medicine. International classification of sleep disorders. Diagnostic and coding manual (2 nd edition). Westchester III, 2005.

2. BROWN WD. The psychosocial aspects of obstructive sleep apnea. Semin Respir Crit Care Med 2005;**26**:33-43.

3. ENGLEMAN H, JOFFE D. Neuropsychological function in obstructive sleep apnoea. Sleep Med Rev 1999;**3**:59-78.

4. DECARY A, ROULEAU I, MONTPLAISIR J. Cognitive deficits associated with sleep apnea syndrome: a proposed neuropsychological test battery. Sleep 2000;**23**:1-13.

5. ENGLEMAN HM, KINGSHOTT RN, MARTIN SE, DOUGLAS NJ. Cognitive function in the sleep apnea/hypopnea syndrome (SAHS). Sleep 2000;**23**:102-8.

6. MCMAHON JP, FORESMAN BH, CHISHOLM RC. The influence of CPAP on the neurobehavioral performance of patients with obstructive sleep apnea hypopnea syndrome: a systematic review. Wis Med J 2003;**102**:36-43.

7. SATEIA MJ. Neuropsychological impairment and quality of life in obstructive sleep apnea. Clin Chest Med 2003;**24**:249-59.

8. ALOIA MS, ARNEDT JT, DAVIS JD, RIGGS RL, BYRD D. Neuropsychological sequelae of obstructive sleep apnea syndrome: A critical review. JINS 2004;**10**:772-85.

9. EL-AD B, LAVIE P. Effect of sleep apnea on cognition and mood. Int Rev Psychiatry 2005;**17**:277-82.

10. BEEBE DW, GOZAL D. Obstructive sleep apnea and the prefrontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioural deficits. J Sleep Res 2002;**11**:1-16.

11. LEZAK MD, HOWIESON DB, LORING DW. Neuropsychological assessment. New York: Oxford University Press, 2004.

12. BURGESS PW. Assessment of executive function. In: Halligan PW, Kischka U, Marshall JC. Handbook of clinical neuropsychology. Oxford: University Press, 2003:302-21.

13. HEATON RK, CHELEME G, TALLEY J, KAY G, CURTISS G. Wisconsin Card Sorting Test Manual. Odessa Psychological Assessment Resources, 1993.

14. Army Individual Test Battery. Manual of directions and scoring. Washington, DC: War Department, Adjutant General Office, 1944.

15. WECHSLER D. Wechsler Intelligence Scale for Children – Third Edition (WISC-III). San Antonio: The Psychological Corporation, 1991.

16. GOLDEN CJ. Stroop Colour and Word Test. Chicago, IL: Stoeting, 1978.

17. OSTERRIETH PA. Le test de copie d'une figure complexe. Arch Psychol 1944;**30**:206-356.

18. WECHSLER DA. Wechsler Adult Intelligence Scale-Revised. New York: The Psychological Corporation, 1981.

19. GIOIA GA, ISQUITH PK, GUY SC, KENWORTHY L. Behavior Rating Inventory of Executive Function. Odessa, FL: Psychological Assessment Resources, 2000.

20. BOLAND LL, SHAHAR E, IBER C et al. Measures of cognitive function in persons with varying degrees of sleep-disordered breathing: the sleep heart health study. J Sleep Res 2002;**11**:265-72.

21. KIM HC, YOUNG T, MATTHEWS CG, WEBER SM, WOODARD AR, PALTA M. Sleep-disordered breathing and neuropsychological deficits. A population-based study. Am J Respir Crit Care Med 1997;**156**:1813-9.

22. BARNES M, HOUSTON D, WORSNOP J et al. A randomised controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med 2002;**165**:773-80.

23. CHESHIRE K, ENGLEMAN H, DEARY I, SHAPIRO C, DOUGLAS NJ. Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. Arch Intern Med 1992;**152**:538-41.

24. ENGLEMAN HM, CHESHIRE KE, DEARY IJ, DOUGLAS NJ. Daytime sleepiness, cognitive performance and mood after continuous positive airway pressure for the sleep apnoea/hypopnoea syndrome. Thorax 1993;**48**:911-4.

25. TELAKIVI T, KAJASTE S, PARTINEN M, BRANDER P, NYHOLM A. Cognitive function in obstructive sleep apnea. Sleep 1993;**16**:74-5.

26. ENGLEMAN H, MARTIS S, DEARY I, DOUGLAS N. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnea syndrome. Lancet 1994;**343**:572-5.

27. NAEGELE B, THOUVARD V, PEPIN J-L et al. Deficits of cognitive executive functions in patients with sleep apnea syndrome. Sleep 1995;**18**;43-52.

28. BORAK J, CIESLICKI JK, KOZIEJ M, MATUSZEWSKI A, ZIELINSKI J. Effects of CPAP treatment on psychological status in patients with severe obstructive sleep apnoea. J Sleep Res 1996;**5**:123-7.

29. MEURICE J-C, MARC I, SERIES F. Efficacy of auto-CPAP in the treatment of obstructive sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1996;**153**:794-8.

30. ENGLEMAN H, MARTIS S, DEARY I, DOUGLAS N. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnea syndrome. Thorax 1997;**52**:114-9.

31. FEUERSTEIN C, NAEGELE B, PEPIN JL, LEVY P. Frontal lobe-related cognitive function in patients with sleep apnea syndrome before and after treatment. Acta Neurol Belg 1997;**97**:96-107.

32. ENGLEMAN HE, MARTIN SE, KINGSHOTT RN, MACKAY TW, DEARY IJ, DOUGLAS NJ. Randomized placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnea/hypopnea syndrome. Thorax 1998;**53**:341-5.

33. KINGSHOTT RN, ENGLEMAN HM, DEARY IJ, DOUGLAS NJ. Does arousal frequency predict daytime function. Eur Respir J 1998;**12**:1264-70.

34. NAEGELE B, PEPIN J-L, LEVY P, BONNET C, PELLAT J, FEUERSTEIN C. Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS) after CPAP treatment. Sleep 1998;**21**:392-6.

35. ENGLEMAN HE, KINGSHOTT RN, WRAITH PK, MACKAY TW, DEARY IJ, DOUGLAS NJ. Randomized placebo-controlled crossover trial of continuous positive airways pressure for mild obstructive sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med 1999;**159**:461-7.

36. KINGSHOTT RN, VENNELLE M, HOY CJ, ENGLEMAN HM, DEARY IJ, DOUGLAS NJ. Predictors of improvements in daytime function outcomes with CPAP therapy. Am J Respir Crit Care Med 2000;**161**:866-71.

37. BARDWELL WA, ANCOLI-ISRAEL S, BERRY CC, DIMSDALE JE. Neuropsychological effects of one-week continuous positive airway pressure treatment in patients with obstructive sleep apnea: a placebo-controlled study. Psychosom Med 2001;**63**:579-84.

38. HENKE KG, GRADY JJ, KUNA ST. Effect of nasal continuous positive airway pressure on neuropsychological function in sleep apnea-hypopnea syndrome. Am Respir Crit Care Med 2001; **163**:911-7.

39. BARTLETT DJ, RAE C, THOMPSON CH, BYTH K et al. Hippocampal area metabolites relate to severity and cognitive function in obstructive sleep apnea. Sleep Med 2004;**5**:593-6.

40. THOMAS RJ, ROSEN BR, STERN CE, WEISS JW, KONG KK. Functional imaging of working memory in obstructive sleep-disordered breathing. J Appl Physiol 2005;**98**;2226-34.

41. LOJANDER J, KAJASTE S, MAASILTA P, PARTINEN M. Cognitive function and treatment of obstructive sleep apnea syndrome. J Sleep Res 1999;**8**:71-6.

42. ADAMS N, STRAUSS M, SCHLUCHTER M, REDLINE S. Relation of measures of sleep-disordered breathing to neuropsychological functioning. Am J Respir Crit Care Med 2001;**163**:1626-31.

43. DAHLÖF P, NORLIN-BAGGE E, HEDNER J, EJNELL H, HETTA J, HÄLLSTRÖM T. Improvement in neuropsychological performance following surgical treatment for obstructive sleep apnea syndrome. Acta Otolaryngol 2002;**122**:86-91.

44. ANTONELLI-INCALZI R, MARRA C, SALVIGNI BL et al. Does cognitive dysfunction conform to a distinctive pattern in obstructive sleep apnea syndrome? J Sleep Res 2004;**13**:79-86.

45. REDLINE S, STRAUSS ME, ADAMS N et at. Neuropsychological function in mild sleep-disordered breathing. Sleep 1997;**20**:160-7.

46. LAAKSO J, HERRALA J, MÄKINEN R et al. Impairment of quality of time and performance in mild form of sleep related breathing disorder. Sleep and hypnosis 1999;**1**:163-72.

47. FERINI-STRAMBI L, BAIETTO C, DI GIOIA MR et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): partial reversibility after continuous positive airway pressure (CPAP). Brain Res Bull 2003;**61**:87-92.

48. GALE SD, HOPKINS RO. Effects of hypoxia on the brain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. JINS 2004;**10**:60-71.

49. BEDARD M-A, MONTPLAISIR J, RICHER F, ROULEAU I, MALO J. Obstructive sleep apnea syndrome: pathogenesis of neuropsychological deficits. J Clin Exp Neuropsychol 1991;**13**:950-64.

50. VERSTRAETEN E, CLUYDTS R. Psychomotor and cognitive performance in nonapnetic snorers: preliminary findings. Percept Mot Skills 1997;**84**:1211-22.

51. BEDARD M-A, MONTPLAISIR J, MALO J, RICHER F, ROULEAU I. Persistent neuropsychological deficits and vigilance impairment in sleep apnea syndrome after treatment with continuous positive airways pressure (CPAP). J Clin Exp Neuropsychol 1993;**15**:330-41.

52. VERSTRAETEN E, CLUYDTS R, VERBRAECKEN J, DE ROECK. Neuropsychological functioning and determinants of morning alertness in patients with obstructive sleep apnea syndrome. JINS 1996;**2**:306-14.

53. VERSTRAETEN E, CLUYDTS R, PEVERNAGIE D, HOFFMANN G. Executive function in sleep apnea: controlling for attentional capacity in assessing executive attention. Sleep 2004;**27**:685-93.

54. SALORIO CF, WHITE DA, PICCIRILLO J, DUNTLEY SP, UHLES ML. Learning, memory, and executive control in individuals with obstructive sleep apnea syndrome. J Clin Exp Neuropsychol 2002;**24**:93-100.

55. LEE MM, STRAUSS ME, ADAMS N, REDLINE S. Executive functions in persons with sleep apnea. Sleep Breath 1999;**3**:13-6.

56. ROULEAU I, DECARY A, CHICOINE AJ, MONTPLAISIR J. Procedural skill learning in obstructive sleep apnea syndrome. Sleep 2002;**25**:401-11.

57. NAISMITH S, WINTER V, GOTSOPOULOS H, HICKIE I, CISTULLI P. Neurobehavioral functioning in obstructive sleep apnea: differential effects of sleep quality, hypoxemia and subjective sleepiness. J Clin Exp Neuropsychol 2004;**26**:43-54.

58. STONE J, MORIN CM, HART RP, REMSBERG S, MERCER J. Neuropsychological functioning in older insomniacs with or without obstructive sleep apnea. Psychol Aging 1994;**9**:231-6.

59. ROEHRS T, MERRION M, PEDROSI B, STEPANSKI E, ZORICK F, ROTH T. Neuropsychological function in obstructive sleep apnea syndrome (OSAS) compared to chronic obstructive pulmonary disease (COPD). Sleep 1995;**18**:382-8.

60. RAVEN JC. Raven's Progressive Matrices: a perceptual test of intelligence. Oxford: Oxford Psychologists Press, 1996.

61. RAVEN JC. Coloured Progressive Matrices sets A, Ab, B. Manual sections 1 & 2. Oxford: Oxford Psychologists Press, 1995.

62. GOLDSTEIN F. LEVIN HS. Question-asking strategies after severe closed head injury. Brain Cogn 1991;**17**:23-30.

63. ROSENBERG D, WILLSON-QUAYLE A, PASNAK R. Preliminary test of effects of cognitive ability, experience, and teaching methods on Verbal Analogy Test scores. Percept Mot Skills 2000;**90**:1261-7.

64. BEN-YISHAY Y, LAKIN P, ROSS B, RATTOCK J, COHEN J, MILLER L. A modular approach to training (verbal) abstract reasoning in traumatic head injured patients: Revised procedures. In: Ben-Yishay Y, ed. Working approaches to remediation of cognitive deficits in brain damaged persons. New York: New York University Medical Center, 1980:128-74.

65. HOUSE A. Wechsler Adult Intelligence Scale – Revised (WAIS-R). In: Newmark CS, ed. Major Psychological Assessment Instruments. Boston: Allyn & Bacon, 1996:320-47.

66. PARK S, HOLZMAN PS. Schizophrenics show spatial working memory deficits. Arch Gen Psychiatry 1992;**49**:975-82.

67. WECHSLER DA. A standardized memory scale for clinical use. J Psychol 1945;**19**:87-95.

68. VILLA G, GAINOTTI G, DE BONIS C, MARRA C. Double dissociation between temporal and spatial processing in patients with frontal and parietal damage. Cortex 1990;**26**:399-406.

69. BRICKENKAMP R. Le test D2 d'attention concentree (2e edition). Paris: Editest, 1966.

70. YOUNG T, PALTA M, DEMPSEY J, SKATRUD J, WEBER S, BADR S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;**328**:1230-5.

71. ALCHANTIS M, ZIAS N, DELIGIORGIS N, AMFILOCHIOU A, DIONELLIS G, ORPHANIDOU D. Sleep apnea-related cognitive deficits and intelligence: an implication of cognitive reserve theory. J Sleep Res 2005;**14**:69-75.

72. SAHAKIAN BJ, OWEN AM. Computerised assessment in neuropsychiatry using CANTAB. J R Soc Med 1992;**85**:399-402.

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

Test method	Domain of executive function
Wisconsin Card Sorting Test (13)	Mental set shifting (4,10) and abstract behaviour (4)
Trails B of Trail Making Test (14)	
Trail Making Test (14)	Conceptual and visuomotor tracking (4)
Mazes (WISC-III; 15)	Planning and foresight (4)
Stroop test (16)	Focal attention, shifting processes (4) and behavioural inhibition (4,10)
Copy of Rey-Osterreith Complex Figure (17)	Organizational skills / analysis-synthesis on the spatial domain (4,10)
Fluency tasks (11)	Analysis / synthesis (10)
Back digit strings (WAIS-R; 18)	Working memory (10)
Visual sequences (11)	
N-back test (11)	
Behavior Rating Inventory of Executive Functioning (19)	Self-regulation of affect and arousal (10)

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

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)		24
of which:		
a) phonological	Language (44,57)	21
	Cognition (22)	
	Planning abilities (44)	
	Verbal cognitive speed and ability to retrieve words from lexical memory (21)	
	Verbal fluency / production ability (26,30,32,47,49,51)	
	Not specified (20,27,31,34,37,38,42,48,54,55,56,)	
b) semantic	Conceptual semantic knowledge (44)	3
	Language (57)	
	Not specified (54)	
Trail Making Test: Trails A and B (14)	Cognitive set shifting and flexibility (47,53)	20
	Attentional capacity (27,31,34)	

	Visuomotor activity and visual search (53)	
	Processing speed (57)	
	General cognitive function (22,24)	
	Not specified (23,25,29,33,35-38,42,45,48,56,57)	
Digit Span forwards and backwards (18)	Short-term, immediate memory (27,31,47,34,59)	14
	Working memory (27,34,46,47,53,55,57)	
	Memory efficiency (31,34)	
	Central executive memory (53)	
	Attention (46,56)	
	Not specified (28,37,38,48)	
Wisconsin Card Sorting Test (13)	Abstract reasoning ability (43)	11
	Contextual flexibility, shifting (43,46)	
	Not specified (27,31,34,42,45,54-57)	
Stroop test (16)	Attentional capacity (22,27,31,34,50,52)	9
	Inhibition (47,50,52)	
	Not specified (27,53)	
Tower tests (11)	Not specified (27,31,34,55,57)	5

Copy of Rey-Osterreith Complex Figure Test (17)	Perceptual organization (46) Visuo-constructional abilities (47) Not specified (49,51,56)	5
Corsi's block-tapping test (11)	Short-term memory (27,31,34,47) Working memory (27,34) Memory efficiency (31) Visual attention (46)	5
Raven's progressive or coloured matrices (60, 61)	Nonverbal reasoning (47) Reasoning in visuospatial modality (44,50,52)	4
Mazes tests (11)	Planning and problem solving (58) Not specified (49,51,56)	4
Double encoding task (e.g. 27)	Short-term memory (27,31,34) Working memory (27,34) Memory efficiency (31,34)	3
Twenty questions procedure (62)	Strategy formation in verbal problem-solving (27,31,34)	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** (20,23-25,28,29,33,35,36,40,41,43,44)*
Two tests	**7** (21,26,30,32,50,52,58)
Three tests	**4** (22,38,48,54)
Four tests	**9** (37,42,44,45,46,49,51,53,59)
Five tests	**0**
Six tests	**1** (57)
Seven tests	**2** (55,56)
Eight tests	**1** (47)
Nine tests	**3** (27,31,34)

* Note: Numbers in parentheses refer to the original articles reviewed.

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

Test	Naegele et al. (27)	Lee et al. (55)	Feuerstein et al. (31)	Verstraeten et al. (53)	Redline et al. (45)	Ferini-Strambi et al. (47)	Rouleau et al. (56)	Salorio et al. (54)	Laakso et al. (46)	Bedard et al. (49)	Bedard et al. (51)	Thomas et al. (40)
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

Abbreviations**:** 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.

Note: '+' 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.

* Note: In the studies by Laakso et al. (46) and Rouleau et al. (56) the Digit Span was reported as a sum of the Digit Span forwards and backwards.

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

Test	Feuerstein et al. (31)	Ferini-Strambi et al.(47)	Naegele et al. (34)	Bedard et al. (51)	Thomas et al. (40)
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

Abbreviations: 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.

Note: '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.