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# Executive Dysfunction in Patients with Obstructive Sleep Apnea Syndrome

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Social Sciences of the University of Tampere,
for public discussion in the Väinö Linna-Auditorium K104,
Kalevantie 5, Tampere,
on November 5th, 2010, at 12 o'clock.

UNIVERSITY OF TAMPERE

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ACADEMIC DISSERTATION
University of Tampere
Department of Psychology
Finland

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Finland

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Fax +358 3 3551 7685
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www.uta.fi/taju
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Cover design by
Mikko Reinikka

Acta Universitatis Tamperensis 1548
ISBN 978-951-44-8204-5 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 994
ISBN 978-951-44-8205-2 (pdf)
ISSN 1456-954X
http://acta.uta.fi

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2010

# ACKNOWLEDGEMENTS

First of all, I would like to thank my supervisor, Docent Mervi Jehkonen from the Department of Psychology at the University of Tampere for her unfailing inspiration and guidance and for always being so easy to approach. I have felt in safe hands throughout this emotional journey and have certainly come to appreciate how extraordinarily satisfying it can be to combine scientific and clinical neuropsychological work.

I wish to thank Professor Jari Hietanen from Department of Psychology. Even though we have not worked closely in the course of this research, he has had a great influence on my work because of his praiseworthy demanding attitude. I am also indebted to Professor Hietanen for the opportunity to work at the Department.

I also wish to thank Professor Sari-Leena Himanen from the Medical School and the Department of Clinical Neurophysiology and Professor Olli Polo from the Medical School and the Department of Pulmonary Medicine for their professional help and for the opportunity to conduct my research at the Tampere University Hospital. For me one of the best things to come out of this research is my friendship with you, Sari-Leena.

I would like to thank the reviewers of this thesis, Docent Erkki Kronholm from the National Institute for Health and Welfare and Docent Matti Laine from the Department of Psychology, Åbo Akademi University for their contribution and comments on the manuscript.

A special note of thanks goes to all the patients and controls who took part in this study. I am grateful to my colleague Riikka Kilpinen for sharing the work of neuropsychological assessments and all the ups and downs of this project. I appreciate the assistance of Virpi Räsänen in organizing the assessments. Many thanks to Dr Eero Huupponen for his professional input in the computational EEG analysis and to David Kivinen for his help with the English language. I would also like to express my gratitude for the grants I received from the Tampere University Hospital, the University of

Tampere, the Finnish Cultural Foundation and the Tampere Tuberculosis Foundation, which made this study financially possible.

I have been privileged to work in two great workplace communities. I wish to thank my colleagues, neuropsychologists and psychologists, at the Department of Neurology and Rehabilitation, Tampere University Hospital, as well as all the professors, lecturers and researchers at the Department of Psychology, University of Tampere. Special thanks go to the members of the clinical neuropsychological research group, especially Pirkko Nieminen, Kati Rantanen, Eija Rosti-Otajärvi and Minna Wäljas.

I feel very privileged that I have had two experienced, precious colleagues and friends throughout my career so far. I have learned my clinical skills from Ritva Hänninen. Her Lurian education has helped me to acquire the soul of a proud clinical neuropsychologist. Another important Lurian guide for me has been Kaija Poutanen. In addition to her professional guidance, she has almost been a mother-figure to me in many minor and major troubles.

I would like to express my warmest thanks to my family, mother Marja-Leena, mother-in-law Soili, brother Jarkko and uncle Leo. Thank you for always listening even when you didn't want to, or didn't necessarily understand. Sadly, my father Jorma is no longer with us to celebrate my achievement, but I know he would have been extremely proud of me. I owe my ambition to him.

Finally, I wish to express my deepest love and gratitude to my husband Marko; for 18 years now the best place in the world has been by your side. Thanks for never questioning my abilities during the hardships of this undertaking and for sharing with me all its joys.

Kangasala, September 2010

Tiia Saunamäki

# ABSTRACT

The aim of this thesis was to investigate executive functions in obstructive sleep apnea syndrome (OSAS). The specific focus was to identify the most affected domains of executive functioning, to establish the severity of dysfunction and to determine the effect of continuous positive airway pressure (CPAP) treatment on executive dysfunction. In addition, verbal and visual cognitive functions were evaluated along with changes in sleep depth.

The first step was to review earlier studies concerning executive functions in OSAS. Next, in a series of original studies, 40 newly-diagnosed OSAS patients and 20 healthy controls underwent a polysomnography and a neuropsychological assessment focusing on executive functions. The 20 regular CPAP users were followed up after six months with a polysomnography and a neuropsychological assessment, and 17 of the 20 controls were followed up with a neuropsychological assessment. A subgroup of 15 patients and 15 controls were included in a separate study on verbal and visual cognitive functions and local sleep depth using EEG.

The review of earlier studies showed that OSAS patients had decline in working memory, set shifting, behavioural inhibition, phonological fluency and visuospatial organizational skills, but the results were not consistent. With CPAP, OSAS patients' performance time in the behavioural inhibition task improved and the number of errors in the set shifting task decreased, but in other domains the deficits continued to persist.

In the original studies for this thesis, OSAS patients showed impaired executive functioning compared to healthy controls in visuospatial organizational skills and set shifting. However, normative analysis suggested that most OSAS patients had normal performance and only a minority had mild to severe dysfunction. CPAP did not improve executive dysfunction, and patients showed no learning effect in executive tests while

healthy controls did. In addition, OSAS patients who showed mild visual cognitive dysfunction also had a reduced amount of deep sleep in the right hemisphere.

Executive dysfunction in OSAS seems to be limited to visuospatial organizational skills and set shifting. Only a minority of patients show impaired performance, but the impairment may persist even after long-term treatment.

# CONTENTS

# LIST OF ORIGINAL PUBLICATIONS

This thesis consists of the following publications, which are referred to in the text by their Roman numerals I - IV:

I Saunamäki, T., & Jehkonen, M. (2007). A review of executive functions in obstructive sleep apnea. Acta Neurologica Scandinavica, 115, 1-11.

II Saunamäki, T., Himanen, S.L., Polo, O., & Jehkonen, M. (2009). Executive dysfunction in patients with obstructive sleep apnea syndrome. European Neurology, 62, 237-242.

III Saunamäki, T., Himanen, S.L., Polo, O., & Jehkonen, M. (2010). Executive dysfunction and learning effect after CPAP treatment in patients with obstructive sleep apnea syndrome. European Neurology, 63, 215-220.

IV Saunamäki, T., Jehkonen, M., Huupponen, E., Polo, O., & Himanen, S.L. (2009). Visual dysfunction and computational sleep depth changes in obstructive sleep apnea syndrome. Clinical EEG and Neuroscience, 40, 162-167.

# ABBREVIATIONS

| | |
|---|---|
| AHI | apnea/hypopnea index, number/hour |
| ARI | arousal index, number/hour |
| BMI | body mass index |
| CANTAB | Cambridge Neuropsychological Test Automated Battery |
| CPAP | continuous positive airway pressure |
| DS% | computational deep sleep percentage |
| EEG | electroencephalography |
| ESS | Epworth Sleepiness Scale |
| IED | Intra-Extra Dimensional Set Shift |
| IQ | intelligence quotient |
| NREM | non rapid eye movement sleep |
| ODI4% | oxygen desaturation index, number/hour |
| OSAS | obstructive sleep apnea syndrome |
| REM | rapid eye movement sleep |
| ROCFT | Rey-Osterrieth Complex Figure Test |
| SAS | supervisory attentional system |
| SAQLI | Calgary Sleep Apnea Quality of Life Index |
| SD | standard deviation |
| SOC | Stockings of Cambridge |
| SWS | slow wave sleep |
| S1-S4 | sleep stages 1-4 |
| TMT | Trail Making Test |
| WAIS-R | Wechsler Adult Intelligence Scale - Revised |
| WCST | Wisconsin Card Sorting Test |

# 1. INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is the most common cause of sleep apnea. It is characterized by repetitive episodes of upper airway obstruction during sleep (American Academy of Sleep Medicine, 2005). The condition results in blood gas abnormalities and fragmented sleep. Up to 4% of men and 2% of women have clinically important sleep apnea (Young et al., 1993). Common daytime symptoms are excessive daytime sleepiness, reduced quality of life, mood changes and cognitive symptoms. OSAS also has social consequences and it increases the risk of impaired working ability and traffic accidents (American Academy of Sleep Medicine, 2005). OSAS is commonly treated with continuous positive airway pressure (CPAP) (McMahon, Foresman, & Chisholm, 2003).

The relationship between OSAS and cognitive symptoms is complex and the research evidence is inconsistent (Aloia, Arnedt, Davis, Riggs, & Byrd, 2004; Beebe, Groesz, Wells, Nichols, & McGee, 2003; Engleman, Kingshott, Martin, & Douglas, 2000). According to Beebe and Gozal (2002) executive functions (e.g. planning, decision-making, flexible thinking) are among the most affected cognitive skills, because fragmented sleep, hypoxemia and hypercapnia associated with OSAS primarily affect the frontal areas of the brain. This thesis investigated executive functions in OSAS both before and after CPAP treatment.

## 1.1 Obstructive sleep apnea syndrome

Alternate terms for OSAS are obstructive sleep apnea, sleep apnea, sleep apnea syndrome, obstructive apnea, mixed sleep apnea, sleep-disordered breathing, sleep hypopnea syndrome and upper airway obstruction (American Academy of Sleep Medicine, 2005). Upper airway resistance syndrome is also subsumed under this diagnosis because the underlying pathophysiology is essentially the same as in OSAS.

Research into OSAS over the past 40 years has helped to give a clearer understanding of the condition (Dempsey, Veasey, Morgan, & O'Donnell, 2010). The syndrome was first described in the latter half of the 19th century (Lavie, 2003). These first descriptions were case reports of obese persons suffering from extreme daytime sleepiness and the syndrome was termed the "Pickwickian syndrome" after a character in Charles Dickens' The Pickwick Papers (Lavie, 2003). Although periodic breathing was also recognized in other patient groups, including heart failure patients (Lavie, 2003), the link between obesity, daytime sleepiness and control of breathing was not understood until the 1950s and the discovery of periodic breathing as part of the Pickwickian syndrome (Bickelmann, Burwell, Robin, & Whaley, 1956). At that time, however, no connection was drawn with sleep disorder but it was thought that daytime sleepiness was caused by "carbon dioxide poisoning" induced by respiratory failure. When the effects of sleep on ventilation were discovered in the 1960s, Gastaut, Tassinari and Duron (1966) developed a comprehensive view on OSAS by linking obesity, sleep-induced airway obstruction, sleep fragmentation and daytime sleepiness.

After these key observations, case reports were published of OSAS and tracheostomies as a treatment method (Lugaresi, Coccagna, Mantovani, & Brignani, 1971). Research was active in the late 1970s and early 1980s, including extensive physiological research on sleep and breathing (Dempsey et al., 2010) and the landmark discovery of non-invasive CPAP treatment (Sullivan, Issa, Berthon-Jones, & Eves, 1981). The association between OSAS, hypertension and cardiovascular diseases was discovered in the 1990s (Fletcher, Lesske, Qian, Miller, & Unger, 1992). Soon after it was discovered that OSAS was highly prevalent in the middle-aged nonclinical population leading to a better understanding of the importance of this undiagnosed syndrome to public health (Young et al., 1993). Since then there has been a huge increase in basic, clinical and population research (Dempsey et al., 2010).

### 1.1.1 Diagnosis and treatment

OSAS refers to repetitive episodes of either complete (apnea) or partial (hypopnea) obstruction of the upper airway during sleep (American Academy of Sleep Medicine, 2005; Dempsey et al., 2010). Obstructive events cause a cessation or reduction of airflow but ongoing respiratory efforts, and an over-compensatory response by the autonomic nervous system (American Academy of Sleep Medicine, 2005; Dempsey et al., 2010). The condition results in significant arterial hypoxemia and hypercapnia and arousals from sleep.

The diagnosis of OSAS takes into account both clinical and polysomnographic features. Nocturnal symptoms of OSAS include loud snoring and breathing interruptions often reported by the bed partner (American Academy of Sleep Medicine, 2005). Other

common symptoms are gasping and choking during sleep, unrefreshing sleep, sweating and nocturia. Daytime symptoms include morning headache, excessive daytime sleepiness, fatigue and unintentional sleep episodes, as well as changes in libido, quality of life, mood and cognition (Aloia et al., 2004; American Academy of Sleep Medicine, 2005; Beebe et al., 2003; Engleman et al., 2000; Harris, Glozier, Ratnavadivel, & Grunstein, 2009; Reimer & Flemons, 2003). The severity of OSAS as measured by the frequency of respiratory breathing events during sleep correlates poorly with the severity of daytime symptoms (American Academy of Sleep Medicine, 2005).

The techniques of polysomnographic recording used in the diagnosis of OSAS are highly standardized (Iber, Ancoli-Israel, Chesson, & Quan, 2007). The apnea-hypopnea index (AHI) is used to describe the number of complete and partial obstructive events per hour of sleep. OSAS severity is usually determined as follows: AHI 5-15 indicates mild, 6-30 moderate and over 30 severe OSAS. The oxygen saturation index (ODI4%) describes the number of at least 4% drops in blood oxygen levels per hour of sleep. Slight hypercapnia also occurs during obstructive events. The arousal index (ARI) indicates the number of arousals per hour and is one indicator of sleep fragmentation (American Academy of Sleep Medicine, 2005).

OSAS can occur in any age group, but its prevalence increases in middle-aged and older adults. In women, the prevalence of OSAS increases after menopause. Obesity is a major predisposing factor to OSAS. Patients with below normal or normal body weight suffer from OSAS mainly because of localized structural upper airway abnormalities, such as maxillomandibular malformation and adenotonsillar enlargement.

Smoking and alcohol also increase the risk of OSAS (American Academy of Sleep Medicine, 2005).

OSAS is associated with other health problems such as hypertension, metabolic syndrome, diabetes and an increased risk of cardiovascular and cerebrovascular diseases (American Academy of Sleep Medicine, 2005; Dempsey et al., 2010), as well as other sleep disorders including parasomnias, insomnia and restless legs syndrome (American Academy of Sleep Medicine, 2005; Rodrigues et al., 2007; Lavie, 2007).

Treatments for OSAS include weight loss, sleep hygiene, postural treatment, mechanical advancement devices, surgical procedures and CPAP treatment (McMahon, Foresman, & Chisholm, 2003). CPAP is a common and effective treatment especially for moderate and severe OSAS. CPAP treatment involves the use of a nasal mask attached to a pneumatic pump which supplies constant positive air pressure to the upper airway, preventing collapses during sleep and stimulating normal breathing. CPAP improves oxygen saturation and reduces sleep fragmentation.

### 1.1.2 Sleep quality and sleep stage fragmentation

Quality of sleep and sleep stage fragmentation can be studied using sleep electroencephalography (EEG). Sleep is divided into REM (rapid eye movement) sleep and NREM (non rapid eye movement) sleep. According to the sleep stages defined by Rechtschaffen and Kales (1968), NREM sleep stage 1 (S1) is a transition phase between wakefulness and sleep; sleep stage 2 (S2) indicates light sleep; and stages 3 (S3) and 4 (S4) consist of deep sleep and together constitute slow wave sleep (SWS). The thinking is that the amount of SWS is especially important to good sleep quality and refreshing sleep

(Kecklund & Åkerstedt, 1997; Åkerstedt, Hume, Minors, & Waterhouse, 1997). SWS seems to vary in different brain areas; EEG changes induced by sleep deprivation suggest that the left hemisphere needs more SWS than the right hemisphere (Achermann, Finelli, & Borbely, 2001), and the frontal cortex seems to need more SWS than more posterior parts of the cortex (Kubicki, Herrmann, & Höller, 1985). This may be explained by the high level of activity of both the left hemisphere and frontal cortex during wakefulness. It seems that the right hemisphere can better maintain its normal functioning when the brain is going to sleep or is in sleep and that it can also better tolerate sleep loss (Casagrande & Bertini, 2008a and 2008b).

The effects of OSAS on sleep fragmentation are stage specific because obstructive events occur more frequently in NREM sleep stages 1 and 2 and in REM sleep than in SWS (American Academy of Sleep Medicine, 2005). In OSAS, the amount of sleep stage 2 increases, while the amount of SWS usually decreases and there is only a minor reduction of REM sleep (Sanchez, Martinez, Miro, Bardwell, & Buela-Casal, 2009). In OSAS patients, fragmented sleep seems to cause frontally located sleep EEG differences compared to healthy controls. In untreated OSAS patients the amount of slow delta wave sequences in the left prefrontal cortex has been reported to be lower than in controls (Himanen, Joutsen, & Virkkala, 2004; Huupponen et al., 2005). In addition, it has been reported that CPAP increases SWS more in the left frontal than in the left central cortex, suggesting that before treatment OSAS patients have a reduced amount of SWS especially frontally, but CPAP moves EEG indices of sleep quality in a more normal direction (Eskelinen, Uibu, & Himanen, 2007). The reduced amount of frontal SWS seen in OSAS patients may impact patients' daytime performance because the

frontal cortex is highly active during wakefulness and needs more recovering slow wave activity during sleep (Rector et al., 2009). Earlier studies have investigated sleep depth changes in OSAS patients in one hemisphere only (Himanen et al., 2004; Eskelinen et al., 2007). An investigation of sleep depth changes in both hemispheres could clarify whether there are hemispheric-specific changes and whether these changes are associated with specific cognitive symptoms.

## 1.2 Cognitive symptoms and executive dysfunction associated with sleep apnea

The relationship between cognitive symptoms and OSAS has received increasing research attention since the 1980s. The very first studies on the relationship between OSAS and cognition reported that some cognitive domains are affected while others are not (Findley et al., 1986; Greenberg, Watson, & Deptula, 1987; Kales et al., 1985). However, from the outset there have also been studies reporting no impairment in OSAS patients' cognitive skills (Knight et al., 1987).

### 1.2.1 General cognitive symptoms

Subjective reports of concentration and memory problems in OSAS are common. In a study using Calgary Sleep Apnea Quality of Life Index (SAQLI) 70% of the 113 OSAS patients reported a decreased ability to concentrate and 66% reported a decreased ability to remember things (Flemons & Reimer, 1998). The prevalence of cognitive symptoms as assessed by objective methods is not known because there are no prevalence studies with large enough samples. Reviews (Aloia et al., 2004; Beebe et al., 2003; Decary, Rouleau,

& Montplaisir, 2000; Engleman & Douglas, 2004) have found that when compared to either control or norm-referenced data, OSAS patients show most consistently impairment in attention, especially vigilance, executive functions, learning and memory, visuoconstructive abilities and psychomotor functioning. The results concerning the effect of OSAS on general cognitive performance level are inconsistent; some reviews report a decline (Decary et al., 2000) while others do not (Aloia et al., 2004; Beebe et al., 2003).

Cognitive deficits are related to the severity of OSAS as determined by the frequency of respiratory breathing events, but the correlation is not clear or linear (Engleman et al., 2000). It is reported that moderate and severe OSAS are associated with cognitive deficits, but in mild OSAS cognitive problems may not be evident (Engleman & Douglas, 2004). The mechanisms behind cognitive deficits are not clearly understood. Possible background variables include OSAS-related biological factors, such as hypoxemia, hypercapnia, increased respiratory effect, sleep fragmentation and excessive daytime sleepiness (Beebe & Gozal, 2002; Decary et al., 2000, Verstraeten, 2007). Cognitive problems may also be increased by other OSAS-related health problems such as hypertension, metabolic syndrome, diabetes or increased risk of cerebrovascular and cardiovascular diseases. Old age may increase cognitive problems because of increased cerebrovascular risk, sleep changes (Antonelli-Incalzi et al., 2004) and impaired compensatory skills (Alchanatis et al., 2008). On the other hand, high primary cognitive level can provide protection against cognitive problems (Alchanatis et al., 2005).

CPAP treatment generally improves cognitive performance but some deficits may persist (Aloia et al., 2004; Sanchez et al., 2009). The positive effects of CPAP treatment

are sensitive to the duration of and adherence to the treatment regimen (McMahon et al., 2003). Attention and vigilance generally improves (Aloia et al., 2004; McMahon et al., 2003). The results from studies investigating the effects of CPAP on memory are inconsistent (McMahon et al., 2003). At least some deficits in executive functions, constructional abilities and psychomotor functioning continue to persist (Aloia et al., 2004; Decary et al., 2000). The persistent cognitive deficits raise the possibility of biochemical or structural brain damage (Aloia et al., 2004; Beebe & Gozal, 2002).

### 1.2.2 Executive dysfunction

Executive functions refer to a person's ability to respond in an adaptive manner to changing situations and to engage successfully in purposive and self-serving behaviour (Lezak, Howieson, & Loring, 2004). Executive functions are the basis for many cognitive, social and emotional skills. Executive dysfunction is associated with abnormalities in the frontal cortex and in the dense connections between the frontal cortex and other cortical or subcortical areas (Lezak et al., 2004).

Among the best known theories of executive functions are those of Norman and Shallice (1986; Shallice, 1988) and Baddeley (1986, 2000). Norman and Shallice's theory of supervisory attentional system (SAS) includes two complementary processes: contention scheduling and SAS. Contention scheduling is for automatically implemented responses and includes schemata or behavioral programs for completing routine tasks and skills. However, when a task is novel or complex, the schemata are not enough but an additional attentional system, SAS, is required. SAS makes it possible to function in novel situations that are not well-known by formatting a new action model that fits the

new situation and that can be flexibly reformatted when the situation changes. SAS compromises different processes: working memory, monitoring, rejection of schemata, spontaneous schema generation, adoption of processing mode, goal setting, delayed intention marker realization, and episodic memory retrieval.

In Baddeley's (1986, 2000) model of working memory, the central executive is a modality-free attentional control system that selects and controls strategies needed in a particular task or situation. The relevant information is temporarily stored by two modality-dependent short-term memory storages, visuospatial sketchpad and phonological loop. In addition, the episodic buffer stores multidimensional information and provides a temporary interface between short-term memory storages and long-term memory. The central executive controls what information is retrieved from the long-term memory to working memory for the purposes of the current task, and what information should be stored from working memory into the long-term memory for later use.

Beebe and Gozal (2002) say that in OSAS patients, executive functions are among the most affected cognitive domains because sleep disruption, hypoxemia and hypercapnia reduce sleep-related restorative processes and disturb cellular and chemical homeostasis, which in turn leads to altered neuronal and glial viability, particularly in the frontal cortex. They suggest that executive dysfunction in OSAS patients can cause impairment in behavioural inhibition, set shifting, self-regulation of affect and arousal, working memory, analysis/synthesis performance and/or contextual memory. Impairment of these skills causes everyday problems in mentally manipulating information, planning, decision-making, organization, flexible thinking and maintaining attention, motivation and emotional state. A recent meta-analysis by Beebe et al. (2003) investigated the effect

of OSAS on different cognitive skills and executive functioning displayed a moderate to large mean effect size indicating substantial executive dysfunction in OSAS. Effects sizes were larger in comparison to control-referenced data than in comparison to norm-referenced data.

On the other hand it has also been suggested that in some cases executive dysfunction may be explained by lower-level attentional deficits. Verstraeten and co-workers (2004a, 2004b, 2007) have pointed out that some earlier studies concerning executive functions in OSAS (e.g. Bedard et al., 1991; Redline et al., 1997) have not taken adequate account of the effects of decreased alertness and therefore their findings of executive dysfunction remain tentative. They conclude that higher-level executive dysfunction in OSAS may actually be explained by impaired lower-level processes, namely attentional capacity deficits such as slowed information processing and decreased short-term memory span, and that these cognitive changes may be caused by basal slowing due to sleepiness, not by frontal dysfunction.

### 1.2.3 Assessment of executive dysfunction

Even mild executive dysfunction in OSAS may adversely impact patients' everyday life, working ability and social relationships (Beebe & Gozal, 2002), which underlines the importance of early detection of these symptoms. Executive functions are not usually impaired across the board, but some skills are impaired while others are not (Burgess, 2003). To clarify the nature of executive dysfunction in OSAS, it is necessary to evaluate different domains. Beebe and Gozal (2002) and Decary et al. (2000) have given their recommendations as to which test methods should be used in the assessment of OSAS

patients' executive functions. These recommendations are summarized in Table 1. Because executive tests are 'one-shot' tests based on novelty and strategy formation, the test-retest reliability of these tests is often poor (Burgess, 2003). It is important to account for possible learning effect when assessing OSAS patients' executive function before and after treatment.

The only way to assess executive functions is via other cognitive skills. This means that executive functions must always be assessed as part of a more comprehensive neuropsychological assessment so that the possible effects of other cognitive deficits can be analysed (Burgess, 2003). The view of Verstraeten and co-workers (2004a, 2004b, 2007) emphasize that cognitive processing speed and short-term memory span are key factors that must be taken into account in the assessment of executive functioning. Other aspects that must be included are general cognitive level and verbal and visual cognitive processes (Crawford & Henry, 2005).

TABLE 1. An overview of methods recommended for the assessment of executive functions in OSAS by Beebe & Gozal (2002) and Decary et al. (2000).

| Domain of executive function | Test method |
|---|---|
| Mental set shifting and abstract behaviour | Wisconsin Card Sorting Test[1] |
| | Trails B of Trail Making Test[2] |
| Conceptual and visuomotor tracking | Trails A of Trail Making Test[2] |
| Planning and foresight | Mazes[3] |
| Focal attention, shifting processes and behavioural inhibition | Stroop test[4] |
| Organizational skills / analysis-synthesis on the spatial domain | Copy of Rey-Osterreith Complex Figure[5] |
| Analysis/synthesis | Fluency tasks[3] |
| Working memory | Back digit strings[3] |
| | Visual sequences[3] |
| | N-back test[3] |
| Self-regulation of affect and arousal | Behavior Rating Inventory of Executive Functioning[6] |

[1]Heaton et al., (1993); [2]Armitage, (1946); [3]Lezak et al., (2004); [4]Golden, (1978); [5]Osterrieth, (1944); [6]Gioia et al., (2000).

### 1.2.4 Verbal and visual cognitive functions

Executive tests are based on either verbal or visual material, and therefore the performance of these tests also requires verbal or visual cognitive functions. In OSAS, verbal cognitive skills such as naming and conceptual formatting are usually intact (Aloia et al., 2004; Beebe et al., 2003), while verbal fluency, which requires both verbal skills and executive functioning, is more often affected (Bedard et al., 1991 and 1993; Ferini-Strambi et al., 2003; Lee et al., 1999; Salorio et al., 2002). Visuoconstructive and visuomotor changes are reported quite often while other aspects of visual functioning seem to be intact (Bedard et al., 1991 and 1993; Ferini-Strambi et al., 2003; Rouleau et al., 2002). According to the meta-analysis by Beebe et al. (2003), OSAS affects especially drawing and fine-motor coordination, but it has less effect on visual perception and motor speed. It seems then that visual cognitive functions that involve both a visual and executive component, are more easily affected in OSAS.

# 2. AIMS OF THE STUDY

It is well-known that executive functions are among the most defected cognitive domains in OSAS, but executive dysfunction is usually examined as a single cognitive domain, without considering which executive domains are most vulnerable to the effects of OSAS. This thesis presents a detailed investigation of executive functions in OSAS. The work was based on the theory of Beebe and Gozal (2002), without forgetting the objections raised by Verstraeten (2007). In addition, because EEG changes during sleep may be related to OSAS patients' cognitive symptoms, hemisphere-related cognitive functions and local sleep depth changes were also investigated. The aims were:

1) to review earlier studies concerning executive functions in OSAS, focusing specifically on the assessment methods used, the executive domains that are most frequently defected, and the impacts of CPAP treatment on executive functions;

2) to investigate whether newly-diagnosed OSAS patients have executive dysfunction when compared to healthy controls, identify the executive domains most affected, and to establish the severity of possible dysfunction;

3) to clarify the impact of long-term CPAP treatment on OSAS patients' executive dysfunction and investigate any possible learning effect in executive tests;

4) to establish whether OSAS patients demonstrate decline in verbal or visual cognitive functions compared to controls and whether they show local sleep depth changes at the same time.

# 3. METHODS

## 3.1 Review of earlier studies

In Study I, earlier research on executive functions in OSAS was reviewed by searching MEDLINE and PSYCHLIT for articles published between January 1990 and December 2005. The search terms used were ‘obstructive sleep apnea and cognitive’ and ‘obstructive sleep apnea or neuropsychological’. The first search yielded 196 articles. After exclusion criteria were applied (non-English articles, articles with non-human and non-adult subjects, case reports, reviews, experimental studies, letters, commentaries, abstracts and chapters of edited volumes) and when the review was narrowed to articles reporting results on at least one executive function, 24 articles remained. The lists of references of these 24 articles were searched, yielding 16 additional articles. The total number of articles reviewed was thus 40.

## 3.2 Original studies

### 3.2.1 Subjects

The subjects of the original studies were investigated at Tampere University Hospital sleep unit. In Study II, the sample included 40 newly-diagnosed male OSAS patients who met the diagnostic criteria, who had received no previous treatment and whose first

treatment choice was CPAP. The control group consisted of 20 healthy male volunteers. In Study III, the 20 patients who used CPAP for at least four hours a night and at least five nights a week for a period of six months or longer were included in a follow-up. After at least six months, 17 of the original controls joined the follow-up assessment. In Study IV, a subgroup of 15 patients who had participated in both baseline and follow-up assessments as well as 15 original controls were included. The demographic, clinical and polysomnographic characteristics of all subjects are presented in Table 2.

TABLE 2. Demographic, clinical and polysomnographic characteristics of patients and controls.

| | Patients (n = 40) | Controls (n = 20) | Difference[1] |
|---|---|---|---|
| Age | 47.2 ± 7.8 (28-65) | 42.9 ± 10.3 (29-63) | ns |
| Education (yrs) | 12.5 ± 3.0 (5-17) | 13.8 ± 3.0 (8-17) | ns |
| ESS | 11.5 ± 3.8 (4-18) | 4.5 ± 2.8 (0-11) | $p < 0.001$ |
| BMI | 30.3 ± 4.6 (24-41) | 24.9 ± 2.7 (20-30) | $p < 0.001$ |
| AHI, n/h | 41.0 ± 22.8 (10-103) | 2.5 ± 2.1 (0-5) | $p < 0.001$ |
| ARI, n/h | 33.8 ± 19.2 (8-100) | 13.0 ± 4.4 (4-23) | $p < 0.001$ |
| ODI4%, n/h | 26.0 ± 22.3 (0-88) | 0.8 ± 1.4 (0-6) | $p < 0.001$ |
| TST | 426.9 ± 49.8 (325-532) | 419.4 ± 54.7 (328-527) | ns |
| SEI% | 90.3 ± 6.2 (74-100) | 89.6 ± 7.0 (74-98) | ns |
| S1% | 6.1 ± 3.9 (1-23) | 6.3 ± 3.6 (2-16) | ns |
| S2% | 68.2 ± 9.7 (48-85) | 60.5 ± 7.7 (45-72) | $p = 0.005$ |
| SWS% | 8.2 ± 7.0 (0-23) | 13.8 ± 6.8 (2-25) | $p = 0.005$ |
| REM% | 17.6 ± 5.0 (6-28) | 19.4 ± 4.7 (13-28) | ns |

[1]Mann-Whitney U test; p-value

Abbreviations

ESS = Epworth Sleepiness Scale; BMI = body mass index; AHI = apnea/hypopnea index; ARI = arousal index; ODI4% = oxygen desaturation index; TST = total sleep time; SEI = sleep efficiency index of total sleep time; S1% = sleep stage 1 percentage of total sleep time; S2% = sleep stage 2 percentage of total sleep time; SWS% = slow wave sleep percentage of total sleep time; REM% = rapid eye movement sleep percentage of total sleep time.

### 3.2.2 Procedure

Both the patients and controls were first interviewed by telephone to make sure they met the initial eligibility criteria: a) age between 20 and 65 years, b) right-handedness, c) no (other) sleep disorders, d) no clinically significant medical disorder (e.g. neurological illness, psychiatric disorder, hypo-/hyperthyroidism or other lung diseases than currently asymptomatic asthma), f) no medication affecting central nervous system, g) no substance or alcohol abuse, and h) no self-reported primary sensory disorders. The patients' OSAS diagnosis and the controls' healthiness were then confirmed in a clinical interview and by means of a diagnostic full-night polysomnography in a sleep laboratory. The diagnosis of OSAS was based on clinical picture and subjective complaints of OSAS (American Academy of Sleep Medicine, 2005) and on an AHI > 10 per hour of sleep. The controls had to be asymptomatic and to have an AHI of ≤ 5 per hour of sleep.

At baseline, patients and controls who according to the first night polysomnography met the eligibility criteria underwent a second full-night polysomnography; the latter recordings were used in the analyses. A neuropsychological assessment focusing on executive functions was conducted the following morning.

After at least six months of CPAP treatment, patients returned for a full-night polysomnography (the treatment night) and a neuropsychological control assessment the following morning. Prior to the treatment night, objective compliance measures were downloaded from CPAP units. The controls underwent a neuropsychological control assessment after an interval of at least six months from the baseline assessment.

### 3.2.3 Measures

Neuropsychological test methods were selected to assess general cognitive level, verbal and visual cognitive functions, and different domains of executive functioning (Table 3).

Subjective sleepiness was assessed with the Epworth Sleepiness Scale (ESS; Johns, 1991). Conventional polysomnographic variables were used as background variables. In addition, in Study IV, deep sleep percentages (DS%) were calculated from six EEG derivations, based on the work by Saastamoinen, Huupponen, Värri, Hasan and Himanen (2007). The value of DS% indicated the proportion of NREM sleep time containing deeper sleep than the threshold of 4.0 Hz.

TABLE 3. Assessment of cognitive functions.

| Domain | Test method used |
|---|---|
| General cognitive level | Wechsler Adult Intelligence Scale-Revised[1] – short version with seven subtests[2] |
| Verbal cognitive functions | Information[1], Digit Span[1], Arithmetics[1], Similarities[1], Semantic fluency[3], Phonological fluency[3] |
| Visual cognitive functions | Picture Completion[1], Block Design[1], Digit Symbol[1], Copy of the Rey-Osterrieth Complex Figure Test[4] |
| Verbal short-term memory span | Digit Span forwards[1] |
| Verbal working memory | Digit Span backwards[1] |
| Visual short-term memory span | Spatial Span[5]: span length |
| Visual working memory | Spatial Working Memory[5]: strategy |
| Verbal fluency | Semantic: Animals[3] |
| | Phonological: letters PAS (Finnish version of FAS[3]) |
| Visuospatial organizational skills | Copy of the Rey-Osterrieth Complex Figure Test[4] |
| | Block Design[1] |
| Visuomotor tracking / processing speed | Digit Symbol[1] |
| | Trails A of Trail Making Test[6]: time |
| Mental set-shifting | Trails B of Trail Making Test[6]: time |
| | Intra-Extra Dimensional Set Shift[5]: stages completed and errors |
| Planning and problem-solving | Stockings of Cambridge[5]: problems solved in minimum moves |

[1]Wechsler, (1981); [2]Ward & Ryan, (1996); [3]Lezak et al., (2004); [4]Osterrieth, (1944); [5]Cambridge Neuropsychological Test Automated Battery, Cambridge Cognition Ltd.; [6]Armitage, (1946).

# 4. RESULTS

## 4.1 Review of earlier studies

The studies reviewed (Study I) consisted mainly of working-age men with mild to severe or moderate to severe OSAS. The most commonly used test methods were the Phonological fluency tasks, Trail Making Test (TMT), Digit Span, Wisconsin Card Sorting Test (WCST; Heaton, 1993), Stroop test (Golden, 1978), Tower tests (Lezak et al., 2004), Rey-Osterrieth Complex Figure Test (ROCFT) and Corsi's block-tapping test (Lezak et al., 2004). There was much variation in terms of what the tests were thought to measure, and some studies failed to determine what executive domain they wanted to assess with the test. Half of the 40 studies reviewed used only one or two methods to assess executive dysfunction, the other half assessed executive dysfunction using three to nine tests.

Among the most commonly used tests, OSAS patients showed defected performance most frequently in the Digit Span, Corsi-block tapping test, Trails B of the TMT, Stroop test, Phonological fluency tasks and ROCFT, and they achieved fewer categories and showed more perseverative errors in the WCST. With CPAP treatment, OSAS patients' performance time improved in the Stroop test and they had fewer perseverative errors in the WCST, but in other domains the deficits continued to persist.

## 4.2 Executive dysfunction before CPAP treatment

In Study II, working-aged male patients had mild to severe OSAS with arousals, hypoxemic events and sleep stage changes, and they were sleepier and more obese than healthy controls. The study groups did not differ in intelligence quotient (IQ). Patients showed poorer set shifting performance than healthy controls as assessed with the Trails B and Intra-Extra Dimensional Set Shift (IED), and lower visuospatial organizational skills as assessed with the ROCFT and Block Design (Table 4). When performance in these executive tests was compared with normative data, most OSAS patients showed normal performance, but some demonstrated either mild (2-12.5%) or from moderate to severe (5-15%) decline. The nine patients who showed moderate to severe deficits were compared to the 31 patients with normal or only mildly impaired performance with regard to age, years of education, IQ, ESS, body mass index (BMI) and polysomnographic variables. No statistically significant differences were found.

## 4.3 Executive dysfunction after CPAP treatment

CPAP had the effect of normalizing OSAS patients' respiratory deficits, arousals and hypoxemic events, improving sleep quality, and decreasing subjective sleepiness (Study III). Mean CPAP adherence was 6.2 hours per night (range 4.3-8.6), and the mean duration of CPAP treatment was 7.4 months (range 6-12). Patients' executive performance showed no improvement, and they continued to perform more poorly than controls. In addition, OSAS patients showed no learning effect in executive tests, while

healthy controls improved their performance in the Block Design, Digit Symbol, Trails A and Stockings of Cambridge (SOC).

TABLE 4. Mean ± SD and (range) of executive tests in patients and controls.

| | Patients (n = 40) | Controls (n = 20) | Difference[1] |
|---|---|---|---|
| IQ | 111.2 ± 9.7 (94-132) | 117.6 ± 9.8 (104-137) | ns |
| Digit Span forwards | 6.9 ± 1.6 (4-10) | 7.1 ± 1.9 (4-11) | ns |
| Digit Span backwards | 6.6 ± 1.3 (4-10) | 6.7 ± 1.6 (4-10) | ns |
| Spatial Span | 6.6 ± 1.4 (3-9) | 7.1 ± 1.4 (5-9) | ns |
| Spatial Working Memory | 30.6 ± 6.6 (19-43) | 29.5 ± 6.9 (19-41) | ns |
| Phonological fluency | 24.8 ± 5.0 (13-34) | 25.6 ± 4.4 (16-31) | ns |
| Semantic fluency | 39.7 ± 11.2 (18-74) | 42.2 ± 11.2 (27-59) | ns |
| ROCFT | 33.6 ± 2.7 (26-36) | 35.1 ± 1.0 (33-36) | p = 0.041 |
| Block Design | 33.2 ± 8.3 (14-49) | 39.1 ± 8.5 (23-51) | p = 0.021 |
| Digit Symbol | 45.4 ± 11.6 (25-86) | 54.0 ± 15.5 (33-88) | ns |
| Trails A | 31.5 ± 13.6 (17-73) | 32.0 ± 10.6 (14-61) | ns |
| Trails B | 73.0 ± 47.4 (42-238) | 61.5 ± 32.5 (31-159) | p = 0.019 |
| IED stages | 8.6 ± 0.7 (7-9) | 9.0 ± 0.0 (9-9) | p = 0.021 |
| IED errors | 18.1 ± 11.5 (7-45) | 13.0 ± 6.4 (7-28) | ns |
| Stockings of Cambridge | 9.7 ± 1.9 (3-12) | 9.9 ± 2.1 (5-12) | ns |

[1]Mann-Whitney U test; p-value

Abbreviations

IQ = intelligence quotient; ROCFT = Copy of Rey-Osterrieth Complex Figure Test; IED = Intra-Extra Dimensional Set Shift.

## 4.4 Verbal and visual cognitive functions and local sleep depth

When verbal and visual cognitive functions were investigated (Study IV), OSAS patients showed lower performance than controls in the Picture Completion, Digit Symbol and ROCFT. The difference between the study groups remained after CPAP treatment in the Picture Completion and ROCFT. Before CPAP, OSAS patients had a reduced amount of deep sleep in both hemispheres frontally, centrally and occipitally compared to controls (Table 5). After six months of CPAP treatment, patients' amount of deep sleep increased to the same level as in controls' frontopolarly and centrally in the left hemisphere, while patients continued to show a reduced amount of deep sleep in all three locations of the right hemisphere and occipitally in the left hemisphere (Table 5). Patients also had a lower amount of deep sleep in the right than in the left hemisphere both frontopolary and centrally, while controls showed this inter-hemispheric difference only frontopolarly.

TABLE 5. Mean ± SD and (range) of deep sleep percentage in the control group and in the patient group before (pre-CPAP) and after (post-CPAP) CPAP treatment.

| | - A - Controls (n = 15) | - B - Patients pre-CPAP (n = 15) | - C - Patients post-CPAP (n = 15) | A vs B[1] | A vs C[1] | B vs C[2] |
|---|---|---|---|---|---|---|
| DS(Fp1)% | 24.8 ± 12.7 (6.2 - 48.8) | 13.1 ± 10.6 (0.0 - 30.2) | 18.3 ± 11.6 (0.0 - 33.3) | p = 0.017 | ns | p = 0.036 |
| DS(Fp2)% | 21.1 ± 12.3 (0.0 - 39.3) | 6.5 ± 7.7 (0.0 - 21.5) | 10.3 ± 9.3 (0.0 - 24.7) | p = 0.002 | p = 0.018 | ns |
| DS(C3)% | 13.2 ± 11.0 (0.0 - 29.6) | 4.8 ± 4.6 (0.0 - 11.8) | 9.2 ± 8.3 (0.0 - 24.4) | p = 0.024 | ns | p = 0.019 |
| DS(C4)% | 12.8 ± 10.2 (0.0 - 29.7) | 2.8 ± 3.3 (0.0 - 11.9) | 5.1 ± 5.4 (0.0 - 15.49 | p = 0.016 | p = 0.013 | p = 0.022 |
| DS(O1)% | 10.0 ± 11.8 (0.0 - 37.4) | 1.1 ± 2.6 (0.0 - 8.3) | 2.2 ± 3.5 (0.0 - 9.89 | p = 0.004 | p = 0.027 | ns |
| DS(O2)% | 11.8 ± 12.6 (0.0 - 42.9) | 1.5 ± 2.6 (0.0 - 9.1) | 1.9 ± 3.1 (0.0 - 11.0) | p = 0.016 | p = 0.022 | ns |

[1]Mann-Whitney U test; [2]Wilcoxon test; p-values

Abbreviations

DS(Fp1)%, DS(Fp2)%, DS(C3)%, DS(C4)%, DS(O1)%, DS(O2)% = computational deep sleep percentages extracted from EEG channels Fp1-A2, Fp2-A1, C3-A2, C4-A1, O1-A2, O2-A1.

# 5. DISCUSSION

The purpose of this thesis was to investigate executive functions in OSAS before and after CPAP treatment. A further concern was with verbal and visual cognitive functions and local sleep depth changes.

## 5.1 Assessment of executive functions

In the studies reviewed (Study I), executive functions were predominantly assessed using the methods recommended by Decary et al. (2000) and Beebe and Gozal (2002). The use of standardized tests makes for easier comparisons. However, the general lack of theoretical agreement how executive functions are defined and operationalized, can be seen also in the studies reviewed. Some studies failed to specify which executive domain they were measuring, but set about assessing executive function as a single global function. This may have led to the false conclusion that executive functions are either totally impaired or totally intact. There were also marked differences in terms of what the test was thought to measure. The use of a wide battery of executive tests helps to overcome the problem that there is no common agreement about which executive aspect even the most commonly used tests actually measure, but the disadvantage is that it increases the likelihood of false-positive errors (Burgess, 2003).

Half of the studies reviewed assessed executive functions with only one or two test methods. This does not provide a sufficiently sound basis for drawing conclusions and it is possible that this narrow assessment fails to recognize some executive dysfunction. It should be also noted that neuropsychological tests may not be sensitive enough to detect mild cognitive change and the positive treatment effects of CPAP, especially in OSAS patients with a high general cognitive level (Lojander et al., 1999). Recent studies (Lim et al., 2007; Lis et al., 2008) have shown that more complex neuropsychological tasks (e.g. PASAT, n-back working memory tasks and Digit Vigilance; see Lezak et al., 2004 for test descriptions), which require cognitive processing speed, vigilance and working memory, seem to be more sensitive to detect even mild changes. Assessment methods developed by experimental cognitive studies may offer in the further more sensitive and specific tests to be used also in clinical practice.

Learning effect in executive tests may be significant when retesting OSAS patients after CPAP treatment. Especially in measurements of the short-term effects of CPAP, OSAS patients seem to improve their performance over time, and without placebo control this improvement may be misattributed to CPAP (Lim et al., 2007). In the placebo-controlled studies reviewed, treatment time ranged from 1 to 8 weeks, which is not necessarily enough to see an improvement in complex cognitive domain such as executive functioning. Only a few studies explored the long-term effects of CPAP on executive functions (Bedard et al., 1993; Ferini-Strambi et al., 2003; Feuerstein et al., 1997; Naegele et al. 1998). These studies used parallel or alternative test versions at the follow-up assessment to decrease the learning effect. However, this is not necessarily

enough; when a patient figures out the basic idea of the test, it may be much easier to do the second time round, even if the material is different from the original test.

## 5.2 Quality and quantity of executive dysfunction

In the original study (Study II) where OSAS patients' executive functions were compared with the control-referenced data, executive functions were only partly impaired and the most defected domains were visuospatial organizational skills and set shifting. The finding regarding lower visuospatial organizational skills is in line with earlier results (Bedard et al., 1991; Ferini-Strambi et al., 2003; Rouleau et al., 2002). In contrast, the finding of reduced set shifting performance as measured by the Trails B has previously been reported only in a study by Bedard et al. (1991 and 1993); most earlier studies have shown no change in this test (Ferini-Strambi et al., 2003; Feuerstein et al., 1997; Lee et al., 1999; Naegele et al., 1995; Rouleau et al., 2002). However, the patients' lower set shifting observed in the present study is also supported by their reduced performance on the IED. The IED is used to assess similar executive function to the WCST, and many earlier studies have reported reduced performance in this test (Feuerstein et al., 1997; Lee et al., 1999; Naegele et al., 1995; Redline et al., 1997; Roulaeu et al., 2002).

The present study did not confirm that OSAS patients have impaired working memory or verbal fluency. Earlier studies have reported inconsistent findings for these executive domains: some studies show impaired working memory (Felver-Gant et al., 2007; Feuerstein et al., 1997; Lis et al., 2008; Naegele et al., 1995) and verbal fluency (Bedard et al., 1991 and 1993; Ferini-Strambi et al., 2003; Lee et al., 1999; Salorio et al.,

2002), while others conclude that working memory (Ferini-Strambi et al., 2003; Lee et al., 1999; Yaouhi et al., 2009) and verbal fluency (Feuerstein et al., 1997; Naegele et al., 1995; Rouleau et al., 2002; Yaouhi et al., 2009) are intact in OSAS.

When compared to norm-referenced data, most OSAS patients performed at normal level and only some patients showed executive dysfunction. Although patients with executive dysfunction seem to be a minority, it is important to detect these patients because even mild executive dysfunction may have a negative impact on patients' working ability, and moderate to severe deficits may cause significant everyday problems. These patients cannot be identified on the basis of their background data: the patients with moderate to severe executive dysfunction did not differ from those with normal or only mildly impaired performance in terms of age, education, IQ, daytime sleepiness, obesity, or conventional polysomnographic variables. Although the severity of OSAS in the present study group varied from mild to severe, most patients had moderate to severe OSAS. It is possible that this made them more vulnerable to cognitive changes. Although patients did not have any other significant medical disorder, it is possible that the existence of OSAS-related co-morbidities increased the risk of cognitive problems.

## 5.3 Effect of CPAP on executive dysfunction

After six months of CPAP treatment, OSAS patients' performance in executive tests showed no change and remained lower than in healthy controls (Study III). This confirms the results of earlier studies that executive functions are not totally reversible even with long-term CPAP treatment (Bedard et al., 1993; Ferini-Strambi et al., 2003; Feuerstein et

al., 1997; Naegele et al. 1998). The results of the present study showing persisting decline in set shifting are in line with the finding of Bedard et al. (1993), who reported that impaired performance in the Trails B remained after six months of CPAP treatment. Feuerstein et al. (1997) and Naegele et al. (1998), by contrast, reported that OSAS patients' set shifting performance as assessed with the WCST improved after 4-6 months of CPAP treatment. Findings of persisting decline in visuospatial organizational skills are consistent with the results of Ferini-Strambi et al. (2003), but in contrast to those of Bedard et al. (1993). In placebo-controlled studies, Engleman et al. (1994; 1997) reported that CPAP produced a greater improvement in set shifting as assessed with the Trails B than did placebo treatment. However, most placebo-controlled studies have found no improvement in either set shifting performance or in visuospatial organizational skills over placebo (Bardwell et al., 2001; Barnes et al., 2002; Engleman et al. 1998; Lim et al., 2007).

After CPAP treatment, OSAS patients showed no learning effect in executive tests, while healthy controls did. This may have to do with the fact that executive dysfunction and long-term memory deficits often overlap: frontal dysfunction may cause poorer learning and memory skills because of deficits in memory organization (Salorio et al., 2002). The recording of new experiences and consolidation of declarative memories are dependent on the cooperation of prefrontal and hippocampal functions, and this process can easily be disrupted by inadequate sleep, especially the lack of SWS (Walker, 2009) that is seen in OSAS patients. It is also possible that the finding of OSAS patients' reduced amount of deep sleep in the right hemisphere have an association with their impaired learning effect. In the study by Huber, Ghilardi, Massimini, and Tononi (2004),

learning in a visuomotor task was followed by an increase in slow wave activity over the right parietal cortex. On the other way round: decreased slow wave activity in the right parietal brain area might decrease learning, at least in visuomotor tasks.

## 5.4 Visual cognitive dysfunction and local sleep depth changes

When verbal and visual cognitive functions and local sleep depth were investigated (Study IV), OSAS patients showed mild visual dysfunction and a reduced amount of deep sleep in the right hemisphere compared to controls even after long-term CPAP treatment. The finding of mild visual cognitive dysfunction is in line with earlier results (Bedard et al., 1991 and 1993; Ferini-Strambi et al., 2003; Rouleau et al., 2002). As in previous reports, also in this study verbal cognitive skills remained intact (Aloia et al., 2004; Beebe et al., 2003). On the other hand, in contrast to many other studies (Bedard et al., 1991 and 1993; Ferini-Strambi et al., 2003; Lee et al., 1999; Salorio et al., 2002), this study found no change either in verbal fluency tasks.

At baseline, OSAS patients showed a reduced amount of deep sleep compared to controls in both hemispheres frontally, centrally, and occipitally. The reduced amount of deep sleep might be connected to cognitive changes because deep sleep is thought to express the refreshing effect of sleep (Kecklund & Åkerstedt, 1997; Åkerstedt et al., 1997). However, even though the amount of deep sleep was reduced bilaterally, only visual cognitive dysfunction was detected, not verbal. It can be speculated whether compensatory mechanisms may explain intact verbal cognitive skills. In a recent study, Aloia et al. (2009) reported that OSAS patients performed at the same level in a 2-back

verbal memory task in the condition where patients were using CPAP and where CPAP was withdrawn. However, in the condition where CPAP was withdrawn, functional magnetic resonance imaging showed overactivation of the right inferior parietal lobule and deactivation of the right posterior insula, suggesting compensatory function.

After CPAP, OSAS patients continued to show mild visual dysfunction and reduced amount of deep sleep in the right hemisphere. This might indicate that this dysfunction was in fact a result of visual cognitive change, although other cognitive functions, especially executive functions, may also have an effect on patients' performance. OSAS patients had a reduced amount of deep sleep compared to controls bilaterally in the occipital brain areas before and after CPAP treatment, and the amount of deep sleep in the occipital area did not increase significantly during treatment. It can be speculated whether occipital deep sleep changes are related to the visual dysfunction observed in OSAS patients.

Another noteworthy finding was the discovery that even healthy controls presented an inter-hemispheric difference in the deep sleep percentage. This might be connected to the findings of Casagrande and Bertini (2008a and 2008b), who proposed that the right hemisphere could better maintain normal functioning during sleep and monitor potential warning stimuli. If this theory is correct, it might be natural that healthy controls have less deep sleep in the right than in the left frontopolar area during normal sleep. However, OSAS patients showed a reduced deep sleep percentage in a larger area of the right hemisphere than controls. This might indicate that in OSAS patients the right hemisphere monitors possible internal warning stimuli such as signals about respiratory deficits and the central cortex is also needed to make this possible. This fits in with the

theory of Sturm et al. (1999) according to which the attention and vigilance system is based on the right fronto-parietal-thalamic-brainstem network.

After CPAP treatment, OSAS patients continued to show inter-hemispheric deep sleep difference in both the prefrontal and central cortex and a reduced amount of deep sleep in the right hemisphere compared to controls. This raises the question as to whether the right hemisphere continues to monitor respiratory deficits, even though CPAP treatment is expected to prevent obstructive events, and whether the right hemisphere is more vulnerable to the harmful effects of OSAS because of its dominance in this vigilance system. In a recent study, Yaouhi et al. (2009) concluded that OSAS patients who did not have notable cognitive deficits showed right-lateralized cerebral changes in terms of both grey matter density and metabolic levels. They suspected that many patients, especially with a high general cognitive level, compensate the functional effects of brain changes at disease onset, but that there is a risk of changes causing more notable cognitive consequences if OSAS is not treated.

## 5.5 Limitations

Most samples in the studies reviewed as well as in the original studies consisted of working-age men. It is not known whether gender has an effect on OSAS patients' cognitive symptoms, but it should be noted that these results can only be generalized to male patients. The number of patients in our study was quite low, but nevertheless comparable to the numbers in earlier studies focusing on OSAS patients' executive functions (Bedard et al. 1991 and 1993; Ferini-Strambi et al., 2003; Feuerstein et al.,

1997; Lee et al., 1999; Naegele et al., 1995 and 1998; Roulaeu et al., 2002; Salorio et al., 2002).

The search of reference lists in the studies reviewed (Study I) yielded a significant number of additional articles. This suggests that the terms used in the literature search were not inclusive enough. In particular, the use of alternative terms for obstructive sleep apnea would have improved the coverage of the search. The use of meta-analysis would also have made the review more exact.

There were some limitations in the original studies. Study II did not investigate the effect of executive dysfunction on patients' daily performance because of the lack of adequate methods. In Study III, the patients who used CPAP adequately tended to be older than those who did not. In addition, patients and controls differed in their sleep conditions prior to the neuropsychological control assessment. This may have had some effect on patients' cognitive performance the following morning because of generally poorer sleep quality in laboratory conditions. This may be particularly true in tasks that require cognitive processing speed (e.g. Trails A). However, the impaired learning effect seen in executive tests is mainly attributable to the long-term effects of OSAS. Study IV used a subgroup of patients from the earlier studies. Verbal and visual cognitive functions were assessed using partly the same test methods as were used to assess executive functions in Studies II and III. However, because executive functions can only be assessed via other cognitive skills, it is impossible to avoid the overlapping use of tests.

## 5.6 Theoretical considerations and future directions

As described earlier, Beebe and Gozal (2002) suggest that executive functions may be easily disturbed in OSAS because the frontal brain area is vulnerable to the cellular and chemical effects of sleep fragmentation, hypoxemic and hypercapnic events. Verstraeten (2007), on the other hand, argues that rather than frontally based executive dysfunction, OSAS patients may in fact be showing decreased alertness and slowed information processing speed due to sleepiness and basal slowing. Bearing in mind that fronto-subcortical circuits of the brain are very dense, it is possible that both views of Beebe and Gozal (2002) and Verstraeten (2007) are correct and that OSAS impacts both higher-level executive functions and lower-level attentional skills. At least recent studies show that OSAS patients' working memory performance may be affected by both executive and attentional deficits (Lis et al., 2008; Naegele et al., 2006). Considering the co-morbidities of OSAS, it is also possible that vascular risk factors disturb mostly the dense fronto-subcortical circuits, although Aloia et al. (2004) suspect that damage to the small vessels of the brain results in cognitive problems that are not restricted to any particular domains.

Future research into the relationship between OSAS and cognitive dysfunction should focus on prevalence issues, using objective neuropsychological assessment methods to establish how large a proportion of OSAS patients have cognitive symptoms. In addition, more research is needed to explore the background variables of cognitive symptoms, especially the effect of co-morbidities of OSAS on patients' cognition. The possible vulnerability of the right hemisphere to the effects of OSAS also needs closer investigation.

## 5.7 Clinical implications

The clinical investigation of OSAS patients does not routinely include a neuropsychological assessment. However, such an assessment should be considered whenever a patient reports cognitive problems in everyday life and a reduced capacity for work or driving. The neuropsychological assessment of OSAS patients should be as comprehensive as possible and include not only neuropsychological tests but also a structured interview and self-assessment inventories. In addition to general cognitive level and different aspects of memory, the assessment should compromise executive functions, attention, information processing speed, visuoconstructive and visuomotor functions. It is also important that clinicians are aware of the limitations of the test methods. The use of tests that require both executive functioning, attention and processing speed seem to be the most sensitive to detect OSAS-related cognitive symptoms and the effects of CPAP treatment. Input is needed to develop assessment methods that focus on the everyday consequences of cognitive symptoms.

# 6. SUMMARY AND CONCLUSIONS

The main findings of the thesis are as follows:

1) The review of earlier research indicated that OSAS patients do not show impairment in all executive functioning, but some domains are impaired while others are not. However, executive dysfunction seems to persist mostly after CPAP treatment.

2) The original studies of this thesis showed that executive dysfunction is restricted especially on impaired visuospatial organizational skills and set shifting, but based on the normative analysis, most OSAS patients have normal performance and only a minority show dysfunction.

3) Even long-term CPAP treatment does not efficiently improve impaired visuospatial organizational skills and set shifting. In addition, OSAS patients show an impaired learning effect in executive tests. This may be explained by the fact that executive dysfunction and impaired learning skills often overlap.

4) Local sleep depth changes may help to better understand cognitive dysfunction in OSAS. At the same time as OSAS patients show mild visual dysfunction, they have a reduced amount of deep sleep in the right hemisphere. The right hemisphere may be more vulnerable to the harmful effects of OSAS because of its dominance in the vigilance system.

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Acta Neurol Scand 2007: 115: 1–11 DOI: 10.1111/j.1600-0404.2006.00744.x

ACTA NEUROLOGICA SCANDINAVICA

# 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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Key words: executive functions; neuropsychological assessment; obstructive sleep apnea

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Accepted for publication August 9, 2006

## 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 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

**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 (≥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-apnetic 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 reported 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) | 21 |
| | 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) | |
| (b) Semantic | Conceptual semantic knowledge (40) | 3 |
| | Language (53) | |
| | Not specified (50) | |
| Trail Making Test: Trails A and B (14) | Cognitive set shifting and flexibility (43, 49) | 20 |
| | 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) | |
| Digit Span forwards and backwards (65) | Short-term, immediate memory (23, 27, 30, 43, 55) | 14 |
| | 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) | |
| Wisconsin Card Sorting Test (13) | Abstract reasoning ability (39) | 11 |
| | Contextual flexibility, shifting (39, 42) | |
| | Not specified (23, 27, 30, 38, 41, 50–53) | |
| Stroop test (15) | Attentional capacity (18, 23, 27, 30, 46, 48) | 9 |
| | Inhibition (43, 46, 48) | |
| | Not specified (23, 49) | |
| Tower tests (11) | Not specified (23, 27, 30, 51, 53) | 5 |
| Copy of Rey-Osterreith Complex Figure Test (64) | Perceptual organization (42) | 5 |
| | Visuo-constructional abilities (43) | |
| | Not specified (45, 47, 52) | |
| Corsi's block-tapping test (11) | Short-term memory (23, 27, 30, 43) | 5 |
| | Working memory (23, 30) | |
| | Memory efficiency (27) | |
| | Visual attention (42) | |
| Raven's progressive or colored matrices (66, 67) | Nonverbal reasoning (43) | 4 |
| | Reasoning in visuospatial modality (40, 46, 48) | |
| Mazes tests (11) | Planning and problem solving (54) | 4 |
| | Not specified (45, 47, 52) | |
| Double encoding task (e.g. 23) | Short-term memory (23, 27, 30) | 3 |
| | Working memory (23, 30) | |
| | Memory efficiency (27, 30) | |
| 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 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 (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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Original Paper

European Neurology

Eur Neurol 2009;62:237–242
DOI: 10.1159/000232156

Received: March 2, 2009
Accepted: June 3, 2009
Published online: August 6, 2009

# Executive Dysfunction in Patients with Obstructive Sleep Apnea Syndrome

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**Key Words**
Cognition · Executive function · Frontal lobes · Obstructive sleep apnea syndrome

**Abstract**
***Aims:*** To clarify whether patients with obstructive sleep apnea syndrome (OSAS) have executive dysfunction, to identify the domains of executive function affected and to establish the severity of any dysfunction. ***Methods:*** A full-night polysomnography and a comprehensive neuropsychological assessment focusing on executive functions were conducted on 40 newly diagnosed OSAS patients and 20 healthy controls. The severity of dysfunction was analyzed using norm-referenced data. ***Results:*** All patients and controls were men. The groups did not differ statistically significantly in terms of age, education or intelligence quotient. Patients showed poorer performance than controls on the copy of the Rey-Osterrieth Complex Figure test, the Block Design, the Trails B of the Trail Making Test and the Intra-Extra Dimensional Set Shifting test. Based on the normative data, most OSAS patients performed at a normal level, but a few patients had either mild dysfunction (2.5–12.5%) or moderate to severe dysfunction (5–15%). ***Conclusions:*** OSAS patients have lower set-shifting and analysis/synthesis performance than healthy controls. According to the normative data, most patients in the present study had normal performance, but there were also a few patients with more serious deficits.



## Introduction

Obstructive sleep apnea syndrome (OSAS) is a common condition [1] characterized by repetitive episodes of complete (apnea) or partial (hypopnea) obstruction of the upper airway during sleep, resulting in oxygen desaturation and arousal from sleep [2]. OSAS is also associated with cognitive changes. Among the cognitive domains most affected is executive function [3–7].

Executive functions refer to 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 [8]. According to Beebe and Gozal [9], executive functions in the context of OSAS can be divided into 6 domains: behavioral inhibition, set-shifting, self-regulation of affect and arousal, working memory, analysis/synthesis and contextual memory. Executive dysfunction is caused by abnormalities in the frontal cortex or in the dense connections between the frontal cortex and other cortical or subcortical areas [8]. Beebe and Gozal [9] hypothesize that executive functions are easily disturbed in OSAS because nocturnal hypoxemia, hypercarbia and sleep disruption reduce the efficacy of sleep-related restorative processes, and this induces biochemical and cellular alterations, especially in the frontal cortex. However, Verstraeten and co-workers [10–12] point out that earlier studies [13, 14] did not adequately take into account the effects of decreased alertness, and therefore their findings

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of executive dysfunction in OSAS remain tentative. They conclude that executive deficits in OSAS may be explained by reference to attentional capacity deficits, slowed information processing and decreased short-term memory span, and that these cognitive changes may be explained by basal slowing due to sleepiness [10–12].

Many previous studies have assessed OSAS patients' executive functions with only 1 or 2 tests; this is not enough to draw generalizable conclusions about executive functions in OSAS [15]. Only a few previous studies have assessed executive functions more comprehensively [16–21]. To clarify the nature of executive dysfunction in OSAS, it is necessary to evaluate different domains. In a recent meta-analysis of studies in OSAS patients [5], the domain of executive functioning displayed a moderate to large mean effect size, indicating substantial executive dysfunction in OSAS. Effects sizes with control-referenced data were larger than with norm-referenced data [5]. The use of both control- and norm-referenced data in analyzing executive functions in OSAS could help us better understand the quantity of these problems. It is also important to consider the significance of executive dysfunction in OSAS patients' daily life [22], because patients often report initiative problems and changes in work efficiency in particular.

To explore executive functions in OSAS in closer detail, we set out in this study to determine (1) whether OSAS patients have executive dysfunction compared to healthy controls, (2) which, if any, domains of executive function are affected and (3) the severity of any changes observed based on norm-referenced data.

## Subjects and Methods

*Subjects*

The study was conducted in a sleep unit of a university hospital. Patients were referred to the unit because of possible OSAS. The sample included 40 newly diagnosed OSAS patients who met the diagnostic criteria and had not had any previous treatment. The control group consisted of 20 healthy volunteers.

Both the patients and controls were first interviewed by telephone to make sure they met the initial eligibility criteria, i.e., (1) age between 20 and 65 years, (2) right-handedness, (3) no (other) sleep disorders, (4) no clinically significant medical disorder (e.g., neurological illness, psychiatric disorder, hypo-/hyperthyroidism or lung diseases other than currently asymptomatic asthma), (5) no medication affecting the central nervous system, (6) no substance abuse or alcohol abuse based on their own report using the criteria of the World Health Organization for alcohol units and (7) no self-reported primary perception disorder. The patients' OSAS diagnosis and the controls' healthiness were then confirmed by means of a clinical interview and a diagnostic full-night polysomnography in a sleep laboratory. The diagnosis of OSAS was based on a clinical picture and subjective complaints of OSAS [2] and on an apnea/hypopnea index (AHI) >10 per hour of sleep. The controls had to be asymptomatic and have an AHI of ≤5 per hour of sleep. The study protocol was approved by the Hospital District Ethical Committee. The subjects gave their written informed consent.

*Procedure and Measures*

The patients and controls who met the eligibility criteria according to the first-night polysomnography underwent a second full-night polysomnography and a neuropsychological assessment on the following morning. The recordings for the second of the 2 diagnostic nights were used in the analyses. Subjective sleepiness was evaluated with the Epworth Sleepiness Scale (ESS) [23].

*Polysomnography*

Subjects retired to bed between 10:00 and 12:00 PM according to their own habitual bedtimes. Six EEG derivations (Fp1-A2, Fp2-A1, C3-A2, C4-A1, O1-A2 and O2-A1), 2 electro-oculography channels, submental muscle tonus, electrocardiogram, airflow pressure via a nasal transducer, thermistor, thoracoabdominal respiratory movements and blood oxygen saturation were recorded. In addition, transcutaneous carbon dioxide tension, leg movements, body position and body movements were recorded. The second diagnostic night was classified by 2 independent scorers into the old sleep stages from C3-A2 channels [24]. Somnologica® software (Medcare/Flaga, Iceland) was used for visual analyses. The level of agreement between the 2 scorers was 86.0% ($K = 0.76$). Based on the 2 coders' independent scorings, a consensus classification was developed for use in the statistical analyses. AHI was calculated as the number of obstructive apneas and hypopneas per hour of sleep. Obstructive apnea was defined as at least a 90% reduction in the thermal signal amplitude, whereas hypopnea was scored as a respiratory event lasting 10 s or more and presenting a nasal pressure signal drop of 50% or more from baseline with over 3% desaturation or an arousal [25]. Microarousals were scored according to the criteria of the American Sleep Disorders Association [26].

*Neuropsychological Assessment*

Both patients and controls underwent a neuropsychological assessment on the morning after the second night. The assessment was always conducted at the same time. General cognitive performance was assessed with a short form [27] of the Wechsler Adult Intelligence Scale-Revised [28], which included the following subtests: Information, Digit Span, Arithmetics, Similarities, Picture Completion, Block Design and Digit Symbol. The executive tests (table 1) were chosen for inclusive coverage of the different domains of executive functions.

*Statistical Analyses*

Mean values, standard deviations and ranges were used as descriptive values. Since some of the parameters were not normally distributed and the sample sizes were small, nonparametric tests were chosen. The 2 subject groups were compared using the Mann-Whitney U test. The significance level was set at 0.05 for all analyses. All reported p values are based on two-tailed tests.

To evaluate the severity of a possible dysfunction on tests in which the 2 groups differed, norm-referenced analysis was con-

**Table 1.** Assessment of executive functions

| Domain of executive function | Test method |
|---|---|
| Verbal short-term memory span | Digit Span forwards [28] |
| Verbal working memory | Digit Span backwards [28] |
| Visual short-term memory span | Spatial Span[1]: span length |
| Visual working memory | Spatial Working Memory[1]: strategy |
| Verbal fluency | semantic: animals [8] |
| | phonological: letters PAS (Finnish version of FAS) [8] |
| Visuospatial organizational skills | copy of the Rey-Osterrieth Complex Figure Test (ROCFT) [30] |
| | Block Design [28] |
| Visuomotor tracking | Digit Symbol [28] |
| | Trails A of Trail Making Test: time [31] |
| Mental set-shifting | Trails B of Trail Making Test: time [31] |
| | Intra-Extra Dimensional Set-Shifting[1]: stages completed and errors |
| Planning and problem-solving | Stockings of Cambridge[1]: problems solved in minimum moves |

[1] Subtest of the Cambridge Neuropsychological Test Automated Battery.

ducted using the Wechsler Adult Intelligence Scale-Revised manual [28], the meta-analysis of Mitrushina et al. [29] and normative data from the Cambridge Neuropsychological Test Automated Battery. Performances on the Rey-Osterrieth Complex Figure Test [30], the Block Design [28] and the Intra-Extra Dimensional Set Shifting (IED; Cambridge Neuropsychological Test Automated Battery) were corrected for age, and performance on the Trails B of the Trail Making Test [31] was corrected for both age and education. In this study, the scores were scaled as follows: Z values equal to or smaller than –3 were considered indicative of severe deficit; Z values from –2.99 to –2 were indicative of moderate deficit, and Z values from –1.99 to –1 were indicative of mild deficit. Scores equal to or greater than –0.99 were considered to demonstrate normal performance.

## Results

All patients and controls were men. The patients' mean age was 47 years (range 28–65) and that of the controls was 43 years (range 29–63). The mean length of education for patients was 13 years (range 5–17), and for controls it was 14 years (range 8–17). The groups did not differ statistically significantly in terms of age or education. The patients were sleepier, as assessed with the ESS, and had a higher body mass index (BMI) than controls (table 2). The patients had mild to severe OSAS with sleep fragmentation and hypoxemic episodes. The values for subjective sleepiness, BMI and polysomnographic data are presented in table 2.

The mean intelligence quotient (IQ) for patients was 111 (range 94–132), and for controls it was 118 (range 104–137); this difference was nonsignificant. The results of the executive tests are presented in table 3. The patients had poorer scores than controls on the copy of the Rey-Osterrieth Complex Figure Test, the Block Design, the Trails B of Trail Making Test and the IED levels completed. On the IED, all controls performed at the optimal level, completing 9 levels, while 8 of the OSAS patients showed difficulties and completed only 7 or 8 levels. The number of errors on the IED did not differ significantly between the groups. The severity of executive dysfunction from these 4 tests is presented in table 4. Most OSAS patients did not show any deficits on these tests based on the normative values, while a few patients showed either mild deficits or moderate to severe deficits. Although patients performed worse than controls on the Block Design, almost every patient had normal normative performance on this test. For 4 of the 40 patients, test performance was lower on more than 1 test.

The 9 patients who showed moderate to severe deficits were compared to the 31 patients who performed at a normal normative level or who showed only mild deficits with regard to age, years of education, ESS, BMI, IQ and polysomnographic variables (AHI, arousal index, oxygen desaturation index, total sleep time, sleep efficiency as a percentage of the total sleep time, percentages of sleep stage 1, sleep stage 2, slow wave sleep and rapid eye movement sleep). No statistically significant differences were found between these groups.

**Table 2.** Results of subjective sleepiness, obesity and polysomnographic variables in patients and controls

| | Patients (n = 40) | Controls (n = 20) | p value |
|---|---|---|---|
| ESS score | 11.5 ± 3.8 (4–18) | 4.5 ± 2.8 (0–11) | <0.001 |
| BMI | 30.3 ± 4.6 (24–41) | 24.9 ± 2.7 (20–30) | <0.001 |
| TST | 426.9 ± 49.8 (325–532) | 419.4 ± 54.7 (328–527) | n.s. |
| SEI, % | 90.3 ± 6.2 (74–100) | 89.6 ± 7.0 (74–98) | n.s. |
| AHI, n/h | 41.0 ± 22.8 (10–103) | 2.5 ± 2.1 (0–5) | <0.001 |
| ARI, n/h | 33.8 ± 19.2 (8–100) | 13.0 ± 4.4 (4–23) | <0.001 |
| ODI4%, n/h | 26.0 ± 22.3 (0–88) | 0.8 ± 1.4 (0–6) | <0.001 |
| S1, % | 6.1 ± 3.9 (1–23) | 6.3 ± 3.6 (2–16) | n.s. |
| S2, % | 68.2 ± 9.7 (48–85) | 60.5 ± 7.7 (45–72) | 0.005 |
| SWS, % | 8.2 ± 7.0 (0–23) | 13.8 ± 6.8 (2–25) | 0.005 |
| REM, % | 17.6 ± 5.0 (6–28) | 19.4 ± 4.7 (13–28) | n.s. |

Values shown are means ± standard deviations (ranges in parentheses). TST = Total sleep time; SEI = sleep efficiency index as a percentage of the total sleep time; ARI = arousal index; ODI4% = oxygen desaturation index; S1 = sleep stage 1 as a percentage of total sleep time; S2 = sleep stage 2 as a percentage of total sleep time; SWS = slow wave sleep as a percentage of total sleep time; REM = rapid eye movement sleep as a percentage of total sleep time; n.s. = not significant.

**Table 3.** Results of executive tests in patients and controls

| | Patients (n = 40) | Controls (n = 20) | p value |
|---|---|---|---|
| Digit Span forwards | 6.9 ± 1.6 (4–10) | 7.1 ± 1.9 (4–11) | n.s. |
| Digit Span backwards | 6.6 ± 1.3 (4–10) | 6.7 ± 1.6 (4–10) | n.s. |
| Spatial Span | 6.6 ± 1.4 (3–9) | 7.1 ± 1.4 (5–9) | n.s. |
| Spatial Working Memory | 30.6 ± 6.6 (19–43) | 29.5 ± 6.9 (19–41) | n.s. |
| Semantic fluency | 24.8 ± 5.0 (13–34) | 25.6 ± 4.4 (16–31) | n.s. |
| Phonological fluency | 39.7 ± 11.2 (18–74) | 42.2 ± 11.2 (27–59) | n.s. |
| ROCFT | 33.6 ± 2.7 (26–36) | 35.1 ± 1.0 (33–36) | 0.041 |
| Block Design | 33.2 ± 8.3 (14–49) | 39.1 ± 8.5 (23–51) | 0.021 |
| Digit Symbol | 45.4 ± 11.6 (25–86) | 54.0 ± 15.5 (33–88) | n.s. |
| Trails A | 31.5 ± 13.6 (17–73) | 32.0 ± 10.6 (14–61) | n.s. |
| Trails B | 73.0 ± 47.4 (42–238) | 61.5 ± 32.5 (31–159) | 0.019 |
| IED stages | 8.6 ± 0.7 (7–9) | 9.0 ± 0.0 (9) | 0.021 |
| IED errors | 18.1 ± 11.5 (7–45) | 13.0 ± 6.4 (7–28) | n.s. |
| Stockings of Cambridge | 9.7 ± 1.9 (3–12) | 9.9 ± 2.1 (5–12) | n.s. |

Values shown are means ± standard deviations (ranges in parentheses). ROCFT = Copy of Rey-Osterrieth Complex Figure Test; n.s. = not significant.

## Discussion

OSAS patients had lower visuospatial organizational skills and mental set-shifting performance than controls. When performance in these executive domains was compared to the normative data, most OSAS patients showed normal performance, but a few patients had either mildly impaired performance or moderate to severe deficits. Controls performed otherwise at a normal normative level, but 20% of them had mildly impaired performance on the time-limited mental set-shifting task.

Our results regarding the lower visuospatial organizational skills of OSAS patients are in line with earlier findings [13, 19, 21]. In contrast, our finding of reduced mental set-shifting performance as measured by the Trails B has previously been reported only in a study by Bedard et al. [13]; most earlier studies reported no change on this test [16–19, 21]. In this study, we controlled for possible

**Table 4.** Severity of executive dysfunction based on Z values in OSAS patients and healthy controls

| | Normal (Z >–1) | Mild (–2 < Z ≤ –1) | Moderate (–3 < Z ≤ –2) | Severe (Z ≤–3) |
|---|---|---|---|---|
| *Patients (n = 40)* | | | | |
| ROCFT | 33 (82.5) | 5 (12.5) | 1 (2.5) | 1 (2.5) |
| Block Design | 39 (97.5) | 1 (2.5) | – | – |
| Trails B | 29 (72.5) | 5 (12.5) | 1 (2.5) | 5 (12.5) |
| IED stages[1] | 31 (77.5) | 5 (12.5) | 3 (7.5) | – |
| *Controls (n = 20)* | | | | |
| ROCFT | 20 (100) | – | – | – |
| Block Design | 20 (100) | – | – | – |
| Trails B | 16 (80) | 4 (20) | – | – |
| IED stages | 20 (100) | – | – | – |

Values shown are numbers of patients/controls (percentages in parentheses). ROCFT = Copy of Rey-Osterrieth Complex Figure Test.

[1] One missing value.

attentional capacity deficit, e.g. slowed information processing, by including in the test battery not only an executive subtest (Trails B), but also a subtest that measures attentional capacity (Trails A), as Verstraeten and coworkers [10–12] have recommended. The groups did not differ on Trails A, but on Trails B, the OSAS patients showed poorer performance. This suggests that executive dysfunction such as decreased mental set-shifting occurs in OSAS patients and that it is not explained by slowed processing speed only. However, it is noteworthy that some of the controls in our study had mildly reduced performance on Trails B based on the normative data. It is possible that there is wide variety in performance on this test even in the healthy population.

Our finding of lower mental set-shifting in OSAS patients is also supported by their reduced performance on the IED. The IED is used to assess similar executive function to the well-known Wisconsin Card Sorting Test [32]. Earlier studies have reported that OSAS patients have impaired mental set-shifting performance as assessed by the Wisconsin Card Sorting Test, either in terms of the stages completed [16, 19] or in the number of perseverative errors [16–18].

Our results did not confirm the results of Naëgele et al. [16] and Feuerstein et al. [17] that OSAS patients have impaired working memory. This may be due to the insensitivity of the working memory tasks used in this study. N-back working memory tasks seem to be more sensitive in detecting working memory deficits in OSAS [33, 34]. In addition, our results did not indicate reduced verbal fluency in OSAS patients. Earlier results concerning verbal fluency are inconsistent; some studies report impaired verbal fluency [18, 20, 21], while others do not [16, 17, 19]. Our result of normal performance for planning abilities, assessed by the Stockings of Cambridge test, is in line with earlier findings [17, 18]. However, Naëgele et al. [16] reported partly impaired performance on a Tower test [8].

Based on the model of Beebe and Gozal [9], our results show that when compared to the control-referenced data, executive functions of OSAS patients are partly impaired, as are set-shifting and analysis/synthesis performance. However, when compared to the norm-referenced data, most OSAS patients perform at the normal level and only some patients have executive dysfunction. Although patients with executive dysfunction seem to be a minority, it is important to detect these patients because even mild executive dysfunction may have a negative impact on patients' working ability, and moderate to severe deficits may cause definite problems in daily life. These patients cannot be detected on the basis of their background data; our patients with moderate to severe executive dysfunction did not differ from those with normal performance or only mildly impaired performance in terms of age, education, IQ, ESS, BMI or conventional polysomnographic variables. It seems obvious that cognitive dysfunction in OSAS is a multifactorial phenomenon. Sleepiness, sleep fragmentation, hypoxemia and hypercarbia may all have an impact on cognitive function [3, 9, 12, 22]. In addition, cognitive problems may also be increased by other OSAS-related health problems like obesity, hypertension, metabolic syndrome, diabetes and increased risk of cerebrocardiac vascular problems [35].

There is a connection between OSAS and executive dysfunction, but it is not possible to draw any conclusion about the causality. OSAS may cause cognitive dysfunction, but it is also possible that prior cognitive dysfunction can predispose individuals to poor health habits and increase the risk of developing OSAS. To the best of our knowledge, our patients did not have prior cognitive dysfunction. Because patients are not usually assessed neuropsychologically prior to diagnosis with OSAS, age, education and IQ are the variables that can be used to evaluate their premorbid cognitive skills. Thus, one of the strengths of our study is that the patients and controls did not differ significantly in terms of age, years of education or IQ, which adds to the reliability of the results. Older age may contribute to poorer cognitive performance because of higher cerebrovascular risks or additionally disturbed sleep [36]. By contrast, higher education level and

IQ can protect from cognitive changes [37]. A limitation of this study is that the effect of executive dysfunction on patients' daily performance was not investigated in detail. To conclude, not all OSAS patients have executive dysfunction but there are some patients who do suffer more serious deficits.


## Acknowledgements

This study was financially supported by grants from the University of Tampere, Tampere University Hospital, and the Finnish Cultural Foundation.


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Original Paper

European Neurology

Eur Neurol 2010;63:215–220
DOI: 10.1159/000278301

Received: September 29, 2009
Accepted: January 11, 2010
Published online: March 9, 2010

# Executive Dysfunction and Learning Effect after Continuous Positive Airway Pressure Treatment in Patients with Obstructive Sleep Apnea Syndrome

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**Key Words**
Continuous positive airway pressure · Executive functions · Learning effect · Obstructive sleep apnea syndrome

**Abstract**
***Aims:*** To assess the impact of continuous positive airway pressure (CPAP) treatment on executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS). ***Methods:*** At baseline, 20 OSAS patients and 17 healthy controls underwent polysomnography and neuropsychological assessment focusing on executive functions. After at least 6 months of CPAP treatment, the patients returned for one more full-night polysomnography and neuropsychological control assessment, while the controls underwent a neuropsychological control assessment. ***Results:*** All patients and controls were working-age males. OSAS severity ranged from mild to severe. Before CPAP, patients showed poorer performance than controls in the copy of the Rey-Osterrieth Complex Figure Test, the Block Design, the Digit Symbol, the Trails B and the Intra-Extra Dimensional Set-Shifting task. Patients' executive performance showed no improvement after CPAP, and it remained poorer than the performance of controls. In addition, patients showed no learning effect in the executive tests, whereas the controls did. ***Conclusion:*** Even long-term CPAP treatment does not seem to improve OSAS patients' mental set-shifting performance or their visuospatial organizational skills. In addition, OSAS patients have impaired learning effect in executive tests.



## Introduction

Obstructive sleep apnea syndrome (OSAS) is associated with cognitive changes, especially executive dysfunction [1, 2]. Beebe and Gozal [3] argue that executive functions may be easily disturbed in OSAS because hypoxemia, hypercarbia and sleep disruption reduce sleep-related restorative processes and cause biochemical and cellular alterations especially in the frontal brain areas. Executive functions refer to a person's ability to engage successfully in adaptive, independent, purposive and self-serving behavior [4]. Earlier studies have reported decreased mental set-shifting performance, visuospatial organizational skills [5–8], behavioral inhibition [6, 7, 9], and reduced working memory in OSAS patients [6, 7, 10, 11].

It seems that executive dysfunction can be partially reversed with continuous positive airway pressure

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(CPAP) treatment [2, 12]. Seven out of the 15 studies reviewed by Aloia et al. [2] showed improved executive function after CPAP treatment. However, the evidence is inconsistent; some studies report an improvement in executive domains with CPAP [5–7], while others do not [9]. Most placebo-controlled studies report that CPAP does not have a greater effect on executive functioning than placebo treatment [13–16]. Only a few studies have shown the opposite result [17–19].

There is then still no consensus on the long-term impact of CPAP on executive dysfunction. The effects of CPAP are sensitive to the duration of the treatment and to compliance [20]. In placebo-controlled studies, treatment is usually provided from 1 to 8 weeks, which is not necessarily enough to see an improvement in the complex cognitive domain that is executive functioning. There are only a few earlier studies that have explored OSAS patients' executive dysfunction in greater depth, based on CPAP treatment periods of 4 months or longer [5–7, 9].

In our recent study [8], OSAS patients showed lower mental set-shifting and visuospatial organizational skills than healthy controls. Our focus here is on the impact of CPAP treatment on the observed dysfunction after at least 6 months of treatment. Furthermore, possible learning effects in executive tests are investigated using a healthy control group at follow-up assessment.

## Subjects and Methods

The subjects for this study were drawn from the same set of 40 patients whose pretreatment executive functioning was investigated in our recent study [8]. The inclusion criteria were CPAP use at least 4 h per night and at least 5 nights per week over a period of 6 months or longer. Twenty patients met the inclusion criteria, and 20 patients were excluded from post-treatment follow-up because of inadequate CPAP use. The control group was drawn from the same set of 20 healthy controls recruited in our recent study. After an interval of at least 6 months, 17 controls returned for a neuropsychological control assessment; 3 refused to take part.

Both the patients and controls were first interviewed by telephone to make sure they met the initial eligibility criteria: (a) age between 20 and 65 years, (b) right-handedness, (c) no (other) sleep disorders, (d) no clinically significant medical disorder (e.g. neurological illness, psychiatric disorder, hypo-/hyperthyroidism or other lung diseases than currently asymptomatic asthma), (f) no medication affecting central nervous system, (g) no substance abuse or alcohol abuse based on their own report using the criteria of WHO for alcohol units, and (h) no self-reported primary perception disorder. The patients' OSAS diagnosis and the controls' healthiness were then confirmed with a clinical interview and diagnostic full-night polysomnography in a sleep laboratory. The diagnosis of OSAS was based on a clinical picture and subjective complaints of OSAS [21] and on an apnea/hypopnea index (AHI) >10 per hour of sleep. The controls had to be asymptomatic and to have an AHI of ≤5 per hour of sleep. The study was performed in a university hospital and the protocol was approved by the Hospital District Ethics Committee. The subjects gave their written informed consent.

*Procedure and Measures*

At baseline, patients and controls who according to the first night polysomnography met the eligibility criteria underwent a second full-night polysomnography and a neuropsychological assessment focusing on executive functions the following morning. The recordings for the latter polysomnography were used in the analyses. Subjective sleepiness was evaluated with the Epworth Sleepiness Scale [22].

After at least 6 months of CPAP treatment, patients returned for full-night polysomnography (the treatment night) and a neuropsychological control assessment the following morning. Prior to the treatment night, objective compliance measures were downloaded from CPAP units showing the mean hours per night from the past 30 days. In addition, to ensure at least minimum compliance for the whole treatment period, the downloadings were performed 2–3 times during the treatment at nurse controls. The controls underwent a neuropsychological control assessment after an interval of at least 6 months from the baseline assessment.

*Polysomnography*

The second diagnostic night was classified by 2 independent scorers into sleep stages according to the rules presented in the manual by Rechtschaffen and Kales [23]. Visual analyses were performed using Somnologica® software (Medcare/Flaga, Iceland). Statistical analyses were conducted on the basis of the consensus scoring of the 2 independent coders. AHI was calculated as the number of obstructive apneas and hypopneas per hour of sleep. Obstructive apnea was defined as a thermal signal amplitude reduction of at least 90%, and hypopnea as a respiratory event lasting 10 s or more and presenting a nasal pressure signal drop of 50% or more from baseline with over 3% desaturation or an arousal [24]. Microarousals were scored according to the criteria of the American Sleep Disorders Association [25].

*Neuropsychological Assessment*

General cognitive performance was assessed using a short form [26] of the Wechsler Adult Intelligence Scale-Revised [27], which included the following subtests: Information, Digit Span, Arithmetics, Similarities, Picture Completion, Block Design and Digit Symbol. Among the executive domains, short-term memory span was assessed with the Digit Span forwards and the Spatial Span (SSP, span length) of the Cambridge Neuropsychological Test Automated Battery (CANTAB). Working memory was assessed with the Digit Span backwards and the Spatial Working Memory (strategy) of CANTAB. Verbal fluency assessment comprised both semantic (animals) and phonological fluency (letters: PAS, a Finnish version of FAS) [4]. Visuospatial organizational skills were assessed with the Rey-Osterrieth Complex Figure Test (ROCFT) [28] and the Block Design. Visuomotor tracking evaluation was based on Trails A of the Trail Making Test [29] and the Digit Symbol. Mental set-shifting was assessed with Trails B of the Trail Making Test and the Intra-Extra Dimensional Set-Shift-

**Table 1.** Mean ± SD and range of subjective sleepiness, obesity and polysomnographic variables in controls and patients before (pre-CPAP) and after (post-CPAP) CPAP treatment and comparisons

| | Controls: baseline (A) | Patients: pre-CPAP (B) | Patients: post-CPAP (C) | A vs. B[1] | B vs. C[2] |
|---|---|---|---|---|---|
| ESS | 3.8 ± 2.3 (0–9) | 12.4 ± 3.8 (5–18) | 7.5 ± 3.9 (1–17) | <0.001 | 0.002 |
| BMI | 24.4 ± 2.5 (20–28) | 31.0 ± 4.6 (25–41) | 31.0 ± 5.1 (21–41) | <0.001 | NS |
| TST | 428.2 ± 54.1 (328–527) | 434.8 ± 51.8 (375–532) | 400.3 ± 55.7 (264–503) | NS | 0.009 |
| SEI, % | 89.7 ± 6.9 (74–98) | 90.1 ± 6.4 (80–98) | 87.9 ± 9.7 (58–97) | NS | NS |
| AHI, n/h | 2.9 ± 2.0 (0–5) | 47.9 ± 24.3 (14–103) | 2.1 ± 3.6 (0–14) | <0.001 | <0.001 |
| ARI, n/h | 13.1 ± 4.7 (4–23) | 38.1 ± 21.9 (8–100) | 15.4 ± 6.0 (5–27) | <0.001 | <0.001 |
| ODI4%, n/h | 0.9 ± 1.5 (0–6) | 33.0 ± 24.2 (0–88) | 0.8 ± 0.8 (0–3) | <0.001 | <0.001 |
| S1% | 6.6 ± 3.8 (2–16) | 5.1 ± 2.5 (1–11) | 6.1 ± 3.6 (2–16) | NS | NS |
| S2% | 59.8 ± 7.2 (45–72) | 73.1 ± 6.9 (60–85) | 67.0 ± 8.3 (47–79) | <0.001 | 0.005 |
| SWS% | 14.2 ± 5.9 (5–25) | 4.4 ± 4.6 (0–14) | 9.2 ± 7.9 (1–29) | <0.001 | 0.002 |
| REM% | 19.5 ± 5.0 (13–28) | 17.5 ± 4.9 (9–27) | 17.7 ± 4.6 (11–26) | NS | NS |

ESS = Epworth Sleepiness Scale; TST = total sleep time in minutes; SEI = sleep efficiency index of TST; ARI = arousal index; ODI4% = oxygen desaturation index; S1% = sleep stage 1 percentage of TST; S2% = sleep stage 2 percentage of TST; SWS% = slow wave sleep percentage of TST; REM% = rapid eye movement sleep percentage of TST.

[1] Mann-Whitney U test. [2] Wilcoxon test; p values.

ing (IED, stages completed and errors) of CANTAB. Planning and problem solving was assessed with Stockings of Cambridge (SOC, problems solved) of CANTAB.

*Statistical Analyses*

Mean values, standard deviations (SD) and ranges were used as descriptive values. Since some of the parameters were not normally distributed and the sample sizes were small, the decision was made to use nonparametric tests. The patient and control groups were compared using the Mann-Whitney U test. Comparisons within these two study groups from baseline to follow-up assessment were performed using the Wilcoxon test. The significance level was set at 0.05 for all analyses, values from 0.05 to 0.1 were considered to show a tendency towards a significant result. All reported p values are based on two-tailed tests.

## Results

*Pre-CPAP*

The mean age for the 20 OSAS patients was 50 years (range 37–65) and for the 17 controls 44 years (range 30–63). The patient group was slightly older than the control group (p = 0.049). The mean length of education for patients was 13 years (range 5–17) and for controls 14 years (range 8–17); this difference was not significant. The values for subjective sleepiness, body mass index (BMI) and polysomnographic data are presented in table 1. Patients were sleepier than controls as assessed with the Epworth Sleepiness Scale, and more obese than controls. Patients had mild to severe OSAS with fragmented sleep and hypoxemic events. Nine patients did not have any medication, 6 patients had medication for hypertension, 4 patients had medication for high cholesterol, and 1 patient had antiaggregation medication. None of the controls had medication.

Mean IQ was 115 (range 99–125) for patients and 118 (range 104–137) for controls; this difference was nonsignificant. The results of the executive tests (table 2) showed that newly diagnosed OSAS patients performed more poorly in the ROCFT, Block Design, Trails B and IED (stages completed). All controls performed at optimal level in the IED, reaching 9 stages, while 6 patients reached only 7 or 8 levels. Patients also performed more poorly in the Digit Symbol, and the difference between the groups in the SSP showed a tendency towards statistical significance.

*Post-CPAP*

Mean CPAP adherence was 6.2 h per night (range 4.3–8.6), and the mean duration of CPAP treatment was 7.4 months (range 6–12). Neuropsychological follow-up assessment of the controls was conducted on average 7.2 months (range 6–12) after the baseline assessment. The interval between the baseline and follow-up assessments did not differ between the two groups. Patients' post-CPAP values for subjective sleepiness, BMI and polysomnographic data are presented in table 1. Subjective sleepi-

**Table 2.** Mean ± SD and range of executive tests in controls at baseline and at follow-up and in patients before (pre-CPAP) and after (post-CPAP) CPAP treatment and comparisons

| | Controls: baseline (A) | Controls: follow-up (B) | Patients: pre-CPAP (C) | Patients: post-CPAP (D) | A vs. C[1] | B vs. D[1] | A vs. B[2] | C vs. D[2] |
|---|---|---|---|---|---|---|---|---|
| Digit span (f) | 7.0 ± 2.0 (4–11) | 6.7 ± 2.5 (4–10) | 7.0 ± 1.7 (4–10) | 7.0 ± 1.7 (3–10) | NS | NS | NS | NS |
| Digit span (b) | 6.8 ± 1.6 (4–10) | 7.5 ± 1.8 (5–12) | 6.8 ± 1.3 (4–9) | 6.7 ± 1.8 (3–10) | NS | NS | NS | NS |
| SSP | 7.3 ± 1.4 (5–9) | 7.7 ± 1.3 (5–9) | 6.6 ± 1.2 (5–8) | 6.6 ± 1.3 (5–9) | (0.070) | 0.011 | NS | NS |
| SWM | 28.7 ± 6.9 (19–39) | 28.0 ± 6.0 (19–37) | 30.1 ± 7.5 (19–43) | 30.7 ± 7.4 (19–42) | NS | NS | NS | NS |
| Fluency (s) | 25.7 ± 4.7 (16–31) | 24.1 ± 4.1 (18–31) | 24.4 ± 4.7 (16–34) | 24.2 ± 5.2 (15–34) | NS | NS | NS | NS |
| Fluency (p) | 42.1 ± 11.9 (27–59) | 46.2 ± 13.7 (20–79) | 42.9 ± 13.1 (29–74) | 42.6 ± 12.2 (23–66) | NS | NS | NS | NS |
| ROCFT | 35.2 ± 0.9 (34–36) | 35.3 ± 1.0 (33–36) | 33.5 ± 2.4 (29–36) | 34.1 ± 2.2 (28–36) | 0.018 | 0.047 | NS | NS |
| Block design | 40.5 ± 8.3 (23–51) | 43.4 ± 9.3 (22–51) | 34.5 ± 9.3 (14–49) | 34.4 ± 9.7 (15–49) | 0.039 | 0.002 | 0.014 | NS |
| Digit symbol | 57.0 ± 14.9 (35–88) | 59.7 ± 12.5 (39–78) | 45.2 ± 10.8 (28–66) | 45.9 ± 11.8 (23–67) | 0.011 | 0.003 | (0.093) | NS |
| Trails A | 31.9 ± 11.5 (14–61) | 25.8 ± 6.7 (16–39) | 36.6 ± 13.0 (19–66) | 35.6 ± 15.4 (16–76) | NS | 0.025 | 0.024 | NS |
| Trails B | 65.4 ± 30.7 (31–128) | 61.1 ± 30.9 (35–153) | 89.4 ± 47.4 (42–230) | 78.6 ± 30.9 (38–161) | 0.034 | 0.022 | NS | NS |
| IED stages | 9.0 ± 0.0 (9–9) | 9.0 ± 0.0 (9–9) | 8.6 ± 0.7 (7–9) | 8.4 ± 1.5 (3–9) | 0.013 | (0.062) | NS | NS |
| IED errors | 13.1 ± 6.8 (7–28) | 9.4 ± 2.6 (7–18) | 20.0 ± 14.2 (7–45) | 17.1 ± 10.9 (6–39) | NS | (0.054) | NS | NS |
| SOC | 10.1 ± 1.9 (6–12) | 10.6 ± 2.2 (5–12) | 9.6 ± 2.2 (3–12) | 9.4 ± 1.9 (5–12) | NS | 0.021 | (0.051) | NS |

p values in parentheses refer to values showing a tendency towards statistically significant difference. f = Forwards; b = backwards; SWM = spatial working memory; s = semantic; p = phonological.

[1] Mann-Whitney U test. [2] Wilcoxon test; p values.

ness decreased. BMI did not change significantly. Slow wave sleep as a proportion of total sleep time increased, while the proportion of sleep stage 2 decreased. Total sleep time (in minutes) also decreased. Respiratory deficits, arousals and hypoxemic events normalized.

Comparing patients' post-CPAP results with the follow-up results for controls, patients continued to show poorer performance than controls in the ROCFT, Block Design, Digit Symbol and Trails B. The difference between the two groups in the IED showed a tendency towards statistically significant poorer performance for patients. Again, all controls performed in the IED at optimal level, reaching 9 stages, while 1 of the patients now reached only 3 stages, and 3 patients reached 7 stages. In addition, patients now performed more poorly than controls in the Trails A, SSP and SOC. These differences were not statistically significant at the baseline assessment. No significant changes were seen in the patients' executive test performance from pre-CPAP assessment to post-CPAP assessment in any test. The controls' performance, on the other hand, improved statistically significantly from baseline to follow-up assessment in the Block Design and Trails A. Controls also showed a tendency towards statistically significant improvement from baseline to follow-up assessment in the Digit Symbol and SOC.

## Discussion

In this study, we set out to investigate the impact of CPAP treatment on executive dysfunction in OSAS patients. Before CPAP treatment, OSAS patients showed mildly impaired mental set shifting performance and visuospatial organizational skills compared to healthy controls, which is in line with our earlier results with a larger patient sample [8]. After at least 6 months of CPAP treatment, OSAS patients' executive performance showed no improvement and they continued to perform more poorly than healthy controls. In addition, OSAS patients showed no learning effect in executive tests, while healthy controls did.

Our findings confirm the results of earlier studies according to which executive functions are not totally reversible even with long-term CPAP treatment [5–7, 9]. Our result which showed persisting decline in mental set-shifting is in line with the finding of Bédard et al. [5], who reported that impaired performance in the Trails B remained after 6 months of CPAP treatment. Feuerstein et al. [6] and Naegelé et al. [7], by contrast, reported that OSAS patients' mental set-shifting performance normalized after CPAP treatment lasting 4–6 months. In their studies, mental set-shifting was assessed with the Wisconsin Card Sorting Test [30], which is used to measure

similar executive functions as are assessed with the IED used in our study. Our findings of persisting decline in visuospatial organizational skills are supported by the results of Ferini-Strambi et al. [9], who reported that among other executive domains, performance in the ROCFT and Block Design remained impaired both after short-term (15 days) and long-term (4 months) CPAP treatment. However, in contrast to our findings, Bédard et al. [5] reported a normalization of both visuospatial organizational skills and visuomotor tracking after 6 months of CPAP. In placebo-controlled studies, Engleman et al. [17, 18] reported that CPAP produced a greater improvement in mental set-shifting as assessed with the Trails B than did placebo treatment. However, most placebo-controlled studies have found no improvement in either mental set-shifting performance or in visuospatial organizational skills over placebo [13, 14, 16, 19].

There are several possible explanations for the inconsistent evidence regarding the impact of CPAP on executive dysfunction. Firstly, executive functions are measured using different tests and therefore the results are not directly comparable. Secondly, the neuropsychological tests used in clinical practice are not necessarily sensitive enough to detect positive treatment effects, especially in patients with high mental functioning [31]. Recent studies [10, 16] have shown that more complex neuropsychological tasks (e.g. PASAT, n-back working memory tasks and Digit Vigilance) [4] that require cognitive processing speed, vigilance and working memory seem to be more sensitive to the effects of CPAP. Thirdly, the comparability of results is affected by the heterogeneity of patient samples and by the differences in CPAP treatment adherence and duration.

A noteworthy finding in our results is that OSAS patients showed no learning effect in executive tests, while healthy controls did. Executive tests are 'one-shot' tests based on novelty and strategy formation [32], and the learning effect may be significant when retesting OSAS patients after CPAP treatment. Especially in measurements of the short-term effects of CPAP, OSAS patients seem to improve their performance over time, and without placebo control this improvement may be misattributed to CPAP [16]. Earlier studies focusing on the long-term effects of CPAP on cognitive and executive functions [5–7, 9] have not used comparison groups after CPAP, but parallel or alternative test versions to decrease the learning effect. However, this is not necessarily enough; when a patient figures out the basic idea of the test, that may be much easier to do the second time round, even if the material is different from the original test. Our finding that healthy controls could improve their performance while OSAS patients could not, raises the possibility that OSAS patients are less well equipped to learn from experience. This may have to do with the fact that executive dysfunction and long-term memory deficits often overlap: OSAS patients may have poorer learning and memory skills because due to frontal dysfunction, they have deficits in memory organization [33]. The recording of new experiences and consolidation of declarative memories are dependent on the cooperation of prefrontal and hippocampal functions, and this process can easily be disrupted by inadequate sleep, especially the lack of slow wave sleep [34] that is seen in OSAS patients.

Cognitive dysfunction in OSAS seems to be a multifactorial phenomenon. Sleepiness, sleep fragmentation, hypoxemia and hypercarbia may all have an impact on cognitive function [3, 35]. In our study group, OSAS patients' disease severity based on AHI was mainly moderate to severe, and it is possible that this made our patients more vulnerable to cognitive changes. Cognitive problems may also be increased by OSAS-related health problems like obesity, hypertension, metabolic syndrome, diabetes and increased risk for cerebrocardiac vascular problems [36]. Comorbidity was seen also in our patient group; half of the OSAS patients had medication for hypertension, high cholesterol or antiaggregation medication.

In this study we took the decision to use a healthy control group not only at baseline, but at the follow-up assessment as well. This allowed us to control the impact of any learning effect on executive test performance. One limitation of our study is that patients who used CPAP adequately tended to be older than those who did not. However, the two groups did not differ in terms of their education or IQ. In addition, the pretreatment findings regarding OSAS patients' poorer performance in mental set-shifting and visuospatial organizational skills were mostly the same as in our previous studies with age-matched study groups [8]. Another limitation is that the study groups had differences in their sleep condition prior to the neuropsychological control assessment. This may have some effect on patients' cognitive performance on the next morning because of generally poorer sleep quality under laboratory conditions. This may be particularly true in tasks that require cognitive processing speed (e.g. Trails A). However, we believe that an impaired learning effect in executive tests is affected mainly by long-term effects of OSAS. Based on our relatively small sample size, we assume that although CPAP may generally have a positive influence on OSAS patients' ex-

ecutive dysfunction, it seems to have only a minor effect on the mild decline seen in their mental set-shifting and visuospatial organizational skills. Our finding of OSAS patients' impaired learning in executive tests should be investigated more thoroughly.


## Acknowledgments

The study was supported by grants from the University of Tampere, Tampere University Hospital and the Finnish Cultural Foundation.


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# Visual Dysfunction and Computational Sleep Depth Changes in Obstructive Sleep Apnea Syndrome

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Key Words

Cognitive Performance
Continuous Positive Airway Pressure
Deep Sleep
Electroencephalography
Obstructive Sleep Apnea Syndrome

**ABSTRACT**

The aims of this study are to clarify whether patients with obstructive sleep apnea syndrome (OSAS) have a decline in verbally or visually-based cognitive abilities and whether the possible decline is related to particular sleep depth changes. In addition, the effect of continuous positive airway pressure (CPAP) on the possible changes is investigated. Fifteen OSAS patients and 15 healthy controls joined two full-night polysomnographies, including a computational measure of deep sleep percentage (DS%) bilaterally from the frontal, central and occipital channels, and a neuropsychological assessment. After a 6-month CPAP the patients underwent one more full-night polysomnography with computational DS% analysis and a neuropsychological assessment.

At the baseline, the OSAS patients had poorer performance in the Picture Completion, in the Digit Symbol and in copying the Rey-Osterrieth Complex Figure Test (ROCFT) compared to the controls. The patients also showed reduced DS% in all 6 electrographic (EEG) channels compared to controls. The patients had an inter-hemispheric difference showing less deep sleep in the right hemisphere than in the left hemisphere both frontopolarly and centrally, while the controls showed this inter-hemispheric difference only frontopolarly. After CPAP the patients still had poorer performance in the Picture Completion and in the ROCFT. The patients continued to show reduced DS% in all 3 channels of the right hemisphere and occipitally in the left hemisphere, also the inter-hemispheric difference frontopolarly and centrally remained. OSAS patients have mild visually based cognitive dysfunction and reduced amount of deep sleep in the right hemisphere even after CPAP.

**INTRODUCTION**

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of complete (apnea) and partial (hypopnea) obstructions of the upper airway during sleep and results in oxygen desaturation and fragmented sleep.[1] OSAS is associated with cognitive decline. Deficits in executive functions, information processing speed, vigilance and long-term memory are the most obvious.[2-4] In contrast, the findings of changes in verbal and visual abilities are inconsistent. Verbal abilities like naming and conceptual formatting are usually intact,[3,4] but verbal fluency is adversely affected more often.[5-10] However, verbal fluency is also reported to be preserved in some studies.[11,12] Changes in visuoconstructive and visuomotor performance are quite common,[3,6,9,10,13] but not all studies have confirmed the visuomotor deficits.[14] Continuous positive airway pressure (CPAP) treatment improves visual skills,[9] but visuoconstructive and visuomotor problems may persist.[3,6] Also reduced verbal fluency may remain.[6,9,15]

The left hemisphere of the brain is dominant in verbal cognitive function and the right hemisphere in visual cognitive function. While the left hemisphere is found to be superior during wakefulness, the right hemisphere seems to be capable of operating at reduced arousals levels.[16,17] EEG changes induced by sleep deprivation suggest that the left hemisphere needs more sleep than the right hemisphere, maybe because it is more active during wakefulness.[18] Also, the prefrontal cortex seems to need more slow wave sleep (SWS) than the central cortex.[19] The amount of SWS seems to be especially important to good sleep quality and refreshing sleep.[20,21] The fragmented sleep in OSAS patients has been reported to cause anterior located unihemispheric sleep EEG differences; in untreated OSAS patients, the amount of slow delta wave sequences in the left prefrontal EEG-derivation was reduced when compared to healthy controls,[22] and CPAP treatment increased SWS more on the left prefrontal than on the left central area.[23]

It is possible that sleep depth changes might be related to daytime cognitive functioning. In the present study, we were interested in investigating if the possible verbal and visual cognitive dysfunction in OSAS is related to sleep EEG changes. We used the previously described computational method in quantifying the amount of deep sleep.[24-26] We set out to examine: 1) whether OSAS patients have a decline in verbally or visually-based cognitive skills; 2) whether OSAS patients show deep sleep changes; and 3) whether CPAP treatment has an effect on the possible changes.

**SUBJECTS AND METHODS**

**Subjects**

All the subjects, 15 OSAS patients and 15 healthy volunteer control subjects, were male. The mean age for the patients was 50 years (range: 37-59) and for the controls 44 years (range: 30-63). The mean length of education for the patients was 12 years (range: 5-17) and for the controls 13 years (range: 8-17). The groups did not differ significantly in terms of age ($p = 0.085$) or education ($p = 0.356$). The study was conducted in a sleep unit of a university hospital. Patients were referred to the unit because of possible OSAS. The sample

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Received: July 16, 2008; accepted September 12, 2008.

included 30 OSAS patients who met the diagnostic criteria and whose first treatment choice was CPAP. Fifteen of them used CPAP treatment regularly for 6 months and were included into this study.

Both the patients and the controls were first interviewed by telephone to make sure they met the initial eligibility criteria: a) age between 20 and 65 years, b) right-handedness, c) no (other) sleep disorders, d) no clinically significant medical disorder (e.g., neurological illness, psychiatric disorder, hypo-/hyperthyroidism or other lung diseases than currently asymptomatic asthma), f) no medication affecting central nervous system, g) no substance or alcohol abuse, and h) no self-reported primary perception disorder. The patients' OSAS diagnosis and the controls' healthiness were then confirmed with a clinical interview and a diagnostic full-night polysomnography in a sleep laboratory. The diagnosis of OSAS was based on a clinical picture and subjective complaints of OSAS[1] and on an apnea/hypopnea index (AHI) > 10 per hour of sleep. The controls had to be asymptomatic and had an AHI of ≤ 5 per hour of sleep. The study was approved by the Ethical Committee of the Hospital District. The subjects gave their written informed consent.

**Procedure and measures**

The patients and controls who according to the first night polysomnography met the eligibility criteria underwent a second full-night polysomnography and a neuropsychological assessment on the following morning. Subjective sleepiness was evaluated with the Epworth Sleepiness Scale (ESS).[27] Of the 2 diagnostic nights, the recordings for the latter night were used in the analyses. After 6 months of CPAP treatment the patients underwent one full-night polysomnography (the treatment night) and a neuropsychological control assessment on the following morning. The minimum required CPAP treatment time was 6 months and minimum adherence at least 4 hours per night and at least 5 nights per week. Objective compliance measures were downloaded from CPAP units prior to the treatment night.

**Polysomnography**

Subjects retired to bed between 10pm and 12pm according to their own habitual bed times. Six EEG derivations (Fp1-A2, Fp2-A1, C3-A2, C4-A1, O1-A2 and O2-A1), 2 electro-oculography channels, submental muscle tonus, electrocardiogram, airflow pressure by nasal transducer, thermistor, thoracoabdominal respiratory movements and blood oxygen saturation were recorded. In addition, transcutaneous carbon dioxide tension, leg movements, body position and body movements were recorded. The second diagnostic night and the treatment night were classified by 2 independent scorers into the old sleep stages from C3-A2 channels.[28] The Somnologica, software (Medcare/Flaga, Iceland) was used for visual analyses. The level of agreement between the 2 scorers was 86.0% (p = 0.76). Based on their independent scorings, the 2 scorers formed a consensus sleep staging, which was used in the statistical analyses. The AHI was calculated as the number of obstructive apneas and hypopneas per hour of sleep. Obstructive apneas were defined as at least 90% reduction in the thermal signal amplitude, whereas hypopneas were defined as diminution of at least 50% of the nasal pressure signal. For hypopneas a concomitant desaturation of 4% was used as an additional criterion. Microarousals were scored according to the criteria of the American Sleep Disorders Association.[29]

**Computational deep sleep percentage (DS%)**

A computational EEG mean frequency measure can be used to quantify sleep depth.[24-26,30] In the present work, EEG signal segmentation of 2-s duration was used, selection based on the work by Saastamoinen and coworkers.[24] The 2-s long signal segment was centered at the kth second in the recording. After the mean removal, each 2-s long EEG signal segment was windowed with a Hanning window function, denoted as $w_n$, where n = 1,…, L, and L= 400. This sequence was then zero-padded to a length of 1024 and the fast Fourier Transform (FFT) was taken of the entire sequence providing the complex-valued spectrum, denoted as R(f) = X(f) + jY(f), where f denotes the frequency and j denotes the imaginary unit. The spectrum was then scaled to the amplitude spectrum, denoted as A(f), as follows:

$$A(f) = \frac{2 \cdot \sqrt{X^2(f) + Y^2(f)}}{\sum_{n=1}^{L} W_n}$$

A frequency band of 0.58-30.1 Hz was utilized in the present mean frequency computation, selected based on the work by Saastamoinen and coworkers.[24] A cumulative distribution function, denoted as c(f), ranging from 0 to 1, was first formed as follows:

$$C(f) = \sum_{fi=0.58Hz}^{f} A(fi) \,/\, \sum_{fi=0.58Hz}^{30.1Hz} A(fi)$$

The mean frequency was then obtained as the frequency f where c(f)= 0.5. Six EEG channels were examined in the present work. A mean frequency value at each second k was first computed from each EEG channel separately. This provided six sleep depth curves during the night. A 201-s long median filtering was then applied to smooth the sleep depth curves, as in the studies by Huupponen and coworkers.[25,26]

In the present study, the visual sleep staging was utilized and the deep sleep percentage (DS%) was extracted during the NREM sleep time from each of the six smoothed sleep depth curves. The value of DS% therefore is, in percentage, the proportion of NREM sleep time containing deeper sleep than the threshold of 4.0 Hz. The resulting DS% value computed from the EEG channel Fp1-A2 was denoted as DS(Fp1)%, and the others values, respectively as DS(Fp2)%, DS(C3)%, DS(C4)%, DS(O1)%, and DS(O2)%.

**Neuropsychological assessment**

General cognitive performance was assessed with a short form[31] of the Wechsler Adult Intelligence Scale -Revised (WAIS-R[32]), as Décary and coworkers[33] have recommended. The verbally-based cognitive abilities were assessed with the WAIS-R verbal subtests: Information, Digit Span, Arithmetics and Similarities, and visually-based cognitive abilities with visual subtests: Picture Completion, Block Design and Digit Symbol. In addition, the Controlled Word Association Test (COWAT[34]) including semantic (animals) and phonemic (letters P-A-S; a Finnish version of F-A-S) fluency was used to assess verbal abilities, and the copy of Rey-Osterrieth Complex Figure Test (ROCFT[35]) to assess visual abilities.

**Statistical analyses**

Mean values, standard deviations (SD) and ranges were used as descriptive values. Since some of the parameters were not normally distributed and the sample sizes were small, nonparametric tests were chosen. The 2 subject groups were compared using the Mann-Whitney U test. The patient group at baseline and at follow-up was compared using the Wilcoxon test. The Wilcoxon test was also used to compare inter-hemispheric DS% differences within the groups. A significance level was set at 0.05 for all analyses. All reported p-values are based on two-tailed tests.

**Table 1**

Mean (SD) and range of subjective sleepiness, body mass index, polysomnographic data and deep sleep percentage in the control group and in the patient group before (pre-CPAP) and after (post-CPAP) CPAP treatment and the comparisons

| | - A - Controls | - B - Patients pre-CPAP | - C - Patients post-CPAP | A vs B[1] | A vs C[1] | B vs C[2] |
|---|---|---|---|---|---|---|
| ESS | 4.1 (3.1) | 12.0 (4.0) | 7.9 (4.2) | p < 0.001 | p = 0.012 | p = 0.014 |
| | 0 – 11 | 5 – 17 | 1 - 17 | | | |
| BMI | 24.1 (2.5) | 31.8 (4.6) | 32.3 (4.7) | p < 0.001 | p < 0.001 | ns |
| | 20.1 – 28.1 | 25.4 - 41.4 | 26.0 - 41.0 | | | |
| AHI | 2.9 (2.0) | 49.5 (24.0) | 2.6 (4.0) | p < 0.001 | ns | p = 0.001 |
| | 0 – 5 | 16 – 103 | 0 - 14 | | | |
| ARI | 13.1 (5.0) | 38.2 (22.6) | 14.5 (13.7) | p < 0.001 | ns | p = 0.001 |
| | 4.3 - 22.8 | 8.0 - 99.6 | 4.6 - 27.0 | | | |
| ODI4 | 1.0 (1.6) | 33.6 (25.1) | 0.8 (0.9) | p < 0.001 | ns | p = 0.001 |
| | 0.0 - 6.0 | 2.0 - 88.0 | 0.0 - 3.0 | | | |
| S1% | 5.7 (3.0) | 4.7 (2.4) | 5.8 (4.0) | ns | ns | ns |
| | 2.2 - 15.0 | 1.2 - 11.2 | 1.5 - 16.1 | | | |
| S2% | 62.6 (6.2) | 74.4 (6.0) | 68.8 (7.7) | p < 0.001 | p = 0.038 | p = 0.006 |
| | 52.0 – 71.7 | 65.8 - 85.3 | 56.2 - 79.0 | | | |
| SWS% | 11.5 (11.9) | 3.5 (3.3) | 6.4 (6.1) | p < 0.001 | p = 0.007 | p = 0.011 |
| | 2.1 - 20.6 | 0.0 - 11.7 | 0.6 - 24.2 | | | |
| REM% | 20.2 (4.9) | 17.4 (4.7) | 19.0 (4.4) | ns | ns | p = 0.001 |
| | 13.6 – 27.8 | 8.6 - 27.3 | 12.4 - 26.4 | | | |
| DS(Fp1)% | 24.8 (12.7) | 13.1 (10.6) | 18.3 (11.6) | p = 0.017 | ns | p = 0.036 |
| | 6.2 - 48.8 | 0.0 - 30.2 | 0.0 - 33.3 | | | |
| DS(Fp2)% | 21.1 (12.3) | 6.5 (7.7) | 10.3 (9.3) | p = 0.002 | p = 0.018 | ns |
| | 0.0 - 39.3 | 0.0 - 21.5 | 0.0 - 24.7 | | | |
| DS(C3)% | 13.2 (11.0) | 4.8 (4.6) | 9.2 (8.3) | p = 0.024 | ns | p = 0.019 |
| | 0.0 - 29.6 | 0.0 - 11.8 | 0.0 - 24.4 | | | |
| DS(C4)% | 12.8 (10.2) | 2.8 (3.3) | 5.1 (5.4) | p = 0.016 | p = 0.013 | p = 0.022 |
| | 0.0 - 29.7 | 0.0 - 11.9 | 0.0 - 15.4 | | | |
| DS(O1)% | 10.0 (11.8) | 1.1 (2.6) | 2.2 (3.5) | p = 0.004 | p = 0.027 | ns |
| | 0.0 - 37.4 | 0.0 - 8.3 | 0.0 - 9.8 | | | |
| DS(O2)% | 11.8 (12.6) | 1.5 (2.6) | 1.9 (3.1) | p = 0.016 | p = 0.022 | ns |
| | 0.0 - 42.9 | 0.0 - 9.1 | 0.0 - 11.0 | | | |

[1]Mann-Whitney U test; [2]Wilcoxon test

ESS = Epworth Sleepiness Scale; BMI = body mass index; AHI = apnea/hypopnea index; ARI = arousal index; ODI4 = oxygen desaturation index; S1% = sleep stage 1 percentage of total sleep time; S2% = sleep stage 2 percentage of total sleep time; SWS% = slow wave sleep percentage of total sleep time; REM% = rapid eye movement sleep percentage of total sleep time; DS(Fp1)%, DS(Fp2)%, DS(C3)%, DS(C4)%, DS(O1)%, DS(O2)% = computational deep sleep percentages extracted from EEG channels Fp1-A2, Fp2-A1, C3-A2, C4-A1, O1-A2, O2-A1

## RESULTS

### Pre-CPAP

Descriptive values of subjective sleepiness, body mass index (BMI), polysomnographic data and DS% are presented in Table 1. At baseline the patients were sleepier as assessed with the ESS and had a higher BMI than the controls. The patients had moderate to severe OSAS with sleep fragmentation, hypoxemic episodes, and reduced SWS% of the total sleep time.

The mean estimated intelligence quotient (IQ) for the patients was 113.4 (SD: 7.6; range: 99-125) and for the controls 118.2 (SD: 11.2; range: 104-137). The groups did not differ significantly in terms of IQ (p = 0.430). The other results of the neuropsychological assessment are presented in Table 2. The patients performed more poorly compared to the healthy controls in the Picture Completion and the Digit Symbol subtests of the WAIS-R, and in the copy of ROCFT.

The patient group had reduced DS% values in all 6 EEG channels compared to the control group. The patients showed a lower DS% in the right hemisphere than in the left hemisphere both frontopolarly and centrally (p-values 0.001 and 0.009, respectively), but occipital recordings showed no significant inter-hemispheric difference. The controls presented a lower DS% in the right prefrontal derivation (p = 0.011) compared to the left side but had no other significant inter-hemispheric differences.

### Post-CPAP

The mean CPAP treatment time was 7.2 months (range: 6-12) and the mean adherence 6.1 hours per night (range: 4.3-8.6). The descriptive values of subjective sleepiness, BMI, polysomnographic data and DS% are presented in Table 1. After CPAP treatment the patients' subjective sleepiness reduced but was still higher than controls'. BMI did not change significantly. Respiratory deficits, arousals and hypoxemic

**Table 2**

Mean (SD) and range of cognitive performance in the control group and in the patient group before (pre-CPAP) and after (post-CPAP) CPAP treatment and the comparisons

| | - A - Controls | - B - Patients pre-CPAP | - C - Patients post-CPAP | A vs B[1] | A vs C[1] | B vs C[2] |
|---|---|---|---|---|---|---|
| Information | 25.9 (4.2) | 24.1 (5.0) | 24.1 (4.5) | ns | ns | ns |
| | 7 – 31 | 11 – 30 | 13 - 30 | | | |
| Digit Span | 13.4 (2.7) | 13.5 (3.0) | 13.9 (2.6) | ns | ns | ns |
| | 10 – 20 | 8 – 18 | 9 - 18 | | | |
| Arithmetics | 19.3 (3.2) | 19.1 (2.4) | 18.9 (2.4) | ns | ns | ns |
| | 14 – 24 | 13 – 24 | 14 - 22 | | | |
| Similarities | 27.2 (2.8) | 27.7 (2.8) | 28.5 (2.7) | ns | ns | ns |
| | 21 – 32 | 23 – 32 | 23 - 33 | | | |
| Phonemic Fluency | 42.5 (11.9) | 41.7 (12.1) | 41.6 (10.9) | ns | ns | ns |
| | 28 – 59 | 29 – 74 | 23 - 56 | | | |
| Semantic Fluency | 25.3 (5.0) | 23.7 (4.1) | 24.3 (4.4) | ns | ns | ns |
| | 16 – 31 | 16 – 32 | 16 - 31 | | | |
| Picture Completion | 19.1 (1.3) | 17.4 (2.1) | 18.1 (1.6) | p = 0.010 | p = 0.048 | ns |
| | 16 – 21 | 13 – 20 | 16 - 22 | | | |
| Block Design | 40.2 (9.1) | 34.3 (10.0) | 34.3 (10.5) | ns | ns | ns |
| | 23 – 51 | 14 – 49 | 15 - 49 | | | |
| Digit Symbol | 56.0 (15.4) | 43.7 (10.4) | 45.2 (11.4) | p = 0.038 | ns | ns |
| | 35 – 88 | 28 – 66 | 23 - 65 | | | |
| ROCFT | 35.1 (1.0) | 32.5 (2.4) | 33.5 (2.2) | p = 0.002 | p = 0.023 | ns |
| | 33 – 36 | 29 – 36 | 28 - 36 | | | |

[1]Mann-Whitney U test; [2]Wilcoxon test

ROCFT = Copy of Rey-Osterrieth Complex Figure Test

events normalized. The percentage of sleep stage 2 of the total sleep time (S2%) decreased, SWS% and the percentage of rapid eye movement sleep of the total sleep time (REM%) increased, but the patients still showed higher S2% and lower SWS% than the controls.

In the neuropsychological tests the patients' results did not change statistically significantly in the Digit Symbol based on the Wilcoxon test, but the patients did not differ statistically significantly from the controls any more. The patients still showed lower performance in the Picture Completion and in the copy of ROCFT (Table 2).

The DS% increased frontopolarly in the left hemisphere and centrally on both hemispheres but not occipitally. CPAP treatment normalized the DS% to the same level as the controls' frontopolarly and centrally in the left hemisphere whereas the patients continued to show reduced DS% in other derivates. During CPAP treatment the inter-hemispheric differences within the patient group remained. The DS% persisted lower both frontopolarly and centrally in the right hemisphere than in the left hemisphere (p-values 0.001 and 0.008, respectively).

## DISCUSSION

In this study, OSAS patients showed slightly lower performance in tests of visually-based cognitive skills. Differences compared to healthy controls were observed in visual perception, visuospatial or visuoconstructive organizational skills, and visuomotor performance. Before CPAP treatment, OSAS patients showed a reduced deep sleep percentage (DS%) compared to controls in both hemispheres frontally, centrally and occipitally. After 6 months of CPAP treatment, patients continued to show mild visual dysfunction and a reduced DS% compared to controls in all 3 derivations of the right hemisphere and occipitally in the left hemisphere. In the examination of inter-hemispheric differences within the study groups, OSAS patients showed a lower DS% in the right hemisphere than in the left hemisphere both frontopolarly and centrally, while controls showed this inter-hemispheric difference only frontopolarly.

Most of our findings on visual dysfunction are in line with earlier results.[3,6,9,10,13] In keeping with the findings here, earlier studies have reported only minor differences between OSAS patients and controls,[6,13] especially when OSAS is moderate.[10] However, our finding concerning the mild decline in visual perception in OSAS patients is less common. According to the meta-analysis by Beebe and coworkers,[4] OSAS markedly affects drawing and fine-motor coordination, but has less effect on visual perception and motor speed. As in previous reports, we found that verbal cognitive skills remained intact in OSAS.[3,4,11,12] On the other hand, we found no change in verbal fluency tasks.[5-10]

At baseline, OSAS patients showed a reduced DS% compared to controls in all selected EEG locations. This is possibly explained by the effect of apneas, hypopneas and desaturations which disturb the sleep process in OSAS and make it difficult to reach enough deep sleep. The reduced amount of deep sleep might be connected with the cognitive changes because it is thought that the amount of deep sleep expresses the goodness and refreshing effect of sleep.[20,21] However, even though the amount of DS% was reduced bilaterally, only visual-based cognitive and not verbal dysfunction was detected. This raises the question as to whether the left hemisphere is more capable of maintaining cognitive functions even in the event of sleep quality changes.

The finding that healthy controls present an inter-hemispheric difference in the amount of DS% is noteworthy. According to Casagrande and Bertini,[16] the left hemisphere seems to fall into sleep earlier than the right hemisphere as judged by both behavioral and EEG criteria. This might be indicative of a high need for restorative sleep in

the left hemisphere, which is known to be very active during the daytime. Indeed, Casagrande and Bertini[17] and Achermann and coworkers[18] have suggested that the right hemisphere might not need as much deep sleep as the left one. Casagrande and Bertini[17] have proposed that the right hemisphere could maintain waking ability when the brain is going to sleep or is in sleep and to tolerate sleep loss better than the left hemisphere. This dominance of the right hemisphere in the vigilance system, Casagrande and Bertini[17] hypothesize, would enable it to watch out for potential warning stimuli even in sleep. If this theory is correct, it might be a natural rather than an abnormal situation that healthy controls show less deep sleep in the right frontopolar area than in the left one during normal sleep. However, in our study OSAS patients showed a lower DS% both frontopolarly and centrally in the right hemisphere than in the left hemisphere. This reduced DS% in a larger area of the right hemisphere might indicate that in OSAS patients the right hemisphere is on the lookout for possible warning stimuli such as respiratory deficits and the central cortex is also needed to make this possible. This fits in the theory of Sturm and co-workers[36] according to which the attention and vigilance system is based on the right fronto-parietal-thalamic-brainstem network.

The mild dysfunctions observed in our patients in visual perception and visuospatial or constructive skills persisted during CPAP. Although the number of cortical arousals returned to normal, DS% remained low in the right hemisphere. This might support the view that these dysfunctions are in fact visually-based cognitive changes, although other cognitive functions may also have affected the patients' performance. OSAS patients had reduced DS% bilaterally on the occipital areas compared to controls before and after CPAP treatment, and the amount of DS% in occipital tracings did not increase significantly during treatment. Whether occipital DS% changes are related to the observed visual dysfunction in OSAS patients lies in the realm of speculation.

After CPAP treatment, OSAS patients continued to show inter-hemispheric difference on both prefrontal and central cortex and to have a reduced DS% compared to controls in all recordings from the right hemisphere and occipitally in the left hemisphere. The question remains as to whether the right hemisphere continues to monitor respiratory deficits, even though CPAP treatment is expected to prevent episodes of apnea and hypopnea. Perhaps through this monitoring process the right hemisphere enables the left hemisphere to sleep more deeply.

The strength of our study lies in the inclusion of both computational EEG analysis and neuropsychological methods to assess OSAS patients. The smallness of our material, however, necessitates a larger future study.

## CONCLUSION

OSAS patients have mild visually-based cognitive dysfunctions and less computational deep sleep in the right hemisphere even during CPAP treatment. The analysis of local sleep EEG changes may help explain the cognitive dysfunction in OSAS.

## ACKNOWLEDGMENTS

The study was financially supported by grants from the University of Tampere and Tampere University Hospital, as well as the Finnish Cultural Foundation.

## DISCLOSURE AND CONFLICT OF INTEREST

T. Saunamäki, M. Jehkonen, E. Huupponen, O. Polo, S.-L. Himanen have no conflicts of interest in relation to this article.

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