The Cognitive Effects of Obstructive Sleep Apnoea Syndrome (OSAS): A Comparison Between Untreated Patients and Patients on at Least 3 Months of Continuous Positive Airway Pressure (CPAP) Treatment

By

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COMPULSORY DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works of other people has been attributed, and has been cited and referenced.

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Abstract

Background: Obstructive Sleep Apnoea Syndrome (OSAS) is a relatively common, but also under diagnosed disorder, characterised by periods of breathing stoppage during sleep. Symptoms of OSAS can be divided into nocturnal and diurnal symptoms. The diurnal symptoms, especially excessive daytime sleepiness and cognitive dysfunction, have been found to be the most debilitating of these symptoms, as they disrupt the everyday functioning of OSAS patients. OSAS is most commonly treated with Continuous Positive Airway Pressure (CPAP) therapy.

Objectives: To investigate whether or not OSAS patients from the South African population showed any cognitive impairment relative to healthy individuals from the same population, and to assess whether or not untreated OSAS patients and patients on CPAP treatment differed in their cognitive functioning.

Method: 25 patients, who had previously undergone polysomnographic sleep studies, and had been diagnosed as having moderate to severe OSAS (AHI > 20), were assessed retrospectively using a comprehensive neurocognitive test battery. These patients were divided into a group who had not yet received treatment for OSAS (n = 12), and a group who had been on CPAP treatment for at least 3 months (n = 13). The performances of these two groups on the cognitive test battery were compared to each other, and to a group of normal controls (n = 10). These controls all underwent an overnight polysomnographic sleep study to ensure that they did not have OSAS (AHI < 5). All three groups were matched according to sex, age and years of education. The two OSAS groups were also matched according to AHI (AHI of the untreated OSAS group and pre-treatment AHI of the treated OSAS group). The subjective levels of sleepiness were assessed for all groups, using the Epworth Sleepiness Scale (ESS).

Results: Significant differences were found between the untreated OSAS group and the controls on two of 30 test measures given. These were both measures assessing visual and psychomotor ability. Significant differences were also found between the untreated and treated OSAS groups on two of 30 test measures. However, these were only two of the 18 test measures used to assess executive functioning, and these results do not reflect any specific pattern of improvement after CPAP use. They are therefore likely to be attributable to chance factors, given the small sample

size of the study. No significant differences were found between any of the groups in levels of sleepiness.

Conclusions: Some mild cognitive impairment is shown in untreated OSAS patients, particularly in the areas of visual and psychomotor ability. However, overall, there seems to be little difference between the cognitive functions of OSAS patients and other healthy individuals. Additionally, no substantial differences in cognitive functioning are shown after being on CPAP for at least 3 months. It is recommended that more studies of this nature are conducted – perhaps using a randomised, placebo-controlled crossover design, bigger sample sizes and multiple cognitive batteries that provide a detailed assessment of individual cognitive functions.

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Chapter 1

1 Introduction and Literature Review

OSAS is a relatively common, but also often under diagnosed, respiratory disorder characterized by temporary, repetitive obstruction in the upper airway – typically in the oropharynx or hypopharynx. It occurs during sleep and leads to a reduction in airflow (hypopnoea) or complete cessation of breathing (apnoea) in spite of continued respiratory effort (Skomro & Kryger, 1999; Qureshi & Ballard, 2003; Hopkins & Bigler, 2001; Bédard, Montplaisir, Richer, Rouleau & Malo, 1991, 1993; Valencia-Flores, Bliwise, Guilleminault, Cilveti & Clerk, 1996; Gordon & Sanders, 2005; Ferini-Strambi et al., 2003; Kotterba, Rasche, Widdig, Blombach et al., 1998; Kotterba, Rasche, Widdig, Duscha et al., 1998; Caples, Gami & Somers, 2005; Day, Gerhardstein, Lumley, Roth & Rosenthal, 1999; Engleman & Joffe, 1999; Incalzi et al., 2004). OSAS also results in periodic, nocturnal hypoxaemia, as well as a disturbed pattern of sleep, and episodes frequently end in temporary arousal (Bédard et al., 1991, 1993; Hopkins & Bigler, 2001; Day et al., 1999; Ferini-Strambi et al., 2003; Kotterba, Rasche, Widdig, Blombach et al.1998; Kotterba, Rasche, Widdig, Duscha et al., 1998; Qureshi & Ballard, 2003; Gordon & Sanders, 2005). It is commonly defined by the presence of at least five apnoeas – which are periods of complete airflow cessation lasting for 10 seconds or more; hypopnoeas – which are periods where airflow is reduced by at least 30% for 10 seconds or more; or both (Qureshi & Ballard, 2003; Hopkins & Bigler, 2001). The severity of OSAS is generally measured using the Apnoea-Hypopnoea Index (AHI) or the Respiratory Disturbance Index (RDI). These are both measures of the sum of apnoeas and hypopnoeas experienced during one hour of sleep. The AHI is divided into the categories of mild (with an AHI greater than 5, but less than 15), moderate (with an AHI of 15-30) and severe (with an AHI greater than 30) (Qureshi & Ballard, 2003; Caples et al., 2005; Bédard et al., 1991; Aloia et al., 2004).

A close association has been found between OSAS and older age (that is, over the age of 40 years), obesity, and large neck circumference and these are all important risk and aggravating factors for the disorder (Caples et al., 2005; Qureshi & Ballard, 2003; Hopkins & Bigler, 2001). Additionally, males, postmenopausal women, people who suffer from chronic sleep deprivation

and people who take alcohol and/or sedatives are also considered to have a greater risk of developing OSAS (Qureshi & Ballard, 2003; Hopkins & Bigler, 2001; Caples et al., 2005; Gordon & Sanders, 2005). On the other hand, people who suffer from OSAS are at a high risk of developing other disorders and diseases such as: hypertension, pulmonary hypertension, asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure, cardiac arrhythmias, myocardial infarction, and stroke (Hopkins & Bigler, 2001; Qureshi & Ballard, 2003; Gordon & Sanders, 2005; Bédard et al., 1991; Caples et al., 2005). Subsequently, the death rate among OSAS patients is generally higher than among the general population (Hopkins & Bigler, 2001; Quan et al., 2006).

The symptoms of OSAS can be classified into the categories of nocturnal and diurnal symptoms (Qureshi & Ballard, 2003). The most common nocturnal symptoms include: snoring, witnessed apnoeas, choking, snorting and gasping, nocturia, dry mouth, gastroesophageal reflux, and increased motor activity in sleep (Hopkins & Bigler, 2001; Qureshi & Ballard, 2003). On the other hand, the most frequent diurnal or daytime symptoms include: excessive daytime sleepiness and fatigue; cognitive impairment; personality changes such as moodiness, aggressiveness, anxiety, and depression; sexual dysfunction; and morning headaches (Hopkins & Bigler, 2001; Qureshi & Ballard, 2003). The daytime symptoms are generally found to be far more disturbing and important to the patients than the nocturnal events, as they tend to disrupt and impair the patients' everyday functioning (Engleman & Douglas, 2004; Ferini-Strambi et al., 2003; Day et al., 1999; Valencia-Flores, 1996). Subsequently, these daytime symptoms – especially excessive daytime sleepiness and impairments in memory, concentration and attention – frequently form the primary and presenting complaints of OSAS (Engleman & Joffe, 1999; Engleman & Douglas, 2004; Caples et al., 2005; Bédard et al., 1991, 1993; Ferini-Strambi et al., 2003; Day et al., 1999; Valencia-Flores et al., 1996).

A probable diagnosis of OSAS can be made based on the presence of the above symptoms and predisposing factors (Qureshi & Ballard, 2003). However, in order to make a definitive diagnosis of OSAS, it is essential that a sleep study, using a procedure known as polysomnography, be carried out (Valencia-Flores, 1996; Qureshi & Ballard, 2003; Hopkins & Bigler, 2001; Caples et al., 2005). The polysomnogram is taken overnight, usually in a sleep laboratory, and is generally supervised by an appropriately qualified technician (Qureshi & Ballard, 2003). The

polysomnogram employs a range of different measures - taking electroencephalographic, electro-oculographic, electromyographic, electrocardiographic, oral and nasal airflow, leg movement, respiratory effort, and oxygen saturation recordings (Qureshi & Ballard, 2003; Valencia-Flores, 1996). These measures allow clinicians to obtain a detailed, accurate, and quantifiable picture of the severity and characteristics of the OSAS condition in each individual patient, thus enabling them to make an accurate and definitive diagnosis (Qureshi & Ballard, 2003; Valencia-Flores, 1996).

1.1 Cognitive Impairment in OSAS

Cognitive dysfunction is commonly accepted as being one of the most important and incapacitating daytime symptoms of OSAS, frequently posing as a source of great distress to people suffering from this disorder (Bardwell, Ancoli-Israel, Berry & Dimsdale, 2001; Engleman & Joffe, 1999; Engleman & Douglas, 2004; Qureshi & Ballard, 2003; Hopkins & Bigler, 2001; Bédard et al, 1991, 1993; Valencia-Flores et al., 1996; Gordon & Sanders, 2005; Ferini-Strambi et al., 2003; Kotterba, Rasche, Widdig, Duscha et al., 1998; Caples et al., 2005; Day et al., 1999; Incalzi et al., 2004; Fulda & Schulz, 2001; Henke, Grady & Kuna, 2001; Weaver, 2001; Kim et al., 1997; Roehrs et al., 1995). Furthermore, these cognitive symptoms may frequently impair occupational and psychosocial functioning; lead to a reduced quality of life; and result in an increased risk of automobile and industrial accidents in OSAS patients (Beebe, Groesz, Wells, Nichols & McGee, 2003; O'Donoghue et al., 2005; Weaver, 2001; Engleman & Douglas, 2004; Day et al., 1999; Engleman & Joffe, 1999; Engleman, Kingshott, Martin & Douglas, 2000; Aloia, Arnedt, Davis, Riggs & Byrd, 2004). Consequently, a wide range of empirical studies has been carried out in an attempt to gain a better understanding of the exact nature, causes and quality of the cognitive deficits experienced by OSAS patients (Findley et al., 1986; Cohen-Zion et al., 2001; Mazza et al., 2005; Bédard et al., 1991; Kim et al., 1997; Greenberg, Watson & Deptula, 1987; Adams, Strauss, Schluchter & Redline, 2001; Dealberto, Pajot, Courbon & Alperovitch, 1996; Redline et al., 1997; Naëgelé et al., 1995; Lee, Strauss, Adams & Redline, 1999; Verstraeten, Cluydts, Pevernagie & Hoffman, 2004; Gale & Hopkins, 2004; Thomas, Rosen, Stern, Weiss & Kwong, 2005; Naismith, Winter, Gotsopoulos, Hickie & Cistulli, 2004; Boland

et al., 2002; Bonnet, 1993; Roehrs et al., 1995; Incalzi et al., 2004; Kotterba, Rasche, Widdig, Blombach et al., 1998; Quan et al., 2006).

These empirical studies have primarily taken the form of case-controlled, clinical studies - generally with very small sample sizes of approximately 30-50 patients (Findley et al., 1986; Mazza et al., 2005; Bédard et al., 1991; Greenberg, Watson & Deptula, 1987; Adams et al., 2001; Redline et al., 1997; Naëgelé et al., 1995; Lee et al., 1999; Verstraeten et al., 2004; Gale & Hopkins, 2004; Thomas et al., 2005; Naismith et al., 2004; Bonnet, 1993; Roehrs et al., 1995; Incalzi et al., 2004; Kotterba, Rasche, Widdig, Blombach et al., 1998). However, several epidemiological, population-based studies have also been conducted (Kim et al., 1997; Boland et al., 2002; Dealberto et al., 1996; Cohen-Zion et al., 2001; Quan et al., 2006). Almost all of these studies have found at least mild impairment in some cognitive domains in OSAS patients, and many of them have found that these deficits are wide ranging across a number of different functions (Roehrs et al., 1995; Incalzi et al., 2004; Findley et al., 1986; Bédard et al., 1991; Greenberg et al., 1987; Adams et al., 2001; Naismith et al., 2004). Consequently, deficits have been said to occur in OSAS patients in the domains of: vigilance and various types of attention; concentration; motor skills; immediate and delayed long-term verbal and visual memory; short-term memory; general intelligence; psychomotor efficiency; the various components of the executive functions such as working memory, mental flexibility, complex problem solving, planning, categorizing and inhibition; and visuoconstructional abilities (Findley et al., 1986; Cohen-Zion et al., 2001; Mazza et al., 2005; Bédard et al., 1991; Kim et al., 1997; Greenberg, Watson & Deptula, 1987; Adams et al., 2001; Dealberto, Pajot, Courbon & Alperovitch, 1996; Redline et al., 1997; Naëgelé et al., 1995; Lee, Strauss, Adams & Redline, 1999; Verstraeten et al., 2004; Gale & Hopkins, 2004; Thomas et al., 2005; Naismith et al., 2004; Boland et al., 2002; Bonnet, 1993; Roehrs et al., 1995; Incalzi et al., 2004; Kotterba, Rasche, Widdig, Blombach et al., 1998, Quan et al., 2006). However, each of these studies vary significantly from one another in terms of which of these specific functions they identified as being impaired in OSAS, as well as in the severity of these impairments. These discrepancies in the results of the various studies can probably be attributed to the fact that the different studies assessed different cognitive functions, used different neuropsychological tests to assess these functions – sometimes even when they were testing the same function - and used different OSAS patient groups with various

levels of severity of the disorder (Décary, Rouleau & Montplaisir, 2000; Beebe et al., 2003; Verstraeten & Cluydts, 2004; Naismith et al., 2004; Adams et al., 2001; Incalzi et al., 2004). A number of recent articles have been written with the aim of summarising and reviewing this body of literature (Fulda & Schulz, 2001; 2003; Engleman & Douglas, 2004; Engleman et al., 2000; Beebe et al., 2003; Décary et al., 2000; Aloia et al., 2004; Engleman & Joffe, 1999; Day et al., 1999). As these articles provide a detailed and comprehensive examination of this literature, this review will not discuss the individual studies on cognitive dysfunction in OSAS in detail, but will instead focus on the results and findings of the aforementioned articles written to review these studies.

The review articles that examine previously conducted studies on cognitive impairment in OSAS, like the studies themselves, vary substantially from one another with regards to their findings. This is largely owing to the fact that the authors of these articles use different criteria for deciding which studies to include in their reviews and, subsequently, review slightly different ranges and types of studies. Additionally, the authors of these articles classify and define the cognitive categories in which they organize the results of these studies in different ways. Furthermore, different methods are used to review these studies.

For instance, a number of these articles, such as those written by Décary et al. (2000) and Aloia et al. (2004), present summarised results of various studies on cognitive dysfunction in OSAS in a qualitative, narrative form of review. In the first of these articles mentioned here, Décary et al. (2000) identify and examine the main cognitive domains found to be impaired by the studies reviewed. They classify these cognitive functions as: general intellectual functioning, attentional functioning, memory and learning abilities, executive functions, and motor functions (Décary et al., 2000). Décary et al. (2000) suggest that the inconsistencies in results seen in various studies on cognitive deficits in OSAS are primarily owing to the fact that the different studies use different neuropsychological test batteries to assess the cognitive functioning of their subjects. Consequently, Décary et al. recommend that a standard neuropsychological battery be used instead, and present a proposed battery of cognitive tests that is designed to assess all of the functions mentioned above, based on their review. However, as Verstraeten and Cluydts (2004) note, although it would be useful for all studies investigating cognitive dysfunction in OSAS to be able to utilise a standard battery of tests, the particular battery suggested by Décary et al.

(2000) would take approximately three hours to administer. As time is usually very limited in clinical studies, it would therefore be impractical to administer this suggested test battery in these studies on cognitive dysfunction in OSAS patients (Verstraeten & Cluydts, 2004).

Additionally, in their recent article on the neuropsychological effects of OSAS, Aloia et al. (2004) examined 37 peer-reviewed articles in an attempt to elucidate the pattern of cognitive dysfunction seen in OSAS patients. They classified cognitive functions in a similar way to Décary et al. (2000), using the categories of: language, global cognitive domain (which basically refers to the same function that Décary et al. (2000) termed as "general intellectual functioning"), attention/vigilance, executive functioning, memory, psychomotor functioning, and construction (Aloia et al., 2004). This review of the available literature revealed that the areas of language and global cognitive domain remained relatively unimpaired in sleep apnoeics, whereas attention/vigilance, executive functioning, memory, and to a lesser extent, psychomotor functioning and construction, were reported to be impaired in the majority of studies. However, Aloia et al. (2004) do note that assessments of executive functioning and memory may be subject to some methodological problems. This is due to the fact that both of these broad cognitive domains involve several different functions, each of which is measured with different tests. In the area of executive functioning, in particular, each of the different tests assesses different functions associated with various parts of the frontal lobes in the brain (Aloia et al., 2004). Aloia et al. (2004) therefore note that, seeing as these various tests are assessing completely different functional systems, they are likely to produce relatively discrepant results within a single group of subjects. On the other hand, in the area of memory, test performance can be impaired for various reasons – such as problems with learning new information, problems with forgetting new information that has been learned or problems with retrieving stored information from memory. The different reasons for subjects' poor performance on memory tests reveal which areas of the brain are damaged (Aloia et al., 2004). However, these reasons for impaired performance on tests of memory are seldom investigated, and, consequently, it is not clear to what extent the apparent memory impairment shown in these studies is representative of true memory problems or rather is attributable to or mediated by impairment in executive functions and/or attentional difficulties (Aloia et al., 2004). Additionally, Aloia et al. (2004) also found discrepancies in performance on tests of psychomotor functioning – with OSAS patients generally showing impaired performance

on tests of fine motor co-ordination, but no impairments on tests of simple motor speed. Overall, Aloia et al. (2004) reported that study results were generally inconsistent and ambiguous in most cognitive functions. It is therefore difficult to reach any definite conclusions on the pattern of cognitive impairment in OSAS from the findings of these studies.

Alternatively, other authors have used quantitative, meta-analytical methods to review and analyse the findings of the literature on cognitive dysfunction in OSAS patients (Beebe et al., 2003; Fulda & Schulz, 2003; Engleman et al., 2000). As noted by Fulda & Schulz (2003), Engleman et al. (2000) were the first to use the meta-analytical technique to review the results of case-controlled studies on cognitive impairment in OSAS. This technique involves pooling the quantitative results of the individual studies being reviewed by calculating effect sizes for cognitive impairment (Engleman et al., 2000; Beebe et al., 2003). These effect sizes provide a quantitative way of measuring and comparing dysfunction in the various cognitive domains affected by OSAS (Engleman et al., 2000). Engleman et al. (2000) categorised these domains as: attention and psychomotor skills; memory and learning ability; and executive and frontal lobe function. They found that subjects used in community or population-based studies generally demonstrated mild impairments in the domains of attention and executive functioning, and negligible impairments in the area of memory (Engleman et al., 2000). On the other hand, in subjects involved in clinical studies, moderate and large cognitive impairment was seen in all three cognitive domains – with the largest impairment seen in the area of attention, followed by large impairment also in the area of executive functioning and moderate impairment in the area of memory (Engleman et al., 2000). Engleman et al. (2000) also noted that the severity of cognitive impairment seen in OSAS patients seemed to be at least weakly associated with the severity of disease as measured by AHI. This relationship between the severity of cognitive dysfunction and the severity of OSAS will be discussed in more detail at a later stage of this literature review.

Beebe et al. (2003) note that Engleman et al.'s (2000) narrow focus on published, case-controlled data restricted the cognitive domains that could be analysed and also prevented the statistical investigation of other potential influencing factors, such as disease severity, on cognitive impairment in OSAS. Furthermore, they state that the aforementioned study's (Engleman et al., 2000) use of only published studies may also have resulted in a possible publication bias – where

the number of positive and significant findings may have been misrepresented, since studies with null results have a smaller chance of being chosen for publication (Beebe et al., 2003). Consequently, Beebe et al. (2003) carried out a similar, meta-analytical review of the studies conducted on neuropsychological dysfunction in OSAS, in order to extend the study and findings of Engleman et al. (2000). They included all the available, quantitative data on the cognitive effects of OSAS from studies which had been conducted up to, and including, the year of 2001 (Beebe et al., 2003). This included both case-controlled and uncontrolled studies; studies using control groups, as well as those comparing their results to published norms; and published studies, as well as unpublished dissertations (Beebe et al., 2003). Using this data, they found 10 cognitive domains, namely: intelligence; verbal ability; visual ability; short-term verbal memory; short-term visual memory; long-term verbal memory; long-term visual memory; executive functioning - which included the functions of working memory, mental flexibility, planning, problem-solving, inhibition and verbal fluency -; motor functioning; and vigilance (Beebe et al., 2003). After analysing the various continuous effect sizes of each of these domains from the studies reviewed, Beebe et al. (2003) noted that functioning was relatively unimpaired in the areas of general intelligence and verbal ability in untreated OSAS patients. These results reflect the findings of Aloia et al.'s (2004) narrative review, as described previously. Additionally, Beebe et al. (2003) also found large impairments in the areas of executive functioning and vigilance. On the other hand, they found that performances on tests of visual and motor skills, as well as on tests of memory, were inconsistent across studies. Once again, these results are similar to those found by Aloia et al. (2004).

Finally, in Fulda & Schulz's (2003) detailed review on the current available literature on the neuropsychological effects of OSAS, the authors combined the two aforementioned methods of review. They thus provide both a summarised, narrative review of 54 studies, as well as a meta-analysis of 28 of those studies that provided sufficient statistics to carry out this technique. They classified the cognitive functions measured into the following categories: perception, attention, motor functions, driving simulation, constructional performance, memory, concept formation, reasoning and executive functions, verbal functions and language skills, and general intellectual functioning (Fulda & Schulz, 2003). In this review, Fulda and Schulz (2003) usefully group measures of cognitive dysfunction in as narrow categories as possible and subsequently placed

the results of the tests of the different types of attention, memory and executive functions into separate sub categories. As a result, they were able to attempt to solve the methodological problems described by Aloia et al. (2004) in the domains of memory and executive dysfunction by clarifying which specific functional systems of these areas were being assessed by the various tests used (Fulda & Schulz, 2003). Overall, Fulda & Schulz (2003) found moderate to large impairments in mental flexibility, visual delayed-memory retrieval, and driving simulation performance and small to moderate dysfunction in focused and sustained attention, verbal delayed-memory retrieval, verbal fluency, and general intellectual functioning. They found relatively no impairments in the areas of divided attention, concept formation and reasoning, and verbal or visual immediate memory performance (Fulda & Schulz, 2003). However, they were not able to integrate data from the various studies in the cognitive domains of: various aspects of attention – such as attentional span, selective attention, alertness and vigilance -; motor functions; perception; constructional performance; learning; executive functions; and some measures of general intellectual functioning - such as verbal and performance IQ (Fulda & Schulz, 2003). The results of this review study therefore show that impairment varies significantly between the different cognitive domains, as well as within the different functions and sub-functions of these domains (Fulda & Schulz, 2003).

Overall, as previously mentioned, the above reviews of the current available literature on the neuropsychological effects of OSAS have produced somewhat disparate findings. Consequently, they provide only a rather hazy picture of the pattern of cognitive impairment seen in OSAS patients. Nonetheless, these review articles do still provide a basic, broad idea of the cognitive domains that are most likely to be impaired in OSAS patients. Generally, these reviews have most commonly cited the largest degree of cognitive impairment in the areas of attention/vigilance and executive functioning, followed by dysfunction in the domain of memory (Engleman et al., 2000; Aloia et al., 2004; Beebe et al., 2003). Slightly less severe and less consistently reported impairments have also been seen occasionally in the functions of constructional abilities and psychomotor ability (Beebe et al., 2003; Aloia et al., 2004). Bearing these findings in mind, it is therefore not surprising that a number of individual studies have been conducted in order to specifically investigate the effects of OSAS on the executive functions and attention/vigilance of patients suffering from this disorder (Lee et al., 1999; Thomas et al., 2005;

Verstraeten & Cluydts, 2004; Verstraeten et al., 2004; Jones & Harrison, 2001; Naëgelé et al., 1995; Mazza et al., 2005). However, as has been shown to be the case in most of the studies conducted in this area of research, these studies have yielded discrepant results.

For instance, in their study on executive dysfunction in OSAS patients, Naëgelé et al. (1995) examined 17 OSAS patients and 17 normal controls using neuropsychological tests that focused specifically on various frontal lobe functions. They found that OSAS patients had an impaired ability to initiate new, and to inhibit automatic, mental processes (Naëgelé et al., 1995). They also found that these patients had a tendency to make more perseverative errors than controls, had an impaired ability to learn new verbal and visual information, and had decreased memory spans (Naëgelé et al., 1995). However, the OSAS patients in this study did not evidence any significant impairment in their abilities to solve problems, to produce adequate generalized strategies for solving problems, or to generate words of a specific letter within a given time – all of which are usually found in people with damage to their frontal lobes (Naëgelé et al., 1995). As a result, therefore, the authors concluded that their results suggested that OSAS patients did show some executive dysfunction, but not to the extent seen in patients who have had frontal lobe, or related subcortical, damage (Naëgelé et al., 1995).

On the other hand, Verstraeten & Cluydts (2004) have argued in their theoretical article on executive functioning in OSAS that studies on this cognitive function have assumed that any impairment in this area is due to damage to the (pre)frontal lobes, resulting from the intermittent, nocturnal hypoxaemia experienced by these patients. However, they note that such studies have neglected to bear in mind the effects that deficits in functions of attention and vigilance – such as in the areas of arousal or alertness – can have on the cognitive processes involved in executive functioning (Verstraeten & Cluydts, 2004). Seeing as OSAS patients are known to suffer from deficits in these areas of attention and vigilance, owing to the sleep fragmentation that they experience – which leads to a decreased quality and quantity of sleep -, the authors therefore suggest that these problems may underlie the apparent deficits of executive functions sometimes seen in OSAS patients (Verstraeten & Cluydts, 2004). They therefore propose that the effects of attention on executive functioning should be controlled for in order to assess the true impact of OSAS on executive functions (Verstraeten & Cluydts, 2004). This can be done through statistical methods, as well as by encouraging the patients in order to ensure that they reach a maximum

level of alertness, motivation, and effort when completing tests of executive functioning (Verstraeten & Cluydts, 2004).

Verstraeten et al. (2004) subsequently conducted a study in which they assessed executive functions, while using both of the aforementioned methods to control for the possible effects that attentional deficits may have on these functions. They found clear evidence of vigilance and attentional impairment in the OSAS patients in their study, while finding no indications of executive dysfunction when controlling for the role of the aforementioned attentional deficits experienced by these patients. This study therefore provided support for their proposed idea that the apparent executive dysfunction seen in OSAS patients was not likely to result from permanent brain damage to the frontal lobes, owing to the intermittent hypoxaemia experienced by OSAS patients (Verstraeten et al., 2004). Instead, these results suggest that these apparent executive deficits are in fact simply a function of the underlying, sleep-related attentional and vigilance problems commonly experienced by sleep apnoeics (Verstraeten et al., 2004). Similarly, in their study assessing executive functioning in OSAS patients, Lee et al. (1999) found only slight impairment in two tests of executive functions and found no evidence of deficits in working memory – an important aspect of executive functioning. Consequently, the findings of this study also lend support to the idea that OSAS patients do not suffer the significantly large deficits in executive functioning previously reported and found in other studies (Lee et al., 1999; Verstraeten & Cluydts, 2004; Naëgelé et al., 1995). Additionally, in their study on neuroimaging and neuropsychological impairment in carbon monoxide poisoning and OSAS, Gale and Hopkins (2002) found that the executive impairment seen in their OSAS patients improved following CPAP treatment. This therefore provides further evidence that the executive dysfunction commonly seen in OSAS patients is not caused by permanent damage to the frontal lobes of the brain (Gale & Hopkins, 2002).

However, as is evidenced from the varied findings described above, no firm conclusions can yet be drawn about the exact nature or cause of the executive dysfunction frequently seen in OSAS patients. As a result, there is a need for more studies to be conducted which carefully examine executive functioning in OSAS patients, using tests that specifically assess the different systems involved in both attentional/vigilance and frontal lobe functions (Verstraeten & Cluydts, 2004). Additionally, similar such studies need to be conducted which investigate the various functions

involved in the cognitive domain of memory, since studies have often been found to have inconsistent results in this area in particular (Aloia et al., 2004; Beebe et al., 2003). Furthermore, in order to overcome the methodological concerns often associated with studies testing attentions/vigilance, executive functions, and memory – as mentioned above when describing Aloia et al.'s (2004) study, and as has been described by a number of other authors -, each function of these cognitive domains need to clearly defined and assessed individually (Jones & Harrison, 2001; Fulda & Schulz, 2003; Décary et al., 2000).

1.2 Cognitive Dysfunction and Severity of OSAS

Several authors have suggested that there is a relationship between the severity of OSAS – as measured by AHI or RDI and/or measures of hypoxaemia, such as oxygen desaturation levels – and the severity of the cognitive dysfunction commonly seen in sleep apnoeic patients (Engleman & Joffe, 1999; Redline et al., 1997; Bédard et al., 1991; Adams et al., 2001; Engleman et al., 2000; Engleman & Douglas, 2004; Kim et al., 1997). Consequently, a few studies have been carried out which investigate this relationship, although they have yielded somewhat inconsistent findings (Bédard et al., 1991; Redline et al., 1997; Engleman et al., 2000; Adams et al., 2001; Boland et al., 2002; Cohen-Zion et al., 2001). For instance, in their study on mild sleep disordered breathing, Redline et al. (1997) found that patients with mild levels of OSAS (that is, patients who had an RDI of 10-30) only evidenced cognitive impairment in a task of vigilance and working memory, but did not differ significantly from non-apnoeic patients in any other cognitive domains. Furthermore, in their recent study examining the neurocognitive functioning of 67 patients with mild to moderate OSAS (that is patients with an AHI of 10-50) from a non-clinical population, Quan et al. (2006) found no significant differences between the OSAS group and a group of 74 controls on any of the neuropsychological tests used. These results therefore show that patients with mild OSAS experience no, or only mild, cognitive deficits (Redline et al., 1997; Quan et al., 2006). Additionally, in their study comparing 10 normal controls to 10 patients with moderate OSAS and 10 patients with severe OSAS, Bédard et al. (1991) found that, while both groups of OSAS patients were more cognitively impaired than the controls in a wide range of cognitive functions, the severely apnoeic patients showed greater neuropsychological deficits

than the moderately apnoeic group. This study provides further evidence for a dose-response relationship between level of severity of OSAS and level of severity of cognitive dysfunction.

However, several other authors have reported no, or only small, associations between disease severity and severity of neuropsychological impairment in OSAS patients (Naismith et al., 2004; Cohen-Zion, 2001; Boland et al., 2002). For instance, Boland et al. (2002) found no consistent relationship between the RDI and cognitive functioning in the mild to moderate sleep apnoeics participating in their epidemiological, population-based study. Alternatively, Aloia et al. (2004) have suggested that perhaps there is a non-linear relationship between severity of OSAS and severity of cognitive dysfunction, whereby a threshold of severity of OSAS needs to be reached before cognitive dysfunction is evident. Overall, however, as evidenced in other aspects of the research on cognitive dysfunction in OSAS, no definite conclusions can be drawn about this relationship, and further studies are needed to examine it further.

1.3 Aetiology of Cognitive Impairment in OSAS

Another controversial topic in this area of research is the aetiology of the neuropsychological impairment frequently seen in OSAS patients (Engleman & Joffe, 1999; Engleman & Douglas, 2004; Naismith et al., 2004; Cohen-Zion et al., 2001; Adams et al., 2001; Bédard et al., 1991; Hopkins & Bigler, 2001; Day et al., 1999). Researchers are divided as to whether this impairment results from the excessive daytime sleepiness or the nocturnal hypoxaemia associated with OSAS, or whether it results from a combination of these two factors (Engleman & Joffe, 1999; Engleman & Douglas, 2004; Naismith et al., 2004; Cohen-Zion et al., 2001; Adams et al., 2001; Engleman et al., 2000; Greenberg et al., 1987; Findley et al., 1986; Hopkins & Bigler, 2001; Bliwise, 1993; Day et al., 1999; Roehrs et al., 1995; Kotterba, Rasche, Widdig, Blombach et al., 1998; Quan et al., 2006). Studies conducted to clarify this matter have once again yielded discrepant results, and evidence has been given to support each of these possible causes of cognitive dysfunction in OSAS (Engleman & Joffe, 1999; Engleman & Douglas, 2004; Naismith et al., 2004; Cohen-Zion et al., 2001; Adams et al., 2001; Engleman et al., 2000; Findley et al., 1986; Hopkins & Bigler, 2001; Day et al., 1999; Roehrs et al., 1995; Kotterba, Rasche, Widdig, Blombach et al., 1998; Quan et al., 2006).

For instance, in their study comparing patients with sleep apnoea associated with hypoxaemia and non-hypoxaemic apnoeic patients, Findley et al. (1986) found that the patients with sleep apnoea associated with hypoxaemia had more severe cognitive dysfunction than the non-hypoxaemic OSAS patients had. Furthermore, they found that the severity of hypoxaemia significantly correlated with the level of overall cognitive dysfunction (Findley et al., 1986). Additionally, Greenberg et al. (1987) found that patients with sleep apnoea associated with hypoxaemia experienced neuropsychological impairment that extended beyond what could be explained by the effects of aging or excessive sleepiness. Furthermore, in their study of 100 patients with sleep disordered breathing of various levels of severity, Adams et al. (2001) found a linear relationship between severity of hypoxaemia and/or RDI and cognitive dysfunction in OSAS. They also noted that only the cognitive domain of vigilance was predicted by the level of sleepiness in these patients (Adams et al., 2001). Moreover, Quan et al. (2006) found that, although there were no significant differences between the OSAS patients and healthy controls on any of the neuropsychological test measures used in their study, the cognitive function of motor speed was significantly disturbed in the patients who were more hypoxaemic. They also found that the patients with more severe desaturation in oxygen levels showed more deficits in the areas of motor speed and processing speed, even when the authors controlled for the effects of sleepiness, age, gender and education. Their results therefore show that any deficits that may be found in OSAS, however mild, seem to be primarily related to the hypoxaemia seen in these patients (Quan et al., 2006).

Further evidence has been given to support the aetiological role of hypoxaemia in the neuropsychological dysfunction in OSAS patients by some brain imaging studies conducted on these patients (Gale & Hopkins, 2004; Morrell et al., 2003; Macey et al., 2002). For instance, in their study on neuroimaging and neuropsychological dysfunction in victims of carbon monoxide poisoning and OSAS patients, Gale and Hopkins (2004) found hippocampal atrophy in OSAS patients. Intermittent hypoxic events have been known to cause damage to the CA1 region of the hippocampus and, subsequently, the results of this study suggest that the nocturnal hypoxaemia experienced by OSAS patients may cause permanent damage to the brain, leading to at least some of the cognitive impairments seen in OSAS (Gale & Hopkins, 2004; Morrell et al., 2003). Morrell et al. (2003) similarly found significantly lower concentration of grey matter in the left

hippocampal region of sleep apnoeic patients. Furthermore, Macey et al. (2002) found significant loss of grey matter in several regions of the brain, including the frontal and parietal cortex; temporal lobe; anterior cingulate; hippocampus; and cerebellum – many of which are particularly susceptible to the effects of hypoxaemic episodes, and are known to be associated with some of the cognitive deficits seen in OSAS patients.

However, O'Donoghue et al. (2005) conducted a very similar, but better controlled, study to the one mentioned above and found no evidence of differences in volume of grey matter or of any focal structural changes in OSAS patients. Seeing as their study was better controlled than that of Macey et al. (2002), used more optimised imaging techniques, and excluded any patients with co-morbidities that were likely to affect their results – which Macey et al. (2002) neglected to do - the findings of their study hold more weight than those of Macey et al.'s (2002) study. Additionally, in Verstraeten et al.'s (2004) study investigating executive dysfunction in OSAS, which has been described above, the researchers found that the cognitive deficits seen in their OSAS patients closely resembled those seen in normal, sleep deprived individuals. Furthermore, the picture of cognitive decline seen in these patients was rather different to that seen in COPD patients, who suffer from chronic hypoxaemia (Verstraeten et al., 2004). These authors also found no evidence to suggest the type of cognitive impairment seen in patients with permanent damage to the prefrontal lobes (Verstraeten et al., 2004). Consequently, Verstraeten et al. (2004) conclude from these findings that the neuropsychological dysfunction seen in OSAS patients is primarily caused by their sleepiness rather than by structural brain damage resulting from the intermittent hypoxaemia that they experience. These findings are further supported by Cohen-Zion et al.'s (2001) study, where the authors found that the severity of cognitive deficits – as measured by scores on the Mini-Mental State Examination – was associated with levels of sleepiness, but not with differences in oxygen saturation levels – which are an indication of the severity of hypoxaemia. Furthermore, Bonnet (1993) also noted that the pattern of cognitive deficits seen in sleep apnoeics is consistent with that seen in normal people after a period of sleep deprivation.

Alternatively, a number of other studies have yielded results suggesting a differential contribution of both sleepiness and nocturnal hypoxaemia in causing cognitive dysfunction in OSAS (Engleman et al., 2000; Bédard et al., 1991; Naismith et al., 2004). For instance, in their

study aimed at investigating the aetiology of cognitive impairment in OSAS, Bédard et al. (1991) found that deficits in general intellectual functioning; executive functioning and psychomotor tasks were related to the severity of nocturnal hypoxaemia, while impairment in memory and attention were associated with impairment in daytime vigilance. Similarly, in their study on neurobehavioural functioning in OSAS, Naismith et al. (2004) also found differential effects of nocturnal hypoxaemia and daytime sleepiness on cognitive dysfunction in OSAS. However, the respective functions that they found to be associated with hypoxaemia and sleepiness differed from the Bédard et al.'s (1991) findings. Subsequently, whereas Bédard et al. (1991) noted an association between executive functioning and hypoxaemia, Naismith et al. (2004) found executive dysfunction to be related to the level of daytime sleepiness. Naismith et al. (2004) observed a relationship between nocturnal hypoxaemia and impairment in visuoconstructional abilities, processing speed and mental flexibility. Differences in findings between these studies may be attributable to the fact that they each assessed slightly different cognitive functions, and also defined and measured these functions in different ways. Overall, therefore, the question about the aetiology of the cognitive deficits seen in OSAS patients is still basically left unanswered. However, other studies which explore this subject further in different ways will be discussed in more detail in the following section of this literature review.

1.4 Treatment and Cognitive Impairment in OSAS

The most popular and commonly used form of treatment for OSAS is nasal continuous positive airway pressure (CPAP) therapy (Hopkins & Bigler, 2001; Engleman & Joffe, 1999; Qureshi & Ballard, 2003; Gordon & Sanders, 2005; Valencia-Flores et al., 1996; Day et al., 1999; Bédard et al., 1993; Caples et al., 2005; Kingshott et al., 2000; Barbé et al., 2001; Engleman et al., 1998; Engleman & Martin, 1994; Borak, Cieslicki, Koziej, Matuszewski & Zielinski, 1996). CPAP therapy treats OSAS by introducing a small amount of positive pressure through a lightweight mask – which the patients wear when they are sleeping – into the upper airway, via the nasal cavity (Valencia-Flores et al., 1996; Hopkins & Bigler, 2001; Qureshi & Ballard, 2003). This positive pressure then splints open the airway, thus preventing obstruction (Valencia-Flores et al., 1996; Hopkins & Bigler, 2001; Qureshi & Ballard, 2003; Gordon & Sanders, 2005). CPAP

therapy has been proven to be highly effective in improving sleeping patterns and sleep fragmentation, breathing pauses, hypoxaemia, and, subsequently, both objective and subjective excessive daytime sleepiness (Kingshott et al., 2000; Engleman & Joffe, 1999; Engleman & Douglas, 2004; Engleman et al., 1993, 1998; Gordon & Sanders, 2005; Ferini-Strambi et al., 2003; Qureshi & Ballard, 2003; Caples et al., 2005; Bédard et al., 1993; Hopkins & Bigler, 2001; Valencia-Flores et al., 1996; Borak et al., 1996; Naëgelé et al., 1998; Barbé et al., 2001; Day et al., 1999). Additionally, improvements in psychological functioning and mood have also been found in several studies (Day et al., 1999; Engleman et al., 1993; Engleman & Joffe, 1999; Engleman & Martin, 1994; Hopkins & Bigler, 2001). However, the efficacy of CPAP therapy in improving the cognitive symptoms of OSAS is less clear, and, as a result, a number of studies have been carried out in order to investigate the effect that CPAP therapy has on cognitive dysfunction in OSAS patients (Engleman & Joffe, 1999; Engleman & Douglas, 2004; Engleman et al., 1993, 1998, 2000; Engleman & Martin, 1994; Gordon & Sanders, 2005; Ferini-Strambi et al., 2003; Bédard et al., 1993; Hopkins & Bigler, 2001; Valencia-Flores et al., 1996; Bardwell et al., 2001; Day et al., 1999; Kotterba, Rasche, Widdig, Duscha et al., 1998; Henke et al., 2001; Montplaisir, Bédard, Richer & Rouleau, 1992; Kingshott et al., 2000; Lojander, Kajaste, Maasilta & Partinen, 1999; Borak et al., 1996; Naëgelé et al., 1998; Barbé et al., 2001).

The results of the majority of CPAP treatment studies generally show at least partial improvements in cognitive functioning after the use of CPAP (Engleman & Joffe, 1999; Engleman & Douglas, 2004; Ferini-Strambi et al., 2003; Bédard et al., 1993; Hopkins & Bigler, 2001; Valencia-Flores et al., 1996; Bardwell et al., 2001; Kotterba, Rasche, Widdig, Duscha et al., 1998; Henke et al., 2001; Borak et al., 1996; Kingshott et al., 2000; Naëgelé et al., 1998). However, there are a few studies which have found no or only mild improvement in neuropsychological functioning after the use of CPAP therapy (Engleman et al., 1993, 1998, 2000; Lojander et al., 1999; Barbé et al., 2001; Bardwell et al., 2000). For instance, in their study investigating the effects of CPAP on daytime sleepiness, cognitive functions, and mood, Engleman et al. (1993) found that, while objective measures of daytime sleepiness and mood improved after 3 months of CPAP therapy, cognitive functioning showed no major changes. Similarly, in Engleman et al.'s (1998) randomised placebo controlled study, no major improvements were found in the cognitive functioning of OSAS patients after 4 weeks of CPAP

treatment. However, this study had a relatively small sample size of 23 participants and the authors suggest that this may have influenced their results (Engleman et al. 1998). Alternatively, in their study comparing the effects of surgical treatment to CPAP therapy on cognitive functions in OSAS patients, Lojander et al. (1999) – who utilised a bigger sample of 50 OSAS patients – found only slight improvement in neuropsychological functioning both 3 and 12 months after both types of treatment. It is important to note that the patients who participated in this study only showed mild cognitive impairment before receiving treatment, despite the fact that they suffered from moderate to severe OSAS (Lojander et al., 1999). Consequently, Lojander et al. (1999) attribute their findings to the insensitivity of the neuropsychological battery used in identifying improvements in patients with relatively high levels of overall cognitive functioning.

Alternatively, as previously mentioned, a vast number of CPAP therapy studies have been conducted which show positive changes in cognitive functioning following this type of treatment (Engleman & Joffe, 1999; Engleman & Douglas, 2004; Ferini-Strambi et al., 2003; Bédard et al., 1993; Hopkins & Bigler, 2001; Valencia-Flores et al., 1996; Bardwell et al., 2001; Kotterba, Rasche, Widdig, Duscha et al., 1998; Henke et al., 2001; Borak et al., 1996; Kingshott et al., 2000; Naëgelé et al., 1998). However, as in the studies on the quality and nature of cognitive impairment in OSAS (described in the previous section of this literature review), these studies have shown variable results in terms of the extent of cognitive improvement, as well as the specific cognitive areas that are improved, after CPAP treatment (Bardwell et al., 2001; Day et al., 1999; Hopkins & Bigler, 2001; Engleman & Joffe, 1999; Borak et al., 1996; Montplaisir et al., 1992; Valencia-Flores et al., 1996; Ferini-Strambi et al., 2003; Engleman & Martin, 1994). For instance, some studies have shown positive changes in almost all neuropsychological functions or in overall cognitive functioning in OSAS patients (Bardwell et al., 2001; Henke et al., 2001; Borak et al., 1996). For example, in their study on the effects of CPAP treatment on psychological status in OSAS patients, Borak et al. (1996) found improvements in several areas of cognitive functioning after 3 months of CPAP therapy, and found positive changes in almost all tests of neuropsychological functioning after 1 year of treatment. Additionally, in their placebo-controlled study, which assessed neuropsychological functions in 36 OSAS patients before and after one week of effective or placebo CPAP treatment, Bardwell et al. (2001) found that the patients on effective CPAP therapy showed improvements in overall cognitive

functioning. However, when they did a further analysis to assess which particular cognitive functions had improved, they did not obtain significant results in any particular area of cognition (Bardwell et al., 2001). Similarly, the results of another placebo-controlled treatment study also showed that OSAS patients improved in their overall cognitive functioning after being on effective CPAP therapy (Henke et al., 2001) However, the researchers of this study also found that the group of patients who had been on ineffective CPAP treatment also improved equally in their cognitive functioning (Henke et al., 2001).

On the other hand, some other studies have shown only partial reversibility of cognitive dysfunction after CPAP treatment – evidencing significant improvements in some areas of cognition after treatment, but not others (Bédard et al., 1993; Ferini-Strambi et al., 2003; Valencia-Flores et al., 1996; Hopkins & Bigler, 2001; Engleman & Joffe, 1999; Engleman & Martin, 1994; Montplaisir et al., 1992; Naëgelé et al., 1998). Although the specific cognitive areas that were found to improve or remain impaired after treatment varied from study to study, many studies found similar patterns of improvement and remaining impairment after CPAP therapy (Montplaisir et al., 1992; Ferini-Strambi et al., 2003; Bédard et al, 1993). For instance, in their study on the effectiveness of short- and long-term CPAP therapy in improving cognitive functioning in OSAS, Ferini-Strambi et al. (2003) found improvements in the areas of attention, visuospatial learning, and motor performances after 15 days of CPAP therapy. They also found no additional improvements after 4 months of treatment (Ferini-Strambi et al., 2003. However, they found that the cognitive areas of executive functioning and constructional abilities remained impaired after both 15 days and 4 months of CPAP treatment. Similarly, Bédard et al. (1993) found that all areas of cognitive functioning returned to normal levels after 6 months of CPAP treatment, except for planning abilities – which form a part of the executive functions – and manual dexterity. The cognitive functions that have been shown to remain impaired after CPAP treatment, such as executive functions and visuoconstructive abilities, are areas of neuropsychological functioning that have also been found to be related to the nocturnal hypoxaemia that OSAS patients experience (Montplaisir et al., Bédard et al., 1993; Ferini-Strambi et al., 2003). Additionally, it has been suggested that those areas that are commonly found to improve after treatment are associated with daytime sleepiness and vigilance impairment in OSAS patients (Montplaisir et al., 1992). Consequently, the results of these

studies have been used as evidence to show that both daytime sleepiness and vigilance impairment, as well as hypoxaemia, differentially affect and cause cognitive dysfunction in OSAS patients (Engleman et al., 2000; Valencia-Flores, 1996). Furthermore, some authors have proposed that the areas that remain impaired after CPAP treatment may reflect irreversible damage to the brain – particularly to the frontal lobes, which are the main areas involved in executive functioning – resulting from the intermittent hypoxaemia experienced by these patients (Ferini-Strambi et al., 2003; Bédard et al., 1993; Kotterba, Rasche, Widdig, Duscha et al., 1998; Montplaisir et al., 1992; Hopkins & Bigler, 2001).

Further evidence to support this idea is provided by Kotterba, Rasche, Widdig, Duscha et al. (1998) in their study on neuropsychological functioning and event-related potentials in OSAS before and after treatment on CPAP. These researchers found impairments in the areas of alertness, selective attention, and continuous attention before CPAP therapy (Kotterba, Rasche, Widdig, Duscha et al., 1998). They found that these cognitive deficits were not related to measurements of vigilance, the arousal index, or AHI in these patients, but were correlated with the degree of nocturnal hypoxaemia (Kotterba, Rasche, Widdig, Duscha et al., 1998). Furthermore, the P3 event related potential latencies – which are electric signals from the brain - were prolonged (Kotterba, Rasche, Widdig, Duscha et al., 1998). It has been found that structures such as the prefrontal cortex and limbic system play a role in generating these signals (Kotterba, Rasche, Widdig, Duscha et al., 1998). Consequently, the authors conclude that these prolonged signals may represent hypoxaemic damage in these areas (Kotterba, Rasche, Widdig, Duscha et al., 1998). Furthermore, after 6 months of CPAP therapy, these prolonged signals remained (Kotterba, Rasche, Widdig, Duscha et al., 1998). Additionally, although improvements were shown on most of the cognitive tests given after CPAP therapy, some deficits still remained in individual patients (Kotterba, Rasche, Widdig, Duscha et al., 1998). As a result, Kotterba, Rasche, Widdig, Duscha et al. (1998) note that their findings provide positive evidence suggesting permanent hypoxaemic damage in some areas of the brain, such as the prefrontal cortex and limbic system – areas which are involved in cognitive functions previously found to be affected in OSAS and to remain after CPAP treatment in other studies (Naëgelé et al., 1998; Ferini-Strambi et al., 2003).

Alternatively, some authors have suggested that these residual cognitive deficits seen after CPAP therapy may also represent reversible, functional damage to the brain – also related to the hypoxaemia experienced by OSAS patients – rather than structural, irreversible damage (Bédard et al., 1993; Ferini-Strambi et al., 2003). These authors propose that this functional damage may result from interference in neurotransmitter synthesis caused by hypoxaemia (Ferini-Strambi et al, 2003). However, more studies using functional brain imaging techniques are needed in order to confirm this hypothesis (Ferini-Strambi et al., 2003).

Furthermore, as Engleman et al. (2000) note in their meta-analytical review article on cognitive impairment in OSAS - described in the previous section of this literature review - the results of these studies may be also be attributable to other factors, and may not necessarily reflect any sort of hypoxaemic brain damage in OSAS patients. For instance, they observe that many CPAP studies use samples with relatively mild cognitive dysfunction, which may account for the lack of improvement in some cognitive functions (Engleman et al., 2000). Additionally, these study findings may also be attributable to the relatively low level of treatment given in some studies (Engleman et al., 2000). Furthermore, several authors have noted that patients' levels of compliance on CPAP treatment are likely to have an impact on the efficacy of this treatment in improving cognitive dysfunction in OSAS (Kotterba, Rasche, Widdig, Duscha et al., 1998; Aloia et al., 2004; Day et al., 1999). Several of the studies that have investigated the effectiveness of CPAP in improving cognitive deficits in OSAS have not systematically measured patients' rates of compliance on CPAP treatment. Subsequently, these studies may have found no or little changes in cognitive functioning after treatment because their participants had not been using the CPAP therapy for a sufficient amount of hours per night or nights per week (Aloia et al., 2004; Day et al., 1999; Kotterba, Rasche, Widdig, Duscha et al., 1998). Moreover, Day et al. (1999) also note that there is a possibility that some patients may have inherent poor sleeping habits, even when they are compliant on CPAP therapy. This may also contribute to their having residual cognitive deficits even after treatment (Day et al., 1999).

Overall, therefore, it can be seen that, although treatment studies have shown some common patterns of cognitive improvement after CPAP therapy, they have produced disparate results. This could be due to the differences in tests used to assess cognitive functions in various studies, different cognitive areas tested, differences in levels of compliance on CPAP by some of the

participants in the various studies, differences in the period of time in which the patients were on treatment, differences in sample sizes used, differences in severity of OSAS before treatment, and learning and placebo effects in some studies (Aloia et al., 2004; Day et al, 1999; Henke et al., 2001; Bardwell et al., 2001; Engleman & Martin, 1994; Engleman & Joffe, 1999; Lojander et al., 1999; Kingshott et al., 2000). Regardless of the reasons, the findings of many of these studies are equivocal, and consequently, current knowledge on the efficacy of CPAP therapy in treating cognitive dysfunction in OSAS patients is still inconclusive. There is therefore a need for more studies to be carried out in this area of research.

Chapter 2

2 Objectives of Study

Cognitive impairment is one of the most debilitating symptoms of OSAS and it has consequently been the subject of numerous studies, as discussed above. Furthermore, several studies have investigated the efficacy of CPAP treatment – the most widely used form of treatment for OSAS – in improving these symptoms. However, as explained in the preceding literature review, these studies have generally produced disparate results and more studies are needed in this area of research. Moreover, no study on the cognitive impairment of OSAS patients has yet been carried out in the South African context.

It is extremely important to investigate the effectiveness of CPAP treatment in improving cognitive dysfunction in OSAS in South Africa, since CPAP machines are extremely costly. Additionally, most medical aid plans available in this country only cover a small percentage of the cost of CPAP machines or do not provide any compensation at all for the purchase of these machines. As a substantial percentage of the South African population comes from a low socio-economic background, and would not be able to afford the cost of CPAP treatment, it will be especially useful to assess the efficacy of CPAP treatment in improving cognitive impairment in OSAS in this country. This will enable one to gauge whether the benefits of CPAP treatment are worth the expense.

The topic of cognitive dysfunction in OSAS, and the effectiveness of CPAP in improving this dysfunction, is an extremely broad area of research, covering a wide range of more specific topics. This is evidenced by the large variability in the focus of, and methods used in, the studies on the neuropsychological effects of OSAS that have been discussed in the literature review above. The scope of this study was narrowed to focus specifically on the effects of cognitive dysfunction in OSAS and the effectiveness of CPAP in improving this dysfunction, given the study's time constraints and lack of available resources. Consequently, investigations around the questions of the aetiology of cognitive impairments in OSAS, and the relationship between

cognitive dysfunction and the severity of OSAS, could not be covered in this study. This study therefore attempted to answer the following two specific questions:

1.) Do OSAS patients in the South African population show any cognitive deficits in comparison to other healthy people from the same population?

2.) Do OSAS patients receiving CPAP treatment show less cognitive deficits than untreated OSAS patients do from the same South African population?

Chapter 3

3 Design and Methodology

3.1 Sample

The sample in this study comprised of 35 participants, divided into three groups: a group of untreated OSAS patients, a group of OSAS patients on CPAP treatment, and a group of healthy controls. A breakdown of the sample into these specific participant groups can be found in Figure 1 below. The participants ranged in age from 24 to 67 years (mean age = 47 years), and the sample consisted of 29 males and 6 females. All participant groups were required to meet the following criteria:

1.) Aged between 20 and 70 years at time of testing
2.) Fluent in English
3.) No known or suspected history of alcohol or narcotic abuse
4.) No presence or history of sleep disorders (other than OSAS for patient groups), such as narcolepsy or insomnia
5.) No presence or history of any neurological disease
6.) No history of head trauma
7.) No use of medications that could have an adverse effect on cognitive functioning

Additionally, only patients who had been given a definitive diagnosis of OSAS by a recognised medical practitioner were included in the 2 patient groups, and all OSAS patients were required to have an AHI of more than 20 (for the OSAS patients on CPAP treatment, the pre-treatment AHI was used).

The sample was restricted to participants with a minimum age of 20 years, as this study was only examining the cognitive effects of OSAS in adults. Furthermore, participants aged over 70 years were excluded from the study in order to minimise the possibly confounding effects of normal, age-related cognitive decline found in elderly persons. The criterion of fluency in English (one of the 11 official languages in South Africa) was included for practical purposes, as the majority of the tests being administered were only available in English. The exclusion criteria described in

points 3-7 listed above were established in order to eliminate the potentially confounding effects of other medical conditions and treatments on neuropsychological functioning (Adams et al., 2001; Redline et al., 1997; Greenberg et al., 1987; Naismith et al., 2004; Naëgelé et al., 1995; Roehrs et al., 1995; Bédard et al., 1991, 1993; Verstraeten et al., 2004; Ferini-Strambi et al., 2003). However, the use of these rigorous criteria did lead to a substantially smaller sample size.

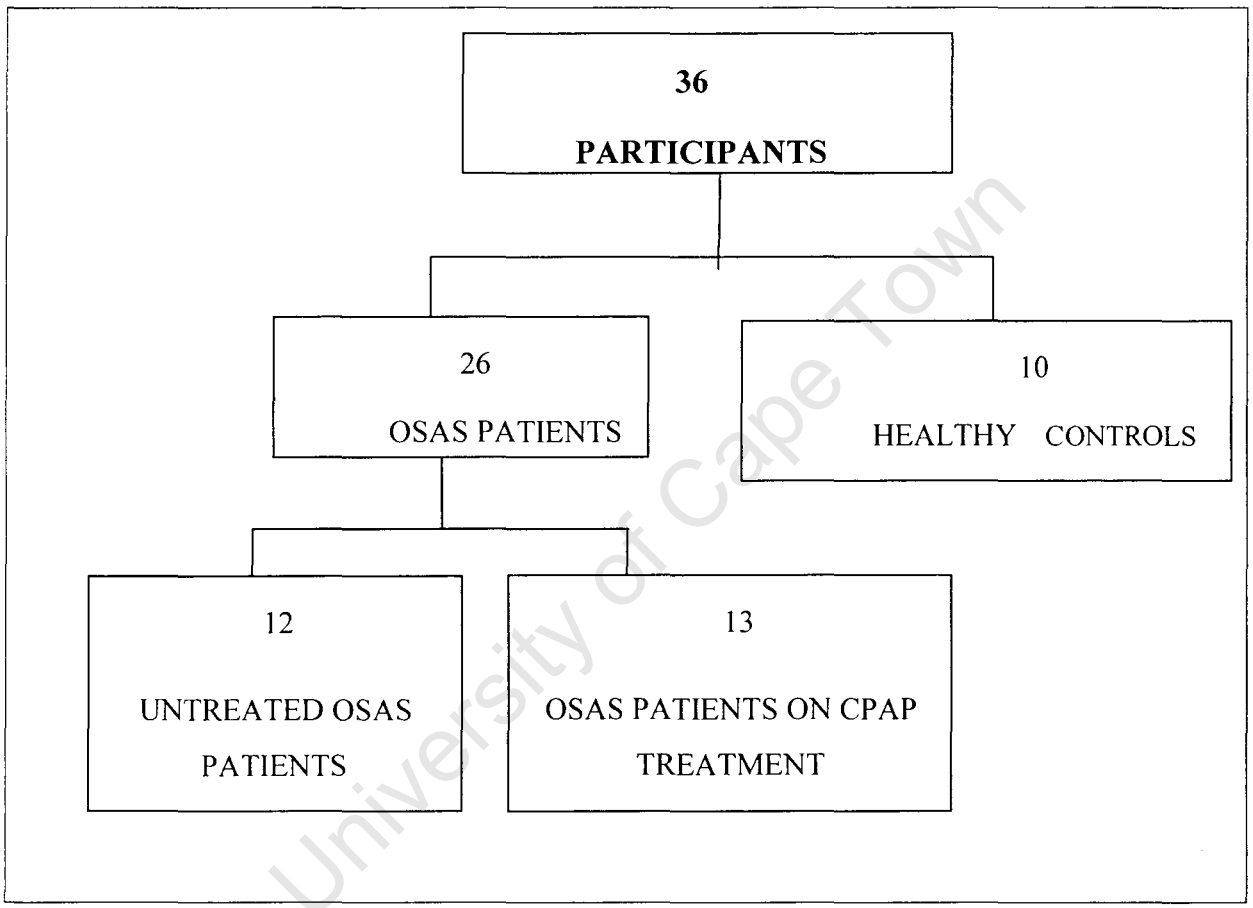


Figure 1: Breakdown of Sample Group

A total of 68 OSAS patients (21 untreated patients and 47 patients on CPAP treatment) and 22 healthy controls were requested to participate in this study. Of all the OSAS patients (both treated and untreated), 40 were excluded prior to the assessment or analysis stages of the study, either because they did not meet one of the required criteria listed above; they could not be reached; or they were unwilling or unable to participate for some reason – commonly due to time constraints

on the part of the patients. In addition, two OSAS patients who had previously been using CPAP treatment regularly had now stopped using it completely for at least 2 months. These patients were therefore not included in the study, as their results would not accurately reflect the effects of CPAP treatment on cognitive functioning. Additionally, a further two patients from the treated OSAS group were excluded because they had been on CPAP treatment for substantially longer than the other patients in that group had (5 and 14 years respectively; mean length of treatment for the treated OSAS group = 1 year and 2 months). Furthermore, seven of the healthy controls were excluded because they did not meet all of the necessary criteria, could not be contacted, or were unwilling or unable to participate. Additionally, five of the control participants were unable to find a suitable date to undergo a full, overnight polysomnographic sleep study within the time confines of this study. As previously mentioned, OSAS can only be diagnosed definitively on the basis of a polysomnographic sleep study, and is a commonly under diagnosed disorder (Valencia-Flores, 1996; Qureshi & Ballard, 2003; Hopkins & Bigler, 2001; Caples et al., 2005; Skomro & Kryger, 1999). Subsequently, these five patients could not be included in the study, as it was unclear whether or not they suffered from OSAS. Information on the participants who were excluded from this study can be found in Table 1 below.

Table 1: Excluded Patients

REASONS FOR EXCLUSION:	UNTREATED OSAS GROUP	OSAS GROUP ON CPAP	HEALTHY CONTROLS
Age	0	1	0
Language	1	3	0
History of alcohol or narcotic abuse	2	1	1
History or presence of sleep disorder	0	0	2
History or presence of neurological disease	0	0	0
History of head trauma	0	0	0

Use of medications that adversely affect cognitive functions	0	0	0
Period on CPAP less than 3 months	0	2	0
Patient previously on CPAP, but now stopped completely for > 2 months	0	2	0
Period on CPAP substantially longer than other participants	0	2	0
AHI < 20	2	2	0
Unable to complete polysomnographic sleep study	0	0	5
Patient could not be contacted	1	8	1
Patient unwilling or unable to participate	3	13	3
Total No. of Excluded Patients	9	34	12

Each individual participant group that was included in the study will be discussed in more detail below.

3.1.1 Untreated OSAS Patients

This group consisted of 12 patients, who had previously undergone a full polysomnographic sleep study and who had been given a definitive diagnosis of OSAS by a qualified medical practitioner at either Groote Schuur Hospital (GSH), Gatesville Medical Centre (GMC) or Milnerton Medi-clinic. The AHI ratings of these patients ranged from 26 to 112.5 (mean AHI = 53.69). Most of these patients were on some form of medication (n = 9) – primarily anti-hypertensive medications (n = 8), insulin (n = 3), anti-inflammatory medications (n = 1), or

medications to lower cholesterol (n = 1). None of these medications has any significant impact on cognitive functioning. The majority of these patients (n = 8) had not yet received CPAP treatment, as they had only recently been diagnosed with OSAS and, subsequently, had not yet purchased CPAP machines. On the other hand, a few of these patients (n = 4) had not received treatment because their respective medical aid schemes did not cover the cost of the CPAP machine, and they could not afford to buy the machine without this financial support. This could introduce a possible bias, as the latter of these two groups is likely to come from a lower socio-economic background than the former group, and this could have had an impact on their respective performances on the various neuropsychological tests. However, an examination of the years of education of all of the untreated OSAS patients reveals that none of the patients differs substantially from one another in terms of the amount of education received. Moreover, one of the patients who could not afford CPAP treatment (S2) has received the highest number of years of education (16 years; mean years of education for untreated OSAS group = 12 years) of all of these patients. Subsequently, this reduces the likelihood that the different reasons for not being on CPAP treatment had an important effect on the results of this study. The results of all the neuropsychological tests for this group of patients can be found in Appendix 1, and the clinical information of this group is shown in Table 2 below.

Table 2: Clinical Information for Untreated OSAS Group

Patient	Sex	Age	Years of Education	AHI	Sleepiness
S1	M	47	10	31.9	8
S2	M	45	16	52	7
S3	M	53	10	55.9	15
S4	F	61	12	39.6	15
S5	M	54	12	59.3	9
S6	M	45	12	36.4	13
S7	M	24	15	112.5	12

S8	M	61	10	32	13
S9	M	46	12	77.1	18
S10	M	69	12	26	9
S11	F	58	9	64.7	6
S12	M	34	15	56.9	5
MEANS		49.75	12.08	53.6916667	10.83

3.1.2 Treated OSAS Patients

Fourteen OSAS patients, who had been using CPAP treatment for a period of at least 3 months, were identified from the hospital files and sleep study reports of OSAS patients at GSH and Milnerton Medi-clinic, and were recruited for this study. The patients in this group had pre-treatment AHIs ranging from 20.1 to 87 (mean pre-treatment AHI = 59.16). The majority of the sleep study reports and files of these patients did not include information about their post-treatment AHIs, so these could not be recorded for this study. The length of time for which these patients had been on CPAP treatment ranged from 3 months to 2 years and 3 months (with a mean period of 1 year and 2 months on CPAP). The period for which these patients had been receiving treatment was calculated from the day when they began treatment to the day of their neuropsychological assessment for this study. It was not possible to obtain objective CPAP compliance rates in any of these patients, as the CPAP machines used did not have in-built time monitors (Henke et al., 2001; Engleman et al., 1993, 1997, 1998, 1999; Bardwell et al., 2001; Engleman & Martin, 1994; Barbé et al., 2001; Muñoz et al., 2000; Naëgelé et al, 1998). All of the patients in this group were asked to give a subjective indication of compliance rates, and 11 of the 13 patients tested reported that they used the CPAP machines every night for the entire night (approximately 5-8 hours per night). However, patients are likely to be reluctant to report non-compliance, and, subsequently, the accuracy of these subjective ratings of compliance is questionable. Of the two patients who reported non-compliance, one (S21) indicated that he used the machine for the entire night approximately twice a week. On the other hand, the other patient

(S18) explained that she would be completely compliant on the CPAP machine during the months of summer, but would not use it at all during winter, as she did not have a humidifier for her machine and found that the CPAP would have a drying effect that was extremely uncomfortable, and which caused greater disturbances in her sleep than the OSAS. This patient showed a substantially higher level of sleepiness than the other patients in this participant group did (a score of 19 out of 21 on the Epworth Sleepiness Scale (ESS); the mean score on the ESS for the treated OSAS group was 7). However, an examination of the results of these two patients on the cognitive measures assessed reveals that they attained results which were the same as, or above, the mean for their participant group for a large number of these tests (25 out of 30 and 18 out of 30, respectively; the results of all tests for this group of patients can be found in Appendix 2 of this thesis). Nonetheless, the low compliance rates of these two patients and the lack of objective compliance rates for all of the treated OSAS patients may have affected the results of the neuropsychological tests in this study, as higher compliance rates have been associated with greater improvements in cognitive functioning after CPAP use (Aloia et al., 2004; Kotterba, Rasche, Widdig, Duscha et al., 1998).

As in the untreated OSAS group, the majority of the treated OSAS patients were taking some form of medication (n = 10) – primarily anti-hypertensive medication (n = 9) and medication to lower cholesterol (n = 3) – none of which had any adverse effects on cognitive functioning. The clinical information for the treated OSAS group is shown below in Table 3.

Table 3: Clinical Information for Treated OSAS Patients

Patient	Sex	Age	Years of Education	AHI	Sleepiness	Time on CPAP (months)
S13	M	59	12	20.1	4	12
S14	M	46	9	23.6	6	24
S15	M	48	13	52.3	7	12
S16	M	52	17	80	7	11
S17	M	47	15	76.9	3	16

S18	F	45	12	82	19	12
S19	M	47	15	71.4	0	3
S20	M	40	18	87	5	29
S21	M	43	13	87	2	12
S22	M	40	15	27.5	8	10
S23	M	67	16	78	17	24
S24	M	67	12	22.4	7	7
S25	M	43	12	60	9	8
MEANS		49.54	13.77	59.09	7.23	13.85

3.1.3 Healthy Control Group

Ten healthy controls were recruited through two different means. The first group of controls (n = 6) consisted of people who had previously undergone polysomnographic sleep studies and who had been diagnosed as not having OSAS. These participants were referred for this study by the sleep technologist at GMC. These participants had all been referred for polysomnographic sleep studies following various medical complaints – most commonly daily headaches. The other group of controls (n = 4) were obtained through an advertisement placed in GSH and sent to the staff members at the University of Cape Town. All of these participants underwent a full, overnight polysomnographic sleep study, conducted by a qualified sleep technologist at GMC, in order to ensure that they did not suffer from undiagnosed OSAS. The results of these sleep studies were confirmed by a qualified medical practitioner. These patients were compensated for any expenses incurred to travel to and from GMC for the overnight sleep study. Obtaining healthy controls by these two different means could introduce a possible bias in this study, as it could establish a division between a "healthy control group" and a "healthier control group" (that is, the group who had gone for a sleep study following medical complaints as opposed to the group who had taken place in the study in response to an advertisement). Furthermore, the

subjects in the latter of these two groups (S27, S28, S31 and S36) had the highest number of years of education of all the participants in the complete control group. Additionally, two of the participants (S30 and S35) who had been referred for this study by the sleep technologist at GMC obtained much higher scores of sleepiness than the other people in the control group (17 and 16 out of 21 on the ESS, respectively; mean score for the control group on the ESS = 7). However, a close examination of the results of these two participants, as well as of all the other participants in the control group, reveals that none of them generally differs substantially from one another in their cognitive functioning (see Appendix 3 for the scores for all cognitive tests for the control group). Moreover, although the participants who had been referred for a sleep study by a medical practitioner had originally sought medical attention for numerous health concerns, all of these patients were found to be generally healthy - having no neurological problems or other serious medical conditions. Furthermore, the concerns for which they had originally sought medical help – such as daily headaches - were generally attributed to high stress levels and were alleviated through simple techniques such as taking paracetomol for their headaches, beginning exercise regimes or decreasing their workload. Furthermore, the only two participants in this group who were taking any form of medication (S27 and S28) were participants who had taken part in the study in response to an advertisement. Subsequently, it appears that the two groups of participants within the control group are very similar to one another in terms of health status.

Participants were included in the healthy control group if they met all of the inclusion criteria described previously, and if they were diagnosed as not having OSAS after undergoing a full polysomnographic sleep study. Patients are assessed as not having OSAS if they have an AHI of less than 5. The AHI ratings of the participants in this control group ranged from 0 to 4.2 (mean AHI for the healthy control group = 1.1).

It is important to note that comparing the cognitive outcome of the two OSAS patient groups to a healthy control group is limited in that the control group is not subjected to the same level of psychological and emotional stress as OSAS patients are. OSAS patients suffer with severe disturbances in sleep and pathological levels of sleepiness, and the psychological and emotional effects that these stressors have on these patients and their everyday functioning should not be underestimated (Bédard et al., 1991, 1993; Hopkins & Bigler, 2001; Day et al., 1999; Ferini-Strambi et al., 2003; Qureshi & Ballard, 2003; Gordon & Sanders, 2005). However, it was

necessary to include a control group in this study, as normative data was not available for this sample population for the cognitive tests used. The clinical information for the group of healthy controls is shown in Table 4 below.

Table 4: Clinical Information for Healthy Control Group

Patient	Sex	Age	Years of Education	AHI	Sleepiness
S27	M	50	18	1.5	7
S28	M	65	17	0.2	4
S29	M	37	13	1.2	7
S30	F	36	10	0.5	17
S31	M	32	20	0	9
S32	F	41	12	0.7	0
S33	M	38	13	1.8	3
S34	M	48	12	4.2	4
S35	F	26	13	0.9	16
S36	M	57	15	0	4
MEANS		43	14.3	1.1	7.1

3.2 Comparability of the Participant Groups

All three of the participant groups used in this sample were matched according to age, sex and years of education, as much as was practically possible. However, these patients could not be matched on a case-to-case basis, as it was extremely difficult to find a sufficient number of participants in each group who met all of the prescribed inclusion criteria for this study and who could be accurately matched to one another in terms of age, sex and years of education. Consequently, the three groups differed from one another in terms of these factors to some extent. In order to establish whether these differences were statistically significant, a one-way Analysis of Variance (ANOVA) was carried out for the factors of age and years of education, using the level of disorder (OSAS, OSAS on CPAP treatment, healthy controls with no disorder) as the independent variable. Conventional significance levels ($p<0.05$) were used and both the assumptions of homogeneity and normality were met. As can be seen from the univariate one-way ANOVA results (shown below in Tables 5 and 6), there were no significant differences between the three groups concerning age or years of education. The means of these two factors for each group are also shown below in Figure 2.

Table 5: Univariate ANOVA Results for Age

	df	SS	MS	F	p
GROUP	2	315.2	157.6	1.2616	0.296905
Error	32	3997.48	124.92		
Total	34	4312.68			

Table 6: Univariate ANOVA Results for Years of Education

	df	SS	MS	F	p
GROUP	2	30.561	15.281	2.25	0.121818
Error	32	217.324	6.791		
Total	34	247.885			

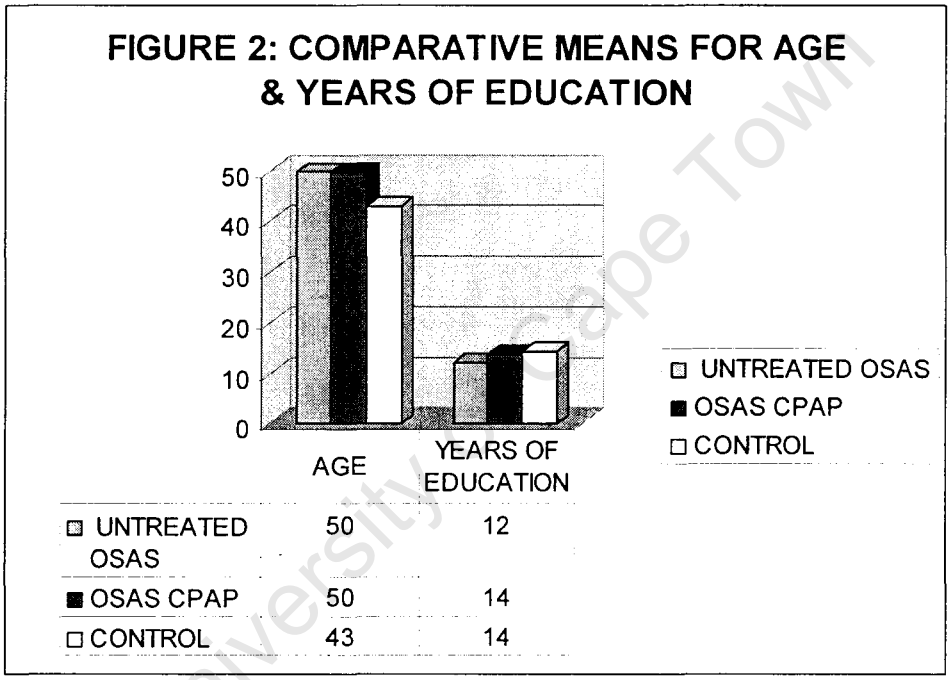


Figure 2: Comparative Means for Age and Years of Education

Additionally, the two OSAS groups (untreated and treated) were also matched as far as was possible according to their AHI (AHI of untreated OSAS group matched to pre-treatment AHI of treated OSAS group). Once again, it was not possible to match these two groups on a case-to-case basis. Subsequently, in order to investigate whether or not any differences between these two groups in terms of level of severity (as measured by AHI) were significant, a one-way ANOVA was performed. Significance levels of $p<0.05$ were used and both the assumptions of

homogeneity and normality were met. The ANOVA results, which are shown in Table 7 below, indicate that there were no significant differences between the two OSAS groups concerning AHI.

Table 7: Univariate ANOVA Results for AHI

	df	SS	MS	F	p
GROUP	1	182	182	0.2809	0.601213
Error	23	14903.98	648		
Total	24	15085.98			

3.3 Procedure

Before the study commenced, the protocol was approved by an ethics committee in the department of Psychology at the University of Cape Town, and at GSH. Permission was given to the author by specialist physicians at GSH and Milnerton Medi-clinic to peruse the files and sleep study reports of all the recent OSAS patients. These were examined for information on patients' past medical history, past and current medications and AHI. Additionally, several other patients who had been given a definitive diagnosis of OSAS were referred for this study by the sleep technologist at GMC. The contact details and AHI of these patients were given. Patients were then contacted and were provided with basic information about the purposes and procedure of the study, and were subsequently asked whether they would like to participate. Furthermore, the GMC patients were asked some general questions about their past medical history and general health status in order to establish whether or not they were eligible to take part in this study. If the patients agreed to participate in the study, appointments were made for the neuropsychological testing. Testing took place in private offices at GSH or GMC, at the patients' bedside prior to polysomnographic sleep studies, at patients' private homes or in another quiet location that was easily accessible to the patient. Regardless of the testing location, every effort was made in order to ensure that the environment was as quiet and undisturbed as possible. Before the testing began, every patient was given an informed consent form (see Appendix 4),

which gave basic information about the study, as well as about the patients' roles and rights as participants in the study. Additionally, the assessor would further expound the information given on the informed consent form and would answer any questions posed by the participants. The participants would then give written consent to participate in the study. Each patient was assessed individually and was given the exact same neuropsychological battery, administered in the same order. The neuropsychological tests used were all administered in the standardised manner specified by the relevant administration and scoring manuals. The testing process took approximately 2-3 hours, depending on the performance of the individual patient, as some tests had no time limit. Some patients did not complete the entire neuropsychological battery due to time constraints on their part. As motivation is an important factor in OSAS patients, all patients were given constant encouragement by the assessor and were also allowed to take as many breaks as they wished (Jones and Harrison, 2001). Furthermore, patients were reminded of the importance of using the maximum amount of effort in completing the tests and were informed that if they were feeling tired or bored, it would be better for them to take a break than to continue the testing in that manner (Jones & Harrison, 2001). All assessments were conducted and scored by the author

3.3.1 Assessment

3.3.1.1 Polysomnography

All of the participants in this study were required to undergo a full, overnight polysomnographic sleep study. The participants in the OSAS groups had already undergone sleep studies and had been given a definitive diagnosis of OSAS prior to the commencement of this study. All of these sleep studies took place at either GMC, the University of Cape Town Lung Institute or Milnerton Medi-clinic. Additionally, all healthy control participants were required to undergo a sleep study in order to ensure that they did not suffer from undiagnosed OSAS. These sleep studies were all carried out at GMC. All of the polysomnographic studies were carried out by trained and fully qualified sleep technologists, and the results were analysed and assessed by qualified medical practitioners with relevant experience in the field. Sleep studies were all conducted using the standard, recognised procedures. After the completion of the sleep studies and sleep study reports, information regarding the AHI of each patient was given to the author.

3.3.1.2 General Information

All participants were required to complete a general information sheet, requiring details about their age, date of birth, sex, handedness, years of education, occupational history, medical conditions and current medications.

3.3.1.3 Sleepiness

As excessive daytime sleepiness is one of the most important daytime symptoms of OSAS, it was deemed necessary to include a measure of sleepiness in this study (Hopkins & Bigler, 2001; Qureshi & Ballard, 2003; Engleman & Joffe, 1999; Engleman & Douglas, 2004; Caples et al., 2005; Bédard et al., 1991, 1993; Ferini-Strambi et al., 2003; Day et al., 1999; Valencia-Flores et al., 1996). Subsequently the ESS – a commonly used measure of sleepiness, which has been proven to be effective in detecting excessive daytime sleepiness – was administered in order to assess subjective levels of sleepiness (Day et al., 1999; Engleman & Joffe, 1999; Engleman & Douglas, 2004).

3.3.1.4 Neuropsychological Assessment

The neuropsychological tests used were chosen to assess a wide range of cognitive functions that are commonly known to be impaired in OSAS patients. These specifically include the following functions: verbal and visual memory, attention and concentration, executive functioning, constructional abilities and psychomotor efficiency (Bardwell et al, 2001; Bédard et al., 1991, 1993; Engleman & Joffe, 1999; Engleman et al., 2000; Engleman & Douglas, 2004; Hopkins & Bigler, 2001; Incalzi et al., 2004; Ferini-Strambi et al., 2003; Day et al., 1999; Valencia-Flores et al., 1996; Kotterba, Rasche, Widdig, Blombach et al., 1998; Kotterba, Rasche, Widdig, Duscha et al., 1998; Caples et al, 2005; Weaver, 2001; Kim et al., 1997). The process of choosing which particular neurocognitive tests to include in the test battery was directed by a number of important considerations (Greenberg et al., 1987). Firstly, the tests chosen needed to assess the full range of neuropsychological functions listed above, which are commonly affected in OSAS patients. Secondly, the tests chosen needed to be ones that could be easily administered in as short time as possible and in a single session, considering the fact that OSAS patients struggle with pathological levels of daytime sleepiness.

Tests were selected by first choosing appropriate reliable and valid test batteries, which are able to assess the wide range of cognitive functions known to be affected in OSAS. Subsequently, the Wechsler Memory Scale-Revised (WMS-R, 1987) was chosen to assess memory functions and the Delis-Kaplan Executive Function System (D-KEFS, 1995) was chosen to assess executive functions. Individual subtests were then chosen from these two batteries and additional individual tests were chosen from past studies assessing cognitive functioning in OSAS. Consequently, the following neurocognitive tests were selected to assess each of the functions listed below:

Verbal Memory:

Wechsler Memory Scale-Revised (WMS-R, 1987) Logical Memory test

Visual Memory:

Wechsler Memory Scale-Revised (WMS-R, 1987) Visual Reproduction test

Attention and Concentration:

Wechsler Memory Scale-Revised (WMS-R) forwards and backwards Digit Span test. (Wechsler, 1987)

Delis-Kaplan Executive Function System (D-KEFS) Trail Making test (conditions 1 and 4) (Delis et al., 1995)

Delis-Kaplan Executive Function System (D-KEFS) Colour-Word Interference test (conditions 3 and 4) (Delis et al., 1995)

Executive Functioning:

Delis-Kaplan Executive Function System (D-KEFS) Word Fluency task (Delis et al., 1995)

Wisconsin Card Sorting test (Heaton, 1981)

Delis-Kaplan Executive Function System (D-KEFS) Tower test (Delis et al., 1995)

Delis-Kaplan Executive Function System (D-KEFS) Trail Making test (condition 4) (Delis et al., 1995)

Delis-Kaplan Executive Function System (D-KEFS) Colour-Word Interference test (conditions 3 and 4) (Delis et al., 1995)

Constructional Ability:

Benson and Barton Stick Test (Lezak, 1995)

Psychomotor Ability:

Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (condition 5) (Delis et al., 1995)

Digit Symbol Substitution test

Where applicable, patients were permitted to answer questions or complete tests (such as the D-KEFS verbal Fluency task) in Afrikaans if they so desired in order to minimise the chance of language bias. Please refer to Appendix 5 for details on the descriptions of each test used, the cognitive functions assessed by the various tests, and the particular conditions and scores utilised in this study.

3.4 Data Analysis

All of the statistical analyses were conducted using STATISTICA version 7.0. One-way ANOVAs were carried out for each dependent variable (each measure of cognitive outcome), and, subsequently, there were 30 individual one-way ANOVAs that were performed for this study. Levene's test was used to ensure that the assumption of homogeneity was met and a histogram and normal P-Plot was obtained and examined in order to ensure that the assumption of normality was fulfilled for each dependent variable. With regards to post-hoc tests, Fisher's

Least Significant Difference (LSD) test was used in order to analyse any statistically significant results, as is suggested by Howell (2002) for comparisons involving three groups, such as in this study. An important concern in the analysis of this data is the substantial rise in the Type I error rate due to the large amount of analyses being performed, given the number of measures used to assess cognitive functioning. However, Bonferroni adjustments on significance levels would yield extremely small probability values, and, considering the small sample size and subsequently low power of this study, it was decided that the high rate of the occurrence of Type I errors and the low power of the study would balance each other out. As a result, conventional significance levels ($p<0.05$) were used for all statistical tests.

Chapter 4

4 Results

4.1 Sleepiness

The untreated OSAS group obtained a higher mean sleepiness score than the other two groups (mean for untreated group = 11 out of 21, mean for treated OSAS group = 7 out of 21 and mean for healthy control group = 7 out of 21). However, these differences in sleepiness did not reach statistically significant levels on the one-way ANOVA. Both the assumptions of homogeneity and normality were fulfilled for this variable. Univariate results for the ANOVA for sleepiness and the mean sleepiness scores for each participant group are shown below in Table 8 and Figure 3, respectively.

Table 8: Univariate ANOVA Results for Sleepiness

	df	SS	MS	F	p
GROUP	2	105.697	52.849	2.08046	0.141439
Error	32	812.874	25.402		
Total	34	918.571			

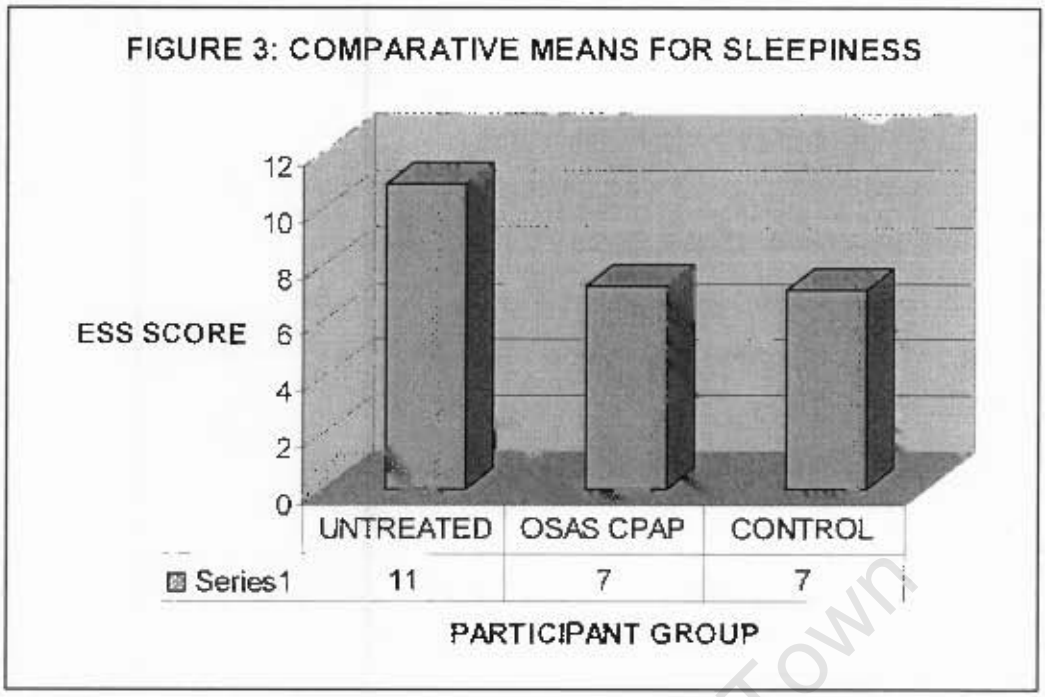


Figure 3: Comparative Means for Sleepiness

4.2 Neuropsychological Assessment Data

The assumption of homogeneity of variances, as well as the assumption of normality was met for the dependent variables (the 30 measures used to assess neuropsychological functioning). Overall, the untreated OSAS group performed more poorly than the control group on 26 of the 30 test measures, and than the treated OSAS group on 19 of the 30 test measures used. Additionally, the treated OSAS group obtained worse results than the healthy controls in 23 of the 30 measures used to assess cognitive functioning in this study (see Appendices 1, 2 and 3 for the results of all the cognitive tests for each of the three participant groups). However, statistically significant results were only attained for the following three of these 30 measures:

-The D-KEFS Trail Making test (condition 5) score for completion time

-The Digit-Symbol Substitution test – score for total number of items completed

-The Wisconsin Card Sorting test – score for total number of errors

The univariate results for the ANOVAs and the comparative means for these tests can be found below in Tables 9-11 and Figure 4, respectively. Please note that for the D-KEFS Trail Making test (condition 5): completion time and the Wisconsin Card Sorting test: total number of errors, a higher figure indicates a poorer result.

Table 9: Univariate Results for D-KEFS Trail Making Test (Condition 5): Completion Time

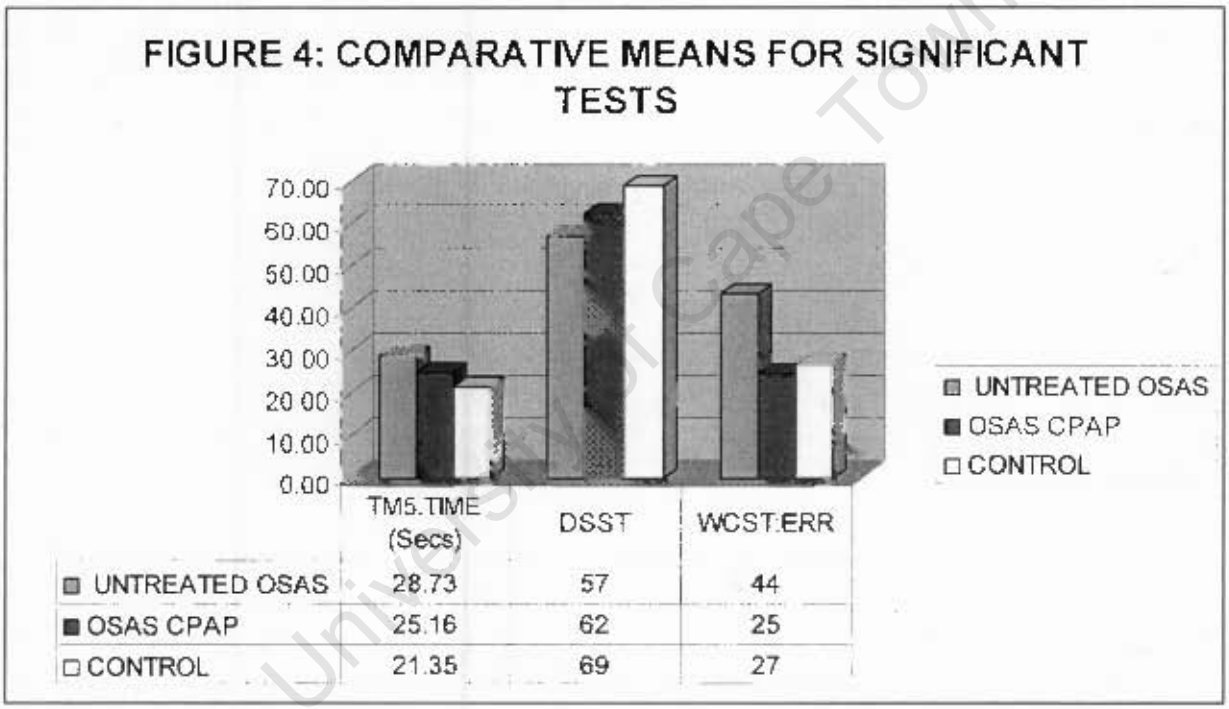
	df	SS	MS	F	p
GROUP	2	297.42	148.71	3.6344	0.037814
Error	32	1309.37	40.92		
Total	34	1606.79			

Table 10: Univariate Results for Digit Symbol Substitution Test: Total No. of Items Completed

	df	SS	MS	F	p
GROUP	2	805.2	402.6	3.750	0.034417
Error	32	3435.5	107.4		
Total	34	4240.7			

Table 11: Univariate Results for Wisconsin Card Sorting Test: Total No. of Errors

	df	SS	MS	F	p
GROUP	2	2558.45	1279.23	3.52337	0.041404
Error	32	11618.23	363.07		
Total	34	14176.68			



ABBREVIATIONS: TM5: TIME = Trail Making test (condition 5): completion time; DSST = Digit Symbol Substitution test: total no. of items; WCST: ERR = Wisconsin Card Sorting test: total no. of errors

Figure 4: Comparative Means for Significant Tests

Post-hoc Fisher's LSD tests were carried out in order to identify where the differences lay on each of the statistically significant test measures. The results of these analyses are shown below in Tables 12-14.

Table 12: Fisher's LSD Results for Trail Making Test (Condition 5): Completion Time

	GROUP	1 28.727	2 25.157	3 23.348
1	UNTREATED OSAS		0.172815	0.011140
2	OSAS CPAP	0.172815		0.166540
3	CONTROL	0.011140	0.166540	

Table 13: Fisher's LSD Results for Digit Symbol Substitution Test: Total No. of Items Completed

	GROUP	1 56.75 (57)	2 62.231 (62)	3 68.9 (69)
1	UNTREATED OSAS		0.195756	0.009996
2	OSAS CPAP	0.195756		0.135778
3	CONTROL	0.009996	0.135778	

Table 14: Fisher's LSD Results for Wisconsin Card Sorting Test: Total No. of Errors

	GROUP	1 43.5 (44)	2 24.538 (25)	3 27
1	UNTREATED OSAS		0.018338	0.051559
2	OSAS CPAP	0.018338		0.760736
3	CONTROL	0.051559	0.760736	

As can be seen from Tables 12 – 14 and Figure 4 above, the untreated OSAS group yielded significantly poorer results than the control group on both the Trail Making test (condition 5): completion time, and Digit Symbol Substitution test: total number of items completed, measures. On the other hand, the untreated OSAS group made significantly more errors than the treated OSAS group on the Wisconsin Card Sorting Test. More specifically, it can be seen that the untreated OSAS group took the longest of all three groups to complete the Trail Making (condition 5) task, taking an average of approximately 5 seconds longer than the control group to complete the task. Furthermore, the untreated OSAS group also completed the least amount of items within 2 minutes on the Digit Symbol Substitution test out of all the participant groups, with the OSAS group completing an average of 12 items less then the control group. On the Wisconsin Card Sorting test, the untreated OSAS patients once again yielded the poorest results of all three groups and made an average of about 19 more errors than the treated OSAS group. It is important to note that, although only the difference in errors between the untreated and treated OSAS groups reached statistical levels of significance, the untreated OSAS patients did also make an average of about 17 more errors than the control group on this test, with statistical probability levels being very close to significance ($p = 0.051559$).

Chapter 5

5 Discussion

OSAS is a relatively common, yet often under diagnosed disorder, characterized by periods of cessation of breathing during sleep (Skomro & Kryger, 1999; Qureshi & Ballard, 2003; Hopkins & Bigler, 2001; Bédard et al., 1991, 1993; Valencia-Flores et al., 1996; Gordon & Sanders, 2005; Ferini-Strambi et al., 2003; Kotterba, Rasche, Widdig, Duscha et al., 1998; Kotterba, Rasche, Widdig, Blombach et al., 1998; Caples et al., 2005; Day et al., 1999; Engleman & Joffe, 1999; Incalzi et al., 2004). This disorder has a number of nocturnal and diurnal symptoms, but the diurnal symptoms – especially excessive daytime sleepiness and cognitive dysfunction – are commonly found to be the most debilitating, as they are disruptive to the everyday functioning of the patients (Douglas, 2004; Ferini-Strambi et al., 2003; Day et al., 1999; Valencia-Flores, 1996). As a result, a large number of studies – discussed in detail in previous sections of this paper - have been conducted to investigate the effects of OSAS on cognitive functioning, and also to assess the efficacy of CPAP treatment in improving cognitive dysfunction in OSAS patients. Subsequently, this study aimed to build on this existing body of literature by examining cognitive dysfunction, and the effectiveness of CPAP treatment in improving this dysfunction, in OSAS patients in the South African population. It specifically aimed to answer the following two questions:

1.) Do OSAS patients in the South African population show any cognitive deficits in comparison to other healthy people from the same population?
2.) Do OSAS patients receiving CPAP treatment show less cognitive deficits than untreated OSAS patients do from the same South African population?

In order to investigate these two questions, a test battery containing 30 neurocognitive test measures was given to 12 untreated OSAS patients, 13 OSAS patients on CPAP treatment and 10 healthy controls – all of whom were matched for age, sex and years of education. The results of these tests for all three groups were analysed and compared, and it was shown that, overall, both the untreated and treated OSAS groups performed more poorly than the control group in a large number of the tests given (26 out of 30 and 19 out of 30, respectively). Furthermore, the

untreated OSAS group yielded worse results than the OSAS group on CPAP treatment in 19 of the 30 tests used to assess neurocognitive functions in these patients. Nonetheless, statistically significant results (with significance levels of $p<0.05$) were only found for 3 of the 30 test measures given, namely: the D-KEFS Trail Making test (condition 5) – a test of motor speed and visuomotor ability (Delis et al., 1995); the Digit Symbol Substitution test – a test of general cognitive capacity and intelligence, sustained attention, response speed, visuomotor co-ordination, motor persistence and psychomotor performance (Kim et al., 1997; Wechsler, 1987); and the Wisconsin Card Sorting test – a test of abstract behaviour, concept formation, mental shifting and problem solving (Décary et al., 2000; Fulda & Schulz, 2001; Heaton, 1981). In the Trail Making and Digit Symbol Substitution tests, the untreated OSAS group performed significantly worse than the healthy controls, and on the Wisconsin Card Sorting test, the untreated OSAS group made significantly more errors than the OSAS group on CPAP treatment.

Consequently, it can be seen that the OSAS patients on CPAP treatment did not differ significantly from the healthy controls in their cognitive functioning. On the other hand, the untreated OSAS group differed significantly from the healthy control group on two test measures – condition 5 of the Trail Making task and the Digit Symbol Substitution test. In examining the implications of these findings, it is important to bear in mind that the tests used to assess neuropsychological functioning are complex in nature – commonly requiring the use of the "primary" function identified by the actual test, as well as numerous other cognitive functions (Walsh & Darby, 1999; Pantelis, 2005). Subsequently, poor performances in any of these tests could result from disturbances in any individual, or combination of, the neurocognitive functions required to complete the task (Walsh & Darby, 1999, Pantelis, 2005). For instance, in the case of the Digit Symbol Substitution test, the untreated OSAS patients may have performed significantly worse than the healthy controls because of impairments in any of the individual cognitive functions assessed by the test - such as general cognitive ability and intelligence, sustained attention, response speed, visuomotor tracking and co-ordination or fine manual motor functions – or in any combination of these functions (Kim et al., 1997; Weschler, 1987, Walsh & Darby, 1999). Similarly, the significantly poorer performance of the untreated OSAS patients than the control group on condition 5 of the Trail Making task may be attributable to problems in psychomotor efficiency, visuomotor skills, or a combination of the two. As a result, one needs to

be careful not to hastily conclude that patients suffer deficits in one specific area of cognitive functioning following poor performance on an individual test cited to assess a particular function (Walsh & Darby, 1999). It is therefore vital that one examines and interprets the results of individual tests within the context of patients' performances on the other tests of cognitive functioning (Walsh & Darby).

Subsequently, one needs to examine the two tests for which the untreated OSAS patients obtained significantly poorer results than the healthy controls in light of this group's performance on all of the cognitive tests used in this study. Given the fact that these were the only two tests on which statistically significant results were obtained for the OSAS group in comparison to the normal controls, it is unlikely that the group performed more poorly in the Digit Symbol Substitution test because of disturbances in general cognitive ability and intelligence. Furthermore, if examined together with the results of condition 5 of the Trail Making test – the other test in which significant results were attained for the untreated OSAS group in comparison to the control group – it can be seen that these two tests both involve the use of visuomotor tracking and motor speed, as they both require the patient to visually keep track of a specific pattern (circles which need to be connected in a specified pattern, in the case of the Trail Making task, and a variety of symbols substituting for the digits 1-9 that need to be drawn in a given order, in the case of the Digit Symbol test) and to respond using manual motor movements (drawing lines to connect circles in the case of the Trail Making test, and drawing specific symbols in the case of the Digit Symbol test). It therefore appears that the untreated OSAS group performed more poorly in tasks that required the use of the functions broadly and commonly defined as visual ability and motor ability or psychomotor functioning, in the literature (Beebe et al., 2003; Aloia et al., 2004).

However, caution needs to be taken in drawing specific and definitive conclusions about the pattern of impairment found in the general South African population of untreated OSAS patients from these findings, given the small sample size and large number of tests used in this study (Pantelis, 2005). Moreover, the methodological differences between, and large variability in results in, previous studies in this area of research – as described in the literature review above - make it difficult to draw comparisons between the results of this study and previous findings (Aloia et al., 2004; Pantelis, 2005). However, it is still valuable to ascertain areas where the

results of this study are similar to, or differ from, other studies investigating the neuropsychological effects of OSAS.

A review of the current literature on OSAS reveals that a number of other studies have similarly reported impaired performance in the cognitive functions of visual and psychomotor ability (Naismith et al., 2004; Ferini-Strambi et al., 2003; Gale & Hopkins, 2004; Aloia et al., 2004; Beebe et al., 2003; Kim et al., 1997; Engleman et al., 2000). However, as described in the preceding literature review, findings concerning these functions have been inconsistent across studies – with some studies showing significant impairment, and others not showing any significant differences in OSAS patients in these areas of functioning relative to a normal control group (Aloia et al., 2004; Beebe et al., 2003). These discrepancies in results between different studies were further investigated by both Aloia et al. (2004) and Beebe et al. (2003). Both of these sets of authors reported that the tests assessing the functions broadly defined as visual and psychomotor ability could be further divided into those that tested fine motor co-ordination and drawing, and those that assessed simple motor speed or visual perception. It was found that those studies which yielded significant results in the areas of visual and psychomotor functioning were those that used tests of fine motor co-ordination and drawing, whereas those studies using tests of simple motor speed and/or visual perception were those which found visual and psychomotor ability to be unimpaired in OSAS patients relative to normal controls (Beebe et al., 2003; Aloia et al., 2004). Aloia et al. (2004) note that these two different areas of visual ability and psychomotor functioning may involve the use of different regions in the brain – with the areas of the brain such as the basal ganglia sub serving fine motor co-ordination. Furthermore, they suggest that, since the brain regions involved in the more specific area of fine motor co-ordination appear to be those that are especially vulnerable to the effects of the chronic, intermittent hypoxaemia from which OSAS patients commonly suffer, this particular function is less likely to improve after CPAP treatment than the function of simple motor speed (Aloia et al., 2004).

Interestingly, in this study, 1 of the 2 tests assessing visual ability and psychomotor functioning - both of which yielded significant results – measured simple motor speed and/or visual perception (condition 5 of the Trail Making task), while the other tested motor speed as well as fine motor co-ordination and drawing (the Digit Symbol Substitution test). Furthermore, although untreated

OSAS patients performed more poorly than the OSAS patients on CPAP treatment in both of these two tests, none of these differences reached statistical levels of significance. As a result, it appears that the findings of this study differ slightly from those reported by Aloia et al. (2004) and Beebe et al. (2004). However, in order for the test battery used in this study to meet all of the necessary requirements described above in the method section of this paper, only two tests aiming to assess the areas of visual and psychomotor ability were included. As a result, if more tests assessing each of the specific areas of visual and psychomotor functioning (that is, fine motor co-ordination and drawing, and simple motor speed and/or visual perception) were used, this study may have yielded similar findings to those described by Aloia et al. (2004) and Beebe et al. (2003).

Consequently, in response to the first of the two investigative questions posed by this study, and highlighted above, it can be seen that untreated OSAS patients taken from the South African population only differed significantly from normal controls in the cognitive areas of visual and psychomotor ability. These results differ from the findings of most of the other studies in this area of research that have also examined OSAS patients from a clinical population (Beebe et al., 2003; Aloia et al., 2004; Engleman & Joffe, Hopkins & Bigler, 2001; Engleman et al., 2000; Bédard et al., 1991, Weaver, 2001; Engleman & Douglas, 2004; Caples et al., 2005). These other studies have commonly found OSAS patients to be impaired in a wide range of cognitive functions – especially attention and concentration, executive functioning, memory, and to a lesser degree, constructional abilities - in comparison to normal controls (Beebe et al., 2003; Aloia et al., 2004; Engleman & Joffe, Hopkins & Bigler, 2001; Engleman et al., 2000; Bédard et al., 1991, Weaver, 2001; Engleman & Douglas, 2004; Caples et al., 2005). The discrepancy between these results and those of previous studies may be attributable, firstly, to the sample size used in this study and, subsequently, the low statistical power of this study. Additionally, in order to ensure that the test battery used included tests of all the cognitive functions found to be impaired in OSAS, and was also practically administrable in a minimum amount of time, the tests chosen could not fully cover every aspect of the complex functions being assessed. For instance, in the case of memory, only two measures were used to test verbal memory - testing immediate free recall and delayed recall – and two measures were used to assess visual memory. Consequently, this study was only able to test one aspect of verbal and visual memory and it is possible that, had

other areas of memory been tested, significant differences may have been found. The same can be said of the other areas of cognitive functioning, such as attention and concentration. As each of these cognitive functions is extremely complex, it would take a substantially long amount of time to assess every aspect of them thoroughly. Subsequently, considering the fact that OSAS patients suffer from pathological levels of daytime sleepiness, which also has adverse effects on their levels of motivation, it would not be possible to fully assess each aspect of each of these functions within a test battery that covers a wide range of functions. As a result, it is recommended that future studies establish test batteries containing tests assessing each of these functions individually, perhaps conducted over a series of days or in separate studies, rather than testing all of the functions together in one single battery.

With regards to the second question that this study aimed to answer, it can be seen that the untreated OSAS patients performed more poorly than the OSAS patients on CPAP on only one measure – the total number of errors made on the Wisconsin Card Sorting Test. It should also be noted that, although no significant differences were found on the measure for perseverative responses on the Wisconsin Card Sorting test at the conventional significance level ($p<0.05$), the untreated OSAS group made 12 more perseverative responses than the OSAS group on CPAP, and 10 more perseverative responses than the control group. It is therefore likely that if this study had a larger sample size and, subsequently, greater statistical power to detect differences between groups at the same significance level ($p<0.05$), the results for this measure would reach statistically significant levels (Lee et al., 1999). Both of these measures are scores for the Wisconsin Card Sorting test – a test of executive functions, including: abstract behaviour, concept formation, mental shifting and problem solving (Décary et al., 2000; Fulda & Schulz, 2001; Heaton, 1981). If these results are considered in isolation, one might therefore hastily conclude that untreated OSAS patients show impairments in executive functioning – which are commonly sited to not improve after CPAP treatment - in comparison to patients on CPAP therapy (Décary et al., 2000; Beebe et al., 2003; Aloia et al., 2004). However, as explained earlier, one needs to interpret and analyse patients' performances on one specific test in light of their performances on the other cognitive tests taken – especially those of a similar nature, designed to assess the same cognitive function. In view of this, it can be seen that these are the only 2 of 18 test measures designed to assess executive functioning – some of which tested the

same specific aspects of executive functions as these two measures - that yielded significant results. It is therefore unlikely that the significant differences found between the untreated and treated OSAS groups could be attributed to disturbances in executive functioning, and they are more likely to be due to chance factors. Consequently, it can be seen that the patients on CPAP did not perform significantly better than the untreated OSAS patients on the majority of cognitive tests given. It therefore appears that being on CPAP treatment for at least 3 months does not make any substantial difference to the neuropsychological functioning of OSAS patients.

As previously mentioned in the literature review above, the majority of studies investigating the effects of CPAP treatment on cognitive functioning have found at least some improvements. However, a few studies have found similar results to the current study - reporting little or no differences in the neuropsychological functions of OSAS patients after being on CPAP treatment for varying periods of time (Barbé et al., 2001; Engleman et al., 1993, 1998, 2000; Bardwell et al., 2001; Lojander et al., 1999). For instance, in their placebo-controlled study on 36 OSAS patients, Bardwell et al. (2001) found that, although the OSAS patients on effective CPAP showed better overall cognitive functioning than the group on the placebo treatment, significant results were found on only 1 of 22 specific measures used to assess various neurocognitive functions. These authors suggest that these findings may be attributable to the fact that the OSAS patients were only on treatment for a period of one week, although other authors have found significant differences after a few days on CPAP treatment (Bardwell et al., 2001). Additionally, as described in the preceding literature review, both Engleman et al. (1993) and Engleman et al. (1998) found significant improvements in sleepiness, but not in cognitive functioning in OSAS patients after being on CPAP treatment for periods of 3 months and 4 weeks, respectively. Engleman et al. (1998) propose that the small sample size and low statistical power had likely played a role in these results, and it is probable that these same factors similarly had an effect on the findings of this current study too.

However, it is important to note that the current study, unlike all of the other treatment studies described above, did not investigate one single group of OSAS patients, conducting a cognitive battery of tests on them before and after being on CPAP treatment for a specific period. Instead, this study retrospectively examined a group of OSAS patients who had previously been diagnosed with the disorder and who had already been on CPAP treatment for at least 3 months,

and compared them to a matched group of previously diagnosed OSAS patients who had not yet received any form of treatment. The use of this method removed the possible practice effects that may have influenced the results of the other treatment studies described. However, this also introduces an additional limitation in this study not seen in the ones described above, as no comparative information is available about the pre-treatment levels of intelligence and cognitive functioning of the treated OSAS patients. Subsequently, the patients used in the treated OSAS group may have had poorer levels of pre-treatment cognitive functioning than the untreated OSAS group currently display, thus leading to the small number of significant differences between the two groups in an investigation of cognitive functioning after the treated group had been on CPAP treatment for at least 3 months. Matching the two groups in terms of age and years of education limits the possibility of large differences in intelligence and cognitive functioning between the two OSAS groups to only some extent. However, as the test battery used in this study was designed to be administrable in as short time as possible, no tests were included to assess current levels of overall intelligence or to estimate pre-morbid and pre-treatment levels of intelligence – such as the Weschler Adult Reading Test (WART). It is therefore recommended that future studies include these measures of general intelligence to ensure that there are no substantial differences in this area between the sample groups used. It should also be noted that drawing comparisons of the CPAP group with a group of untreated OSAS patients and a group of normal, healthy individuals - matched for age and years of education – is useful in providing a measure of pre-morbid and pre-treatment cognitive functioning, but is also limited, as it can only provide estimates of these levels of functioning. A more effective study design would therefore be one that monitored a single group of OSAS patients, assessing their levels of general intelligence and cognitive functioning before and after at least 3 months of CPAP treatment. Additionally, previous studies have also demonstrated the importance of using a placebo control, such as ineffectual CPAP, in studies investigating the effectiveness of CPAP treatment (Bardwell et al., 2001; Henke et al., 2001). An ideal CPAP treatment study would therefore also include this type of placebo control in a randomised, crossover trial. However, it was not possible to employ this ideal type of study design in the current study, given its time constraints and lack of available resources.

A further limitation in this study that may have contributed to the relative lack of significant differences between the untreated and treated OSAS groups is the fact that no reliable, objective measure of treatment compliance was available. As explained in the literature review above, compliance on treatment appears to be an important factor in whether or not cognitive functioning improves after CPAP, and the extent to which it improves (Aloia et al., 2004; Day et al., 1999; Kotterba, Rasche, Widdig, Duscha et al., 1998). In this study, patients were asked to give a subjective estimate of the length of time they spend on CPAP treatment per night, and of the number of nights per week on which they use the CPAP machines. However, as previously mentioned, patients are likely to be reluctant to report non-compliance, especially at high levels. As a result, it is possible that few differences were seen on the neurocognitive test measures between the untreated OSAS group and the OSAS group on CPAP treatment because the treated group were not consistently compliant on their treatment.

In addition to investigating differences in cognitive functioning between the untreated OSAS patients, OSAS patients on CPAP treatment, and the healthy control group, this study also examined whether or not these three groups differed in levels of subjective sleepiness – as measured by the ESS. It was found that there were no significant differences between the three groups in terms of subjective sleepiness, suggesting that any differences in cognitive functioning between the three groups was not attributable to differences in sleepiness. Most previous studies conducted on the cognitive effects of OSAS have found differing results from those of this study, showing significant improvements on ESS scores or measures of objective sleepiness after CPAP treatment (Muñoz et al., 2000; Montplaisir et al., 1992; Engleman et al., 1993, 1998, 1999; Engleman & Martin, 1994; Ferini-Strambi et al., 2003; Bédard et al., 1993). Furthermore, those studies that found no differences in levels of sleepiness after CPAP treatment or compared to normal controls were investigating mild OSAS patients (Engleman et al., 1997; Redline et al., 1997). However, one other study yielded similar results to the current study, finding no significant differences in subjective levels of sleepiness (as measured by the Stanford Sleepiness Scale - a measure of subjective sleepiness similar to the ESS) between a group of moderate to severe OSAS patients and a group of normal controls. Moreover, if one examines the ESS scores of each participant group in this study more closely, it is evident that the untreated OSAS group did obtain lower scores than both the treated OSAS group and the healthy control group (the

untreated OSAS group obtained a mean score of 11 out of 21 on the ESS, while both the treated and control groups scored 7 out of 21). Consequently, it appears that the OSAS group not receiving treatment was generally sleepier than the OSAS group on CPAP treatment and the normal control group, although not to a level that reached statistical significance.

It is important to bear in mind the limitations and constraints of a study when considering all analyses and interpretations of results. Many of the limitations of the current study have already been described and addressed above. However, this study was subject to a number of other limitations, which need to be highlighted at this point. The first of these is the fact that each patient was assessed at a different time of the day. This was done for practical reasons, as all of the participants in this study were volunteers and many held full time jobs. As a result, assessment times needed to be planned according to participants' convenience, and differed from person to person. This is a limitation in this study, as OSAS patients suffer from excessive daytime sleepiness, so participants' performance in the cognitive tests given may differ substantially if they are tested in the early or late morning, in the early or late afternoon, or in the evening. The times at which patients were tested may have therefore affected the results of this study.

A further limitation to this study is the possible problem of cultural bias, owing to the fact that the tests used to assess cognitive functioning were not designed specifically for the South African population. This therefore leads one to question whether or not these tests were suitable to assess the neuropsychological functioning of the current sample. However, this problem was managed by comparing the scores of these tests for the OSAS patient groups to the test scores of a healthy control group, rather than to published test norms. This ensured that test scores of the OSAS patients were compared to those of a group that came from the same South African population, and from a similar psychosocial background. Additionally, as previously mentioned, patients were allowed to complete some tests in Afrikaans if this was required.

The application of stringent inclusion and exclusion criteria in this study may also have been a limitation, as it may have led to the creation of a "super healthy" sample group that is not representative of OSAS patients in general (Mark, 2005). This is especially important to consider, given the fact that OSAS patients have an increased risk of developing other diseases

such as: congestive heart failure, cardiac arrhythmias, myocardial infarction and stroke, as previously mentioned (Hopkins & Bigler, 2001; Qureshi & Ballard, 2003; Gordon & Sanders, 2005; Bédard et al., 1991; Caples et al., 2005). However, this study wanted to investigate the specific effects of OSAS alone on neuropsychological functioning, and the use of strict inclusion and exclusion criteria was therefore necessary.

The final limitation of this study is that fact that all the tests were administered and scored by the author, thus leading to a possible experimenter bias. However, in order to limit the likelihood of experimenter bias, the author was blind to the diagnosis of the patients when scoring the tests.

In conclusion, therefore, this study, within the bounds of its limitations, has demonstrated a significant impairment in untreated OSAS patients in the areas of visual and psychomotor ability, compared to normal controls. However, it has otherwise shown no substantial differences in any area of cognitive functioning between both untreated and treated OSAS patients and other healthy individuals. It has further shown no substantial differences between untreated OSAS patients and OSAS patients receiving CPAP treatment. Nonetheless, it is vital to remember that impairments in any area of cognitive functioning, however slight, can be highly debilitating and can greatly disturb one's ability to function in everyday life. One must therefore be careful not to underestimate the practical significance of these findings and the implications that they may have for the patients that participated in this study. Furthermore, this study was subject to severe time constraints and limited available resources, thus introducing several limitations that may have affected its findings. This study is the first of its kind to be conducted in South Africa and therefore serves to provide a foundation for further similar studies to be conducted in this country. In South Africa, CPAP machines are extremely costly and most medical aid schemes in this country are reluctant to cover these high costs. If it is shown that CPAP treatment can enable OSAS patients to have a better quality of life by improving the cognitive functioning of these patients, then perhaps the medical aid companies will be more willing to provide financial aid for the cost of CPAP machines. Alternatively, if it is found that CPAP treatment makes little difference to the cognitive dysfunction and other daytime symptoms of OSAS – known to be the most debilitating symptoms of the illness – then it may be decided that the benefits of this treatment are not worth the cost, and other conservative or surgical treatments may be favoured over CPAP. Consequently, it is of utmost importance that more studies are conducted in South

Africa to continue to investigate the effectiveness of CPAP treatment in improving the cognitive functioning of OSAS patients in the South African population – perhaps utilising a more effective, randomised placebo-controlled crossover design, bigger sample sizes, and multiple test batteries that can provide a detailed assessment of each cognitive function individually.

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Appendices

Appendix 1 – Tables of Scores for Sleepiness and All Cognitive Tests for the Untreated OSAS Group

ID	SLEEPINESS	TM1 TIME	TM1 ERR	TM4 TIME	TM4 ERR	TM5 TIME	DIGIT SYMBOL	DS FWD	DS BWD	DS TOTAL
S1	8	24.84	0	61.84	0	28.68	45	7	7	14
S2	7	20.59	1	136.41	2	26.89	73	9	6	15
S3	15	21.47	0	218.56	4	23.5	54	10	4	14
S4	15	20.04	0	93.96	0	26.36	62	8	6	14
S5	9	21.17	2	90.92	0	29.69	46	11	10	21
S6	13	24.38	0	85.86	0	24.77	53	6	5	11
S7	12	21.75	0	51.6	0	17.66	63	10	11	21
S8	13	35.95	0	142	2	47.03	45	8	4	12
S9	18	16.5	0	56.97	2	24.67	73	7	6	13
S10	9	32.13	0	129.51	2	30.75	47	10	7	17
S11	6	19.94	0	95.89	0	33.02	47	5	5	10
S12	5	16.66	0	51.5	0	31.71	73	9	9	18
MEANS	10.83	22.95	0.25	101.25	1.00	28.73	56.75	8.33	6.67	15.00

ABBREVIATIONS: TM1 TIME = Trail Making test (condition 1): completion time; TM1ERR = Trail Making test (condition 1): no. of errors; TM4 TIME = Trail Making test (condition 4): completion time; TM4 ERR = Trail Making test (condition 4): no. of errors; TM5 TIME = Trail

Making test (condition 5): completion time; DIGIT SYMBOL = Digit Symbol Substitution test: total no. of items ; DS FWD = Digit Span forwards; DS BWD = Digit Span backwards; DS TOTAL = combined scores of Digit Span backwards & forwards

ID	LM 1	LM 2	VR 1	VR 2	ST REVERSE	WCST CATS	WCST ERR	WCST PER	VF 1	VF 1 ERR	VF 2
S1	28	26	31	33	3	2	48	29	28	2	43
S2	20	15	34	34	0	6	16	10	45	3	46
S3	13	10	25	22	0	3	64	32	48	4	39
S4	25	21	27	25	2	6	23	14	44	0	38
S5	22	12	30	13	2	4	49	31	29	2	26
S6	19	18	32	36	0	6	13	7	18	2	26
S7	30	27	33	35	2	6	19	10	45	2	61
S8	21	13	33	31	4	1	86	52	20	2	29
S9	30	18	31	30	1	3	53	29	46	3	48
S10	18	14	27	14	2	3	63	46	51	1	33
S11	29	27	33	28	5	4	55	31	42	1	34
S12	29	31	36	41	0	6	33	18	73	0	52
MEANS	23.67	19.33	31.00	28.50	1.75	4.17	43.50	25.75	40.75	1.83	39.58

ABBREVIATIONS: LM1 = Logical Memory I; LM2 = Logical Memory II; VR1 = Visual Reproduction I; VR2 = Visual Reproduction II; ST Reverse = Benson & Barton Stick test: reverse condition; WCST CATS = Wisconsin Card Sorting test: no. of categories completed; WCST ERR = Wisconsin Card Sorting test: no. of errors; WCST PER = no. of perseverative responses; VF1 = Verbal Fluency (condition 1): completion time; VF1 ERR = Verbal Fluency (condition 1): no. of errors; VF2 = Verbal Fluency (condition 2): completion time

ID	VF 2 ERR	VF 3	VF 3 ERR	C-W 3 TIME	C-W 3 ERR	C-W 4 TIME	C-W 4 ERR	TOWER A	TOWER TIME	TOWER VIOL
S1	0	16	0	55.85	1	66.27	5	9	436.82	5
S2	0	15	1	48.84	2	51.51	0	23	409.2	0
S3	3	11	0	103.48	4	146.19	7	16	458.47	2
S4	0	16	0	60.73	0	55.53	1	17	461.79	0
S5	0	16	0	71.29	0	72.34	0	15	581.17	0
S6	1	11	2	99.72	5	120.05	3	14	602.93	1
S7	1	18	0	47.47	3	58.5	3	19	411.62	1
S8	0	13	1	82.16	6	76.75	4	20	430.84	1
S9	0	17	1	57.92	3	53.85	0	19	472.57	1
S10	0	13	1	102.71	2	114.36	2	12	801.88	8
S11	1	12	4	59.76	0	54.77	0	17	456.7	1
S12	1	17	0	44.96	2	44.24	2	17	174.89	1
MEANS	0.58	14.58	0.83	69.57	2.33	76.20	2.25	16.50	474.91	1.75

ABBREVIATIONS: VF 2 ERR = Verbal Fluency (condition 2): no. of errors; VF3 = Verbal Fluency (condition 3): completion time; VF3 ERR = Verbal Fluency (condition 3): no. of errors; C-W 3 TIME = Colour-Word Interference test (condition 3): completion time; C-W 3 ERR = Colour-Word Interference test (condition 3): no. of errors; C-W 4 TIME = Colour- Word Interference test (condition 4): Completion TIME; C-W 4 ERR = Colour- Word Interference test (condition 4): no. of errors

Appendix 2 – Tables of Scores for Sleepiness and All Cognitive Tests for the Treated OSAS Group

ID	SLEEPINESS	TM1 TIME	TM1 ERR	TM4 TIME	TM4 ERR	TM5 TIME	DIGIT SYMBOL	DS FWD	DS BWD	DS TOTAL
S13	4	24.95	0	86.2	0	19.69	69	11	6	17
S14	6	32.06	1	195.15	4	20.24	37	6	5	11
S15	7	18.07	0	68.14	1	26.26	72	10	7	17
S16	7	23.3	0	61.23	0	25.47	65	12	10	22
S17	3	29.51	0	72.71	0	23.85	42	5	6	11
S18	19	14.86	1	87.9	2	19.67	73	7	6	13
S19	0	18.4	1	100.69	0	17.76	62	11	7	18
S20	5	16.56	1	82.04	1	26.69	72	11	10	21
S21	2	19.19	0	58.76	1	31.91	73	8	6	14
S22	8	30.44	0	88.37	0	26.93	67	10	5	15
S23	17	17.06	0	84.09	2	23.94	60	8	7	15
S24	7	33.37	1	112.61	2	42.77	54	7	4	11
S25	9	19.98	0	52.7	0	21.86	63	8	6	14
MEANS	7.23	22.90	0.38	88.51	1.00	25.16	62.23	8.77	6.54	15.31

ABBREVIATIONS: TM1 TIME = Trail Making test (condition 1): completion time; TM1ERR = Trail Making test (condition 1): no. of errors; TM4 TIME = Trail Making test (condition 4): completion time; TM4 ERR = Trail Making test (condition 4): no. of errors; TM5 TIME = Trail Making test (condition 5): completion time; DIGIT SYMBOL = Digit Symbol Substitution test: total no. of items ; DS FWD = Digit Span forwards; DS BWD = Digit Span backwards; DS TOTAL = combined scores of Digit Span backwards & forwards

ID	LM 1	LM 2	VR 1	VR 2	ST REVERSE	WCST CATS	WCST ERR	WCST PER	VF 1	VF 1 ERR
S13	18	11	26	24	0	6	25	12	41	1
S14	25	21	27	22	5	3	57	40	31	3
S15	21	17	31	22	0	6	28	13	33	1
S16	31	33	29	20	0	6	13	6	72	0
S17	24	23	32	25	0	6	10	4	37	0
S18	15	12	30	28	4	6	25	12	28	0
S19	23	17	30	16	3	6	12	6	33	3
S20	33	25	34	28	1	6	10	6	65	2
S21	38	33	34	36	0	6	12	3	37	1
S22	28	20	28	32	1	6	10	5	44	5
S23	28	22	29	31	1	2	43	21	29	0
S24	25	20	28	29	3	1	63	45	36	4
S25	38	31	35	37	0	6	11	5	43	1
MEANS	26.69	21.92	30.23	26.92	1.38	5.08	24.54	13.69	40.69	1.62

ABBREVIATIONS: LM1 = Logical Memory I; LM2 = Logical Memory II; VR1 = Visual Reproduction I; VR2 = Visual Reproduction II; ST Reverse = Benson & Barton Stick test: reverse condition; WCST CATS = Wisconsin Card Sorting test: no. of categories completed; WCST ERR = Wisconsin Card Sorting test: no. of errors; WCST PER = no. of perseverative responses; VF1 = Verbal Fluency (condition 1): completion time; VF1 ERR = Verbal Fluency (condition 1): no. of errors

VF 2	VF 2 ERR	VF 3	VF 3 ERR	C-W 3 TIME	C-W 3 ERR	C-W 4 TIME	C-W 4 ERR	TOWER A	TOWER TIME	TOWER VIOL
41	1	19	2	54.96	0	58.53	1	11	684.54	2
33	4	14	0	87.48	3	161.27	12	17	606.44	1
42	0	12	0	54.19	4	58.97	4	18	451.8	0
72	0	18	0	48.51	4	68.33	1	19	445.03	1
37	0	15	0	55.56	1	67.33	2	15	461.8	2
47	1	17	1	42.92	2	64.55	1	19	494.37	1
35	1	13	2	66.05	0	68.19	1	19	600.56	1
52	3	18	0	63.37	3	58.61	1	18	515.28	0
50	0	16	0	43.77	0	43.86	0	17	444.17	0
52	1	21	0	62.43	0	60.86	1	17	616.96	1
29	0	10	2	69.19	1	69.99	3	15	676.81	2
40	0	17	0	74.44	13	72.5	4	18	380.95	2
40	0	14	0	53.73	1	78.4	0	23	293.15	0
43.85	0.85	15.69	0.54	59.74	2.46	71.65	2.38	17.38	513.22	1.00

ABBREVIATIONS: VF2 = Verbal Fluency (condition 2): completion time; VF 2 ERR = Verbal Fluency (condition 2): no. of errors; VF3 = Verbal Fluency (condition 3): completion time; VF3 ERR = Verbal Fluency (condition 3): no. of errors; C-W 3 TIME = Colour- Word Interference test (condition 3): completion time; C-W 3 ERR = Colour- Word Interference test (condition 3): no. of errors; C-W 4 TIME = Colour-Word Interference test (condition 4): completion time; C-W 4 ERR = Colour-Word Interference test (condition 4): no. of errors

Appendix 3 – Tables of Scores for Sleepiness and All Cognitive Tests for the Control Group

ID	SLEEPINESS	TM1 TIME	TM1 ERR	TM4 TIME	TM4 ERR	TM5 TIME	DIGIT SYMBOL	DS FWD	DS BWD	DS TOTAL
S27	7	21.62	0	66.61	0	20.05	73	10	10	20
S28	4	22.68	0	66.63	0	30.33	73	11	12	23
S29	7	22.71	0	68.44	0	15.36	57	7	6	13
S30	17	23.03	0	57.38	1	17.08	73	8	8	16
S31	9	23.82	1	56.3	0	19.12	72	11	11	22
S32	0	16.57	0	130.14	2	29.24	73	7	7	14
S33	3	28.6	1	84.75	0	24.81	62	9	6	15
S34	4	18.97	0	43.44	1	17.24	73	12	10	22
S35	16	17.27	0	62.98	0	20.04	72	7	6	13
S36	4	20.52	0	63.09	1	20.21	61	10	7	17
MEANS	7.1	21.579	0.2	69.976	0.5	21.348	68.9	9.2	8.3	17.5

ABBREVIATIONS: TM1 TIME = Trail Making test (condition 1): completion time; TM1 ERR = Trail Making test (condition 1): no. of errors; TM4 TIME = Trail Making test (condition 4): completion time; TM4 ERR = Trail Making test (condition 4) no. of errors; TM5 TIME = Trail Making test (condition 5): completion time; DIGIT SYMBOL = Digit Symbol Substitution test: total no. of items ; DS FWD = Digit Span forwards; DS BWD = Digit Span backwards; DS TOTAL = combined scores of Digit Span backwards & forwards

ID	LM 1	LM 2	VR 1	VR 2	ST REVERSE	WCST CATS	WCST ERR	WCST PER	VF 1	VF 1 ERR
S27	29	28	31	29	0	6	13	6	30	0
S28	39	35	36	25	1	6	17	7	53	1
S29	13	7	31	22	4	6	31	18	37	2
S30	19	13	31	23	3	6	25	20	30	2
S31	29	29	36	34	4	6	17	14	45	1
S32	22	21	30	27	3	6	19	8	41	0
S33	25	23	31	32	0	5	36	27	48	7
S34	29	28	35	37	1	6	13	8	28	0
S35	21	18	30	25	3	3	50	24	43	1
S36	25	15	33	35	0	5	49	28	34	1
MEANS	25.1	21.7	32.4	28.9	1.9	5.5	27	16	38.9	1.5

ABBREVIATIONS: LM1 = Logical Memory I; LM2 = Logical Memory II; VR1 = Visual Reproduction I; VR2 = Visual Reproduction II; ST Reverse = Benson & Barton Stick test: reverse condition; WCST CATS = Wisconsin Card Sorting test: no. of categories completed; WCST ERR = Wisconsin Card Sorting test: no. of errors; WCST PER = no. of perseverative responses; VF1 = Verbal Fluency (condition 1): completion time; VF1 ERR = Verbal Fluency (condition 1): no. of errors

ID	VF 2	VF 2 ERR	VF 3	VF 3 ERR	C-W 3 TIME	C-W 3 ERR	C-W 4 TIME	C-W 4 ERR	TOWER A	TOWER TIME	TOWER VIOL
S27	27	0	13	0	58.38	0	55.86	0	16	756.53	0
S28	59	1	19	1	52.18	1	51.03	0	15	488.87	1
S29	47	1	15	2	56.34	1	56.67	1	16	539.67	1
S30	36	0	16	0	42.26	1	56.43	0	17	458.22	0
S31	43	1	15	0	70.38	3	44.2	0	16	378.8	1
S32	51	1	19	2	73.15	8	82.47	6	16	592.2	2
S33	43	0	19	0	58.18	2	88.45	1	24	380.03	0
S34	39	0	13	0	50.24	5	50	0	27	245.55	0
S35	28	0	15	0	45.36	2	74.52	9	20	388.54	0
S36	42	0	17	0	54.43	0	87.27	4	16	707.18	0
MEANS	41.5	0.4	16.1	0.5	56.09	2.3	64.69	2.1	18.3	493.559	0.5

ABBREVIATIONS: VF2 = Verbal Fluency (condition 2): completion time; VF 2 ERR = Verbal Fluency (condition 2): no. of errors; VF3 = Verbal Fluency (condition 3): completion time; VF3 ERR = Verbal Fluency (condition 3): no. of errors; C-W 3 TIME = Colour- Word Interference test (condition 3): completion time; C-W 3 ERR = Colour- Word Interference test (condition 3): no. of errors; C-W 4 TIME = Colour- Word Interference test (condition 4): completion time; C-W 4 ERR = Colour- Word Interference test (condition 4): no. of errors

Appendix 4 – Informed Consent Form

To meet the responsibility to you, the participant of this study, and to the University of Cape Town, which is supporting this research project, I wish to inform you about this study and about your rights as a participant in this study.

You have been invited to participate in this study, which will be assessing the cognitive functions (such as memory and attention) of people with Obstructive Sleep Apnoea Syndrome (OSAS). You have been chosen to participate in this study because you have received a definitive or probable diagnosis of this disorder, or because you will be a part of a comparative group of people from the general population.

In this study, you will be required to undergo a full polysomnographic sleep study (if you have not already done so), where you will be observed for a night while you are sleeping, and various measurements will be taken. This study will not hurt or harm you in any manner; it will simply measure various aspects of your breathing and sleeping patterns in order to obtain a detailed, accurate, and quantifiable picture of the severity and characteristics of the sleep apnoea condition if you have this disorder. In addition to this, your cognitive functions will be assessed using a variety of simple tests, which will be carried out by me, Andrea Wong, a neuropsychology student, under the supervision of a fully trained and qualified neuropsychologist or behavioural neurologist. This assessment will take approximately 2 hours.

This study is completely voluntary and you will not be forced in any way to participate in it. Additionally, should you feel too tired or uncomfortable to continue with any part of the study, or should you wish to withdraw from the study for any other reason, you will be free to do so. Furthermore, if you would like a break while the testing process is being carried out, you can request this at any time.

All information obtained about you from this study will be completely private and confidential and no one will have access to it, except for my supervisors and me. Additionally, no personal details or names will appear in the published study, so you will remain completely anonymous. You will be given a copy of the final study if you so desire.

It is important that you understand and are aware of everything that the study entails, as well as of the rights that you have as a participant in this study. As an indication that you understand this, I ask that you please sign in the place provided below:

Signature: _____

Date: _____

Appendix 5 – Neuropsychological Tests Used in the Study

Test	Procedure of Test	Cognitive Function Assessed	Specific Sub-Score selected
Epworth Sleepiness Scale (ESS)	Patients are required to give a rating from 0 – 3 of their likelihood of dozing in 7 given sedentary situations (0 = no chance of dozing; 3 = high chance of dozing)	Subjective sleepiness (Naismith et al., 2004)	Total score out of 21
Digit Symbol Substitution Test	This task requires the substitution of symbols for corresponding numbers from 1-9 under time constraints (120 seconds)	General cognitive capacity and intelligence, sustained attention, response speed, visuomotor co-ordination, motor persistence and psychomotor performance (Kim et al., 1997; Weschler, 1987)	Total number of items completed

Digit Span Subtests of WMS-R	Subjects are required to repeat digits that are presented orally, in a sequence of increasing length. They are required to repeat the sequence either in the same, or the reverse, order given	Test of working memory, mental tracking and attentional capacity (Pantelis, 2005; Beebe et al., 2000; Walsh & Darby, 1999)	Total score for digit span forwards Total score for digit span backwards Combined total score
Trail Making Subtest of D-KEFS (Conditions 1, 4 and 5)	Condition 1 is a cancellation task in which patients are required to cancel out the target number "3", which is interspersed among a range of numbers and letters on a page In condition 4, patients are required to connect numbers, from 1-16 and letters, from A-P, in ascending order, alternating between numbers and letters In condition 5, patients are required to join a series of circles, following a set pattern demarcated by dotted lines in as short time as possible	Test of visual scanning and sustained attention (Delis et al., 1995; Kim et al., 1997) Test of visual search speed, cognitive flexibility, rule observance, attention and motor function. Primary executive task (Pantelis, 2005; Kim et al., 1997; Mark, 2005) Test of motor speed and visuomotor ability (Delis et al., 1995)	Completion time Number of errors Completion time Number of errors Completion time

Colour-Word Interference Subtest of D-KEFS (Conditions 3 and 4)	In condition 3, participants are required to name ink colours that are printed in incongruent colour names. In condition 4, participants are required to complete the same task as in condition 3, except when the colour names are written in a box - in which case the actual colour name, rather than the colour of ink in which it is written, must be given.	Both of these conditions are tests of the executive functions including: inhibition, selective focused attention and rule observance (Ferini-Strambi et al., 2003; Mark, 2005)	Completion time Number of errors Completion time Number of errors
Tower Subtest of D-KEFS	Patients are required to move an increasing number of disks across three pegs in order to build a specified tower. Patients also need to follow several rules while completing this task	Test of executive functions including: planning, rule observance, set maintenance and shifting (Pantelis, 2005; Naismith et al., 2004; Mark, 2005)	Completion time Total achievement score Total number of rule violations

Verbal Fluency Subtest of D-KEFS (Conditions 1, 2 and 3)	In condition 1, participants are required to give as many words as possible that begin with a specified letter In condition 2, participants are required to give as many words as possible that belong to a specified category In condition 3, participants are required to give as many words as possible in two specified categories, alternating between giving a word in each category	All 3 conditions measure executive functions such as: initiation, simultaneous processing (observing multiple rules at the same time), speed of processing, spontaneous verbal generation and cognitive flexibility (Mark, 2005; Pantelis, 2005; Delis et al., 1995).	Completion time Number of errors Completion time Number of errors Completion time Number of errors
Benson and Barton Stick Test	Patients are required to construct a pattern specified by the assessor with a varying number of wooden sticks (2-4). Patients are first required to copy the examiner's pattern exactly as they see it. The examiner then sits across from the participants, and participants must construct the pattern to be the mirror image to what they see if they look directly at the examiner's pattern.	Test of constructional abilities (Lezak, 1995)	Number of errors on match condition Number of errors on reverse condition *Please note that only the score for the reverse condition was included in the study, as only 1 error was made by 1 participant out of all the participants in this study on the match condition of this test.

Logical Memory I Subtest of WMS-R	Participants are required to recall as much information as they can about two stories immediately after these have been read to them by the assessor	Test of immediate verbal memory, specifically free recall (Wechsler, 1987)	Total recall score
Logical Memory II Subtest of WMS-R	Participants are required to recall as much detail as they can about two stories that had been read to them after a delay of approximately 1 hour	Test of delayed verbal memory, specifically delayed recall (Wechsler, 1987; Pantelis, 2005, Mark, 2005)	Total recall score
Visual Reproduction I Subtest of WMS-R	Patients are required to draw, in as much detail as they can remember, four figures immediately after they have been presented to them for approximately 10 seconds	Test of immediate visual memory, specifically free recall (Weschler, 1987)	Total recall score
Visual Reproduction II Subtest of WMS-R	Patients are required to draw, in as much detail possible, 4 figures that had been presented to them after a delay of approximately 1 hour	Test of delayed visual memory, specifically delayed recall (Weschler, 1987)	Total recall score

Wisconsin Card Sorting Test	Participants are required to sort a set of 128 cards according to a specific category (colour, form or number) so that they match one of four target cards. These categories are not told to the participants, but the participants are instead required to alter their response according to the feedback given by the assessor	A test of abstract behaviour, concept formation, mental shifting and problem solving (Décary et al., 2000; Fulda & Schulz, 2001; Heaton, 1981)	Total number of categories achieved (maximum = 6) Total number of errors Total number of perseverative responses