DEFICITS OF COGNITIVE EXECUTIVE FUNCTIONS IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

by

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ABSTRACT

Although a broad range of neuropsychological deficits have been reported to occur in patients with Obstructive Sleep Apnea Syndrome (OSAS), few studies have examined the executive functions in this patient group. The executive functions provide conscious control of the more basic cognitive functions and play an important role in daily living. They include capacities such as concept formation, planning, cognitive flexibility and resistance to interference. This study compared the performance of groups of moderate and severe OSAS patients with a group of unaffected individuals (N=24), on five tests of executive functioning. Two indices of sleep disordered breathing, sleep fragmentation and hypoxemia, obtained from overnight polysomnography, were respectively used to categorise participants. In patients with severe OSAS, executive function deficits were evident, while in those with moderate OSAS these abilities appeared largely intact. Further analyses revealed that the observed findings could not be attributed to differences in vigilance. These results suggest a discontinuity in the manifestation of executive function deficits between moderate and severe OSAS patients. There may be a threshold of OSAS severity, which if exceeded, impairments tend to occur. The magnitude of the impairment in patients with severe OSAS may be sufficient to interfere with daily cognitive functioning. Further research is needed both to replicate these findings and to establish the underlying pathogenesis of these deficits.

PREFACE

The experimental work described in this thesis was conducted at City and St Augustines Hospitals, in Durban from February to June 2001.

This study represents original work by the author and has not otherwise been submitted in any form for any degree or diploma to any University. Where use has been made of the work of others, it has been duly acknowledged in the text.

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LIST OF ABBREVIATIONS

AHI	Apnea Hypopnea Index
AI	Apnea Index
ASDA	American Sleep Disorders Association
BiPAP	Bilevel positive airway pressure
BMI	Body Mass Index
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPT	Continuous Performance Test
CT	Computed tomography
DB	Digits Backward
DF	Digits Forward
ECG	Electrocardiogram
EDS	Excessive daytime somnolence
EEG	Electroencephalogram
EMG	Electromyogram
EOG	Electro-oculogram
ESS	Epworth Sleepiness Scale
FCRTT	Four Choice Reaction Time Test
FP	False-positives
FPT	Five-Point Test
LTM	Long-term memory
MMPI	Minnesota Multiphasic Personality Inventory
MR	Magnetic resonance
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
NES2	Neurobehavioral Evaluation System 2
NR	Non-responses
NREM	Non rapid-eye-movement
OSAS	Obstructive sleep apnea syndrome
REM	Rapid-eye-movement

SaO_2	Blood oxygen saturation
SAWAIS	South African Wechsler Adult Intelligence Scale
SWS	Slow wave sleep
SDB	Sleep disordered breathing
STM	Short-term memory
TMT-A	Trail Making Test, Part A
TMT-B	Trail Making Test, Part B
UPPP	Uvulopalatopharyngoplasty
WAIS	Wechsler Adult Intelligence Scale
WAIS-R	Wechsler Adult Intelligence Scale Revised
WCST	Wisconsin Card Sorting Test
WMS	Wechsler Memory Scale

CHAPTER 1. OVERVIEW AND STATEMENT OF AIM

1.1 Overview

Obstructive Sleep Apnea Syndrome (OSAS)[1] is a disorder in which obstruction of the upper airway during sleep causes repeated cessations of breathing. Although it was first discovered by Gastaut, Tassinari and Duron (1965), while researching the pathophysiology of Pickwickian Syndrome (as cited in Guilleminault, 1994); subsequent investigations revealed that sleep apnea is not limited to Pickwickians. Epidemiological studies have estimated OSAS to occur in 4% of men and 2% of women in the middle-aged workforce (Young et al., 1993) and it is even more common in elderly populations (Ancoli-Israel et al., 1991).

OSAS results in chronic intermittent hypoxemia (deficient oxygenation of the blood) and sleep fragmentation. It is also associated with numerous medical complications and daytime symptoms. Patients commonly report hypersomnolence, morning headaches, mood alterations and cognitive impairments. A growing number of studies have investigated the nature and pathophysiology of the cognitive deficits (Bédard, Montplaisir, Richer, Rouleau, & Malo, 1991; Berry, Webb, Block, Bauer & Switzer, 1986; Cheshire, Engleman, Deary, Shapiro & Douglas, 1992; Findley et al., 1986, Kales, Caldwell, et al., 1985, Greenberg, Watson & Deptula, 1987; Naëgelé et al., 1995; Redline et al., 1997; Roehrs et al., 1995, Telakivi et al., 1988; Valencia-Flores, Bliwise, Guilleminault, Cilveti, & Clerk, 1996). General intellectual ability, attention, memory, motor and executive functions have all been reported to be negatively affected. However, there are inconsistencies between the findings and clear patterns of the nature and extent of the difficulties have not yet emerged. In addition, research has tended to place more emphasis on certain aspects of cognitive functioning, such as attention and memory, with other areas being relatively neglected.

Knowledge of the executive functioning of OSAS patients tends be based on a few studies

[1] The North American spelling for apnea and hypopnea, which is preferred to the British spelling (i.e. apnoea and hypopnoea) in American-international scientific journals (e.g. *Journal of the International Neuropsychological Society* and *Journal of Clinical and Experimental Neuropsychology*) is used in this thesis.

that have included isolated executive function tests as part of larger neuropsychological test batteries. Bédard et al. (1991) studied a broad range of cognitive abilities in OSAS patients. Their results suggest a discontinuity in the development of executive function impairments between moderate and severe OSAS patients. While no deficits were apparent in the moderate group, executive functions concerned with shifting and constructive abilities were compromised in severe patients. Only one recorded study (Naëgelé et al., 1995) has directly examined the executive functions in OSAS patients. The results suggest that subtle deficits may be present, but further research is needed to confirm these findings. Hypoxemia, and to a lesser degree, sleep fragmentation are implicated in the pathogenesis of these executive function impairments. In a recent review article, Décary, Rouleau & Montplaisir (2000) reiterate this as an area requiring investigation.

The executive functions are "necessary to deal with novel tasks that require us to formulate a goal, to plan, and to choose between alternative sequences of behaviour to reach this goal, to compare these plans in respect of their relative probabilities of success and their relative efficiency in attaining the chosen goal, to initiate the plan selected and to carry it through, amending it as necessary, until it is successful or until impending failure is recognised" (Rabbitt, 1997, p. 3). The executive functions provide conscious control of the more basic or routine cognitive skills (e.g. motor, reading, or language skills), which become over-learned through practice and repetition (Burgess, 1997). They play an important role in daily living, as most situations require at least some adaptation of these skills. Norman & Shallice (1980) describe five types of situations where routine automatic activation of behaviour would not be sufficient for optimal performance: (a) those that involve planning or decision making; (b) those involving error correction or troubleshooting; (c) situations where responses are not well-learned or contain novel sequences of actions; (d) dangerous or technically difficult situations; (e) situations which require the overcoming of a strong habitual response or resisting temptation (as cited in Burgess, 1997). Intact executive functions are necessary to effectively manage and respond in such situations.

In brain-injured patients, the integrity of the executive functions can determine the individual's capacity to compensate for lower level cognitive deficits (e.g. slowing of information processing or memory deficits) and adapt to the altered situation by

restructuring activities (Spikman, Deelman & van Zomeren, 2000). It follows that cognitive deficits will hamper brain damaged individuals only when they lack the compensational executive skills or when the situation does not allow the individuals to use these skills. Because such lower level deficits have been demonstrated to occur in patients with OSAS, an investigation of the integrity of the executive functions is highly relevant.

Neuropsychological assessment remains the primary tool for evaluating the functional consequences of neurological impairment (Long, 1996) and, as such, has an important role to play in the research and management of OSAS. Knowledge of which physiological mechanism (sleep fragmentation or hypoxemia) impairs daytime performance would improve the ability to classify the severity of OSAS from polysomnography results and assist in the selection of patients for treatment.

1.2 Aim

The aim of this research was to contribute to the understanding of the relationship between OSAS and the executive functions, by extending the limited data available. The study sought to compare the performance of groups of moderate and severe OSAS patients with a group of unaffected individuals on a battery of neuropsychological tests, selected to assess the executive functions. The specific capacities assessed included planning, the ability to form abstract concepts, cognitive flexibility, resistance to interference and error utilisation. Impairments of cognitive executive functions are expected to occur in association with sleep fragmentation and nocturnal hypoxemia. Both of these mechanisms have been linked with cognitive dysfunction in humans, although the effect of hypoxemia appears to be more important when considering the executive functions (Bédard et al., 1991; Naëgelé et al., 1995). Repeated arousals, occurring at the termination of apneic events, disrupt sleep architecture and result in a reduction of slow wave sleep (Raine, 1997), while hypoxemia may interfere with the synthesis of neurotransmitters involved in the regulation of cognitive functions or even cause irreversible structural damage to the brain (Bédard et al., 1991).

The following hypotheses were proposed:

Hypothesis 1

There is a discontinuity in the manifestation of executive function deficits in OSAS patients. Patients with severe OSAS will score significantly lower on measures of executive function than both normals and those with moderate OSAS. Patients with moderate OSAS will not differ significantly from normals on measures of executive function

Hypothesis 2

Indices of sleep fragmentation and hypoxemia will be associated with different patterns of impairment, as measured by the neuropsychological tests.

1.3 Organisation of chapters

Chapter 2 describes the clinical symptoms and pathophysiology of OSAS and examines the treatment alternatives. Chapter 3 provides reviews the neuropsychological impairments associated with OSAS. The nature of the executive functions, together with considerations for assessment are discussed in Chapter 4. The methodology chapter (Chapter 5) describes the characteristics of the study sample and the methods used to collect and analyse the data. The results are presented in Chapter 6. Chapter 7 contains a discussion of the results, together with the limitations of the current study and directions for future research.

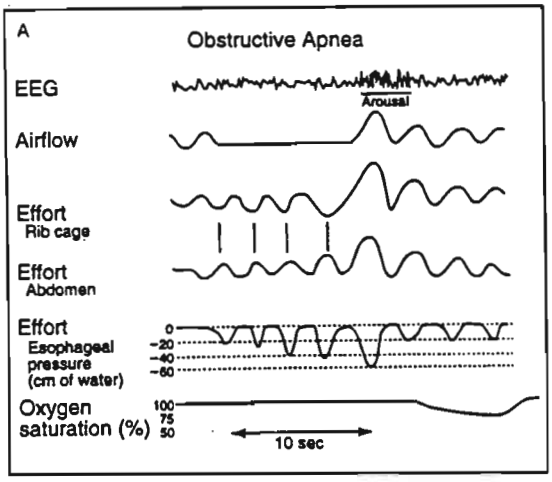
CHAPTER 2. OBSTRUCTIVE SLEEP APNEA SYNDROME

2.1 Definitions

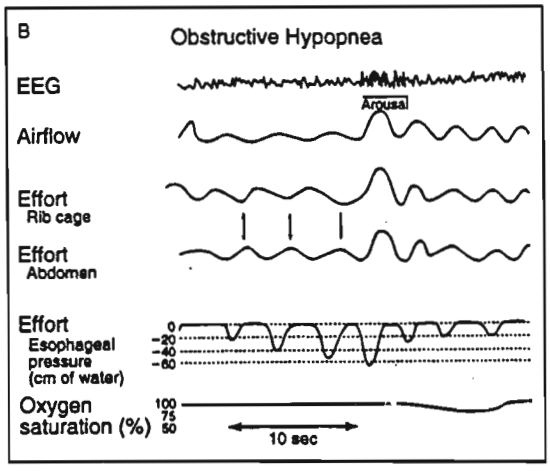
Obstructive sleep apnea syndrome (OSAS) is a sleep-related breathing disorder that is characterised by recurrent episodes of upper airway obstruction during sleep, which usually result in oxygen desaturation, recurrent arousals and daytime symptoms (American Sleep Disorders Association [ASDA], 1997). Kryger (1994) emphasises that OSAS is not a single disease entity, but rather a syndrome, with typical clinical and physiological features. Affected persons experience fragmented sleep, nocturnal hypoxemia and excessive daytime sleepiness, which may be associated with numerous medical complications and cognitive deficits. OSAS is distinguished from central sleep apnea, in which cessations of breathing result from a loss of central respiratory drive (White, 1989).

The diagnosis of OSAS is made when overnight monitoring demonstrates five or more apneas plus hypopneas per hour of sleep (ASDA, 1997). An obstructive apnea occurs when there is complete closure of the upper airway preventing airflow, despite continued respiratory efforts. The diagnostic criteria for an apneic event are (a) cessation of airflow, (b) continued respiratory effort/thoraco-abdominal movement during airflow cessation, and (c) the event lasts 10 seconds or longer. A hypopnea is a temporary reduction, but not complete cessation of airflow. It is defined by (a) a 50% or more decline in amplitude of breathing, or (b) a clear amplitude reduction that is associated with either an oxygen desaturation of greater than 3% or an arousal, and (c) the event lasts 10 seconds or longer. Upper-airway resistance can also result in arousals and cause clinical symptoms without the presence of apnea or hypopnea. The distinctive physiological features of obstructive apnea, obstructive hypopnea and upper-airway resistance are shown in Figure 2-1.

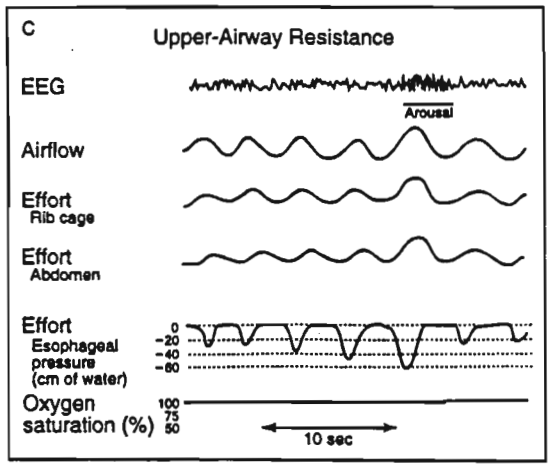
Polysomnography is necessary to confirm the diagnosis and to ascertain severity of OSAS. Several indices are used to grade the severity of the syndrome and serve as guidelines for therapy. The Apnea/Hypopnea Index (AHI) refers to the number of apneas and hypopneas



Panel A depicts obstructive apnea. Increasing ventilatory effort is seen in the rib cage, the abdomen, and the level of oesophageal pressure, despite lack of oronasal airflow. Arousal on the EEG is associated with increasing ventilatory effort, as indicated by the oesophageal pressure. Oxyhaemoglobin desaturation follows the termination of apnea. During the apnea, the movement of the rib cage and the abdomen (Effort) are in opposite directions (arrows) as a result of attempts to breathe against a closed airway. Once the airway opens in response to arousal, rib-cage and abdominal movements become synchronous.



Panel B depicts obstructive hypopnea. Decreased airflow is associated with increasing ventilatory effort (reflected by the oesophageal pressure) and subsequent arousals on the EEG. Rib cage and abdominal movements are in opposite directions during hypopnea (arrows), reflecting increasingly difficult breathing against a partially closed airway. Rib cage and abdominal movements become synchronous after arousal produces airway opening. Oxyhaemoglobin desaturation follows the termination of the hypopnea.



Panel C depicts upper-airway resistance. Asynchronous movements of the rib cage and abdomen are not seen. Arousal on the EEG is associated with increased ventilatory effort due to increased airway resistance, as reflected by the oesophageal pressure. There is no significant oxyhaemoglobin desaturation

Figure 2-1. Manifestations of Upper-Airway Closure (adapted from Strollo & Rogers, 1996, p.100).

that occur per hour of sleep. However, there is presently no consensus between laboratories regarding the cut-off criteria for rating severity. European and South African laboratories tend to apply a more conservative minimum frequency (AHI>10) for the diagnosis of OSAS, than recommended by ASDA (1997). This is reflected in both research (e.g. Bédard et al., 1991; Naëgelé et al., 1995) and clinical practice (M. Baker, personal communication, April 3, 2001). There appears to be more agreement regarding the cut-off for distinguishing moderate (AHI<30) and severe (AHI>30) patients, but this too is not universally applied. Although apneas and hypopneas exceeding 10 seconds are considered clinically significant, it is not uncommon for events to exceed 60 seconds. There are also numerous measures used to quantify hypoxemia. These include (a) number of events below a specified oxygen saturation level (usually 4% from baseline), (b) the percentage of total sleep time below a specific level of desaturation (e.g. 85% or 80%), and (c) the minimal desaturation recorded.

2.2 Prevalence of OSAS

Population data on the prevalence of OSAS are limited. Polysomnography, which is the current standard for diagnosis, is costly and requires subjects to sleep in a laboratory overnight. Screening techniques that involve home monitoring have been developed, but these still require further validation (Keenan, Anderson, Wiggs & Fleetham, 1992a, 1992b). As a result, large-scale epidemiological studies remain extremely expensive and impractical. According to the National Institute of Health (USA), sleep apnea is extremely common and affects more than twelve million Americans (American Sleep Apnea Association, 2001). One study by Young et al. (1993) estimated that the condition affects 2% of women and 4% of men in the middle-aged workforce. The prevalence in the elderly (over 65 years) is reported to be as high as 25% (Ancoli-Israel et al., 1991). Young et al., (1993) conclude that undiagnosed sleep-disordered breathing is common and represents a major public health burden. Although there are no statistics on the prevalence of OSAS in South Africa, Raine (1997) suggests that that the prevalence figures are unlikely to differ from other regions.

2.3 Pathogenesis of OSAS

OSAS is caused by repetitive upper airway obstructions during sleep that result from the narrowing of the respiratory passages. Different factors will predominate in the pathogenesis between individuals, but it is likely that all patients with clinically significant sleep apnea have a multifactorial aetiology, rather than any single cause (McNicholas, 1996). Both anatomical and physiological factors combine to cause pharyngeal narrowing and collapse.

2.3.1 Anatomical features

Patients with OSAS have narrower airways on average than normal subjects when awake (Bradley, Brown & Grossman, 1986). Schwab et al. (1996) observed that the predominant anatomic factor causing airway narrowing in apneics was an enlargement of the lateral pharyngeal muscular walls. They typically have short thick necks and increasing neck size has been shown to correlate with severity of apnea (Flemons, Remmers, Whitelaw & Brant, 1992; Katz, Stradling, Slutsky, Zamel & Hoffstein, 1990). Patients are often, but not always, overweight, with associated enlargement of the parapharyngeal fat pads (Schwab et al., 1996). Guilleminault (1994) report that two-thirds of the more than 1000 patients diagnosed with OSAS, at the Stanford Sleep Disorders Clinic, were overweight (above 20% of ideal body weight for age and height). Body Mass Index (BMI) correlates significantly with severity of OSAS as measured by AHI (Flemons et al., 1992). Many patients with OSAS have craniofacial abnormalities, which may include a small chin, maxilla and mandible, as well as a large tongue. A diminutive or receding jaw may result in insufficient room for the tongue, pushing it posteriorly to impinge on the hypopharyngeal space (Victor, 1999). Retrognathia may predispose non-obese individuals to airway narrowing or obstruction during sleep (Strollo & Rogers, 1996). An elongated and enlarged soft palate is also frequently observed in patients with OSAS (Victor, 1999). Excess peripharyngeal tissue decreases the size of the posterior airway, thereby increasing the chance of obstruction during sleep. However, recurrent exposure to vibratory trauma (snoring) and high negative inspiratory pressure can cause oedema, resulting in the

lengthening of the soft palate due to stretching and thickening. Thus, changes in the soft palate may be the consequence of breathing against upper-airway resistance, as opposed to the cause of increased resistance (Strollo & Rogers, 1996).

2.3.2 Pathophysiology

Pharyngeal patency is dependent on the action of dilator muscles, which contract during inspiration to prevent the upper airway being closed by suction. During sleep, muscle tone of the upper airway is reduced, decreasing pharyngeal patency and impeding airflow during respiration (Douglas & Polo, 1994). The pull of gravity in the supine position causes the posterior movement of the tongue, uvula and free edge of the soft palate and can result in further narrowing of the oropharynx (Remmers, 1989). Initially partial obstruction may occur and lead to snoring. Secondary changes cause tissues to collapse further and the airway may become completely obstructed. During the apneic event, the oxygen saturation of arterial blood drops progressively and carbon dioxide levels increase. These changes in arterial blood gas promote increased efforts to breathe, which become progressively urgent. The apnea is finally terminated when the individual is aroused by the stimulation of chemoreceptors sensitive to hypercapnia and hypoxemia (Remmers, 1989). The influence of the chemoreceptors may be mediated by mechanoreceptor impulses arising in the contracting respiratory muscles (Kimoff et al., 1994).

Upon awakening, the pharyngeal musculature regains tone and airway patency is restored, which permits the resumption of airflow. Vigorous ventilation follows, reversing the hypoxemia and hypercapnia and restoring blood gases towards normal. Soon afterwards, the patient returns to sleep, the tongue and soft tissues again relax, with consequent partial or complete obstruction of the airway and the cycle repeats. Cycles of sleep, snoring, obstruction, arousal and sleep occur throughout the night and may happen hundreds of times, with the length of apneas increasing from the beginning to the end of the night (Montserrat, Kosmas, Cosio & Kimoff, 1996).

Although the arousals are usually only partial and the patients may not recollect them, they cause marked sleep fragmentation. Sleep architecture is disrupted and patients may have reduced amounts of slow-wave sleep (Stages 3 and 4) and rapid-eye-movement (REM) sleep. Severe cases may develop recurrent apnea during the early stages of sleep, and never progress to slow-wave sleep (SWS) or REM sleep at all (Raine, 1997). In addition to the negative effect of sleep fragmentation, it is not uncommon for arterial blood oxygen saturation to drop below 70% and occasionally below 60% (Flemons & Tsai, 1997). The extent of the oxygen desaturations are predicted by the duration of the apneic events, with the mean fall rate reported to range from 0.1 - 1.6 percent per second. Baseline saturation levels and residual lung oxygen volumes further influence the extent and rate of arterial oxyhaemoglobin desaturation (Shepard, 1994).

2.3.3 Aggravating factors

Alcohol or sedative ingestion may precipitate or aggravate obstructive apneas in certain individuals (Robinson & Zwillich, 1989). Patients with OSAS, typically develop more frequent and more prolonged apneas following alcohol ingestion. The hypercapnic ventilatory response decreases by approximately 50% during NREM sleep in adult humans and, in men the hypoxic ventilatory response is also lower during REM and NREM sleep compared to wakefulness (Sleep Research Society, 1997a). Moderate degrees of intoxication have been demonstrated to further decrease these chemoreceptor responses. Central nervous system depressants, such as sedative hypnotics and tranquillisers, tend to cause obstructive apneas by impairing the pharyngeal dilating properties of upper airway muscles and exacerbating upper-airway hypertonia during sleep (Issa & Sullivan, 1982). Allergic rhinitis and chronic sinusitis may contribute to upper-airway closure and affect the severity of apneas (Flemons & Tsai, 1997).

2.4 Clinical symptoms

OSAS disrupts both sleep architecture and breathing and can result in a wide range of clinical symptoms (Table 2-1, p.14). Patients may be unaware of many of the nocturnal symptoms and these are usually reported by their bed-partners.

2.4.1 Symptoms During Sleep

Snoring

Snoring is defined as the noise produced by the vibration of the soft parts of the oropharyngeal walls during inspiration (Lugaresi, Cirignotta & Montagna, 1989) and is the most common reason for referral. The intensity of snoring may exceed 65dB, the noise level considered safe in the work place by the Occupational Health and Safety Administration (USA) and can significantly disrupt a spouse's sleep. The spouse often becomes sleep deprived, which can result in mood alterations or familial disruption through the use of separate bedrooms (Guilleminault, 1994). A retrospective study (Kales, Cadieux, et al., 1985) reports snoring to precede all other symptoms and may be a precursor of OSAS.

Abnormal Motor Activity during Sleep

Patients may report restless sleep, characterised by frequent tossing and turning. Some describe more agitated behaviour including periodic leg movements and large movements of the arms and legs, which sometimes unwittingly hit or kick a bed partner. Cerebral hypoxic attacks, resembling seizures, and sleepwalking are less common (Kelly, Claypoole & Coppel, 1990). The increased motor activity is associated with heavy sweating in two thirds of patients.

Choking during sleep

Some patients report shortness of breath and the sensation of choking or gagging following the awakenings during the night. Airway patency is usually quickly restored, allowing immediate gas exchange. However, some patients may experience a total inability to

breathe when first awoken, which causes extreme anxiety. Inspiratory efforts continue to intensify while awake, increasing negative intrathoracic pressure and maintaining the obstruction. Coughing can eliminate the problem (Guilleminault, 1994; Whyte, Allen, Jeffrey, Gould & Douglas, 1989).

Oesophageal reflux

Symptoms of heartburn and acid reflux are regularly reported by OSAS patients. Apneic events are associated with significant changes in oesophageal and gastric pressures that could allow backflow of stomach acid into the oesophagus, causing a burning sensation in the chest area (Guilleminault, 1994).

Nocturia and Nocturnal Enuresis

Nocturnal enuresis occurs in a limited number of patients. This may be due to increased abdominal pressure (resulting from increased gastric pressure) combined with confusion arising from disturbed sleep. More common is nocturia, with one survey (Guilleminault, 1994) reporting 28% of the sample going to the toilet four to seven times in a night.

2.4.2 Daytime symptoms

Excessive Daytime Somnolence (EDS)

Excessive daytime somnolence and fatigue are among the most frequently reported and often most debilitating daytime symptoms. Daytime tiredness may be disabling and result in reduced work efficiency and job disruption. In one study (Kales, Caldwell, et al., 1985) 84% of patients described work problems, including decreased capacity (79%) and falling asleep at work on several occasions (62%). Individuals often complain of falling asleep during sedentary activities (e.g. attending uneventful meetings, watching TV, sitting in a cinema). Patients fall asleep and stay asleep in inappropriate settings and at inappropriate times. Many patients admit to falling asleep while driving and OSAS has been associated with increased risk of motor vehicle accidents (Findley, Unverzacht, & Suratt, 1988; George, Nickerson, Hanly, Millar, & Kryger, 1987; Teran-Santos, Jiménez-Gómez, & Cordero-Guevara, 1999). Compared with a group of controls, OSAS patients had a

sevenfold greater rate of motor vehicle accidents (Findley et al., 1988). Teran-Santos et al. (1999) reported a strong association between OSAS severity, as measured by the AHI, and traffic accidents.

Cognitive Impairments

OSAS is associated with a range of cognitive impairments that may occur secondary to sleep hypersomnolence and nocturnal hypoxemia. The list includes attention, concentration, memory, visuomotor coordination and planning difficulties. The cognitive functioning of OSAS patients is the focus of this study and is reviewed in more detail in Chapter 3.

Mood alterations

Mood alterations and pronounced psychosocial stress may result from a loss of sleep. Aggressiveness, marked irritability and abrupt bursts of anxiety are often described (Guilleminault, 1994). In sample of 50 patients with severe OSAS, MMPI test results indicated that more than half were seriously depressed (Kales, Caldwell, et al., 1985). Sixty-four percent also attributed marital and family problems to their illness. Millman, Fogel, McNamara, and Carlisle (1989) report an improvement in depressive symptoms with treatment.

Morning Headaches

Morning headaches are generally described as frontal headaches or diffused pain over the scalp. These headaches, which usually dissipate over several hours, are probably caused by hypercapnia-induced cerebral vasodilation during sleep and severe oxygen desaturations (Kryger, 1994). Headaches may also follow long afternoon naps (Guilleminault, 1994).

Sexual Dysfunction

A loss of sexual drive or impotence was reported by 28% of respondents in a survey of 200 OSAS patients by Guilleminault (1994).

Table 2-1 Clinical Symptoms of Obstructive Sleep Apnea

DAYTIME SYMPTOMS	SLEEP SYMPTOMS
Hypersomnolence	Snoring
Cognitive Impairments	Restless sleep
Mood alterations	Recurrent arousals
Morning headaches	Choking
Sexual dysfunctions	Oesophageal reflux
	Nocturia
	Heavy Sweating

Many individuals with OSAS are never diagnosed, as the two most common symptoms of loud snoring and daytime somnolence are often accepted as normal and they do not seek medical attention. Furthermore, many patients are dismissed by their medical practitioners as having no significant illness, despite not undergoing formal assessment (McNicholas, 1996).

2.5 Medical Risk Factors

OSAS is becoming increasingly recognised as a major public health hazard (Phillipson, 1993). In addition to the risk of motor-vehicle accidents, left untreated this condition is associated with a range of cardiovascular and pulmonary complications. Hypertension is highly prevalent, occurring in 50-90% of patients (Dorasamy, 1998). Hla et al. (1994) have further demonstrated that the relationship between OSAS and diurnal hypertension is independent of obesity, age, and sex. Hypertension and obesity, which frequently co-occur in OSAS patients, increase the risk of cardiac disease (Victor, 1999).

OSAS has been associated with increased risk of angina (Wei & Bradley, 1992), stroke (Partinen & Guilleminault, 1990) and myocardial infarction (Hung, Whitford, Parsons &

Hillman, 1990). In patients with coexisting chronic obstructive pulmonary disease (COPD), repetitive severe nocturnal desaturations may lead to persistent pulmonary hypertension and eventually right-sided heart failure (cor pulmonale) (Victor, 1999). During normal sleep, the physiological workload of the cardiovascular system decreases. Blood pressure, heart rate and ventilation are reduced. However, apneic events are associated with activation of the sympathetic nervous system, increased blood pressure, asphyxia and in some cases cardiac arrhythmias (Shepard, 1994). Effective treatment of OSAS has been shown to improve the control of or reverse these problems in most cases (Raine, 1997).

2.6 Mortality

The physiological disturbances associated with OSAS, have been associated with a shortened lifespan. He, Kryger, Zorick, Conway, & Roth (1988) investigated the relationship between mortality and severity of OSAS, as measured by the Apnea Index (AI). They report that the probability of cumulative eight-year survival in patients with an AI<20 was .96 (±0.02) versus .63 (±.17) for AI>20 ($p<.05$). They conclude that left untreated, patients with AI>20 have a higher mortality rate than those with AI<20.

2.7 Treatment of OSAS

2.7.1 Conservative Measures

Weight Loss and Dietary Management

The dietary control of weight is extremely important in the management of OSAS (Guilleminault, 1994). In morbidly obese patients, significant weight loss may produce dramatic improvements and in some cases alleviate symptoms entirely. However, all overweight persons can benefit from even modest amounts of weight loss. In a group of mild to moderately obese patients, a weight loss of less than 10% produced a significant drop in the frequency of apneas and lowered levels of hypoxemia (Smith, Gold, Meyers, Haponik & Bleecker, 1985). This was associated with improved sleep architecture and

decreased daytime somnolence. The authors hypothesize that the widening of a partially obstructed airway, increased lung volumes and secondary metabolic changes may interact to produce these improvements. Browman et al. (1984) report a similar reduction in apnea frequency and occurrence of related sequelae with weight loss. Despite the demonstrated benefits, compliance with weight-control programs is generally poor and many patients are unable to maintain the weight loss. Consequently, this treatment option is usually not successful in the long term (Victor, 1999).

Sleeping Position

In many patients, sleep related breathing difficulties are most severe when lying in the supine position. Some individuals with mild OSAS only experience apneas when they sleep on their backs. Using pillows and other devices (e.g. tennis ball sewn in the back of pyjama top) that help them to sleep on their side can be beneficial. However, Strollo & Rogers (1996) caution that moving from the supine to the lateral-recumbent position may make apnea less apparent or convert it to another form of sleep disordered breathing (e.g. hypopnea or upper-airway resistance). They recommend that the diagnostic polysomnogram be carefully analysed if this the only treatment prescribed.

Abstinence from alcohol and sedatives

The aggravating effect of nervous systems depressants on OSAS symptoms has been described previously. The total avoidance of alcohol and sedatives, especially before bedtime, is effective in reducing both the frequency and length of apneas and is an important part of therapy (Issa & Sullivan, 1982).

2.7.2. Nasal Continuous Positive Airway Pressure

Nasal Continuous Positive Airway Pressure

Nasally applied continuous positive airway pressure (CPAP) has become the treatment of choice in clinically significant OSAS (Sullivan & Grunstein, 1994). CPAP is both safe and non-invasive and is highly effective in most patients. Positive pressure is supplied from an electric pump through a firmly fitting nasal mask, worn during sleep, providing a physical

pressure splint to the airway. The pressure in the system is maintained at a level sufficient to prevent collapse of the upper airway during respiration, thereby reducing or eliminating the incidence of apneas. The minimum pressure necessary to sustain airway patency should be titrated in the sleep laboratory, to control apnea in all sleeping positions and all sleep stages.

Nasal CPAP therapy has immediate effects on snoring, apnea and somnolence. Many patients with severe apnea experience sleep rebound on the first few nights of treatment, characterised by long periods of REM sleep and Stage 4 NREM sleep. This is associated with dramatic improvements in daytime hypersomnolence. Sleep patterns tend to normalise after 4-7 nights (Sullivan & Grunstein, 1994). CPAP therapy is associated with cardiovascular benefits, especially for patients with right-sided heart failure and hypertension, as well as the reversal of endocrine dysfunctions (Sullivan & Grunstein, 1994). Improved cognitive ability, memory and concentration as well psychological functioning have also been reported (Flemons & Tsai, 1997).

Side effects of CPAP include nasal irritation and drying, facial irritation, abdominal bloating, mask leaks, sore eyes and headaches. Some patients report claustrophobia and panic attacks (Kryger, 1994). Variations of the CPAP device attempt to minimise these side effect. To help patients fall asleep, ramp devices start with a low pressure, which gradually increases until the full pressure is applied. Humidifiers may help to prevent dryness. One drawback of CPAP therapy is poor compliance. Published compliance rates tend to vary between 50-80%; although, one study using objective metering (Kribbs, Redline & Smith, 1991) found that only 25% of patients used their machines on a full-time basis. Usually the improvement of daytime sleepiness is a powerful motivating factor. Successful long-term treatment depends on the adequate management of the problems that arise in the first few weeks of therapy.

Bilevel Positive Airway Pressure

Some patients have difficulty exhaling against the constant airway pressure of CPAP. In such cases, bilevel positive airway pressure or BiPAP is an option. Similar in action to CPAP, BiPAP maintains an open airway using positive pressure, but is a biphasic device

that allows separate settings for inspiratory and expiratory pressure. The expiration pressure is set lower than the inspiration pressure, reducing the additional work of breathing that a higher CPAP causes (Sullivan & Grunstein, 1994). The disadvantage of BiPAP is that machines are considerably more expensive than those providing CPAP.

2.7.3. Surgery

Uvulopalatopharyngoplasty (UPPP)

Uvulopalatopharyngoplasty (UPPP) is a surgical procedure that involves the removal of parts of the soft palate, uvula and redundant peripharyngeal tissues (Victor, 1999). The procedure is usually effective in eliminating snoring as most of the vibrating tissues that cause snoring noises are removed; however, it is not necessarily curative for sleep apnea, since parts of the airway other than the soft palate collapse in most patients with OSAS. Patients may still experience severe, but silent obstructive apneas. As a result, success rates vary considerably and are primarily dependent on patient selection following assessment of the upper airways (Guilleminault, Riley & Powell, 1989). Initial complications include the possibility of obstruction of the airway in the postoperative period due to oedema, bleeding and severe oropharyngeal pain. Long-term complications following the removal of palatal tissue may include nasal regurgitation of liquids, difficulty in producing certain sounds, loss of taste, numbness and parasthesias (Guilleminault, 1994). Furthermore, patients who continue to experience obstructive apneas may experience difficulty using CPAP subsequent to UPPP.

Tracheostomy

The availability and acceptance of CPAP therapy have reduced the need for tracheostomy. It is reserved for a subgroup of patients with severe OSAS, who cannot tolerate positive pressure and for whom other interventions are ineffective or unacceptable (Strollo & Rogers, 1996). A small hole is made in the trachea and a tube is inserted into the opening. The tube is kept closed during waking hours, and the person breathes and speaks normally. It is opened at night, providing a patent pathway for ventilation that bypasses the site of upper airway closure (Hudgel, 1989).

Maxillofacial surgery

Patients in whom sleep apnea is caused by deformities of the lower jaw (micrognathia and retrognathia) or other anatomic abnormalities may benefit from surgical reconstruction (Guilleminault et al., 1989). Although not commonly performed, two maxillofacial procedures (mandibular osteotomy and maxillary and mandibular advancement) have been used to correct hypopharyngeal obstruction with long-term success. Both procedures advance the mandible and hyoid bone, consequently advancing the pharyngeal muscles and the base of the tongue, thereby expanding the airway (Riley, Powell, & Guilleminault, 1992).

2.7.4 Management of OSAS

The role of surgery in the treatment of OSAS is limited. It is appropriate only for patients with predominantly heavy snoring or those in whom CPAP cannot be used because of non-correctable nasal obstruction (Sullivan & Grunstein, 1994). CPAP can be used in the majority of patients and in conjunction with conservative methods is the treatment of choice. Polo, Berthon-Jones, Douglas & Sullivan, (1994) have suggested a treatment plan for the first year management of patients with OSAS (see Figure 2-2). After a diagnostic polysomnogram, the patient is treated with nasal CPAP, nasal surgery or conservative measures only. If the nasal surgery does not eliminate all breathing abnormalities, the patient is offered CPAP or further surgery consisting of UPPP or mandibular osteotomy. If the obstruction still persists, bimaxillary advancement is recommended.

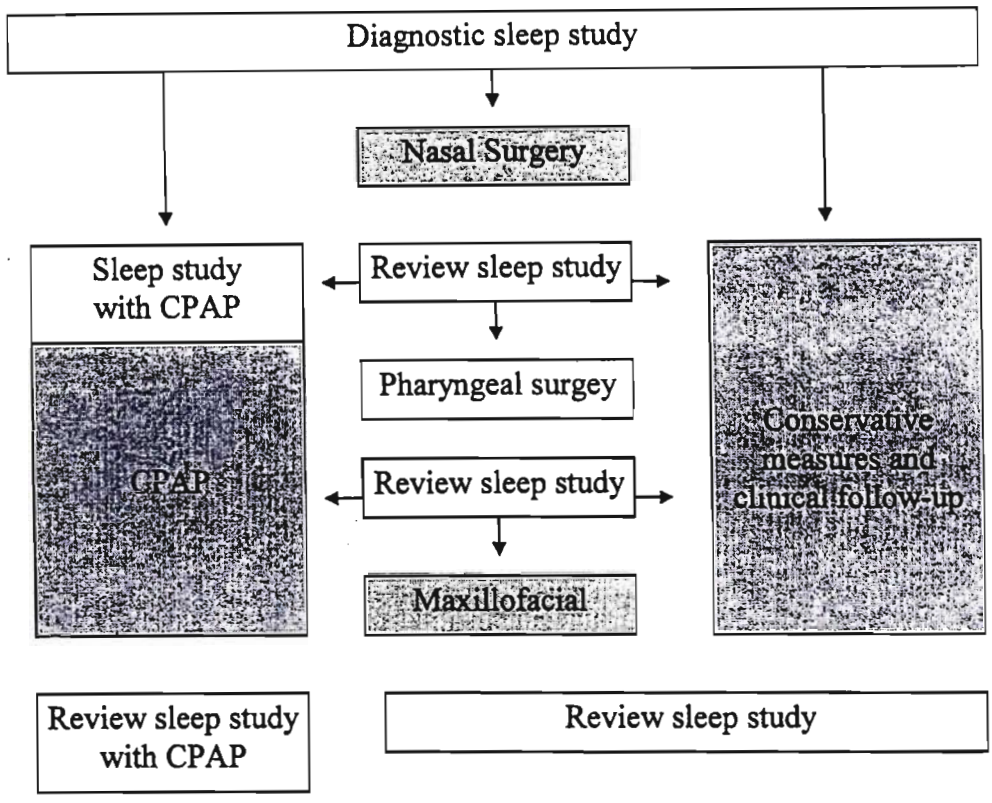


Figure 2-2. First-year Management of Patients with OSAS (Polo et al., 1994, p. 653).

Obstructive sleep apnea is a commonly occurring syndrome that is associated with numerous medical sequelae. Effective treatments are available, but a large proportion of patients remain undiagnosed and are never referred for treatment. In addition to the physiological risk factors, cognitive impairments have also been linked to OSAS. The following chapter reviews the neuropsychological evidence for these deficits, together with proposed theories of pathogenesis.

CHAPTER 3. NEUROPSYCHOLOGICAL MANIFESTATIONS OF OSAS

A wide range of neuropsychological deficits have been associated with OSAS. These include impairments of general intellectual ability, attention, memory, motor and executive functioning, which in turn can have a marked impact on patients' ability to carry out their jobs, complete everyday tasks and seriously reduce their quality of life (Bolitschek et al., 1998). However, the findings often vary between studies and clear patterns of the nature and extent of the cognitive difficulties have not yet emerged.

The lack of consistent findings may, to some extent, reflect methodological differences. Studies differ according to (a) their design, (b) recruitment strategies to obtain samples of patients, (c) severity of OSAS patients, (d) different control populations, and (e) the neuropsychological tests administered. The potential for Type I and Type II errors is also relevant. Some researchers have included large numbers of variables in their analyses, without correcting significance values for multiple comparisons, increasing the probability of chance findings. Many of the studies report small sample sizes, due to the high cost of overnight polysomnography. This results in limited statistical power, even when effect sizes are reasonable, and the potential for Type II errors occurring.

Differences in the interpretation of neuropsychological test results may further contribute to inconsistencies in the literature. Although not unique to OSAS research, divergent conclusions are often drawn about which functions are responsible for poor performances on a particular test (Décary et al., 2000). This is exemplified by the conclusions drawn from scores on Part B of the Trail Making Test (TMT-B). Findley et al. (1986) and Naëgelé et al. (1995) considered this test to be a measure of attention and concentration, while Bédard et al. (1991) and Greenberg et al. (1987) interpreted it to be a measure of executive functioning. On the other hand Cheshire et al. (1992) described it as a test of motor and conceptual tracking. TMT-B may in fact be sensitive to all three of the described functional areas, but determining which is responsible for poor performances is more difficult. Some of the reported neuropsychological deficits associated with OSAS are discussed below:

3.1 General Intellectual functioning

General intellectual functioning refers principally to the measurement of an IQ score and reflects an individual's general cognitive ability at a given time, in relation to available age norms. IQ is a multifaceted concept and is best measured using a multifaceted instrument (Spreen & Strauss, 1991), such as the Wechsler Intelligence Scales (e.g. WAIS or WAIS-R). Although Lezak (1995) considers the value of composite scores (e.g. Verbal-, Performance-, and Full Scale-IQ) in a neuropsychological assessment to be limited, they do provide some indication of the overall integrity of the cognitive functions and are thus discussed in this review.

Only three studies were located that calculated IQ scores in OSAS patients, based on a complete battery of subtests. In a sample of 28 patients with OSAS of sufficient severity to warrant recommendation for tracheostomy, 11 (39%) were described as impaired, scoring one standard deviation or lower than the standardisation sample on the WAIS or WAIS-R (Kales, Caldwell, et al., 1986). Berry et al. (1986) examined the association between neuropsychological test performance and various indices of sleep disordered breathing in 46 heavy snorers. Using partial correlations, to correct for age, weight and education, significant relationships were observed between the number of desaturations, of 4% or greater, and Verbal IQ (r=-.399) and Performance IQ (r=-.487). Bédard et al. (1991) reported that severe apneics scored lower than moderate apneics and normal controls on the WAIS-R. Similar to the findings of Berry et al. (1996), Performance IQ showed a greater decrement than Verbal IQ. Subtests relying on previously learned material and verbal associations (Vocabulary, Information, and Picture Completion), which are typically more resistant to organicity, were less affected than those dependent on concentration, response speeds and abstract concept formation (Digit span, Similarities, Digit Symbol, and Block Design).

Several studies have estimated IQ, based on the performance of selected WAIS-R subtests, and report mixed findings in OSAS patients. Findley et al. (1986) compared the cognitive functioning of 9 apneic patients who had associated hypoxemia with that of 17 apneic patients who were relatively non-hypoxic. A single measure of general intellectual

functioning was calculated by adding the Vocabulary and Block Design scores of the WAIS-R. The two groups did not differ significantly on this variable. Although these two subtests have the highest correlation with Verbal and Performance IQ respectively, Lezak (1995) cautions against the reliability of individual subtests. Thus, the combined score based on only two subtests may not provide an accurate estimate of general ability and the null result may be misleading.

Cheshire et al. (1992) measured intellectual deterioration by comparing premorbid ability, estimated from National Adult Reading Test (NART) scores with current IQ, based on the prorated estimates from two WAIS-R performance subtests (Block Design and Digit Symbol). The authors use this to demonstrate that the severity of OSAS, as measured independently by the AHI and minimum nocturnal blood oxygen saturation levels, was associated with a drop in IQ scores. However, the WAIS-R subtests and the NART load on different cognitive functions and a comparison of general ability based on these tests is problematic. Both Bédard et al. (1991) and Berry et al. (1986) have shown nonverbal subtests to be more vulnerable to the effects of hypoxemia than verbal subtests. The two performance subtests may have underestimated the patients' overall ability, as well as the extent and significance of intellectual deterioration.

The available data suggest that severe OSAS is associated with a decline in general ability. However, it is difficult to draw any firm conclusions from the above studies and their designs further preclude the inference of causal relationships. The observations, however, are similar to findings in other groups of patients with significant hypoxemia (e.g. COPD), where diffuse cognitive dysfunction has been reported (Kelly et al., 1990).

3.2 Attention

Attention may be subdivided into (a) selective attention (concentration) - the ability to focus on one or two important stimuli, while suppressing awareness of competing distractions; (b) sustained attention (vigilance) - the capacity to maintain an attentional activity over a period of time; (c) divided attention - the ability to respond to more than one

task at a time or to multiple elements or operations within a task; and (d) alternating attention - allows for shifts in focus or tasks (Lezak, 1995).

Concentration difficulties are among the most frequently reported complaints of OSAS patients, and many studies (e.g. Bédard et al., 1991; Findley et al., 1986; Greenberg et al., 1987, Naëgelé et al., 1995; Redline et al., 1997) have included some measures of selective attention in their respective test batteries. The Digit Symbol, Letter Cancellation, Stroop Test, Paced Auditory Serial Addition Test and Trail Making Test have all been used to demonstrate impaired concentration in OSAS patients. However, the pathogenesis of these deficits remains uncertain. Some studies have emphasised the effects of hypoxemia (Findley et al., 1986; Greenberg et al., 1987), while others attributed the deficits to excessive daytime somnolence (Bédard et al., 1991; Naëgelé et al., 1995). Décary et al. (2000) suggest that hypersomnolence appears to be the major factor contributing to the patients' difficulties on relatively simple attentional tasks. Yet, the severity of hypoxemia becomes more important when faced with more demanding tasks of divided attention (e.g. Stroop, TMT-B).

Investigations into the cause of vigilance impairments in OSAS patients are also inconclusive. Redline et al., (1997) reported that a group of patients with mild sleep disordered breathing (10<AHI<30) performed significantly worse than a control group (AHI<5) on a test of sustained attention. Little hypoxemia was noted in either group, and no differences between objective and subjective measures of sleepiness were found. Sleep fragmentation appeared to underlie the observed deficits. Roehrs et al. (1995) compared the neuropsychological function of OSAS patients to COPD patients, a group with hypoxemia but no hypersomnolence. The OSAS patients performed more poorly than the COPD group on the Continuous Performance Test (CPT), suggesting that hypersomnolence or fragmented sleep may be the cause of the lower vigilance. In moderate to severe OSAS patients, measures of hypoxemia have also been used to predict levels of daytime vigilance. Findley et al. (1986) reported that non-hypoxemic patients performed significantly better than hypoxemic patients on the Four Choice Reaction Time Test (FCRTT). Indices of sleep fragmentation did not correlate significantly with vigilance scores and disturbed sleep did not appear to have contributed to the pathogenesis of vigilance impairments. Bédard et al.

(1991) were also able to discriminate between moderate and severe patients using the FCRTT, with the severe group performing worse on the sustained attention tasks. Patients in this study were grouped on the basis of both AHI and hypoxemia ratings.

In summary, impairments of sustained attention have been consistently observed in OSAS patients. Arousals secondary to respiratory events fragment sleep and disrupt its architecture. Fragmented sleep may explain daytime alertness in non-hypoxemic or mildly hypoxemic patients. In severely affected patients, hypoxemia may be a more important factor in the pathogenesis of lowered vigilance levels.

3.3 Memory

Memory is the generic term for describing the registration, storage, retention and retrieval of information (Lezak, 1995). A major functional distinction of the memory system is the division into short- and long-term memory (STM and LTM). STM is primarily responsible for maintaining information that is to be used immediately, while LTM involves the consolidation and maintenance of information over a longer period of time (Décary et al., 2000).

Many OSAS patients report complaints of poor memory in their everyday lives such as misplacing their keys, forgetting to buy certain items at the shops, and not remembering the details of conversations. Both STM and LTM deficits have been observed using formal neuropsychological testing, although most research has focused on LTM. Kales, Caldwell and co-workers (1985) found memory impairments in 50% of the 22 OSAS patients who were administered the Wechsler Memory Scale (WMS). They do not, however, describe the nature of the impairments. Several other groups of authors (Bédard et al., 1991; Berry et al., 1986; Findley et al., 1986; Greenberg et al., 1987; Telakivi et al., 1988) have also used the WMS to demonstrate memory deficits in OSAS patients. Difficulties with the immediate and delayed recall of both verbal (WMS - Logical Memory) and non-verbal (WMS - Visual Reproduction) information have been reported, but the delayed recall of logical stories appears to be the most consistently impoverished area. The degree of

impairment has been associated with the severity of OSAS, as measured by the number of apneas per hour (Berry et al., 1986) and the frequency of hypoxic episodes (Berry et al., 1986; Telakivi et al., 1988). Bédard et al. (1991) studied the effects of both hypoxemia and daytime vigilance on cognitive function. Their findings suggest that memory deficits are primarily related to a decrease in daytime vigilance.

In contrast to the above studies, Telakivi, Kajaste, Partinen, Brander and Nyholm (1993) and Lojander, Kajaste, Maasilta and Partinen (1999) failed to demonstrate memory deficits using formal testing, despite subjective complaints by the participants. They propose that standard neuropsychological instruments, developed to identify patients with severe neuropsychological disorders, may not be suited to detect the impairments associated with OSAS. In particular, individuals with a high cognitive capacity may be able to compensate for fatigue in the short term. Redline et al. (1997) found no differences on tests of memory between a group of patients with mild sleep disordered breathing and matched controls.

Naëgelé et al. (1995) argue that LTM deficits in OSAS patients are related to a learning impairment rather than forgetting difficulties. They reason that the retention deficits observed in the above studies were an artefact of the procedures used, since they did not control for the amount of learning. To ensure that initial retention levels were equivalent, these authors used the Selective Reminding Test to compare the performance of OSAS patients with controls. As predicted, the patient group had more difficulty on the learning part of the test and acquiring the information for memory. The percentage recalled after a 30-minute delay did not differ between the groups. The authors suggest that the nature of the impairments are more consistent with the deficits found in frontal lobe patients than in amnesics with temporal lesions. However, a criticism of the selective reminding procedures used is that some patients are presented the items more times than others, favouring encoding and consolidation, possibly resulting in better long-term retrieval.

Most studies have focused on patients' abilities to learn and remember information about objects and events (declarative memory). Procedural memory refers to the gradual acquisition and maintenance of motor skills and procedures (Décary et al., 2000) such as how to walk, talk, dress, eat, etc. This knowledge is generally not available to

consciousness and is more difficult to assess (Lezak, 1995). Although there appear to be no studies that have investigated procedural learning in OSAS patients, Décary et al. (2000) hypothesise that this capacity is reduced in this patient group and identify it to be an area requiring further investigation.

3.4 Motor and Visual-Perceptual Functioning

Deficits of motor functioning (reduced speed, dexterity and accuracy) have been described in mountaineers exposed to extremely high altitudes and patients with hypoxemia associated with COPD. Patients with OSAS, who may also experience severe hypoxemia, show similar deficits in dexterity and speed (Décary et al., 2000). Greenberg et al. (1987) used the Purdue Peg Board to compare the fine motor control of OSAS patients and a group of patients with excessive daytime somnolence, but no apnea. The OSAS group performed worse than controls. Manual dexterity was significantly correlated with two measures of hypoxemia severity, the total time not breathing (r=-.52) and the lowest desaturation (r=.51). In another study using the Purdue Peg Board (Bédard et al., 1991), controls, moderate- and severe-apneics all differed significantly on this task. However, in comparison with COPD patients, sleep apneics perform better on the Finger-tapping test (Roehrs et al., 1995). This test loads on motor skill and has shown to be sensitive to the effects of hypoxemia. The increased severity and continuous rather than intermittent nature of the hypoxemia in the COPD patients may account for the greater performance deficit.

Construction tasks combine perceptual activity with a motor response and always have a spatial component (Lezak, 1995). Two broad classes of activities, drawing and assembly tasks, are used in the assessment of construction ability. Of a sample of 50 patients with severe OSAS, the majority displayed some degree of visual-perceptual difficulty on the Bender Gestalt (Kales, Caldwell, et al., 1986). In the study by Greenberg et al. (1987), perceptual organisational skills were related to hypoxemia severity. Scores on Block Design (WAIS-R) correlated with the total time not breathing (r=-.51) and lowest desaturation (r=.48). Similarly, Bédard et al. (1991) report that deficits of visual organisation were linked to levels of nocturnal hypoxemia. Patients with severe OSAS

performed significantly worse than moderate patients on the copy of Rey-Osterreith Complex Figure, and the Block Design and Object Assembly subtests of the WAIS-R. Deficits of spatial orientation have also been observed in a group of habitual snorers using the Clock Test (Telakivi et al., 1988). Performance was negatively associated with the frequency of oxygen desaturations.

3.5 Executive functions

The executive functions refer to a group of skills involved in the initiation, planning and monitoring of goal-directed behaviour. They include the ability to establish and maintain a set, shift from one set to another, use feedback to monitor behaviour, concept formation, and abstract reasoning. The nature of the executive functions are described in more detail in Chapter 4. Several researchers (e.g. Bédard et al., 1991, 1993; Berry et al., 1986; Redline et al., 1997) who have assessed the cognitive deficits associated with sleep apnea have included some tests sensitive to executive functions in their studies and report mixed findings. Bédard et al. (1991) compared the cognitive performance of a group of ten severe OSAS patients with ten moderately affected patients and ten controls on a large battery of neuropsychological tests. Deficits of executive functioning, concerned with shifting abilities as well as verbal fluency were mostly evident in the severe patient group. Although moderates did differ from controls on one test of planning ability (WISC-III Mazes), there is seemingly a discontinuity in the pattern of executive deficits. This capacity appears to be relatively preserved in patients with mild and moderate OSAS, but is impaired in patients with severe OSAS. Further analyses revealed that compromised executive functioning could be attributed to the severity of hypoxemia, rather than impaired vigilance.

Roehrs et al. (1995) also described executive function deficits in a group of OSAS patients, with significant nocturnal hypoxemia. On the Category Test, a measure of abstract reasoning and mental flexibility, the mean scaled score, corrected for age and education, fell within the impaired range (i.e. greater than two standard deviations below the mean).

No significant differences were found between the mean scores of the OSAS patients and a group of COPD patients, suggesting that hypoxemia may be a possible common cause.

In a study of patients with mild sleep disordered breathing, no differences were evident between patients and controls on any of the measures of executive functioning (Redline et al., 1997). Wisconsin Card Sorting Test (WCST) perseverative errors tended to be worse in those with SDB, but this did not reach significance (p=.095). Given that little hypoxemia was noted in either group and that earlier studies have suggested that executive impairments only tend to occur in severe patients with significant hypoxemia (Bédard et al., 1991), these results were not unexpected.

An earlier study of heavy snorers, with mild OSAS [AHI mean (*SD*)=3.2 (9.6)] found no significant correlations between the nocturnal respiratory indices (AI, AHI, and number of desaturations greater than 4%) and a measure of executive functioning (categories achieved on the WCST) (Berry et al., 1986). The authors do not, however, report on the number of perseverative errors, which tends to be the most significant indicator of deficit on this test (Heaton, 1981). Verbal fluency (Controlled Oral Word Association Test), which is also largely dependent on executive functioning, was significantly associated with the number of oxygen desaturations (r=-.291).

Naëgelé et al. (1995, 1998) appear to be the only group of researchers to have examined the executive functioning in OSAS patients directly. A battery of "frontal lobe" related tests was administered to a sample of 17 patients and 17 normal controls. The tasks explored attention, working memory, learning abilities, planning and programming capacities, mental flexibility and verbal fluency. Compared with the controls, the OSAS patients revealed a decreased ability to initiate new mental processes (Tower of Toronto Test) and to inhibit automatic processes (Stroop Test) and reduced working memory capacity (Digits Backwards). Relatively small differences in the patients' ability to form concepts, shift and maintain a set and utilise feedback were observed on the modified WCST. Patients made significantly more perseverative errors, while there was a tendency for controls to complete more categories. There was no difference between groups on the time taken to complete Part B of TMT. To take into account some of the pathological mechanisms likely to

contribute to the cognitive impairments found in the patient group, logistic regression analyses were performed. The dependent variables used for establishing the models were the cumulated sleep time spent at SaO_2 (oxygen saturation) levels <85% (severe hypoxemia: greater than 10 minutes, moderate hypoxemia: less than 10 minutes) and the frequency of respiratory events (severe apnea: AHI>40, moderate apnea: AHI<40). Both the number of errors and the number of categories were predictive of the severity of hypoxemia. However, the criterion used to classify hypoxemia severity (sleep time at SaO_2 levels <85%) was not corrected for the total sleep time of each patient, and might be considered an unreliable index. Of the executive function tests used to predict apnea severity, Digits Backward and the Tower of Toronto were the strongest.

Considered collectively, the above studies suggest a hypothesis that patients with severe OSAS have compromised executive functions and that both apnea and hypoxemia severity may be involved in the pathogenesis thereof. However, the degree of impairment experienced by even the severe OSAS patients does not appear to be as significant as patients with frontal lobe lesions or related subcortical abnormalities.

3.6 Pathogenesis of cognitive impairment

Selected findings regarding the pathogenesis of the various cognitive deficits associated with OSAS have already been discussed. However, the literature reports mixed results and there is still controversy to what extent these daytime deficits are due to sleep fragmentation caused by brief microarousals from sleep, or to intermittent hypoxemia associated with sleep disordered breathing. Traditional measurements of OSAS generally do not correlate well with neuropsychological test performance. In a sample of 150 patients with sleep disordered breathing, Kingshott, Engleman, Deary and Douglas (1998) report only weak relationships between nocturnal variables and neuropsychological performance, while in Borak, Cieslicki, Koziej, Matuszewski & Zielinski (1996) deficiencies in cognitive function did not correlate with any of the sleep variables. Nightly variations in the number and severity of apneas and a ceiling effect in the measurement of nocturnal hypoxemia may partly explain these findings. In addition, the indices currently used to rate

the severity of OSAS (i.e. AHI, AI) may not be adequate. For example, Flemons & Tsai (1997) have observed that some patients may have upper-airway resistance without significant apneas or hypopneas and still experience similar symptoms as those with OSAS and similarly respond to CPAP treatment.

Adequate oxygenation of cerebral tissues is critical as sustained reductions in tissue oxygen tension can impair brain functioning (Kelly et al., 1990). Linear relationships between neuropsychological performance and oxygen saturation levels have been reported in patients with COPD (Grant, Heaton, McSweeney, Wright, & Adams, 1987) and similar correlations between cognitive impairment and the extent of hypoxemia might be expected in OSAS patients. Berry et al., (1986) and Telakivi et al., (1988) both report significant correlations between test scores and the severity of hypoxemia (frequency of desaturations of 4% or more) and conclude that the deficits may reflect brain insult from long-term exposure to intermittent nocturnal hypoxemia. However, these relationships have not been consistently established.

Sleep fragmentation has been shown to be the major cause of excessive daytime sleepiness (Colt, Haas & Rich, 1990; Guilleminault et al., 1988) and has also been suggested as an explanation for the impaired cognitive performance of OSAS patients. Compared with normals, patients with OSAS spend proportionally more time in Stages 1 and 2 sleep, whereas Stages 3 and 4 and REM are significantly reduced or absent (Kelly et al., 1990; Sullivan & Grunstein, 1994). Martin, Engleman, Deary and Douglas (1996) examined the effects of sleep fragmentation on daytime function experimentally and report findings supporting the above hypothesis. Healthy volunteers either slept undisturbed or had sleep fragmented with sound pulses every two minutes. Neuropsychological testing the following day revealed performance decrements in the group with disturbed sleep on two cognitive tests sensitive to attention.

It seems likely that both nocturnal hypoxemia and vigilance impairment due to disrupted sleep architecture may contribute to the observed neuropsychological deficits. Cheshire et al. (1992) studied 29 patients with symptoms of sleep apnea/hypopnea syndrome. Their

findings demonstrate that the extent of sleep fragmentation, hypoxemia and frequency of breathing irregularities are important in determining daytime function in OSAS patients.

Bédard et al., (1991) have provided the most comprehensive account of the pathogenesis of the cognitive deficits. They compared the scores of severe and moderate apneics and controls on a large battery of neuropsychological tests. Compared with the controls, both the severe and moderate apneics showed impairments in numerous areas of functioning. In addition, the performance of the severe apneics was compromised on selected tests on which the moderately affected patients performed normally. Thus, not only were impairments, present at an early stage of OSAS, aggravated in severe patients, but new deficits also appeared. A reduction in general intellectual functioning and executive functions concerned with shifting and constructive abilities were only evident in severe apneics. This suggests a discontinuity in the manifestation of cognitive dysfunctions in moderate and severe OSAS. They further examined the data using Multiple Analysis of Covariance (MANCOVA). First using vigilance, then nocturnal hypoxemia, as covariates, they were able to demonstrate that these variables may contribute to different cognitive deficits. General intellectual functioning and performance on executive and motor tasks were related to the severity of the hypoxemia, while attention and memory problems were attributable to vigilance impairment. Two explanations that could account for these patterns were offered.

Oxygen consumption and cerebral blood flow have been found to be reduced in all regions of the brain in OSAS patients during sleep, but this lowering is more severe in the brainstem-cerebellar area. Brainstem dysfunction is further suggested by recordings of abnormal short-latency evoked potentials in this region. Given the close anatomical location of the neural centres controlling both vigilance and respiration, the authors hypothesize that a localised brainstem hypoxic dysfunction might account for these findings. Furthermore, brainstem lesions have been shown to result in cognitive deficits similar to those in frontal lobe patients, affecting the initiation and planning of activities. Alternatively, the intermittent hypoxic episodes may impair the metabolism of central neurotransmitters. Both the cerebral monoamines and acetylcholine, which are involved in the regulation of cognitive function, are highly sensitive to small and brief hypoxic

variations. Increased blood flow during the periods of hypoxemia may occur too slowly to prevent repetitive hypoxic episodes and altered cerebral metabolism.

In a follow up of their original study, Bédard, Montplaisir, Malo, Richer & Rouleau (1993) reassessed both groups of patients after six months of treatment with CPAP. The results demonstrate that CPAP was effective in treating the physiological symptoms of OSAS, with sleep architecture and nocturnal respiration restored to normal. Daytime vigilance was improved, but even with CPAP, patients remained significantly more somnolent than controls. Most cognitive functions improved with treatment, with scores on tests of attention, verbal memory and constructive abilities returned to normal values. These functions represent those previously attributed to impaired vigilance (Bédard, 1991). However, areas of functioning that were related to the severity of nocturnal hypoxemia, such as tasks requiring verbal fluency, planning ability and manual dexterity, remained impaired. The reversal of many of the cognitive deficits following treatment with CPAP supports a functional impairment hypothesis. However, in those patients with persistent cognitive impairment, hypoxemia may have caused irreversible structural damage to the brain.

Neuropsychological testing prior to and immediately subsequent to successful treatment with CPAP (Bearpark, Grunstein, Touyz, Cannon & Sullivan, 1987; Borak et al., 1996; Douglas, 1998; Engleman et al., 1997; 1999; Montplaisir, Bédard, Richer & Rouleau, 1992; Muñoz et al., 2000; Naëgelé et al., 1998; Valencia-Flores, Bliwise, Guilleminault, Cilveti & Clerk, 1996) confirms findings that cognitive deficits result from both hypoxemia and decreased vigilance, and indicates that some of these deficits are reversible. However, differences in the patterns of impairment, both pre- and post-treatment are difficult to interpret and are not helpful in validating Bédard et al.'s (1991; 1993) model of pathogenesis.

Multiple factors appear to play a role in symptom generation and the physiological measurements available at present cannot account for the complex interactions that take place as a result of repeated cessation of breathing. The shortcomings of neuropsychological assessment methods should also be emphasised. Individual variations

in premorbid ability, poor task specificity and the uncertain ecological validity of widely used neuropsychological tests (i.e. the ability to predict how an individual will function in his or environment) are just some of the issues that need to be addressed. Further research is needed in order to understand how the nocturnal symptoms of OSAS impact on the cognitive functions of individuals in their daily lives.

The executive functions lie at the centre of all socially useful, personally enhancing, constructive and creative activities (Lezak, 1982). However, with the exception of severe forms of pathological inertia, defects in executive functions are not readily observable in themselves and so rarely become self-evident. As a result, their importance is often under emphasised in neuropsychological assessments. The study of OSAS is no exception. Minimal research has directly investigated the executive functions in this patient group. A lack of standardised assessment methods may explain why others researchers have tended to avoid this area. In contrast with other cognitive functions, the development of techniques for the measurement of executive functions has lagged far behind (Lezak, 1982). The following chapter explores the nature of the executive functions, together with considerations for their assessment, in more depth.

CHAPTER 4. THE EXECUTIVE FUNCTIONS

4.1 What are the executive functions?

The executive functions represent a broad and often ill-defined area of psychological functioning. The term refers to a range of loosely connected higher-order cognitive processes that include initiation, planning, hypothesis generation, cognitive flexibility, decision making, regulation, judgement, feedback utilisation, and self perception that are necessary for effective and contextually appropriate behaviour (Spreen & Strauss, 1998). Lezak (1995) suggests a taxonomy that classifies these components into four major classes or functional categories: (a) volition, (b) planning, (c) purposive action, and (d) effective performance. These operations involve distinctive sets of behaviour and all are necessary "capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour" (p. 42).

(a) *Volition* can be described as the capacity for intentional behaviour and formulating goals. Motivation together with a psychological and physical awareness of oneself in relation to the environment are necessary preconditions to self-initiate a planned activity. Individuals with the capacity for goal formulation are able to conceptualise their needs and desires, before acting on them. They can consider behaviours that are distinctive from and far more complex than impulsive acts or automatic responses to physiological needs or environmental stimuli (Lezak, 1982). Those lacking volition appear to be passive, withdrawn and without ambition. They may be able to perform complex activities, but do not initiate them, unless instructed to do so.

(b) *Planning* involves the identification and organisation of a complex sequence of successive steps, necessary to achieve a goal. It includes the ability to conceptualise changes from the present circumstances, generate and evaluate alternatives, make choices, and to develop a conceptual framework that will give direction to the carrying out of a plan. In addition, good impulse control sustained attention and reasonably intact memory functions are required. Patients with compromised planning abilities may show a

haphazard and fragmented approach to tasks, rather than an organised, systematic response (Lezak, 1995).

(c) *Purposive action* or the transformation of a plan into a productive, self-serving activity requires an individual to initiate, maintain, switch, and stop sequences of complex behaviour. Breakdown at this level may manifest as a dissociation between a person's verbalised intentions and plans and their actions. Programming difficulties may impair performance on unfamiliar tasks, while routine, automatic behaviours are relatively unaffected. Deficits may also appear as inflexibility or the inability to shift a course of action according to the demands of the situation. Mental inflexibility may present as the inability to change a perceptual set and concrete or rigid approaches to understanding and problem solving. Inflexibility of response results in perseverative, stereotyped and non-adaptive behaviour (Lezak, 1995).

(4) *Effective performance* requires the ability to self-monitor, self-correct and regulate the intensity and rate of delivery. For example, when an impending failure of intention is noticed and corrected, this can be described as successful monitoring. Defective self-monitoring can impair any type of performance (Lezak, 1995).

A loss of the executive functions compromises the individual's capacity to maintain an independent, constructively self-serving and socially productive life regardless of how well he can see and hear, walk and talk and perform tests. However, with the executive functions intact, a person can suffer many different kinds and combinations of sensory, motor, and cognitive deficits and still maintain the direction of his own life (Lezak, 1982). Kolb & Whishaw (1995) note that it is possible to find impaired planning, thought and judgement without a major change in general intellectual status.

The executive functions involve how mental resources are utilised and are processed, as well as being outcome oriented (Cripe, 1996). As a result, many of the definitions are difficult to operationalise. Rabbitt (1997) emphasises the need to distinguish performances, skills and behaviours characteristic of executive function from those that are not. He has

compiled a list of features that describe the executive functions and differentiate these from non-executive behaviours:

1. Unfamiliar task

A novel or unfamiliar task is necessary to elicit an executive response. Executive control is required where an individual must, for the first time, recognise, evaluate and select among a variety of alternatives. The originality of this course of action is in contrast with the familiarity of a non-executive process, where a previously practised behavioural sequence can be performed without the need to develop and weigh alternatives.

2. Controlled behaviour

Executive behaviours can be initiated and controlled independently of the environmental input. The person retains the flexibility to change plans, even when the environment does not respond as predicted, and no previous experience is available to guide decision-making. Non-executive behaviours are externally driven and proceed automatically, in response to specific stimuli in the surroundings. Even very complex behaviours are possible when an environmental event triggers previously learned "plans" or "programs" that are held in long-term memory. For example, driving a motor vehicle in busy traffic, while at the same time listening to a radio broadcast may largely be performed automatically, under non-executive control. Even the procedures that support very complex activities rapidly become automated by practice.

3. Attentional control

Both the regulation and allocation of attention lie within executive control. Baddeley's (1992) model of the working memory describes the concept of the 'Central Executive', which functions as an "attentional controlling system". Attentional control may occur through either switching attention from one source of information to another, or by strategically allocating attentional resources to more than one input. This enables the switching between one sequence of responses and another, or one aspect of the environment and another (Lowe & Rabbitt, 1997). Attentional control is especially relevant in complex tasks that require several different demands to be met simultaneously. It also permits the suppression of habitual responses to allow for alternatives. Ongoing sequences

of behaviour may be interrupted, while attention is directed to new sources of information. Failure of this process may lead to perseveration.

4. Inhibition of inappropriate responses

Clinical accounts of dysexecutive behaviour frequently include reports of bizarre and socially inappropriate actions. These may be related to observations that patients with executive deficits frequently make more false-positive errors than do controls on recognition memory tasks (Parkin, 1997). The common feature appears to be a failure to judge when an intention, and the resultant response are incorrect or "unacceptable" in a particular context. Although these behaviours also represent a breakdown at the level of self-regulation, they should be distinguished from the inhibition of habitual responses, discussed above. These failures of executive control are not habitual responses, but rather decisions that are made without sufficient information or adequate consideration of the available information.

5. Monitoring of performance

An important component of the executive functions is the monitoring of performance during the execution of a chosen plan. In a novel situation, it is necessary that the individual continuously attempt to detect and correct any errors during the task, in addition to evaluating the likely success of a plan. Should either failure be imminent or new, more desirable goals become available, the person will again need to formulate, initiate and execute new plans. Non-executive error correction is also possible. However, it has been demonstrated that this occurs automatically and too fast to be a conscious intervention and represents a different process.

6. Sustained attention

Recently, Manly & Robertson (1997) suggested that the capacity for sustained attention over long periods should also be considered a characteristic of executive control. In the completion of relatively simple tasks with low or intermittent demand, controlled processing requires the efficient activation of task goals. Allocating only the minimum resources for the perceived demands of the task and retaining spare capacity for the

processing of other, potentially important environmental information may be highly adaptive.

7. Accessibility to consciousness

A final characteristic that distinguishes between executive and non-executive behaviours is the former's accessibility to consciousness. Rabbitt (1997) argues that this feature is often under-emphasised in the literature because of the difficulty of empirically investigating conscious states. During a controlled performance, people can usually remember their last decision before an unexpected interruption. Yet, people can seldom remember the last decision they made before being suddenly interrupted while performing a well-practised task. A behavioural sequence that is performed automatically can apparently be performed unconsciously.

The executive functions are considered to be higher-level functions, which control the more basic cognitive functions and determine how an individual uses his knowledge and skills (Lezak, 1982). When severely impaired, they tend to affect all aspects of behaviour. The individual may no longer be capable of satisfactory self-care, earning a living or maintaining normal social relationships. However, in mild cases the deficits may be subtle and even overlooked in formal testing (Lezak, 1995) or interpreted as non-executive impairments. This study focuses only on the cognitive aspects of executive functioning. This should be understood by Rabbitt's (1997) definition: "... executive control is necessary to deal with novel tasks that require us to formulate a goal, to plan, and to choose between alternative sequences of behaviour to reach this goal, to compare these plans in respect of their relative probabilities of success and their relative efficiency in attaining the chosen goal, to initiate the plan selected and to carry it through, amending it as necessary, until it is successful or until impending failure is recognised" (p. 3).

4.2 An executive function model

Stuss & Benson (1986) have formulated a cognitive-neuroanatomical theory of the role of frontal lobe functioning on mental activity. They have attempted to integrate earlier theories of frontal lobe functioning with purely psychological theories and, in particular, acknowledge the respective contributions by Luria (1966/1980, 1970, 1973) and Shallice (1982) in this regard. Stuss & Benson (1986) conceptualise three levels of mental function that are organised hierarchically (see Figure 4-1, p. 41). Central to this theory is a model of executive functioning, which is responsible for providing conscious direction and control to posterior/basal brain functional systems.

The posterior/basal functions include emotion, language, memory, motor, visual-spatial ability and attention. They are described as integrated and fixed functional systems that perform efficiently in routine, overlearned situations. Although each system has direct and reciprocal connections with the frontal cortex, only their control is directly disturbed by frontal lobe pathology. Basic activities are left intact.

Executive controlled functions are activated in non-routine or novel situations, providing conscious direction to the basal systems for efficient processing of information. The model consists of two frontally-mediated functional systems, *drive* and *sequencing*, which are regulated by a third *control system*. The first provides the drive and motivation for the posterior/basal systems to function effectively. Drive is described as "a basic energizing force, ...while motivation suggests some control of this force" (p. 243). Damage to the frontal lobe may manifest as a change in drive, either a decrease in activity (apathy) or excessive drive (decreased ability to inhibit action). The second system, sequencing, is responsible for the organisation of information from the basal systems and orders behavioural responses. It includes the capacity to extract critical information, to identify and form sets and integrate this data into an understanding of a complex situation. The executive control system monitors and controls this interactive process. It determines both how the basic operations of the system are utilised, and the necessary order to achieve a specified goal within the given limitations of time and space. The prefrontal cortex is the anatomical basis for the function of control and is imperative when a new activity is being

EXECUTIVE FUNCTIONING MODEL

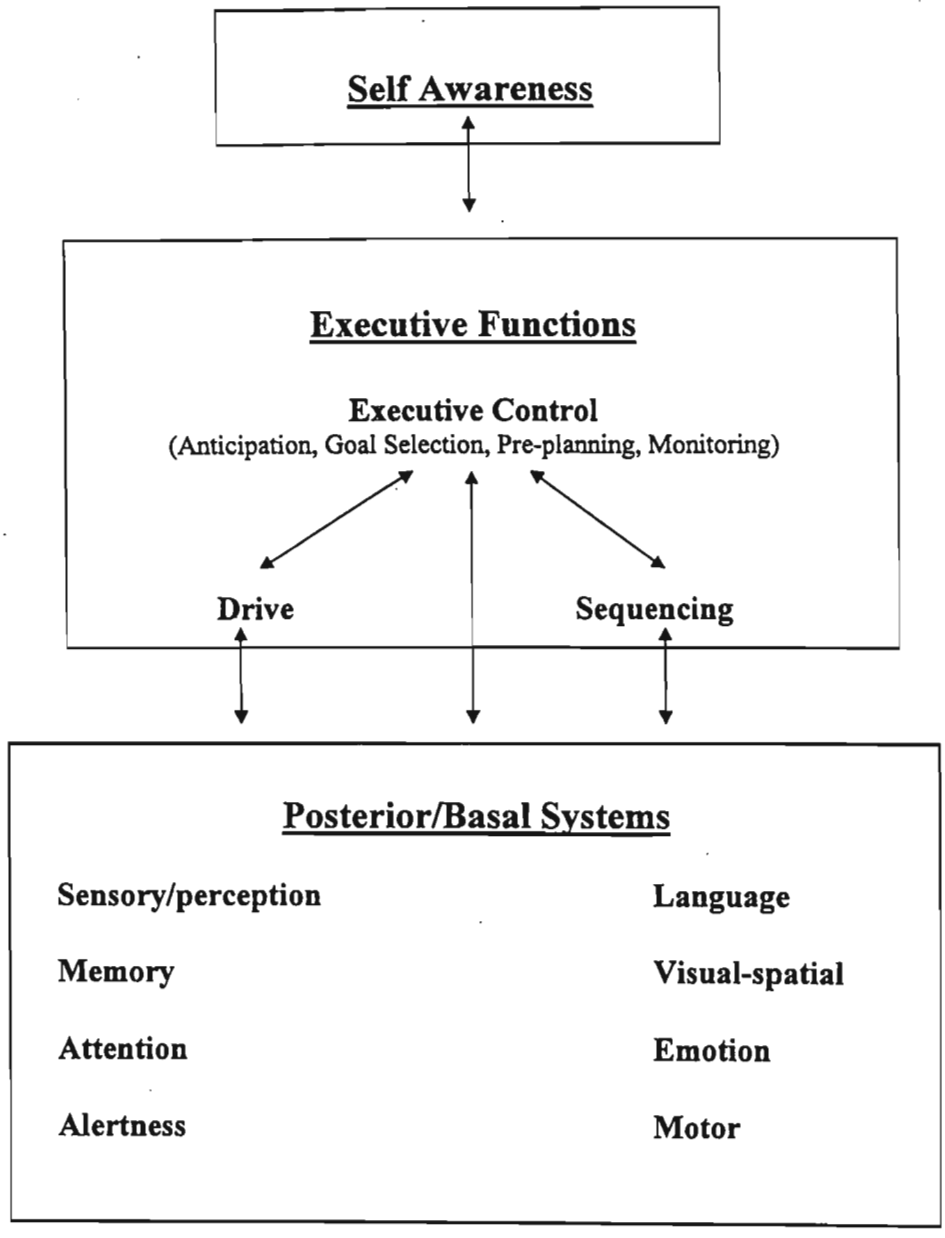


Figure 4-1. Model of executive functioning (adapted from Stuss & Benson, 1986)

mastered and active control is required. It is responsible for anticipation, goal selection, preplanning and monitoring. However, once an activity becomes routine or automatic, frontal participation is no longer required and it can be carried out by other brain areas.

Self-awareness and self-consciousness are considered the highest psychological processes (Stuss & Benson, 1986). As the most advanced mental activities, they are mediated by the most recent phylogenentic region of the brain, the prefrontal lobes. Self-awareness is the behavioural consequence of integrated executive control, utilising posterior/basal systems in a goal-directed manner through drive and sequencing functions.

Stuss & Benson (1986) acknowledge that the theory is incomplete and indeed, it fails to account for all of the proposed executive abilities. More importantly, it reflects the traditional approach in neuropsychology, which seeks connections between specific behaviour manifestations and damage to circumscribed anatomical areas of the brain. Recent advancements in functional neuroimaging have demonstrated that the neuroanatomical structures proposed do not correspond to the various executive abilities and have challenged the exclusive role of the frontal lobes in executive functioning (Reitan & Wolfson, 1994). This relationship is examined in more detail below.

4.3 Executive functions and the frontal lobes

Although a relatively new concept in neuropsychology, the executive processes have historically been associated with the frontal lobes. Luria (1973) never used the term executive function, yet his description of the role of the frontal lobes, fairly comprehensively conveys what is understood by this concept today.

"The tertiary portions of the frontal lobes are in fact a superstructure above all other parts of the cerebral cortex, so that they perform a more universal function of general regulation of behaviour than that performed by the posterior associative centre... the frontal lobes not only perform the function of synthesis of external stimuli, preparation for action, and

formation of programmes, but also the function of allowing for the effect of the action carried out and verification that it has taken the proper course..." (Luria, 1973, p.89-93).

A substantial body of evidence has converged on the opinion that the frontal lobes, rather than themselves performing specific cognitive operations (e.g. memorising, learning, reasoning) are instead concerned with the deployment of the capacity to carry out such processes, which take place elsewhere in the brain. It is thus thought the frontal lobes have a supervisory or executive function (Baddeley, Della Sala, Gray, Papagno & Spinnler, 1997).

In much of the literature concerning the impairment of executive functions, injury to the frontal lobes is implicated. However, Lezak (1995) also cites numerous studies, where subcortical damage may be involved. Recent findings suggest that executive function deficits may result from damage to more widespread brain regions than being truly specific to dysfunction of the frontal areas (Stuss, Eskes & Foster, 1994 in Foster, Black, Buck & Bronskill, 1997). The prefrontal cortex is intricately connected to structures in many other parts of the brain, including the posterior association cortex, limbic structures, the basal ganglia and other subcortical structures. Many of these connections are either reciprocal or form part of a circuit. Thus, damage to other structures in these circuits may cause similar impairments to those caused by prefrontal lesions (Mayes & Daum, 1997).

Reitan & Wolfson (1994) argue that there are fundamental problems with the hypothesis that executive control processes are located in the frontal lobes and emphasise that attempts to associate the capacities characteristic of executive behaviour with particular brain systems have been unsuccessful. Similarly, Foster et al. (1997) conclude that no research has been able to establish the precise brain regions that subserve the mediation of executive abilities.

Despite strong challenges to the assumption that that the frontal lobes are responsible for the executive functions, many neuropsychologists continue to use the terms *executive abilities* and *frontal abilities* interchangeably. However, the terms are not synonymous. Executive dysfunctions can occur without injury to the frontal lobe, while frontal lobes are

also responsible for cognitive functions that are not executive (e.g. motor functions, language expression, olfaction, certain aspects of memory, eye-hand coordination) (Vanderploeg, 2000).

Equally problematic is the interchangeable use of the terms "*frontal lobe test*" and "*executive test*". These tests are often not sensitive or specific to lesions in that particular brain area (Reitan & Wolfson, 1994). Anderson, Damasio, Jones and Tranel (1991) described a study in which they assessed a group of patients with stable MR- and CT-verified focal brain lesion (49 frontal, 24 non-frontal, 18 with frontal but not limited to frontal areas), using the Wisconsin Card Sorting Test (WCST). The WCST is frequently used to make judgements regarding a person's frontal brain system. Anderson et al. (1991) found no differences between groups on WCST performances. A number of the patients with extensive frontal damage performed normally on the tests and cut-off scores produced only a 62% accurate classification. The WCST should be classified as a test of executive- rather than frontal lobe-function.

Given the unreliability with which the cognitive functions map onto specific brain areas, it is imperative to distinguish between anatomical localisation of damage and functional deficit. The terms "frontal" and "executive" are not equivalent and to use them interchangeably is inaccurate and creates conceptual confusion.

4.4 Problems in the measurement of executive functions

A wide variety of neuropsychological tests are currently used to assess the executive functions. The list includes the Wisconsin Card Sorting Test, Category Test, Controlled Oral Word Association Test, Five-Point Test, Ruff Figural Fluency Test, Cognitive Estimation Test, Stroop Test, Trail Making Test, Austin Maze, Porteus Maze, Tinker Toy Test, and Tower of Toronto Test (Lezak, 1995; Spreen & Strauss, 1998). While these tests have some sensitivity to both frontal lobe and executive dysfunctions, none have gone unchallenged (Rabbitt, 1997). Many of the tests have been validated against their sensitivity to frontal lobe lesions, a heterogeneous and unreliable criterion, rather than

through experimental investigation of the processes involved (Phillips, 1997). Circular reasoning is also a problem in some studies (i.e. frontal lobe patients perform poorly on tests thought to measure executive function, therefore any test on which frontal patients perform poorly is an executive test). The validity of many of these tests, thus, remains unknown and their results should be interpreted with some caution.

The nature and complexity of executive functions present numerous methodological problems in test design. Some of these difficulties cannot be easily overcome and may further compromise the validity and reliability of these tests.

4.4.1 Need for novelty

Only novel tasks can be used to measure executive functions. Well practised tasks can be carried out using previously formulated strategies and are likely to require automatic, rather than effortful processing. However complicated, any task can only be novel on its initial presentation, making the assessment of test-retest reliability problematic (Burgess, 1997). Furthermore, it is difficult to ensure that a task is equally novel for all individuals. For any particular test, there may be individual differences, depending on subjects' previous experience, as to how novel the test format and content are. For example, letter fluency tasks are based on the assumption that most searches through knowledge are guided by semantic constraints and a search by phonemic criteria can be considered relatively novel. However, crossword puzzle experts may find the format of these tests somewhat familiar and be able to use previously developed strategies to complete them (Phillips, 1997).

4.4.2 Structure of tests and situations

The classical methodology of human experimental psychology is to control as many variables as possible, in order to isolate the effects of one critical variable. Lezak (1982) argues that traditional testing situations are too controlled and too structured to allow the manifestation of executive problems. Purposive behaviour cannot be assessed when a task

contains a large number of external cues, directing participants how and when to perform a task (Spikman et al., 2000). There is a paradoxical need to structure a test environment in which subjects are provided the opportunity to demonstrate their ability to create a structure for themselves. The responsibility for goal setting, structuring and decision making needs to be transferred from the examiner to the patient. In less structured tasks subjects must actively search for cues, placing a greater demand on self regulated executive abilities (Lezak, 1995).

4.4.3 Task specificity

There is evidence that some patients who fail certain executive tasks, perform successfully on many others (Burgess, 1997). Test performances may be task specific and deal only with specific classes of information. Similarly, performance on a single diagnostic test of executive function may not relate to the individual's capacity to function outside of the test situation and meet the demands of their daily lives (Wilson, Evans, Alderman, Burgess & Emslie, 1997). Executive tasks clearly make demands on a variety of skills, yet it is unclear whether these each involve a different set of functional processes. Kimberg and Farah (1993, in Rabbitt 1997) suggest that multiple working memories may exist, each dedicated to a situation-specific function, where damage to one system has little or no effect on another.

4.4.4 Task impurity

Task impurity is a concern in all areas of neuropsychological assessment, but especially in the study of executive functioning. As higher order functions, they make demands on a variety of other cognitive skills that are supported by a variety of different brain structures (Phillips, 1997). One is unable to measure the executive functions in isolation because the tests also assess a range of processes incidental to their main purpose (e.g. visuospatial processing, memory and motor and language functions). Failure of any of these functions may impact negatively on executive performance. To determine that a problem an

individual demonstrates is selectively executive in nature, it is necessary to know the state of all other non-executive systems (Burgess, 1997).

4.4.5 Reductionistic scores

Executive functions are complex, dynamic processes and considerable data are excluded or lost in the evaluation process. Test scores are reductionistic, symbolic representations of real events (Cripe, 1996). As real events become more complex, interactive and dynamic, the reductionistic symbols become a poorer representation of reality. Summary scores reveal very little about the process of task performance. This typically results in missing information, an oversimplification and a poor understanding of the realities being represented, and poor ecological validity.

4.4.6 Unpleasantness of tasks

Tests of executive function are frequently unpleasant to complete. Unlike tasks that are reasonably automated and require minimal effort, the executive tests demand effortful processing. The tasks are designed to be challenging, but may distress and demotivate some subjects and in turn confound their performance.

Despite the above difficulties, Phillips (1997) does not consider the assessment of executive functions impossible (as some have argued; see Reitan & Wolfson, 1994). There is reasonable consensus about the processes thought to be involved and most of the executive tests have face validity. They are generally novel, require effort in terms of on-line monitoring or response inhibition and most make demands on working memory. Until more information is available, Cripe (1996) recommends the use of tests that have demonstrated some sensitivity to executive functioning, and it remains that caution should be exercised in the interpretation of any findings.

CHAPTER 5. METHODOLOGY

5.1 Considerations in the design

A number of different research strategies have been used in the investigation of neuropsychological deficits in OSAS patients and were available for this study. The decision to compare executive functions across groups of subjects was determined by the research question and aim. A discontinuity in the manifestation of executive function deficits between moderate and severe OSAS patients was hypothesised, which could not be assessed using correlational techniques or linear regression. Separate analyses using (a) the frequency of apneas/hypopneas, and (b) the severity of hypoxemia as the independent variables were conducted to determine whether these indices are associated with different patterns of test scores. Due to the cost of overnight recording, it was not possible to recruit and assess age-matched controls. Patients whose polysomnograms were determined to be negative (i.e. no indication of OSAS) were used as controls.

5.2 Hypotheses

5.2.1 Hypothesis 1

There is a discontinuity in the manifestation of executive function deficits in OSAS patients. Patients with severe OSAS will score significantly lower on measures of executive function than both normals and those with moderate OSAS. Patients with moderate OSAS will not differ significantly from normals on measures of executive function.

5.2.2 Hypothesis 2

Indices of sleep fragmentation and hypoxemia will be associated with different patterns of impairment, as measured by the neuropsychological tests.

5.3 Subjects

A consecutive series of patients, referred to the Lorne Street EEG and Sleep Laboratory in Durban[2] for the assessment of sleep apnea, were recruited for the study. Subjects were screened to exclude the presence of underlying conditions that could interfere with neuropsychological test performance. This included all patients who reported a history of cerebral insult, epilepsy or other neurological pathology, alcohol or drug abuse, mental illness (defined as the diagnosis or treatment of severe psychopathology) or diurnal impairment of respiratory function. Individuals with co-existing causes of daytime sleepiness (e.g. night or rotating shift workers, self-reported sleep duration less than five hours, or narcolepsy) were also excluded. From the original pool of 41 subjects, three refused participation, two reported a history of stroke, one reported head injury, three were currently being treated for major depression or bipolar disorder and one patient was diagnosed with epilepsy. During the clinical interview one subject's understanding of English was determined to be insufficient for a valid assessment[3]. Two participants failed to complete the assessment battery and were excluded (the examiner was not aware of their apnea or hypoxemia severity). Furthermore, upon examination of the physiological records, two recordings contained significant artefact on the oxygen saturation recording and were judged to be inadequate for analysis.

The remaining 24 participants, of whom 23 were men, making up the final sample had a mean (*SD*) age of 41.2 (10.4) years, and 14.9 (2.5) years of education. Fifty-eight percent were considered overweight (above 20% of the ideal body weight for height and age). The mean Body Mass Index (BMI) for the sample was 32.6 (11.5).

Upon scoring and examination of the overnight polysomnogram, subjects were separately classified, according to the frequency of apneic events, as measured by the AHI and the severity of nocturnal hypoxemia. Subjects with AHI less than 10 were classified as normal (n=6). Patients with AHI greater than 10, but less than 30 were considered as moderately

[2] During the course of the study, the sleep clinic was relocated from City Hospital to St Augustine's Hospital. The procedures and recording equipment, however, remained constant

[3] All remaining participants had English as their home language.

apneic[4] (n=5), while those with an AHI above 30 were considered as severe apneics (n=13). These cut-offs reflect European and South African trends for classifying patient severity, used in both clinical practice and research. The percentage of total sleep time with arterial oxygen saturation (SaO_2) under 80% (% sleep SaO_2<80%) was used to classify the severity of hypoxemia. Criteria for inclusion in the severe hypoxemic group (n=7) was % sleep SaO_2<80% greater than five. Patients with % sleep SaO_2<80% more than zero, but less than five were assigned to the moderate group (n=7), and those with % sleep SaO_2<80% equal to zero were considered non-hypoxemic (n=10). Although previous studies have used a combination of apnea frequency and the level of hypoxemia to classify the severity of OSAS patients, sleep fragmentation due to event related arousals, and hypoxemia are hypothesised to affect neuropsychological performance differently. Separate analyses enabled the differential effect of these two pathological mechanisms to be examined. Furthermore, using the two criteria together would have resulted in the exclusion of a significant proportion of subjects from the analysis. While many patients who were classified as severely and moderately apneic, were also classified as severely and moderately hypoxemic respectively, there remained patients with severe apnea, but without significant hypoxemia and moderate apneics with severe hypoxemia. Both residual lung volumes and the duration of apneas influence the extent of oxygen desaturation (Shepard, 1994).

This research was conducted in accordance with ethical guidelines, as described in the *Psychological Association of South Africa: Ethical Code for Psychologists*. The protocol was approved by the School of Psychology, University of Natal (Pietermaritzburg) and the Lorne Street EEG and Sleep Laboratory. Prior to their participation, all eligible subjects were briefed about the nature of the research, including both the objectives and the procedures involved. Participation in the study was on a volunteer basis, with subjects free to withdraw at any time. Written consent was obtained from all subjects participating in the study (Appendix 1). Participants were given feedback regarding their individual neuropsychological performance[5].

[4] Although the groups are classified according to the frequency of both apneas and hypopneas, the labels non-apneics (normals), moderate apneics and severe apneics are applied for economy of expression.
[5] Three subjects could not be contacted on follow-up and never received feedback.

5.4 Procedure

Subjects were recorded overnight with the neuropsychological assessment taking place the following morning. The patients arrived at the sleep laboratory between 18h00 and 19h30. After eating dinner, they met with the principal researcher who administered a standard intake questionnaire (Appendix 2) as part of a semi-structured interview. The questionnaire, which is given to all patients who undergo a sleep study at the laboratory, focuses primarily on the individual's sleep habits and daytime symptoms.

All patients were then fully briefed about the purpose of the research. They were explained important background information regarding the pathophysiology and symptoms of OSAS, the nature of the neuropsychological examination, how the results would be used, how and when feedback would be given and the nature and extent of their informed consent.

A second questionnaire (Appendix 3) detailing demographic and anthropometric (e.g. height, weight) information, educational, medical and psychiatric history was administered. Levels of daytime sleepiness were measured using the Epworth Sleepiness Scale (ESS) (Johns, 1991, Johns & Hocking, 1997). The ESS is a four-point rating scale that measures sleepiness as the tendency to fall asleep during specific, non-stimulating activities (e.g. watching TV or sitting quietly after a lunch without alcohol). It is a well-established, validated measure that demonstrates significant differences between hypersomnolent subjects and controls. An ESS score greater than 10 is considered indicative of EDS. Although two objective measurements, the Multiple Sleep Latency Test (MSLT) and Maintenance of Wakefulness Test (MWT) (Mitler, 1993) are frequently used to assess sleepiness, limited resources precluded their inclusion in this study. These procedures are extremely costly and time consuming, as both necessitate repetitive intervals of electroencephalogram (EEG) monitoring in a sleep laboratory for an 8-hour period.

In addition to eliciting important information, the interview served two important functions:

(1) It provided participants with the necessary and sufficient information to ensure that their consent was well informed.

(2) Participants were able to meet with the examiner, and clarify any uncertainties regarding the procedures and how their results would be stored and used. This served to reduce anxiety and to develop the rapport necessary for maximum performance in the neuropsychological assessment the following morning.

5.5 Polysomnogram

All subjects underwent full-night polysomnography, the standard prescribed by ASDA (1997) and American Thoracic Society (1989) for the diagnosis and evaluation of sleep-related breathing disorders. This involved the simultaneous monitoring of multiple physiological parameters while the patients slept. The following parameters were recorded in this study:

- Central and occipital EEG for the staging of sleep and to determine arousals.
- Electro-oculogram (EOG) to record eye movement observations and detect REM sleep.
- Electrocardiogram (ECG) to detect arrhythmias.
- Sub-mental electromyogram (EMG) for staging REM sleep.
- Oral and nasal thermistors to measure airflow at the mouth and nose.
- Thoraco-abdominal plethysmography for monitoring the amplitude of respiratory movements and the differentiation between types of SDB.
- Snore microphone to detect snoring.
- EMG attached to the anterior tibialis to record periodic leg movements.
- Pulse oximeter attached to the index finger, used to monitor the ratio of oxygenated haemoglobin to total haemoglobin in arterial blood or SaO_2 (Hanning & Alexander-Williams, 1995).
- Positional changes - the transducers and wires permitted normal positional changes during sleep.

Data were recorded and computer scored using Sleep Lab® for Windows (Aequitron Medical, 1995). In preparation for the final analysis, a clinical technologist reviewed and corrected the computer-analysed data and the results were subsequently confirmed by a neurologist. Sleep variables included the time in each sleep stage as a percentage of total sleep time.

Sleep fragmentation was scored using the (a) Apnea/Hypopnea Index (AHI) - the number of apneas plus hypopneas per hour of sleep, (b) Apnea Index (AI) - the number of apneas per hour of sleep and (c) Arousal Index - the number of arousals per hour of sleep. The AHI was judged to be the most important of these indices. It not only appears to be the most consistently reported index in the literature, but is also widely used to make clinical judgements. The AI excludes recurrent hypopneas, which like apneas, can result in significant sleep disruption. Gould et al. (1988), observed that patients with frequent hypopneas were clinically indistinguishable from patients with recurrent apneas and confirm the clinical importance of this group. The number arousals per hour of sleep varies widely in the normal population and was not considered to be a reliable measure of sleep disordered breathing.

Hypoxemia was quantified by (a) minimal SaO_2 recorded during total sleep time, (b) desaturation index - the number of 4% desaturations from baseline per hour of sleep, (c) average low SaO_2 during desaturations, and (d) the percentage of total sleep time with SaO_2 below a specified level. Although records were carefully scanned and rechecked for artefact, isolated errors are possible. The minimum SaO_2 value is more likely to be biased by single errors than the other hypoxemia variables, and as a result may be less reliable. The desaturation index is measure of frequency, and provides no estimate of the extent or duration of the desaturations. Similarly, the average low SaO_2 does not control for the frequency of desaturations. The amount of time a patient spent below a specified level of desaturation during sleep was determined to be the best estimate of hypoxemia. This figure was corrected for differences in recording time and expressed as a percentage per hour of sleep. Various cut-offs (i.e. 90%, 85%, 80%) were available and have been used by different researchers. Hanning & Williams (1995) note that visual, cognitive and EEG changes occur when the oxyhaemoglobin saturation is less than 80-85% in normal subjects.

Given the intermittent nature of oxygen desaturations experienced by OSAS patients, the more conservative lower limit of this range was selected as the criteria. The cut-off values (% sleep SaO_2<80%) greater than five, between zero and five, and zero for the severe, moderate and non-hypoxemic groups respectively correspond with those used by Bédard et al. (1991, 1993).

5.6 Neuropsychological assessment

Neuropsychological testing was conducted in the morning following overnight polysomnography. The recording was interrupted between 05h15 - 05h45 and electrodes and monitoring equipment removed. The assessment commenced once the participants had showered and reported adequate arousal. All assessments were conducted in the sleep laboratory, a quiet environment, largely free from outside distraction. The tests were administered and scored before the analysis of the polysomnogram, thus the examiner was blind to the severity of the patients' apnea.

The choice of neuropsychological measures selected for this study was based on a number of considerations:

(1) The executive functions comprise numerous cognitive capacities. The battery should be sufficiently broad based to sample the diversity of these skills.

(2) While acknowledging the methodological difficulties in validating executive function tests (discussed in Chapter 4, pp. 44-47), the instruments should have reasonably established validity. All of the tests administered are commonly used in both research and clinical practice for the assessment of executive functions (Spreen & Strauss, 1998).

(3) Both the individual tests and the overall battery should be of short duration to enable participants to maintain maximum performance throughout the assessment. OSAS patients are especially susceptible to fatigue and have been reported to have difficulty sustaining concentration, which might otherwise compromise their performance.

(4) Since the hypothesized deficits are subtle, the tests should be sensitive to minor cognitive impairments. Tests that are not sufficiently sensitive may result in ceiling effects, where a clustering of test scores occurs at the upper limit of the variable being measured.

(5) The battery should permit convergence of findings, with several tests measuring a single capacity. This provides a stronger base for claims of impaired or intact ability.

(6) To permit comparison with existing data and future replication, only standard tests with uniform administration and scoring procedures were included. Décary et al. (2000) proposed a standardised neuropsychological test battery for the evaluation of OSAS patients that will allow for the comparison of results from different laboratories. Five of the six instruments used in this study are included in the suggested battery.

Standardised administration procedures were followed, using the instructions, directions regarding test materials and time limits specified in the test manuals. The battery comprised both paper-and-pencil and computer-administered tests. The same order of presentation was maintained for all subjects and is presented in Table 5-1. While it could be argued that a randomised order might have been preferred, it was considered important to begin with the least threatening tasks to reduce participants' anxiety. The difficulty level and response format was varied thereafter, to maintain subjects' interest and minimise the potential effect of fatigue. A more detailed description of the individual tests follows.

Table 5-1 Neuropsychological Test Battery

Test	Approximate Duration (Minutes)
Five Point Test	5
Digits Forward & Backward	5
Stroop Test	5
Trail Making Test	5-10
Continuous Performance Test	8
Wisconsin Card Sorting Test	15
TOTAL	**43-48**

5.6.1 Five-Point Test

The Five-Point Test (Regard, Strauss & Knapp, 1982) is a nonverbal figural fluency task, which measures the production of novel designs under time constraints (Spreen & Strauss, 1998). The test is thought to be a sensitive measure of fluid and flexible thinking and the ability to create novel responses without repetitions (Lee et al., 1997). Poor performances on fluency tasks have been attributed to an inability to generate appropriate task strategies and are generally interpreted to reflect executive dysfunction (Lezak, 1995). Scores on the Five-Point Test are moderately correlated with other measures of executive control (e.g. Wisconsin Card Sorting Test) as well as visuospatial and visuocontructive measures (Picture Completion and Block Design).

The task consists of a page with 40 boxes, each of which contains five dots arranged symmetrically, identical to the five-dot arrangement on dice. Subjects were instructed to produce as many different designs as possible within 3 minutes by joining the dots in each box using straight lines. Scores include the total number of unique designs and the number of repeated figures (perseverative errors). Since more productive individuals have a greater

chance of making more perseverative errors, the percentage of perseverative errors [(perseverative errors / total unique designs) x 100] was also calculated (Lee et al., 1997).

The Five-Point Test is more dependent on intact executive functioning than letter fluency tasks (e.g. Controlled Oral Word Association), as it requires the generation of novel figures, rather than retrieval of information from long-term memory. As a result, the task is likely to be less familiar and is therefore less susceptible to previously used strategies. Phillips (1997) examined the susceptibility of verbal and figural fluency performance to secondary tasks. In the dual task paradigm, a target task is performed simultaneously with a secondary task thought to load on executive function. It is reasoned that if there is significant interference between the two tasks, then the target task involves executive functioning. The results suggested that letter fluency tasks might not be as sensitive to the executive functions as previously assumed, as there was no significant effect of random generation on letter fluency. Significant interference between random generation and figural fluency on the Five-Point Test supported the use of this test as a measure of executive function.

Normative data for the Five-Point Test are limited. Lee et al. (1997) report no significant associations between age, gender or education and tests scores in a sample of 196 neurological and psychiatric patients. However, data regarding the correlation between demographic variables and the performance of normal subjects on this test remain limited.

5.6.2 Digit Span

The Digit Span forms part of both the Wechsler Intelligence and Memory Scales. It comprises two separate tests, Digits Forward and Digits Backward, which involve different mental activities and are affected differently by brain damage (Lezak, 1995). While both tests are dependent on short-term retention capacity, Digits Forward is a more passive process, measuring the efficiency of attention or freedom from distractibility. It serves as a control for the more demanding Digits Backward, a measure of double tracking. Both memory and reversing operations must proceed simultaneously in the latter task,

demanding increased effort that involves the working memory and the central executive. Banken (1985) recommends that the scores be considered separately to avoid confounding the data and obscuring important information.

The South African Wechsler Adult Intelligence Scale (SAWAIS) (National Institute for Personnel Research, 1983) version of the Digit Span was administered. In Digits Forward, the examiner read out a randomly generated sequence of digits, at a rate of one per second. The subject was asked to repeat the numbers in the identical order. The test began with a three-number sequence and the length was increased after each successful trial, until the subject failed two consecutive trials of the same length. The score is the number of correctly repeated digits. In Digits Backward, sequences of numbers were presented as above, but with the instruction to recall the digits in reverse order. Testing continued until the subject failed a pair of sequences. The score was the number of digits in the longest trial passed. The discrepancy between the two scores can be a useful diagnostic sign (Lezak, 1995). Adults typically produce forward spans that are two digits longer than backward spans. A deficit of three or more points is more common in brain-damaged groups than intact populations. Although clinically useful, the interpretation of the difference-score has not been validated. As the executive functions were the focus of this investigation, only Digits Backward was included in the analyses.

5.6.3 Stroop Test

The Stroop Test measures the relative speed of reading names of colours, naming colours, and naming colours used to print an incongruous colour name (e.g. the word 'blue' printed in green ink) (Mitrushina, Boone & D'Elia, 1999). The latter presents an interference situation, known as the Stroop Effect, which requires the ability to inhibit an over-learned response in favour of an unusual one (Spreen & Strauss, 1998). Performance on this test is associated with resistance to interference, cognitive flexibility, as well as ease and rapidity of shifting from one perceptual set to another.

Stroop tests are based on observations that it takes longer to call out the ink colour of coloured patches than to read out words, and even longer to name the ink colour of the incongruous words (Lezak, 1995). Attending to the lexical features of words is highly automatic, whereas attending to ink colour is not (Macleod, 1991). In the interference task, executive control processes are required to suppress the automatic tendency to attend to lexical features and shift the focus of attention towards colour features, thereby increasing response times (Brown et al., 1999). The shape of the word acts as a prepotent stimulus and as a distracter when combined with a stimulus (the different colour) that has a less habituated response. Alternative hypotheses that account for the Stroop effect have been put forward and Macleod (1991) provides a thorough review.

Several versions of this test have been published and differ according to the number of colours used, number of items presented, administration procedures and scoring (Lezak, 1995; Mitrushina et al., 1999). Golden's (1978) version was selected for the purpose of this research, primarily because of its short administration time. Alternative formats may take up to 2-3 times longer to complete and yield no additional information. Lezak (1995) notes that the Stroop test may be extremely unpleasant to do and can cause extreme frustration in impaired subjects and a refusal to continue. It was important to minimise any unnecessary frustration for participants by limiting the test length. Furthermore, OSAS patients are frequently susceptible to fatigue and the purpose of including this test was to assess the capacity to resist interference, rather than vigilance, which longer versions may measure.

The test consists of three A4 pages, each with 100 items, presented in 5 columns with 20 rows. The first page (W) contains the words RED, GREEN, BLUE printed in black ink. Subjects are required to read the words, scanning the columns vertically, beginning on the left side of the page and working right. The second page (C) consists of items, all written as 'XXXX', printed in either red, green or blue ink and the task is to name the colours. On the third page (CW), the colour-words and the ink in which they are printed in are incongruent. Subjects are required to name the colour of the ink, ignoring the word (interference task). The scores (W, C, CW) are the number of correctly identified items on each page in 45 seconds. Errors are not counted, although they result in a lower overall score since subjects are made to repeat the item. Secondary scores, which are not dependent on the subjects

reading or colour naming speed, may also be calculated. Golden (1978) recommends finding the difference between CW and predicted CW (Interference Score). The following formula is used for calculating the predicted CW scores:

$$\text{Predicted CW} = \frac{C \times W}{C + W}$$

Test-retest reliability is satisfactory and Spreen & Strauss (1991) report reliability estimates ranging between .83 and .91 for the three parts. Mitrushina et al., (1999) provide an extensive review of the normative data and propose that both age and education may impact on Stroop performance. Increasing age is associated with a slowing in colour naming and an increase in the interference effect. Some studies have shown a small correlation between the interference score and education, while others report no significant associations.

5.6.4 Trail Making Test

Originally developed as part of the Army Individual Test Battery and now included in the Halstead Reitan battery, the Trail Making Test (TMT) is a widely used neuropsychological test that is sensitive to the effects of brain damage of diverse aetiologies (Mitrushina et al., 1999). It provides information regarding speed for visual search, attention, information processing and motor functioning as well as mental flexibility, or the ability to alternate between two sets of stimuli (an executive function) and working memory functions (Crowe, 1998).

Administered in two parts (TMT-A, TMT-B), participants were required to perform a tracing task, under two conditions. TMT-A consists of a series of circles, each enclosing a number from 1-25, scattered at random on the page. The subjects were required to connect

the circles in numerical order, as quickly as possible, using pencil lines. TMT-B, is a more complex double tracking task, with numbers 1 though 13 and letters A though L within the circles. The subjects' task was to join the encircled numbers and letters in alternating order (e.g. 1-A-2-B-3-C, etc.). The examiner pointed out errors, so that they could be corrected, and these are reflected in the total time to complete each section.

The scores are the time taken in seconds to complete the two parts. A negative correlation exists between test scores and level of performance (i.e. the lower the score, the better the performance). In addition, two derived scores are often calculated to assess the relative performance on the two parts: the B-A difference, and the B/A ratio. These scores provide measures that are relatively independent of both motor and visual scanning speed (Corrigan & Hinkeldey, 1987). Clinically, a B/A ratio less than 2.0 indicates a greater impairment on TMT-A, a score between 2.0 and 3.0 an equivalent performance on the two parts, and a ratio greater than 3.0 shows relative impairment on TMT-B. Lezak (1995) observes that when the time taken to complete TMT-B is relatively much longer than that taken to complete TMT-A, the subject probably has difficulty in complex conceptual tracking. Slow performance on Part A or Parts A and B may indicate motor slowing, incoordination, visual scanning difficulties, poor motivation or conceptual confusion.

Two recent studies (Gaudino, Geisler & Squires, 1995; Vickers, Vincent & Medvedev, 1996) have suggested that TMT-B and TMT-A differ not only in cognitive demands, but also in the length of the completed trails and the degree of interference in the visual scanning element of the tasks and have questioned the validity of the derived scores. However, Arbuthnott & Frank (2000) have subsequently provided strong evidence that the relative performance on TMT-B and TMT-A is associated with set switching costs and provides a measure of cognitive control. The authors concluded, "the assumption underlying the clinical interpretation of the TMT appears to be valid, and the test can continue to be used as an efficient means to assess executive function" (p.527).

Reliability coefficients vary considerably between studies, but are generally in the .70 -.90 range (Spreen and Strauss, 1998). A number of demographic factors (e.g. age, education and intelligence) are reported to influence test performance. Age accounts for most of the

variance, with performance times increasing with age (Greene & Far, 1985 in Mitrushina et al., 1999). Higher education is associated with faster times, as is intelligence. No gender differences have been consistently tied to test performance. According to Corrigan & Hinkeldey (1987) the effect of age and education on the ratio score (B/A) is practically insignificant and, to some extent, it controls for the effect of these variables on performance. The times for TMT-B and the ratio score were included in the data analyses in this study.

5.6.5 Continuous Performance Test

The Continuous Performance Test (CPT) is used to measure vigilance or an individual's ability to sustain attention over time (van Zomeren & Brouwer, 1994). Although the CPT is not an executive function test, it was included in the current battery to explore the possible contribution of vigilance on neuropsychological performance. OSAS patients frequently report difficulties concentrating (Décary et al., 2000). A diminished capacity for sustained attention, which could affect the participants performance on the other cognitive tests and confound any findings.

The CPT measures the ability to detect and respond to specific stimulus changes occurring infrequently and at random intervals over a prolonged time period, while simultaneously inhibiting responses to extraneous stimuli (Ballard, 1996). Many versions of the CPT are available and vary with regard to modality (visual or auditory), the types of stimuli (letters, numbers, colours or geometric figures) and the nature of the task. In some versions subjects must respond to a single stimulus (e.g. the letter 'X'), while in others the target is a designated sequence of stimuli (e.g. 'A' followed by 'X') (Halperin, 1991). The single stimulus ('X') version was preferred to the serial sequence stimulus ('AX') version, as it is cognitively less complex and the rationale for administering the CPT was only to measure sustained attention.

The Neurobehavioral Evaluation System 2 or NES2 (Letz, 1998) version of the CPT was used. In this computer-administered task, several large letters were flashed briefly (50

msec) on the screen at a rate of one per second for eight minutes. Participants were asked to respond as quickly as possible, by pushing a computer key, to the appearance of the letter 'S' on the video display, but not to the appearance of any of five distracter letters. Each stimulus was randomly selected, except that a given stimulus was rejected if it was identical to the previous one, i.e. no two stimuli in a row were the same. Seven blocks of trials, each with 12 critical stimuli, were presented. The programme records the response latency for each critical stimulus, allowing the computation of the total mean reaction time and mean reaction times for each block. To measure the loss of performance over time, the difference between mean reaction times of Block 7 and Block 2 were calculated. Block 1 was not used to allow for any learning effects that may occur during the early stage of the test.

No practice effects have been reported on repeated examination and the test-retest reliability is good. In fact, a slight negative practice effect occurs, due to the tedious nature of this task (Spreen & Strauss, 1998). There is a fall off in performance in the later years, with the vigilance hit rate varying as an inverted U-shaped function of age across the lifespan (Ballard, 1996).

5.6.7 Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST), developed by Grant & Berg (1948), is used to assess an individual's ability to form abstract concepts, to shift and maintain a set, and utilise feedback (Spreen & Strauss, 1998). It is considered to be a measure of executive functioning as successful performance requires strategic planning, organised searching, the ability to use environmental feedback, to shift cognitive sets, goal orientated behaviour and the ability to modulate impulsive responding. Test scores provide an overall indication of success and information on particular sources of difficulty on the task (Heaton, 1981).

The standardised version of WCST, described by Heaton (1981) consists of 4 stimulus cards that are placed in front of the subject. The first has a single red triangle, the second has 2 green stars, the third has 3 yellow crosses, and the fourth has 4 blue circles. The

examiner then gives the subject 2 packs of 64 cards with designs similar to the stimulus cards, but varying in colour, geometric form and number. The object is to place the cards, one by one, under the four stimulus cards. To do this successfully, the subject must work out from the examiner's verbal responses (only permitted to say "right" or "wrong"), the principle by which the cards should be sorted. After a run of ten consecutive correct placements, the examiner changes the principle being used for placement. The test begins with colour as the basis for sorting, shifts to form, then to number and returns again to colour, etc.

In this study, a computerised version (Ormond Software Enterprises, 1999) of the WCST was administered. The subjects were seated in front of a personal computer and given a printed copy of the instructions. After reading the instructions, all subjects were given the opportunity to practise moving the cards and familiarise themselves with using the mouse. Cards were moved either by dragging and dropping or pointing to the preferred placeholder and clicking. Testing proper followed, with the computer administering the test and providing both auditory and visual feedback about whether a card was correctly or incorrectly placed. Testing continued until all 128 cards were sorted.

The results were then computer-scored according to the criteria defined by Heaton (1981), providing the following: (*a*) *completed categories* - number of categories (sequence of 10 correctly sorted cards)*; (b) number of errors; (c) perseverative responses* - responses that would have been correct in the previous stage of the test, e.g. sorting according to colour, when the current rule is form; *(d) perseverative errors* - incorrect perseverative responses.

A computerised version was preferred to manual administration, which is complicated and susceptible to errors. Examiners are required to provide feedback to the patients, keep track of the correctly matched cards and responses, and record the attributes of the sorted response cards. Mistakes are common, even among experienced clinicians. Paolo, Axelrod, Ryan & Goldman (1994) report errors in 71.4% of protocols of manually administered tests. Computer administration eliminates these errors. Scoring is also complex, with inter-rater reliability varying between .75 and .97 (Axelrod, Goldman, Woodard, 1992), whereas computer scoring has a reliability of 1.

Test-retest reliability, as with many executive function tests, is low. Lezak (1995) observes that once the category sort and shift principle have been identified, the WCST no longer measures problem solving in individuals with a reasonably intact memory. Performance remains fairly stable in adults under 70 years, whereafter a decline in some aspects of performance becomes evident. There is a modest, but positive correlation between WCST scores and education, with higher education levels associated with somewhat better performance (Spreen & Strauss, 1998).

5.7 Analysis

The results were analysed using the Statistical Package for the Social Sciences (SPSS®) for Windows, version 9.0.1 (SPSS, Inc., 1999). Given the hypothesised discontinuity in executive function deficits in OSAS patients, subjects were allocated into research groups and the performance across groups compared. Mean scores and standard deviations of each of the demographic, physiological and neuropsychological variables were calculated for the three groups (according to apnea severity) of subjects. The distributions were then examined for deviations from normality (Shapiro-Wilk Test) and homogeneity-of-variance (Levene Statistic). With the exception of BMI scores and percentage of Stage 1 sleep, the demographic and physiological variables were normally distributed, with homogenous variances. Of the 33 neuropsychological test scores, 7 (21%) were identified as having non-normal distributions and one of the ten variables reflected heterogeneous variances (FPT percent perseveration). Transformations failed to correct all of the non-normal distributions and heterogeneous variances. The data were reexamined using the hypoxemia (% sleep<5%) groups as the independent variable. Of the demographic and physiological variables, only the Levene Statistic for BMI was significant. Eight (24%) of the neuropsychological test scores deviated from normality and one of the variables (WCST Categories) had unequal variances. Transformations were only successful in correcting a selection of these distributions.

One way analyses of variance (ANOVA) were used to compare group means for demographic and sleep staging variables (transformed values were used where

appropriate). Multiple pairwise comparisons were made using t-Tests with Bonferroni adjusted significance levels. Although ANOVA is considered to be a very robust statistical procedure and the assumptions can be violated with relatively minor effects (Howell, 1997), Lezak and Gray (1984) observe that violations of the parametric requirements of normality and homogeneity of variance may lead to an overestimation of the Type I error rate. In effect, this results in a loss of power and an increased chance of overlooking a potentially significant finding. For this reason, non-parametric methods were preferred for the analysis of neuropsychological test scores. The Kruskall-Wallis Test was used to compare overall group performances, with the significance level set at .05. The Mann-Whitney Test was used for pairwise comparisons. Applying a procedure to decrease vulnerability to Type I errors, described by Marascuilo & McSweeney (1977), the critical p-value was divided by the number of comparisons, resulting in significance level of .017.

In addition to comparing the raw neuropsychological test scores across groups, standard (z) scores were calculated using available norms (described in Appendix 5). Z-scores are expressed in standard deviation units, the amount a score deviates from the mean of the normative population. This approach provides for a more clinical evaluation of the data. Specifically, an overall rating of impairment was calculated for each subject and analysed for group differences. The frequency of "borderline/impaired" and "non-impaired" scores across the research groups were also calculated and chi-square analyses conducted to determine the clinical significance of the findings. Several classification models are available to researchers and clinicians. Lezak (1995) provides a widely used system (Table 5-2), where each ability level represents a statistically defined range of scores. These criteria were used in the analysis of the standard scores.

Table 5-2 Classification of Ability Levels.

Classification	Z-score	Percent Included	Lower Limit of Percentile Range
Very superior	+2.0 and above	2.2	98
Superior	+1.3 to 2.0	6.7	91
High average	+0.6 to 1.3	16.1	75
Average	±0.6	50.0	25
Low average	-0.6 to -1.3	16.1	9
Borderline	-1.3 to -2.0	6.7	2
Impaired	-2.0 and below	2.2	-

(Lezak, 1995, p. 159)

CHAPTER 6. RESULTS

6.1 Apnea severity

The mean (*SD*) AHI for the sample was 44.0 (34.8) and for the three groups of subjects: non-apneics 4.0 (2.7), moderate apneics 19.4 (8.0) and severe apneics 72 (19.9). The group demographic characteristics, along with univariate F-values (ANOVA) and pairwise comparisons (t-Tests with Bonferroni adjusted significance levels), are presented in Table 6-1. All three groups were of comparable age and education. The severe group had a substantially higher BMI (p=.022) than the moderate group. There were no significant differences between groups with regard to the severity of self-reported symptoms of daytime sleepiness on ESS.

Table 6-1 Demographic variables for apnea groups

	A NORMAL (*n*=6) mean (*SD*)	B MODERATE (*n*=5) mean (*SD*)	C SEVERE (*n*=13) mean (*SD*)	F-VALUE *df*(2,21)	A-B	A-C	B-C
					p-values[a] (Bonferroni-adjusted)		
Age	41.3 (11.3)	40.2 (14.9)	41.5 (8.9)	.02	1.000	1.000	1.000
Education	15.7 (3.7)	14.4 (1.8)	14.7 (2.0)	.42	1.000	1.000	1.000
BMI[b]	28.2 (2.4)	23.8 (4.4)	38.0 (13.1)	5.13*	1.000	.166	.022*
ESS	10.0 (5.8)	12.4 (4.8)	12.6 (4.0)	.68	1.000	.805	1.000

[a] t-Tests

[b] Values of p based on transformed values (square-root)

*: p<.05

Table 6-2 contains the sleep staging analysis for the three levels of apnea severity. Significant differences for the percentage of SWS [F(2,21)=6.27, p=.007] and percentage of Stage 2 sleep [F(2,21)=5.05, p=.016] were observed between the groups. Pairwise comparisons showed severe apneics spent proportionally less time in SWS than moderates (p=.012) and a greater percentage of time in Stage 2 than non-apneics (p=.015).

Table 6-2 Sleep staging variables for apnea groups

	A NORMAL (n=6) mean (SD)	B MODERATE (n=5) mean (SD)	C SEVERE (n=13) mean (SD)	F-VALUE df(2,21)	A-B p-values [a] (Bonferroni-adjusted)	A-C	B-C
% Stage 1 [b]	36.2 (20.8)	19.9 (9.5)	29.7 (10.1)	1.60	.367	1.000	.361
% Stage 2	38.4 (13.9)	52.0 (11.8)	54.4 (7.9)	5.05*	.126	.015*	1.000
% Stage SWS	14.1 (7.0)	17.7 (6.1)	6.6 (6.5)	6.27**	1.000	.088	.012*
% REM	11.4 (10.5)	10.4 (6.5)	9.3 (7.1)	.14	1.000	1.000	1.000

[a] t-Tests

[b] Values of p based on transformed values (natural logarithm)

*: p<.05, **: p<.01

The results of the various neuropsychological test scores/indices are summarised in Table 6-3. Overall comparison of group scores was significant for Stroop Colour-Word [χ^2 (2)=10.10, p=.006], with severe apneics performing worse than both moderates [U(5,13)= 5.5, p=.002] and controls [U(6,13)=11.5, p=.007). Group performances also differed on WCST categories [χ^2 (2)=5.91, p=.046]. Pairwise comparisons revealed a difference between normals and the severely apneic group [U(6,13)=12.5, p=.008]. In completing fewer categories, the severe group also committed more errors than did the normals [U(6,13)=14, p=.014]. No tests of executive function differentiate moderate apneics from normals. Noteworthy is the non-significant difference between the three groups on CPT difference score [χ^2 (2)=1.41, p=.565]. The difference in reaction times (milliseconds), between blocks two and seven, provides an index of sustained attention. Large positive values indicate a loss of performance over the course of the test and suggest poor concentration. Pairwise comparisons on this index were also non-significant, suggesting that concentration is not a factor affecting group performance on the executive function tests.

Table 6-3 Comparison of neuropsychological test scores for apnea groups

	A NORMAL (*n*=6) mean (*SD*)	B MODERATE (*n*=5) mean (*SD*)	C SEVERE (*n*=13) mean (*SD*)	χ^2 VALUE[a] (*df*=2)	P-VALUE	A-B	A-C	B-C
						p-values (Mann-Whitney Test)		
FPT unique designs	33.5 (10.7)	28.8 (6.8)	25.3 (7.4)	2.80	.248	.214	.066	.212
FPT percent perseveration	3.5 (2.7)	1.2 (1.7)	13.3 (9.3)	2.76	.250	.132	.264	.062
Digits Backwards	5.2 (.8)	4.8 (.8)	4.5 (1.6)	2.70	.268	.353	.077	.185
Stroop Colour-Word	41.8 (7.3)	42.0 (3.4)	33.1 (5.7)	10.10	.006**	.448	.007**†	.002**†
Stroop Interference	.1 (6.6)	.8 (6.5)	-6.0 (6.2)	3.32	.200	.465	.122	.059
Trail Making Test B	51.8 (9.8)	65.4 (22.4)	81.4 (53.1)	3.36	.186	.123	.043*	.360
TMT-B/TMT-A	2.1 (.7)	1.8 (.4)	2.6 (1.7)	1.07	.584	.268	.483	.168
WCST categories	5.5 (2.2)	4.2 (3.0)	2.9 (2.4)	5.91	.046*	.240	.008**†	.114
WCST errors	44.0 (13.0)	57 (19.8)	65 (19.6)	5.55	.062	.080	.014*†	.174
WCST perseverative errors	11.0 (5.9)	11.6 (5.9)	20.2 (12.1)	3.73	.155	.457	.046*	.097
CPT difference score	20.3 (37.4)	27.2 (47.9	47.3 (49.3)	1.41	.565	.535	.146	.317

[a] Kruskall- Wallis Test

* p<.05, ** p<.01, † p<.017 (Mann-Whitney Test)

As the overall sample size in the study was small (n=24), with the normal and moderate apneic groups containing only five and six cases respectively, the power of the statistical tests is a relevant consideration. Even where the effect size was reasonably large, the risk of a Type II error (i.e. overlooking a potentially significant finding) was considered to be high. Since this study was partly exploratory in nature, mean plots of the most important executive function test scores were generated (Figure 6-1) to allow visual inspection of the data. Five of the eight variables (63%) showed a trend of progressively poorer performance across the normal, moderate and severe groups. On three tests, although there were no obvious differences between normals and moderate apneics, a distinct drop in scores between moderate and severes is evident. This pattern would be the expected if the hypothesis of a discontinuity in the occurrence of executive function deficits in OSAS patients were correct.

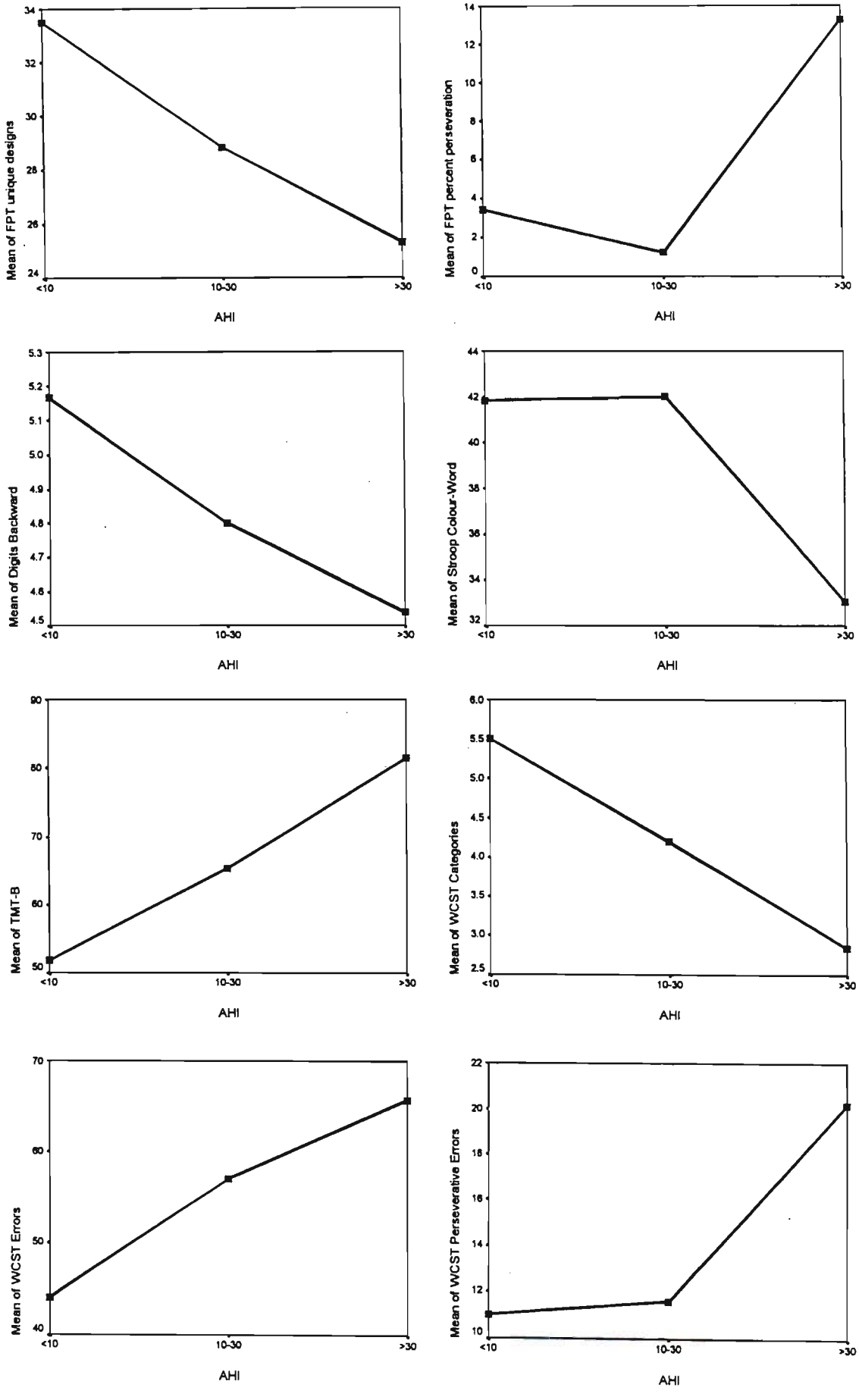


Figure 6-1. Mean plots of executive function variables according to AHI severity

6.2 Hypoxemia severity

Descriptive statistics [mean (*SD*)] of % sleep SaO_2<5% were calculated for the overall sample [8.4 (15.4)], in addition to the three subgroups: non-hypoxemic [0.0 (0)], moderately hypoxemic [1.7 (.91)] and severely hypoxemic [27.5 (17.3)]. No significant group differences were evident for age, education, BMI or ESS (Table 6-4).

Table 6-4 Demographic variables for hypoxemia groups

	A NORMAL (*n*=10) mean (*SD*)	B MODERATE (*n*=7) mean (*SD*)	C SEVERE (*n*=7) mean (*SD*)	F-VALUE *df*(2,21)	A-B p-values[a] (Bonferroni-adjusted)	A-C	B-C
Age	40.1 (9.8)	46.1 (11.8)	37.7 (9.4)	1.27	.739	1.000	.420
Education	14.7 (3.0)	16.4 (1.0)	13.6 (1.9)	2.80	.418	.982	.088
BMI[b]	28.1 (4.3)	30.1 (5.9)	41.4 (17.6)	2.81	1.000	.094	.304
ESS	11.0 (5.6)	11.1 (3.3)	14.0 (4.0)	1.02	1.000	.598	.772

[a] t-Tests

[b] Values of p based on transformed values (natural logarithm)

*: p<.05

The distributions of the sleep staging analysis are outlined in Table 6-5. Overall comparison of group differences were significant for percentage of SWS [F(2,21)=5.57, p=.011] and percentage of Stage 2 sleep [F(2,21)=3.75, p=.041]. The severely hypoxemic patients showed decreased SWS relative to both the non-hypoxemic (p=.015) and moderately hypoxemic groups (p=.045). Normals spent proportionally less time in Stage 2 sleep than severes (p=.039). All the sleep stages between the non-hypoxemic and moderately hypoxemic groups were comparable.

Table 6-5 Sleep staging variables for hypoxemia groups

	A NORMAL (n=10) mean (SD)	B MODERATE (n=7) mean (SD)	C SEVERE (n=7) mean (SD)	F-VALUE df(2,21)	A-B p-values [a] (Bonferroni-adjusted)	A-C p-values [a] (Bonferroni-adjusted)	B-C p-values [a] (Bonferroni-adjusted)
% Stage 1	31.2 (17.4)	29.1 (9.7)	26.7 (13.3)	.20	1.000	1.000	1.000
% Stage 2	44.4 (13.0)	48.7 (9.3)	58.9 (8.3)	3.75	1.000	.039*	.279
% Stage SWS	14.1 (6.1)	13.2 (8.8)	3.7 (13.6)	5.57*	1.000	.015*	.045*
% REM	10.3 (9.8)	9.0 (5.3)	10.6 (7.3)	.08	1.000	1.000	1.000

[a] t-Tests

*: p<.05, **: p<.01

Table 6-6 presents the neuropsychological test results. The Kruskall-Wallis Test indicated that there were significant differences between the three research groups with regard to the number of categories achieved on the WCST [χ^2 (2)=7.79, p=.015]. On average, patients with severe hypoxemia achieved only 1.7 (SD=.95) categories, significantly less [U(7,7)=10, p=.006] than those with moderate hypoxemia [mean=4.4 (SD=2.3)]and made significantly more errors [U(7,7)=11.5, p=.010]. Although not significant, the overall difference between groups approached significance (p<.10) on four of the test scores/indices FPT unique designs [χ^2 (2)=5.79, p=.055], Stroop Colour-Word [χ^2 (2)=4.74, p=.093), TMT-A/TMT-B [χ^2 (2)=5.73, p=.057], WCST errors [χ^2 (2)=5.61 p=.0.061]. Pairwise comparisons, using the Mann-Whitney Test identified significant differences between groups of subjects for all of these tests. Patients with severe hypoxemia generated fewer unique designs on FPT (U(7,10)=12, p=0.011), and scored lower on Stroop Colour-Word (U(7,10)=10.5, p=.007) than did individuals without hypoxemia. The ratio TMT-B/TMT-A revealed that the time taken on the more difficult Part-B (TMT) relative to the time on Part-A was greater for patients with moderate hypoxemia than normals (U(7,10)=11, p=0.009). A further four intergroup comparisons had p-values <.05, suggesting significance. However, when evaluated against the more conservative criteria (p<.017) for multiple comparisons, the results were non-significant. It is unlikely that these

Table 6-6 Comparison of neuropsychological test scores for the hypoxemia groups

	A NORMAL (n=10) mean (SD)	B MODERATE (n=7) mean (SD)	C SEVERE (n=7) mean (SD)	χ^2 VALUE[a] (df=2)	P-VALUE	A-B	A-C	B-C
						p-values (Mann-Whitney Test)		
FPT unique designs	31.0 (8.4)	30.0 (8.4)	22.0 (6.5)	5.79	.055	.378	.011*†	.034*
FPT percent perseveration	5.1 (8.0)	5.9 (9.6)	15.2 (24.6)	.974	.979	.453	.335	.365
Digits Backwards	5.2 (1.4)	4.0 (.58)	4.9 (1.4)	4.20	.121	.023*	.315	.098
Stroop Colour-Word	40.0 (5.0)	37.1 (9.8)	33.0 (5.2)	4.74	.093	.245	.007**†	.238
Stroop Interference	.7 (5.6)	-4.4 (7.6)	-5.0 (7.8)	1.52	.467	.157	.268	.228
Trail Making Test B	59.2 (18.3)	67.9 (26.0)	89.9 (69.6)	1.21	.548	.300	.175	.258
TMT-B/TMT-A	1.8 (.4)	2.8 (1.0)	2.6 (2.3)	5.73	.057	.009**†	.300	.064
WCST categories	4.8 (2.9)	4.4 (2.3)	1.7 (.95)	7.79	.015*	.364	.006**†	.045*
WCST errors	50.8 (19.2)	55.0 (21.4)	73.0 (11.1)	5.61	.061	.443	.010*†	.182
WCST perseverative errors	13.1 (9.6)	15.1 (9.5)	21.3 (12.2)	3.29	.193	.291	.033*	.191
CPT difference score	23.3 (45.3)	61.6 (40.5)	29.9 (48.7)	2.95	.229	.070	.453	.383

[a] Kruskall- Wallis Test

* $p<.05$, ** $p<.01$, † $p<.017$ (Mann-Whitney Test)

represent genuine Type I errors. All group differences were in the expected direction and matched findings in previously reported research. There was no difference between groups in the ability to sustain attention, as measured by CPT (χ^2 (2)=2.951, p=.229).

Mean plots of executive function variables according to hypoxemia severity are presented in Figure 6-2. Five neuropsychological test scores (FPT unique designs, FPT percent perseveration, TMT-B, WCST categories and WCST perseverative errors) showed a marked fall off in performance in the severe hypoxemic group, after a relatively insignificant difference between normals and moderately hypoxemic individuals. Trends of progressively lower scores across non-hypoxemic, moderates and severes were evident for three variables (Stroop Colour-Word, TMT-B and WCST errors). Digits Backward was the only anomaly, with the mildly hypoxemic group performing on average worse than both normals and severes.

The results of the analyses using apnea/hypopnea (AHI) severity and hypoxemia severity (% sleep SaO_2<80%) as the independent variables have been presented separately. Planned comparisons of the two patterns of results were precluded by the non-independence of these variables (r=.63, p=.001). As a consequence, no conclusions regarding their differential effect on the cognitive executive functions of OSAS patients can be drawn.

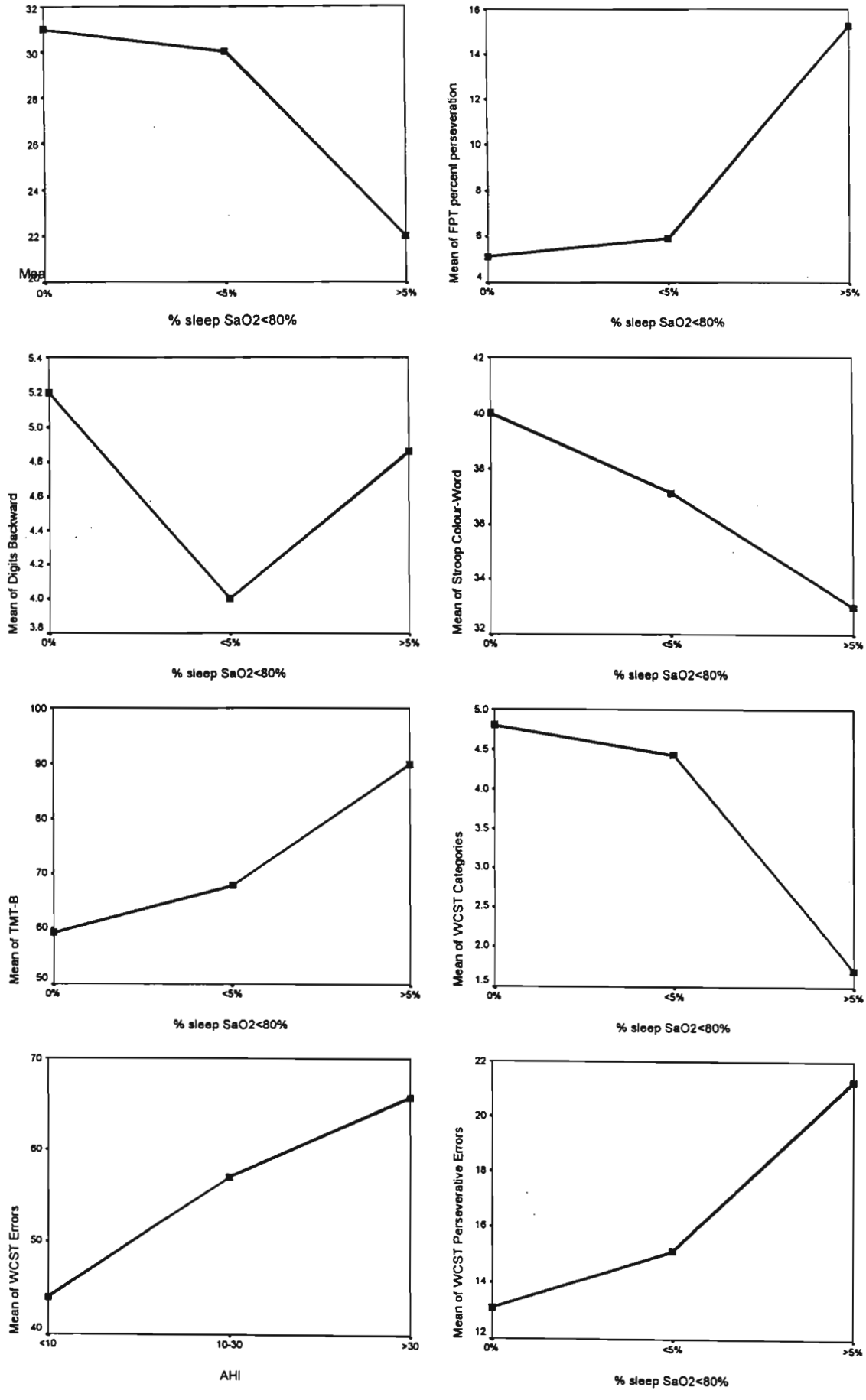


Figure 6-2 Mean plots of executive function variables according to hypoxemia severity

6.3 Prevalence of neuropsychological impairment

Although the comparison of the raw test results across groups is in itself useful, this approach provides little information about the clinical significance of the findings. Standard (*z*) scores were calculated, using available norms, to provide a more clinical evaluation of the data. Standard scores have two important advantages:

(a) Apart from the presence or absence of neuropathology, there may be interindividual variability in neuropsychological test scores. Sources of variability include age, sex, education and other demographic attributes. Uncontrolled variations in these dimensions can dilute the results of data analyses (Lezak & Gray, 1984). Standard scores provide an estimate of how much an individual performance deviates from the mean of the normative population and, depending on how the norms are organised, may correct for anticipated differences in age, sex, education, etc.

(b) By definition, *z*-scores have the same mean (zero) and standard deviation units (one). Thus, to the extent that the normative populations are equivalent, these scores provide a common scale that allow for the comparison of individual performances on different neuropsychological tests.

Since the rationale underlying the use of standard scores was clinical utility, the AHI was the primary independent variable used in the analysis. The AHI is the only objective measurement recommended by ASDA (1997) for evaluating OSAS severity and is an important consideration in patient management. There appears to be no consensus regarding which of the hypoxemia indices are most important and the reporting of these varies widely.

A similar method to that described by Anderson (1997) and De Luca, Johnson, Beldowicz and Natelson (1995), who studied patients with chronic fatigue syndrome (CFS), was adopted for the analysis. An impairment rating (IR), based on Lezak's (1995) classification system (presented in Table 5-2, p. 67), was derived from the *z*-score data. The IR was calculated as follows: test scores within .6 *SD*s or above the published normative

comparison were assigned an IR of 0; scores between .6 and 1.3 *SD*s below the norms were assigned an IR of 1; scores between 1.3 and 2 *SD*s below the norms were assigned an IR of 2; and scores greater than 2 *SD*s received an IR of 3. The IRs were then summed to obtain a summed IR (SIR) of overall performance for each subject. Both the WCST categories and WCST errors are measures of overall success on this test and had identical IRs. To avoid bias in the calculation of SIR, WCST errors were not included. Similarly, the derived indices (Stroop Interference and TMT-B/TMT-A) were also excluded. The two scores on the FPT (unique designs and percent perseveration) were judged to be measuring different aspects of executive functioning, as were WCST categories and WCST perseverative errors and were, therefore, included in SIR.

The overall reliability of the SIR was satisfactory, with a Cronbach alpha of .82. The mean (*SD*) for the normals, mild apneic and severe apneic groups was 1.8 (1.5), 2.8 (2.2), and 8.2 (5.2) respectively (see Figure 6-3). The Kruskall-Wallis Test revealed significant group differences [χ^2 (2)=10.0, p=.007], with the impairment rating of the severe apnea group higher than both the moderate apneics (U(5,3)=10.5, p=.015) and normals (U(6,13)=7.5, p=.001). There was no significant difference between normals and moderate apneics (U(5,6)=11.0, p=.279).

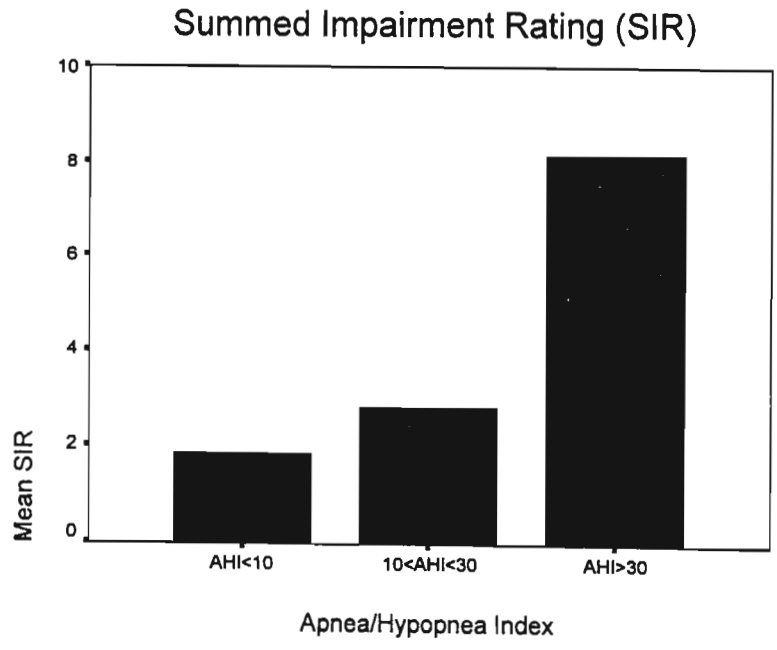


Figure 6-3. Summed impairment rating according to AHI severity

In order to address the question of the proportion of OSAS patients presenting with executive function deficits, the frequencies of unimpaired and impaired subjects were tabulated for the three research groups (Table 6-7). Since impairment on a single test score may be explained by chance (Lezak, 1995), subjects were rated as impaired if two or more scores were greater than 1.3 *SD*s below the mean and unimpaired if zero or one score was more than 1.3 *SD*s below the mean. This approach has also been used by Skoraszewski, Ball and Mikulka (1991) in the study of HIV/AIDS patients and by Anderson (1997). However, the cut-off of 1.3 SDs suggested by Lezak (1995) for identifying borderline/impaired scores is more conservative than 1 *SD* used by Skoraszewski et al. (1991). Furthermore, this study focuses on a specific area of cognitive functioning, and the test battery is considerably smaller than used by Anderson (1997) or Skoraszewski et al. (1991). The occurrence of two or more impaired scores in this sample is unlikely to be a result of chance variability.

Table 6-7. Executive function ratings for apnea groups

	Number of subjects with impaired scores	
	Unimpaired	**Impaired**
Group	Zero or one score >1.3 *SD*s	Two or more scores>1.3*SD*s
Normal (10<AHI)	5 (83%)	1 (17%)
Moderate (10<AH<30)	4 (80%)	1 (20%)
Severe (AHI>30)	5 (38%)	8 (62%)

Since four of the cells (66.7%) in Table 6-7 have expected counts of less than five, a chi-square test could not be performed to test for significant group significance. Table 6-8 presents the same data, but with the rows for normal subjects and moderate apneics collapsed. The chi-square test showed a significant difference between groups [χ^2 (1)=4.6, p=.032]. It is evident from Figure 6-3 that proportionally more subjects with AHI>30 were classified as impaired than those with AHI<30.

Table 6-8. Executive function ratings for AHI<30 and AHI>30

	Number of subjects with impaired scores	
	Impaired	**Unimpaired**
Group	Zero or one score >1.3 *SD*s	Two or more scores>1.3*SD*s
AHI<30 (*n*=11)	9 (82%)	2 (18%)
AHI>30 (*n*=13)	5 (38%)	8 (62%)

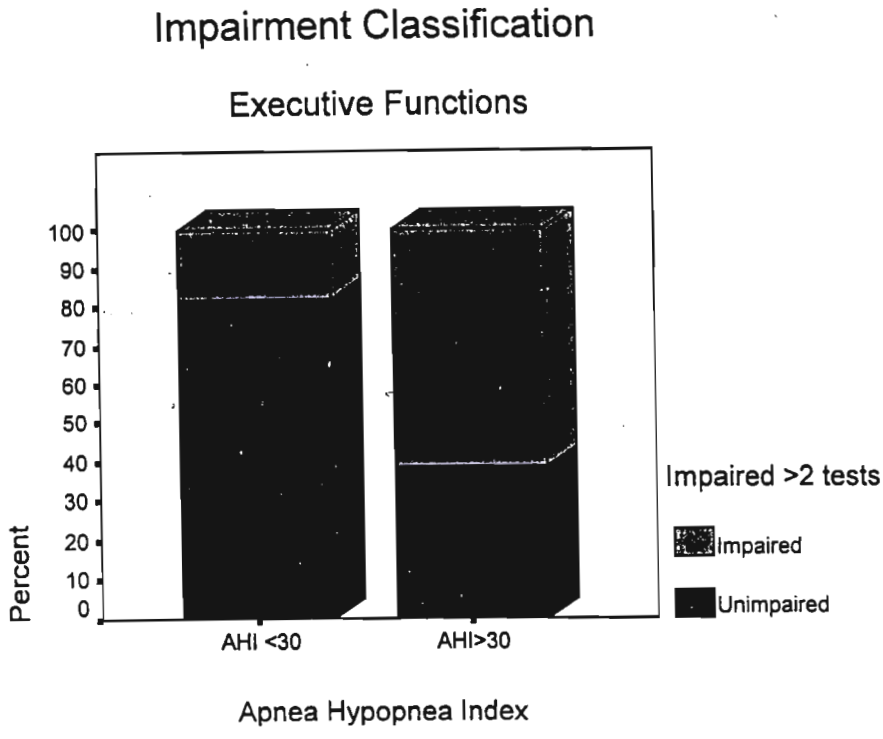


Figure 6-4. Percentage of impaired/unimpaired subjects using AHI=30 as cut-off

The optimal AHI cut-off for classification of impaired and unimpaired subjects in this sample was determined to be AHI=20 [χ^2 (1)=5.5, p=.019] (see Figure 6-4). This cut-off was chosen to maximise accuracy of classification of impaired subjects and as such 90% had an AHI>20. However, the number of false positives was also high, with six (40%) patients with AHI>20 having zero or one score greater than 1.3 *SD*s below the mean.

Examination of the false-positives revealed that only one of these cases was also classified as severely hypoxemic (% sleep<80% greater than five). Using both the frequency of apneic events (AHI>20) and severity of hypoxemia (% sleep<80% greater than five) as criteria for impairment, the whole sample could be correctly classified with 92% accuracy.

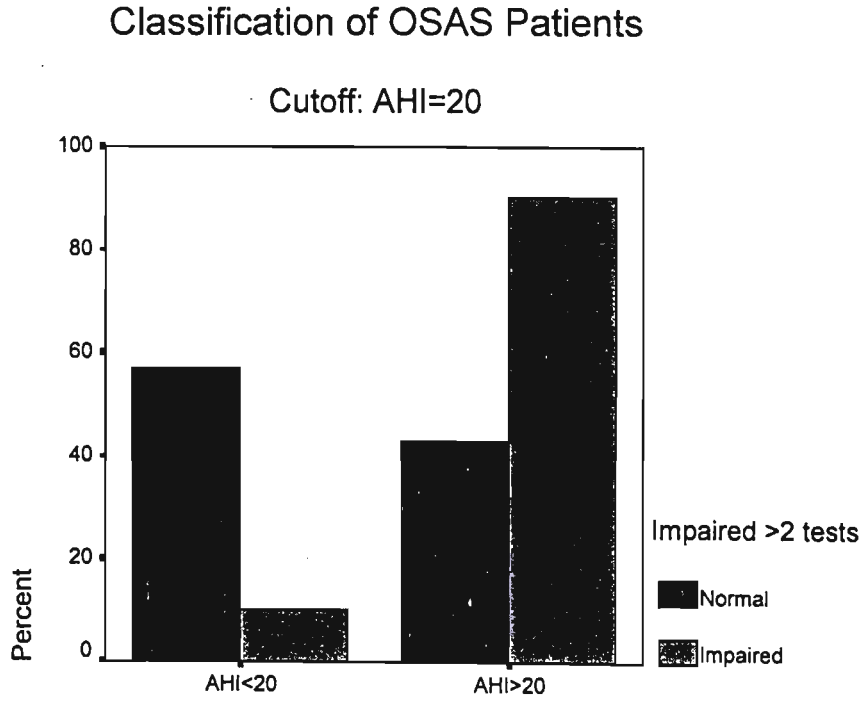


Figure 6-5. Percentage of impaired/unimpaired subjects using AHI=20 cut-off

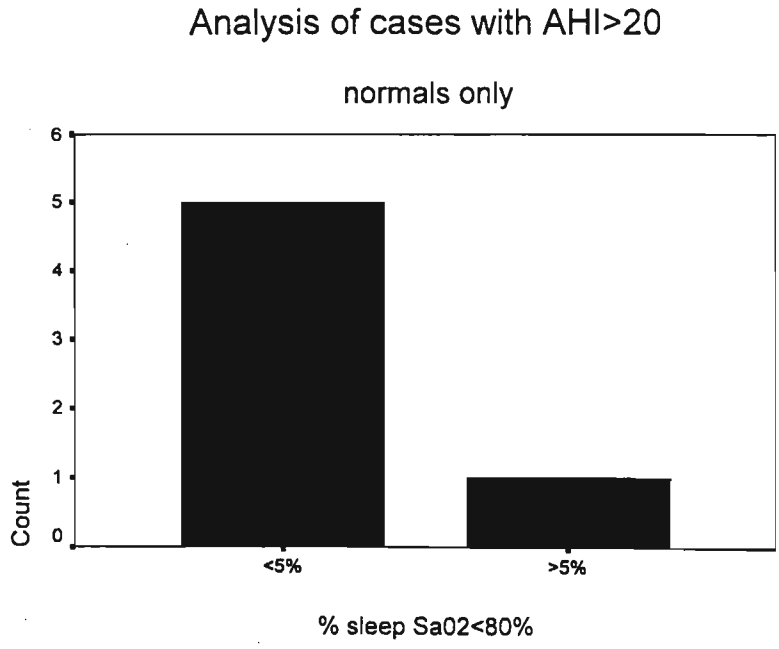


Figure 6-6. Number of unimpaired subjects (AHI>20) using % sleep SaO_2<80% cut-off

CHAPTER 7. DISCUSSION

7.1 Neuropsychological findings

7.1.1 Individual test scores

The major finding of this study was the observation of differences in the executive functions between groups of subjects, who were classified according to their nocturnal respiratory parameters. The two neuropsychological tests that were most sensitive to differences between groups of both apnea severity and hypoxemia severity were the Stroop Test and WCST. These tests both measure the ability to shift from one cognitive set to another and the capacity to inhibit an automatic or stereotyped response. The convergence of evidence on these two tests strengthens the study's findings.

On the Stroop Test, severe apneics performed worse than both normals and moderately affected patients. Moderates and normals did not differ on this task. The severe hypoxemic patients scored lower than non-hypoxemic subjects did. Performance on the Stroop Colour-Word Test requires an individual to inhibit an overlearned or automatic response in favour of a less familiar one, thus demanding cognitive flexibility and the capacity to shift from one perceptual set to another. Factor analytic studies have revealed that, in addition to conceptual abilities, Stroop tasks load on speed of information processing (Spreen & Strauss, 1998). Thus, at an interpretive level, Stroop performance may reflect the efficiency with which an individual is able to sort information from his or her environment and selectively react to this information. Naëgelé et al. (1995) also administered the Stroop Test to a group of OSAS patients and age-matched controls. Using logistic regression analysis, the Stroop Test was effective in discriminating between these two groups of subjects. It was, furthermore, included in the model that was used to classify patients as either severe apneic (AHI>40) or moderate apneic (AHI<40). These results support the current findings that both the ease and rapidity of shifting from one perceptual set to another and resistance to interference may be compromised in patients with severe OSAS.

On the WCST, group differences were evident when both apnea and hypoxemia severity were respectively used to categorise subjects. Severe apneics performed more poorly than normals, while patients with severe hypoxemia scored lower than both normals and those with moderate hypoxemia. No differences were observed between normals and moderate apneics, or non-hypoxemic and moderately hypoxemic subjects, which supports the discontinuity hypothesis that executive function impairments are evident in only the patients with severe OSAS. The number of categories achieved provides an indication of overall success on this test, with low scores reflecting difficulties in concept formation, the ability to shift and maintain a set and problem solving. A high number of errors is also indicative of poor overall performance. When the rules change in WCST, executive functions are needed to use the feedback to determine that such a change has taken place and to formulate and test new hypotheses. Critical to this process is the inhibition of previously used rules. A tendency for the severe apneics and severe hypoxemic patients to make more perseverative errors than normals suggests a failure to select and use alternative approaches for sorting the cards. Results from previous studies support the current findings. Naëgelé et al. (1995) report that severe apneics and moderate apneics differed with regard to the number of categories achieved and that OSAS patients with moderate hypoxemia made significantly fewer errors than patients with severe hypoxemia. Redline et al (1997) found no differences in WCST performance between patients with moderate apnea (10<AHI<30) and healthy controls.

There was a strong tendency for severe apneics to perform more poorly than normals on TMT-B. Inspection of group means also revealed a trend of progressive slowing across the three groups of increasing hypoxemia severity. The results from previous studies using TMT-B are mixed. Bédard et al. (1991) report that patients with severe OSAS show considerable slowing on this task when compared with moderates and controls; while Findley et al., (1986) observed poorer performance in hypoxemic than non-hypoxemic patients. However, both Greenberg et al. (1987) and Naëgelé et al. (1995) report no differences between OSAS patients and controls in the mean time taken to complete TMT-B. All of these studies use different criteria for classifying the research subjects, which might account for the different findings.

There is disagreement between researchers regarding the interpretation of TMT-B. Effective performance requires concentration, the capacity to shift between cognitive sets, visual scanning and motor skills. Poor performance may reflect difficulties in any of these functional areas. Arbuthnott and Frank (2000) suggest that the ratio score (TMT-B/TMT-A) provides a measure of executive functioning that is relatively independent of individual variations in visual scanning and motor abilities. No differences were observed between either the apnea or hypoxemia groups on this index. Although performance on TMT-B involves shifting processes and mental flexibility, unlike the Stroop Test and WCST, it is less dependent on the capacity to inhibit an automatic response, which could account for only modest differences between groups on this score.

On the FPT, subjects were instructed to produce as many unique designs as possible within a limited time period. Adequate performance is dependent on planning and a systematic approach, thus involving executive processes. Patients with severe hypoxemia were less able to generate effective strategies than normals and tended to be less effective than moderately hypoxemic patients. The FPT has not been used by other researchers to investigate cognitive deficits in OSAS patients and further research is needed to validate these findings.

The CPT required subjects to detect successively identical stimuli over an eight-minute testing period, measuring the capacity for sustained attention. Redline at al. (1997) report that compared with controls, subjects with mild SDB showed a decline in this ability on the latter part of the test. Similar vigilance decrements were not evident in any of the subject groups in the current study. The administered version of the CPT was marginally shorter than the ten-minute version used by Redline et al. (1997), which might contribute to the different findings. Perhaps, more significant is the overall duration of the testing session and the time of day when testing occurred. Neuropsychological testing, interrupted by multiple sleep latency tests, took place between 09h00 and 16h30 (Redline et al., 1997), whereas in the present study the 45-minute assessment was completed by 08h30. Thus, not only was the test battery (a) administered at a different time in the sleep-wake cycle, but (b) was considerably shorter.

Sleepiness is modulated by circadian rhythms and there is a biphasic pattern of sleep tendency over the 24-hour day. In addition to the nocturnal increase, a consistent peak in sleep tendency (and trough in alertness) occurs in the early afternoon (Sleep Research Society, 1997b). During the clinical interviews, OSAS patients regularly described periods of excessive daytime somnolence (EDS) corresponding with this period. Although Redline et al. (1997) do not provide a schedule of test presentation; assessment at a different point in the subjects' circadian rhythm may explain the patients decreased ability to sustain attention. Patients with EDS may be less able to counteract the effect of temporal variations in attention than controls. Furthermore, in the current study OSAS patients may have been able to compensate for attentional deficits, as the total duration of the assessment was relatively short. However, when the CPT was part of a much longer test battery and subjects were required to concentrate for extended periods, patients may have lacked the necessary resources to be able to compensate. Other studies reporting vigilance impairments in OSAS patients (Bédard et al., 1991; Findley et al., 1986; Roehrs et al., 1995) also administered large batteries, with testing conducted in the afternoon, and the same argument may explain their different findings.

The non-significant difference in vigilance scores between groups is of particular relevance in the study of executive functions. Phillips (1997) highlights the problem of task impurity in neuropsychological assessment, where deficits of lower order functions may affect an individual's performance on executive function tests. Similarly, Stuss & Benson (1986) propose a hierarchical model, where the executive functions are responsible for providing conscious control of posterior/basal functional systems (including attention), but are also supported by these systems in a reciprocal relationship. However, based on CPT performance, it is unlikely that the executive function deficits reported in this study can be attributable to impaired vigilance, but rather reflect differences in the executive abilities between groups.

Demographic characteristics are another potential source of variability in neuropsychological test scores. Although no attempts were made to match subjects in the different groups, differences of age and education were not significant. The mean BMI [ratio of weight / $(\text{height})^2$] was significantly higher for severe apneics than moderate

apneics. This finding is to be expected, as OSAS severity has been associated with increased body mass. Flemons et al. (1992) report a positive correlation between AHI and BMI. However, there is no reason why the BMI should in itself affect cognitive performance. All participants were carefully screened to exclude other sources of neuropathology. It is thus unlikely that uncontrolled variations in these dimensions are responsible for the observed differences. A surprising finding was that the mean subjective ratings of daytime sleepiness (ESS) did not differ between groups. OSAS patients would be expected to report greater levels of sleepiness than normals. The selection of non-apneic and non-hypoxemic subjects from a clinically referred population might explain the higher than anticipated means scores for these two groups.

The overall pattern of results supports the discontinuity hypothesis and suggests that there is a threshold of OSAS severity, above which impairment of the executive functions are evident. Patients with severe OSAS scored consistently lower on measures of executive functioning than normals and tended to score lower than moderates. Differences between the performance of the normal and moderate groups were largely non-significant. However, a trend of progressively poorer performance across normals, moderates and severes was evident on selected tests. This implies that some of the moderate patients may show very mild executive function deficits or that the criteria used to classify subjects were not optimal.

7.1.2 Standard scores

As well as contrasting the performance on each neuropsychological measure across groups, it was of interest to obtain a summary of overall executive function impairment. The summed impairment rating (SIR) was significantly higher for severe apneics than both moderate apneics and normals. The pattern of performance for the moderate apneics was similar to that of the normals, with no significant difference between the groups. The results from this analysis provide further support for the discontinuity hypothesis. In patients with moderate OSAS the executive functions appear relatively intact, whereas in patients with severe OSAS statistically significant deficits are observable.

To determine the clinical relevance of the observed deficits, the percentage of impaired versus unimpaired subjects were compared across groups. Considering all subjects with AHI<30 (i.e. those previously classified as normal and moderate apneics), only 18% were rated as having impaired executive functions. In contrast, 62% of patients with AHI>30 were classified as impaired (two or more scores greater than 1.3 *SD*s below the population mean). Given the role of the executive functions in regulating all other cognitive functions, the high proportion of severe apneics classified as impaired is cause for concern. The potential implications thereof are discussed in more detail below (Section 7.7, pp. 90-92). The optimal cut-off for classifying subjects with impaired executive functions was determined to be AHI>20. Combining this with a hypoxemia cut-off (% sleep SaO_2<80% greater than five) resulted in a 90% accurate classification of participants. Although replication studies are still needed to verify these results, patients meeting the above criteria have a high probability of impaired executive functions and should be counselled on this possibility.

7.3 Pathogenesis

OSAS causes sleep fragmentation and chronic intermittent hypoxemia and both have been suggested as explanations for the neuropsychological deficits in these patients. Repeated microarousals from sleep, occurring at the termination of apneic events, disrupt sleep architecture and result in reduced or even absent slow wave sleep (Raine, 1997). Deficits of attention and memory have been primarily attributed to sleep fragmentation, whereas nocturnal hypoxemia is considered to be more important in the pathogenesis of executive function deficits (Bédard et al., 1991). Impairments of executive functions show only partial improvement after treatment (Bédard et al., 1993; Naëgelé et al., 1997), which suggests that such deficits might be, at least partly, the result of irreversible anoxic damage. Both frontal lobe and subcortical structures have been implicated. Hypoxemia may disrupt the biochemical and haemodynamic state of the central nervous system and affect the metabolism of central neurotransmitters that are involved in the regulation of cognitive functions. Increased cerebral blood flow, which ordinarily protects cerebral metabolism

during acute hypercapnia/hypoxemia, may occur too slowly to be effective in preventing the repetitive hypoxic episodes associated with OSAS.

Although this study shows statistically significant differences between groups with different apnea and hypoxemia severity, no direct role of these physiological variables as a cause of executive function dysfunction is proven. Firstly, the research design does not allow for causal inferences to be made. Secondly, apnea/hypopnea severity (AHI) and hypoxemia severity (% sleep<80%) are significantly correlated (r=.63, p=.001) and since many of the severe apneics were also severely hypoxemic, it is not possible to separate the two pathological mechanisms. The results of the sleep staging analysis illustrate this more clearly. Both the severe apneics and severely hypoxemic patients spent proportionally less time in slow wave sleep and proportionally more time in Stage 2 sleep than their respective comparison groups. Thus disrupted sleep architecture may be a causal mechanism in both groups. Using the analysis of covariance, it may be possible to statistically control the effect of sleep fragmentation, to study the impact of hypoxemia on executive function performance and vice-versa. However, failure to meet the parametric assumptions required by this statistical procedure precluded this as an option in the current study. Thirdly, there may be unsuspected variables, which were neither measured nor controlled for, that could account for the differences in neuropsychological test scores reported.

In order to assert that a causal relationship between either sleep fragmentation or hypoxemia and executive function impairments exists, the independent variables must be experimentally manipulated. Martin et al. (1996) used sound impulses to fragment the sleep of healthy volunteers and report performance decrements on tests of attention the following day. However, no tests of executive function were administered and it is not clear whether sleep disruption would affect performance on these tasks. It is recommended that future studies use the above methodology to induce arousals, but include tasks sensitive to the executive functions in the neuropsychological battery.

Determining the contribution of hypoxemia in the pathogenesis of cognitive dysfunctions is more complicated. The experimental ideal of manipulating oxygen saturation levels in research subjects is precluded by ethical considerations. The comparison of

neuropsychological performance in OSAS patients, pre- and post-treatment with CPAP, is not an effective solution either. Since both hypoxemia and sleep architecture are restored to normal with CPAP treatment, it is not possible to partial out the independent contribution of hypoxemia on neuropsychological performance. Furthermore, the executive functions are required for the processing of novel information and as result many of the instruments are considered to be 'one-shot tests' with poor test-retest reliability. Even the use of parallel forms does not circumvent this problem. Although the content of the alternate form may be novel, the format is likely to be familiar and may not activate executive processing.

7.3 Implications

The results from this study support and extend previous research, which suggests that patients with severe OSAS may have compromised executive functions. Specifically, difficulties in the ability to shift and maintain a set, inhibit an automatic response, planning and problem solving were observed. Although the deficits tend to be more subtle than might, for example, be seen in patients with frontal lobe injuries or other forms of severe cerebral trauma, the findings have important implications for both patients and those involved in their management, alike.

The executive functions play an important role in daily living and enable an individual to engage successfully in independent, purposive, self-serving behaviour (Lezak, 1995). They are considered to be higher-level functions, which control and regulate more basic cognitive functions. Hence, deficits tend to be supramodal and affect the expression of all aspects of behaviour (Lezak, 1982). There is growing evidence that lower level cognitive functions, such as attention, memory, motor and visuo-perceptual abilities may be impaired in patients with OSAS (Décary et al., 2000). The integrity of the executive functions might determine whether these patients are able to compensate for such deficits through the restructuring of activities. It follows that in situations that are complex, novel or offer little structure, thus demanding executive control, patients with severe OSAS may lack the compensational skills and be unable to respond effectively. This may create difficulties in both occupational and social settings and ultimately affect their quality of life.

Most occupations require at least some adaptation of routine or overlearned skills. Compromised executive functions may result in a reduction of the quality of work performance. In particular, patients working in situations that are dangerous or technically difficult, or involve troubleshooting, planning or decision making, the negative effect of OSAS on executive functioning can have serious (or potentially fatal) consequences and is cause for concern.

Executive function deficits are not readily observable in themselves and may not be self-evident to affected patients. It is the responsibility of health professionals involved in the management of OSAS patients to alert those individuals, who are determined to be at risk, about the potential consequences. For some, an awareness of the difficulties may be sufficient to allow them to develop compensatory approaches (e.g. use of a structured and systematic format for problem solving). Regrettably, the availability of rehabilitation or retraining programmes in South Africa is limited. Thus, referral for a more thorough neuropsychological assessment to determine the nature and extent of the deficits may not be ethically justifiable, from both the perspectives of the cost involved and not being able to offer viable treatment alternatives, if indicated.

Neuropsychological testing pre- and post-treatment with CPAP reveals significant improvement in patients' memory and vigilance capacities (Bédard et al., 1993). However, the extent to which executive function deficits associated with OSAS are reversible remain unclear. Despite the restoration of both sleep architecture and nocturnal oxygen saturation levels towards normal, persistent deficits on selected tests suggest that irreversible anoxic damage may underlie the executive impairments (Bédard et al., 1993; Naëgelé et al., 1998). Although further research is still needed to determine whether executive functions may improve after extended periods of treatment with CPAP, it is imperative to prevent the risk of further damage. These patients should be referred for urgent treatment. Moreover, the demonstrable benefits for other cognitive functions, together with the health-related benefits are, in themselves, sufficient indicators for treatment.

For neuropsychologists in clinical practice, it is important to consider the risk factors for OSAS in the clinical history of patients referred for assessment. Individuals who report loud snoring, choking or gasping during sleep, or observed apneas by a bed-partner, together with excessive daytime somnolence may have undiagnosed OSAS. Executive function deficits that are incidental to the reason for referral, but rather the result of sleep fragmentation or nocturnal hypoxemia associated with OSAS, may be apparent on formal testing and could create a confusing pattern of results. Without confirmation of a diagnosis from overnight polysomnography, it may be impossible to reach any firm conclusions. Furthermore, an increased awareness of the risk factors for OSAS and accompanying neuropsychological deficits will help to identify those individuals who may benefit from appropriate medical treatment.

7.4 Limitations of the current study and directions for future research

This research has a number of limitations that warrant further discussion and provide direction for future research:

(1) The study was conducted in a clinical-, rather than a research-laboratory, which imposed constraints on the sampling of participants. Split-studies, where upon observation of significant evidence of OSAS in the first-half of the night, the second-half is used to titrate the minimum pressure necessary to control sleep disordered breathing with CPAP, were requested for many of the referrals. Although adequate for clinical purposes, the frequency and duration of apneic events tend to increase during the course of the night, split-studies may underestimate the true severity of OSAS. Only subjects who underwent full-night polysomnography were eligible for inclusion. A limited time period available for data collection, together with restrictive selection criteria, resulted in a relatively small sample size. With a larger sample size, the study would have had greater statistical power and some of the non-significant trends between groups might have proved significant.

(2) The patients studied were a convenient sample and cannot be considered to represent a cross-section of the population. Similarly, the non-apneic and non-hypoxemic subjects

were clinically referred and, despite a negative polysomnogram, are not representative of healthy controls. Thus, all conclusions must be considered specific to this sample and cannot be generalised.

(3) Hein & Magnussen (1999) report intraindividual variability in the apnea/hypopnea index in subjects with mild sleep disordered breathing. Although the nightly variation is usually small, this variability increases with increasing AHI and may impact on the reliability of the polysomnographic data. In defence, grouped data and not the actual scores were analysed and any effect on the overall results is likely to be minimal. Nonetheless, future studies might consider a second overnight recording and using the mean values from the two recordings in the data analyses.

(4) No attempt was made to match the subjects in the different research groups on an estimate of premorbid ability. Given the potential effect of this variable on neuropsychological test performance, this represents a weakness of the study. Subjects were not matched for age and education either, however, this is unlikely to have influenced the results as the group means of these variables were determined to be equivalent.

(5) The normative data, used in the calculation of standard scores was collected on subjects in the United Kingdom and United States of America, as South African norms were not available. However, were South African norms available, the relevance of these might still be questionable, as the sample cannot be considered to be typical of the general population. Using the means and standard deviations of the study sample as the comparison standard is an alternative approach, but this method does not adjust scores for age-related differences.

(6) The executive functions are inherently difficult to assess. Overly structured testing situations, task impurity and familiarity with either the test format or content are just some of the problems encountered (see Chapter 4, pp. 45-47), which may undermine the validity and reliability of these measures. Furthermore, there is only limited evidence to suggest that the available tests are valid predictors of an individual's capacity to manage independently in real life social- and occupational environments (Cripe, 1996). Further

research on the ecological validity of the existing tests, together with development of new instruments is needed to address these shortcomings.

(7) The chronicity of the syndrome may potentially affect the integrity of the executive functions in OSAS patients. Should irreversible hypoxic damage be the underlying cause of these deficits, the chronicity of nocturnal hypoxemia may prove to be cumulative, in which case this may be equally as important to consider as the current rating of severity. At present, there are no reliable indicators to determine the onset or chronicity of OSAS. Research into the development of such a scale would be beneficial.

(8) Finally, the number of studies that have investigated the executive function deficits in patients with OSAS are limited. There is a need for further research to replicate and extend the current findings.

7.5 Conclusion

In addressing the aims and hypotheses set out in Chapter 1, the following conclusions were reached:

(1) Executive function impairments were detectable in individuals diagnosed with severe OSAS. Specifically, difficulties in mental flexibility, resistance to interference, concept formation and planning were observed. The magnitude of these impairments may be sufficient to interfere with daily cognitive functioning in situations that are complex, novel or offer little structure.

(2) In patients with moderate OSAS, the executive functions appeared largely intact. This suggests a discontinuity in the manifestation of executive function deficits between moderate and severe OSAS patients. There may be a threshold of OSAS severity, only above which impairments occur.

(3) No inferences regarding the causal role of either hypoxemia or sleep fragmentation in relation to these deficits can be concluded. While some differences were evident on selected neuropsychological tests, the overall patterns of impairment using these two indices as independent variables were largely similar.

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APPENDIX 1: INFORMED CONSENT FORM

UNIVERSITY OF NATAL
CONSENT FORM

I ..... (name),

of .....

..... (address)

hereby consent to participate in the research being carried out by M.Vonk & Prof. R. Griesel of the School of Psychology, University of Natal, Pietermaritzburg. I am aware that this involves the completion of a series of short neuropsychological tests and a questionnaire.

I consent to the disclosure of records or information requested from

☐ (EEG & Sleep laboratory)
☐ (medical practitioner) .....

I understand that all personal information will be kept confidential with the researchers.

Signed: Date:

....

Your involvement in this project is highly valued.

Should you require further information, please contact:

M. Vonk
School of Psychology
Pvt bag X01, Scottsville, 3209
Tel (031) 207-4104

APPENDIX 2: LORNE STREET EEG AND SLEEP LABORATORY QUESTIONNAIRE

LORNE STREET EEG & SLEEP LABORATORY

BASAL O2 SATS:
SLEEP NO:
DATE:
REFERRING DR:

WELCOME TO OUR SLEEP LAB!

We hope that you will feel comfortable and well cared for.
Please answer the following questions for us in order to enhance the analysis of your sleeping problem.
(Answer YES or NO: elaborate if necessary)

**Do you snore loudly every night?.....*
**Do you have frequent pauses in breathing whilst you sleep?.....*
**Are you restless during sleep, tossing and turning?.....*
**Is your posture unusual during sleep, do you sleep propped up by pillows?*
.....
**Do you wake up a lot during the night?.....*
**Do you get up to urinate several times a night?.....*
**Have you ever wet your bed?.....*
**Have you ever fallen from your bed?.....*
WHILST AWAKE:
**Do you wake up in the morning tired and foggy, not ready to face the day?*
.....
**Do you have headaches in the morning?.....*
**Are you very sleepy during the day?.....*
**Do you fall asleep during the day?.....*
**Do you have difficulty concentrating, being productive, and completing tasks?.....*
**Do you carry out routine tasks in a daze?.....*
**Have you ever arrived home in your car but couln't remember the trip from*

work?.....
ADJUSTMENT AND EMOTIONAL ISSUES:
**Are you having serious relationship problems ?.....*
**Are you afraid that you may be losing your memory, ?.....*
**Do your friends tell you that you've changed?.....*
**Are you depressed?.....*
**Are you emotionally ill? (stress, anxiety,panic).....*
**Are you irritable and angry especially in the mornings?.....*
**Do you fall asleep whilst: Watching tv.....*
Driving.....
Activities.....
MEDICAL,PHYSICAL CONDITION, AND LIFESTYLE.
** Are you overweight?.....*
**Have you had any recent weight gain.....*
**Do you have high blood pressure?.....*
**Do you have pains in your bones and joints?.....*
**Do you have trouble breathing through your nose?.....*
**Do you often have a drink of alcohol before going to bed?.....*
**Are you taken any medications at present?*
Please list:.....
**Do you have any medical disorders:*
e.g. Diabetes/Chronic obstructive airway disease:
.....
****Have you had previous surgery to your upper airway?.....***

COLLAR SIZE :
HEIGHT:
WEIGHT:
B/P:
MEDS TONIGHT:
EXTRA NOTES:

NOTE:
This practice does not take any responsibility for loss of possesions, skin reactions to electrodes or stickers /or personal injury ,whilst you are being tested in this laboratory. Any willful damage to equipment will be charged to your account. It is to be noted that this is a private practice within the premises of City Hospital. Any complaints concerning nursing staff or facilities , must be made in writing to the City Hospital Matron or Manager.

I.....accept the above and absolve this practice from any responsibility other than professional conduct, and the monitoring and reporting of my sleep disorder.

Signed:_____ Date:

APPENDIX 3: DEMOGRAPHIC AND CLINICAL HISTORY QUESTIONNAIRE

STRICTLY CONFIDENTIAL

BIOGRAPHICAL INFORMATION

Name: _____ Date: _____

Date of Birth _____ Age:_____

Address:_____

_____ Code: _____

Telephone: _____

Gender: _____ Male _____ Female

Which hand do you write with? _____ Right _____ Left

Do you wear reading glasses/spectacles? _____ Yes _____ No

On average how many hours do you sleep a night? _____

EDUCATIONAL HISTORY

Highest educational level achieved _____

Do you recall any learning problems?(please describe)_____

_____

OCCUPATIONAL HISTORY

Current or last job _____

Do you currently work nights or shift work? _____

MEDICAL HISTORY

Do you have any medical disorders (e.g. diabetes)? _____

_____

Are you taking any medication at present (please list)?_____

_____

Any side effects experienced as a result of the medication? _____

_____

Have you ever had epilepsy? _____

Have you ever had a stroke or cerebral vascular accident?_____

Have you ever had a serious head injury where you have been knocked unconscious?_____

PSYCHIATRIC

Do you have a history of any emotional disorders or depression? _____

_____

Have you ever been admitted to a psychiatric hospital? (If yes, please describe the details)_____

_____

ALCOHOL & DRUGS

Do you drink alcohol? _____

How much do you drink on average per day? _____

Describe any history of alcoholism? _____

Do you use any recreational drugs? _____

DAY TIME FUNCTIONING

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent times. Even if you have not done some of the things recently try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0 = Would *never* doze

1 = *slight* chance of dozing

2 = *moderate* chance of dozing

3 = *high* chance of dozing

SITUATION	CHANCE OF DOZING
Sitting and reading	
Watching TV	
Sitting inactive in a public place (e.g. a theatre or a meeting)	
Lying down to rest in the afternoon, when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

Thank you for your cooperation

APPENDIX 4: NORMATIVE COMPARISONS

TEST	COUNTRY	REFERENCE
Five-Point Test	USA	Lee et al. (1997)
Digits Backward	UK	Wechsler (1997)
Stroop Test	USA	Golden (1978)
Trail Making Test	UK	Bornstein (1985)
Wisconsin Card Sorting Test	USA	Heaton (1981)