A norm- and control-referenced comparative study of the neuropsychological profiles of shift workers and patients with obstructive sleep apnoea (OSA)

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ABSTRACT

Shift work and Obstructive sleep apnoea (OSA) have been associated with excessive daytime sleepiness and increased risk of road traffic accidents. There is evidence that daytime sleepiness does not provide a satisfactory explanation for accidents, and occupational and social failures associated with sleep disorders. The possibility arises that intermittent hypoxemia and sleep deprivation due to sleep fragmentation in OSA and sleep deprivation secondary to sleep cycle disruption in shift work may underlie neuropsychological deficits, which in turn meditate these functional impairments. The current study uses a control-referenced and norm-referenced design to explore in detail the subcomponents of attention/executive functions and motor coordination of patients with OSA and shift workers with an aim to outline and compare the profiles of any cognitive impairment between these groups. Each of the attentional and executive sub-functions investigated are substantiated by theory-based models and are matched with one or more standardized subtests, which are also in accord with a theory and ecological validity. The Tests of Everyday Attention, selected subtests of the Wide Range Assessment of Memory and Learning, the Stroop Test Interference Score, and the Austin Maze were used to assess selective attention, sustained attention, divided attention, set-shifting, working memory, and inhibition of prepotent responses, as well as complex spatial learning, planning, error utilization, behavioural inhibition and motor coordination. Fifteen patients (13 men and 2 women aged between 34 and 58), who had previously undergone a polysomnographic sleep study and a diagnosis of moderate to severe obstructive sleep apnoea (Apnoea-Hypopnoea Index (AHI) > 20/hr and Epworth Sleepiness Scale (ESS) > 8) had been established and verified by a respiratory physician, were recruited from the Austin and Repatriation, Medical Centre. Fifteen shift workers (9 men and 6 women aged between 25 and 49) and fifteen healthy controls (6 men and 9 women aged between 25 and 69), screened for sleep disorders and excessive sleepiness by Maislin Apnoea Prediction Index and ESS, were recruited from the community. Participants were closely matched for age and educational level. More pervasive and severe attentional and executive function impairments were demonstrated in patients with OSA relative to shift workers, both in control-referenced comparison and norm-referenced comparison. In comparison to controls, shift workers demonstrated significant reductions in the abilities of complex visual selective attention, divided attention, auditory set-shifting, verbal and symbolic working memory, and inhibition of prepotent responses, as well as a reduced spatial learning efficiency. Patients with OSA demonstrated significant reductions in the abilities of visual and auditory selective attention, divided attention,

visual and auditory set-shifting, verbal and symbolic working memory, and inhibition of prepotent responses, as well as impaired spatial learning due to poor planning, error utilization, behavioural inhibition and possibly poor motor coordination, as compared to controls. A pattern of predominant attentional deficiency with a mild verbal working memory deficiency in shift workers and a dual pattern of attentional deficiency and pervasive executive dysfunctions in patients with OSA were revealed in norm-referenced analysis. By comparing the neuropsychological profiles of the two groups in standardized scaled score, it can be deduced that sleep deprivation may be the more important contributing factor to the selective inattention, the trend of reduced sustained attention, and the reduced verbal working memory in patients with OSA; whereas intermittent hypoxemia may be the more important contributing factor to the deficits in divided attention, and the trends of mildly reduced visual and auditory set-shifting abilities and inhibition of prepotent responses. Based on the incremental deficiencies in the divided attention and set-shifting sub-functions evident in the comparative control-referenced analysis between shift workers and patients with OSA, it is possible that sleep deprivation and intermittent hypoxemia may contribute additively/synergistically to these two neuropsychological sub-functions of patients with OSA. Austin Maze results support the notion that the pathophysiology of OSA involves subcortical brain structures and the associated frontostriatal pathways. Overall, results of the current study support the Executive dysfunction model and the Microvascular theory, but not a pure Attentional deficits model. The measured attentional and executive sub-functions are separable constructs and are not in a simple hierarchical relationship. The current study exemplifies how a neuropsychological comparative study using standardized tests may serve as an experimental paradigm allowing detailed contrast of the differences in cognitive sub-functions between clinical groups that share a common pathophysiological factor, so that enriched information about the linking of each factor with various neurocognitive deficits can be deduced. Clinical monitoring of the objective indicators of neuropsychological functions is possible by using repeatable standardized tests with high ecological validity. To conclude, the functional impairment in shift workers in this study was significant enough to be presented as a similar profile as patients with OSA, albeit somewhat less pervasive and less severe. The results indicated the potential hazard of shift work as functional impairment as patients with OSA. Heavy health toll should be considered in all potential shift workers.

DECLARATION

I, Jacen Man Kwan Lee, declare that the Doctor of Psychology (Clinical Neuropsychology) thesis entitled "A norm- and control-referenced comparative study of the neuropsychological profiles of shift workers and patients with obstructive sleep apnoea (OSA)" is no more than 40,000 words in length including quotes and exclusive of tables, figures, appendices, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

Signature: Date: 29th October, 2010

DEDICATION

This thesis is dedicated to the memory of my father Yat-Kwong Lee, for providing me an ideal model of perseverance and showing me how to be empathetic, inquisitive and creative.

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
AASM	American Academy of Sleep Medicine
ANOVA	Analysis of Variance
AHI	Apnoea-Hypopnoea Index
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
ADHD	Attention-deficit/hyperactivity disorder
BMI	Body mass index
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFA	Confirmatory factor analysis
CPT	Continuous Performance Test
CRH	Corticotrophin releasing hormone
DADT	Divided Attention Driving Test
EEG	Electroencephalograph
EOG	Electrooculography
ESS	Epworth Sleepiness Scale
EDS	Excessive daytime sleepiness
FCRTT	Four Choice Reaction Time Test
HPA	Hypothalamic-pituitary-adrenocortical
iNOS	Inducible NOS
IQ	Intelligence Quotient
IH	Intermittent hypoxia
ICSD-2	International Classification of Sleep Disorders, 2^{nd} edition
JLD	Jet Lag Disorder
KSS	Karolinska Sleepiness Scale
LTP	Long-term potentiation
MRI	Magnetic resonance imaging
MAPI	Maislin Apnoea Prediction Index
MTT	Mirror Tracing Task
MID	Multiple Infarct Dementia
MSLT	Multiple Sleep Latency Test
MANOVA	Multivariate analyses of variance
NO	Nitric oxide
NOS	Nitric oxide synthase
NMDA	N-methyl-D-aspartate

OSAHS	Obstructive Sleep Apnoea-Hypopnoea Syndrome
OSA	Obstructive Sleep Apnoea
PASAT	Paced Auditory Serial Additional Test
PET	Positron Emission Tomography
PVT	Psychomotor Vigilance Task
RNG	Random number generation
RT	Reaction time
RDI	Respiratory disturbance index
RNA	Ribonucleic acid
RTA	Road traffic accidents
RMSEA	Root mean square error of approximation
SWD	Shift Work Disorder
SWS	Slow wave sleep
SPSS	Statistical Package for Social Sciences
SDMT	Symbol Digit Modalities Test
TEA	Test of Everyday Attention
TOH	Tower of Hanoi
TOL	Tower of London
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WAIS-III	Wechsler Adult Intelligence Scale-Third Edition
WISC-R	Wechsler Intelligence Scale for Children-Revised
WMS-III	Wechsler Memory Scale-Third Edition
WRAML-2	Wide Range Assessment of Memory and Learning – Second Edition
WCST	Wisconsin Card Sorting Test

CHAPTER ONE: INTRODUCTION

1.1 Driver sleepiness and risk of road traffic accidents (RTAs)

Shift work has been associated with the experience of driver sleepiness (Adam-Guppy & Guppy, 2003; Hakkanen, Summala, Partinen, Tihonen, & Silvo, 1999). The combination of homeostatic and circadian influences produces increased behavioural, subjective and physiological sleepiness (Akerstedt, 1988; Akerstedt, 1990; Akerstedt, 2003; Akerstedt, Kecklund, & Knutsson, 1991). Shift workers commonly suffer with disturbed sleep and decreased sleep duration (Akerstedt & Torsavall, 1981). This sleep reduction also causes daytime sleepiness, inability to concentrate and misperception (Paley & Tepas, 1994). However, obstructive sleep apnoea (OSA) is another condition leading to sleep fragmentation and daytime sleepiness (Stradling & Crosby, 1991; Young, Palta, Dempsey, Skatrud, Weber, & Badr, 1993). OSA has been found to be associated with a significantly increased frequency of falling asleep while driving and increased risk of RTAs (Aldrich, 1989; Barbe et al., 1998; Findley, Unverzagt & Suratt, 1988).

1.2 Cognitive impairments in sleep disorders, risk of driving and social occupational failures

Although sleepiness while driving is believed to be an important cause of accidents, recent evidence suggests that actually falling asleep is much less likely to be the causal event than making attentional and judgmental errors (Philip & Mitler, 2000). There is evidence suggesting that perceived sleepiness as measured by the Epworth Sleepiness Scale (ESS), and the objective sleepiness measured in the Multiple Sleep Latency Test (MSLT) are poor predictors of the accident rates in sleep apnoea patients (Young, Blustein, Finn, & Palta, 1997). Moreover, ESS was not correlated with driving simulator performance in OSA patients (Turkington, Sircar, Allgar, & Elliott, 2001).

If sleep disorders are frequently associated with accidents, but daytime sleepiness does not provide a satisfactory explanation (Philip & Mitler, 2000), it could be that factors such as sleep fragmentation and hypoxemia in OSA (Bedard, Montplaisir, Richer, Rouleau, & Malo, 1991) and sleep deprivation resulting from sleep cycle disruption in shift work (Paley & Tepas, 1994) may underlie both the daytime sleepiness and the cognitive impairment (Engleman, Martin, Deary, & Douglas, 1994). Furthermore, it is the latter which may be the major cause of performance and

judgment errors (Harrison & Horne, 1999), and which, in turn, may mediate the higher accident rate (Harrison & Horne, 2000a).

Basic cognitive functions traditionally found to be associated with sleep deprivation, such as alertness, reaction time, attention and vigilance (Dinges et al., 1997; Horne, Anderson, & Wilkinson, 1983) can be important mediating factors for making performance errors and hence causing accidents. OSA patients have been shown to have more electroencephalograph (EEG) monitored attention lapses and higher lane position variability on a driving test, presumably due to their delayed responses to lane drifts during lapses (Risser, Ware, & Freeman, 2000). Recent research suggests that tests sensitive to sleep deprivation need not necessarily be monotonous and simple; they can be short, stimulating and rely on accuracy rather than speed (Wilkinson, 1992). For example, sleep loss is found to impair certain types of executive functions, such as supervisory control (Nilsson et al., 2005), problem solving, divergent thinking capacity (Horne, 1988; Linde & Bergstrom, 1992), verbal creativity, flexibility, response inhibition (Harrison & Horne, 1998,2000a), and cognitive set shifting (Wimmer, Hoffmann, Bonato, & Moffitt, 1992). Studies have shown that sleep deprivation is associated with perseverations, working memory problems, increased distractibility and concern with irrelevancies (Harrison & Horne, 2000a). Sleep deprivation also significantly reduces prefrontal metabolic activity with associated decrements in executive function task performance (Thomas et al., 2000) and biases the person toward risky decision-making, especially with increasing age, with the pattern resembling that of ventromedial prefrontal cortex lesions (Killgore, Balkin & Wesensten, 2006).

Sleep deprivation alone does affect cognitive performance; however, the fact that deficits related to executive function still persist despite treatment-related resolution of daytime sleepiness (Bedard, Montplaisir, Richer, Malo & Rouleau, 1993; Naegele et al., 1998) suggests non-sleep factors may be contributing to the development of some of the cognitive impairments. Comparison of hypoxemic and non-hypoxemic apnoea patients provides evidence to show that sleep fragmentation is a less important cause of cognitive impairment than hypoxemia (Findley et al., 1986). Moreover, OSA in adults is associated with occupational and social failures attributable to poor planning, disorganization, diminished judgment, rigid thinking, poor motivation, and affective lability (Day, Gerhardstein, Lumley, Roth & Rosenthal, 1999; Dogramji, 1993; Redline & Strohl, 1999). Based on the above evidence, it can be reasoned that neuropsychological deficits of OSA are important mediators leading to occupational and social failures as well as increased driving risk, independent of

daytime sleepiness.

1.3 Aims of current study

In the present study, the aim was to investigate the neuropsychological profile of OSA patients who were affected by hypoxemia and sleep deprivation secondary to sleep fragmentation and that of shift workers who were mainly affected by sleep deprivation due to disruption of their sleep cycle. Sustained attention, selective attention, divided attention, executive functions including inhibition of prepotent responses, set-shifting, verbal and symbolic working memory, planning, error utilization, behavioural inhibition, as well as fine-motor coordination were measured using a battery of neuropsychology tests. Potentially, attentional and executive functions together with motor coordination can serve, besides sleepiness, as mediating factors for the real-life consequences of OSA.

By comparing and contrasting the neuropsychological profiles of patients with OSA and shift workers, it was aimed to further the understanding of the differential contribution of sleep deprivation/sleep fragmentation and hypoxemia to cognitive impairments associated with OSA, as well as to evaluate the relative merits of different pathophysiological models of OSA. The present control-referenced and norm-referenced study used standardized neuropsychological tests with high ecological validity, to explore in detail the theoretically discrete subcomponents of attentional and executive functions. This should facilitate clearer conclusions and better comparison of findings reported in the literature. This also makes it possible to examine individual sub-functions and for these to be systematically monitored by clinicians and easily communicated to patients, thus promoting informed medical decisions.

CHAPTER TWO: LITERATURE REVIEW

2.1 *Shift work and Shift Work Disorder (SWD)*

Shift work is a term that applies to a broad spectrum of non-standard work schedules including occasional on-call over-night duty, rotating schedules, steady and permanent night work, and schedules demanding an early awakening from nocturnal sleep. Shift work is very common; in fact, about one in five workers in the United States do some form of shift work (women more than men) (Presser, 1995). In 2004, for approximately 22 million US adults, shift work was an integral part of their professional life; of these individuals, about 3.8 million regularly performed night-shift work on a rotating basis (McMenamin, 2007; US Bureau of Labor Statistics, 2004).

SWD is experienced by individuals whose work schedule overlaps with the normal sleep period, causing misalignment between the body's endogenous circadian clock and the time at which the worker is able to rest. The International Classification of Sleep Disorders, 2nd edition (ICSD-2) defines SWD as the presence of excessive daytime sleepiness (EDS) and/or insomnia for at least one month, in association with a shift-work schedule (American Academy of Sleep Medicine, 2005). Recent practice parameters from the American Academy of Sleep Medicine (AASM) recommend the use of a sleep diary for at least seven days to aid in the diagnosis of SWD and to rule out other sleep/wake disorders (Morgenthaler et al., 2007; Sack et al., 2007); but there are no standard sleep diaries as yet. ESS is helpful in measuring EDS in the primary care setting (Johns, 1991). This brief questionnaire asks the respondent to subjectively rate his or her chances of dozing in eight sedentary situations, such as reading a book or sitting in a meeting. A score of at least 10 out of a maximum 24 is indicative of clinically significant EDS (Johns, 1991). The diagnosis of SWD is based on patient history and it does not require confirmation with a sleep study (Sack et al., 2007). EDS is also a symptom of the other sleep/wake disorders, including OSA (Aloia, Arnedt, Davis, Riggs, & Byrd, 2004). Exclusion of OSA can be done by a screening questionnaire, the Maislin Apnoea Prediction Questionnaire (Maislin et al., 1995). A high Maislin Apnoea Prediction Index (MAPI) (> 0.5) warrants a sleep study or polysomnogram to confirm the differential diagnosis (Maislin et al., 1995).

It can be seen that the difference between a 'normal' and a pathological response to shift work is not clearly defined. The formal diagnosis of SWD has rarely been used

in research studies, and the validity and reproducibility of the AASM diagnosis criteria need testing (Sack et al., 2007). This classification results in the shift work population being separated into three distinct groups: (1) those who have no impairment; (2) those who have impairment (social, occupational or other), but do not meet the ICSD-2 criteria for the diagnosis of SWD based on history taking; and (3) those who have SWD. Drake and colleagues (2004), using questionnaire data from an epidemiological survey, found that 32.1% of night workers and 26.1% of rotating workers met the minimal criteria for SWD. The boundary between a normal and a pathological response to the circadian stress of an unnatural sleep schedule associated with shift work remains unclear (Sack et al., 2007). Since the latter two groups are intolerant of shift work, it is likely that a much larger number of intolerant shift workers have some impairment and may or may not meet the SWD criteria, remain in the workforce.

Insomnia and EDS (drowsiness and a propensity to sleep) are the defining symptoms of SWD and can result in fatigue (weariness and depleted energy), difficulty concentrating, reduced work performance, headache, irritability, or depressive mood, and hence constitute a significant burden of illness on society (Schwartz & Roth, 2006; Shen et al., 2006). The circadian system functions adequately under usual circumstances, but when an imposed shift in the timing of sleep exceeds the limits of circadian adaptation, misalignment occurs. Being classified under Circadian Rhythm Sleep Disorder, circadian misalignment is considered to play an important part in the primary pathophysiology of SWD, causing a constellation of symptoms that characterize the disorder (Sack et al., 2007). This, however, does not preclude other endogenous factors, such as individual differences in the ability to sleep at an unfavourable circadian phase, from contributing to SWD. Indeed, attempts to sleep at an unusual time are often interrupted by noise, and social factors (Sack et al., 2007). There is also an inevitable degree of sleep deprivation associated with sudden transitions in sleep schedule, for example, a night worker who stays awake for 24 hours on the first night of a rotating roster is acutely sleep deprived in the morning. In fact, the major consequences of shift-work are disturbed sleep and decreased sleep duration (Akerstedt & Torsvall, 1981), producing a cumulative sleep loss, or chronic partial sleep deprivation (Scott, 2000).

Accumulated sleep loss, circadian and ultradian factors have been shown to be significant in determining subjective estimates of sleepiness (Babkoff, Caspy, & Mikulincer, 1991). However, sleep reduction alone causes daytime sleepiness, inability to concentrate and misperception (Paley & Tepas, 1994). Similarly, the

symptoms of Jet Lag Disorder (JLD) are considered to be generated by circadian misalignment, the inevitable consequences of crossing time zones too rapidly for the circadian system to keep pace (Sack et al., 2007). Cho, Ennaceur, Cole, and Kook Suh (2000) demonstrated that chronic jet lag experienced by cabin crew is associated with depressed nonverbal short-term memory processing, and possibly attenuated working memory, whereas short-term verbal memory is spared. Nevertheless, memory consolidation, learning, alertness, and performance are found to be severely affected by sleep deprivation, even in the absence of circadian misalignment (Dijk, Duffy, & Czeisler, 1992; Walker & Stickgold, 2005).

2.2 Obstructive Sleep Apnoea-Hypopnoea Syndrome (OSAHS)

OSAHS is a clinical condition that occurs because the upper airway collapses intermittently and repeatedly during sleep, being characterized by recurrent episodes of partial or complete upper airway obstruction during sleep. This manifests as a reduction in (hypopnoea) or complete cessation (apnoea) of airflow despite ongoing inspiratory efforts (AASM, 1999). An apnoea is arbitrarily defined in adults as a ten second breathing pause and a hypopnoea as a ten second event where there is continued breathing, but ventilation is reduced by at least 50% from the previous baseline during sleep (Bassiri & Guilleminault, 2000). The lack of adequate alveolar ventilation usually results in arterial blood oxygen desaturation (decrease in arterial partial pressure of oxygen, PaO_2) and in cases of prolonged events, a gradual increase in arterial partial pressure of carbon dioxide ($PaCO_2$) (AASM, 1999).

As the sufferer falls asleep, the muscle tone in the upper pharyngeal airway decreases leading to upper airway narrowing. This, in turn, produces an increase in inspiratory effort in an attempt to overcome airway narrowing, which then leads to a transient arousal from deep sleep to wakefulness or a lighter sleep phase allowing restoration of normal airway muscular tone and calibre. The patient then falls more deeply asleep again and the whole cycle repeats itself. This can occur many hundreds of times throughout the night leading to fragmentation of normal sleep architecture and a reduction in the quality of sleep with the generation of restless, disturbed and unsatisfying sleep. Daytime symptoms such as excessive sleepiness, poor concentration, and a reduced alertness are thought to be related to sleep disruption associated with recurrent arousals (sleep fragmentation) and possibly also to recurrent hypoxemia (AASM, 1999).

OSAHS represents one end of a spectrum with normal quiet regular breathing at one

end, moving through worsening levels of snoring, to increased upper airways resistance, and to hypopnoeas and apnoeas at the other end. The frequency of apnoeas and hypopnoeas hourly is used to assess the severity of the OSAHS and is called the apnoea/hypopnoea index (AHI) or the respiratory disturbance index (RDI) (Bennett, Langford, Stradling, & Davis, 1998). In an attempt to standardize definitions of apnoeas/hypopnoeas and related indices, the AASM (1999) has published an arbitrary operational guideline to stratify the severity of OSAHS by varying degrees of breathing abnormality, or sleep related obstructive breathing events as defined by AHI:

- Mild: AHI 5 to 14 events/hour
- Moderate: AHI 15 to 30 events/hour
- Severe: AHI greater than 30 events/hour

To fulfill the diagnostic criteria, the individual must have an overnight monitoring and demonstrate five or more obstructed breathing events per hour during sleep. Recorded events may include any combination of obstructive apnoeas/hypopnoeas or respiratory effort related arousals. In addition, the individual must show either excessive daytime sleepiness that is not better explained by other factors, or two of the other features of OSAHS, including choking or gasping during sleep, recurrent awakenings from sleep, unrefreshed sleep, daytime fatigue, or impaired concentration.

Stratification is used to assign patients to an approximate level of severity when considering treatment strategies. Stratification also depends on the severity of symptoms and the level of impairment of social and occupational function. In general, the more severe the breathing abnormality, the more symptomatic the patient becomes, but there may be cases where the severity of the symptoms does not correlate with the degree of breathing abnormality (Duran, Esnaola, Rubio, & Iztueta, 2001).

The incidence of OSAHS increases after the age of 40 and is more common in men than in women (Young, Evans, Finn & Palta, 1997). In the middle-aged population from the Wisconsin Sleep Cohort Study, Young and colleagues (1993) estimated that the prevalence of an AHI of 5 or higher per hour to be 25 percent for men and 9 percent for women. An Australian study which used home monitoring to measure sleep apnoea in 294 men aged 40 to 65 years from the volunteer register of the Busselton Health Survey, showed that 26% had an RDI of at least 5, and 10% had an RDI of at least 10; 81% snored for more than 10% of the night and 22% for more than

half the night. Hence, in middle-aged men, both snoring and sleep apnoea are extremely common, and it was also found that in this age range both are associated more with obesity than with age itself (Bearpark et al., 1995).

In terms of the pathophysiology of OSAHS, during the repeated complete (apnoea) or partial (hypopnoea) cessations of breathing, blood oxygen saturation can drop to dangerously low levels, resulting in increased respiratory effort and arousals from sleep to resume breathing. Recurrent hypoxemia and fragmented sleep are therefore significant consequences of the disorder (Bassiri & Guilleminault, 2000). The primary daytime sequelae of the disorder include EDS, mood changes and self-reported cognitive problems (Aloia et al., 2004).

2.3 Sleep fragmentation = Sleep deprivation

A number of studies have shown that both increased daytime sleepiness in healthy subjects and EDS in patients, whether due to total sleep deprivation, sleep restriction, sleep disruption or sleep fragmentation, impairs cognitive functions (Bonnet, 1986a, 1986b; Downey & Bonnet, 1987; Stepanski, Lamphere, Roehrs, Zorick & Roth, 1987).

Sleep fragmentation refers to the punctuation of sleep with frequent, brief arousals characterized by increases in EEG frequency or bursts of alpha activity, and occasionally, transient increases in skeletal muscle tone (Roth, Hartse, Zorick, & Conway, 1980). These arousals last approximately 3-15 seconds, usually do not result in prolonged wakefulness, and sometimes may not even alter standard sleep stage scoring. In some sleep disordered patients, the arousing stimulus (e.g., apnoeas) can be identified (Miles & Dement, 1980; Roth et al., 1980). In other situations, the arousing stimulus cannot be identified. For example, the sleep of healthy “normal” elderly is often fragmented (Carskason, Brown & Dement, 1982), and out-of-phase sleep, such as occurs in shift work or jet lag, is also fragmented (Wegman et al., 1986). Thus, sleep fragmentation is a common cause of EDS.

Sleep fragmentation has been experimentally studied by inducing arousals in normal subjects with external stimuli. Several studies have employed an auditory stimulus to awaken subjects at various intervals during the night (Bonnet, 1985, 1986a, 1986b; Lumley et al., 1986). Decrements in cognitive performance and results of a single sleep latency test were found to be related to the periodicity of disturbance and not to sleep staging variables. In another study, tones were presented to subjects during the night at 5.5-minute intervals, and a subsequent increase in EDS was

observed, without increased wakefulness during the sleep period (i.e., subjects were not awakened behaviourally) (Stepanski et al., 1987). This was accomplished by terminating the tones upon arousal as defined by a speeding of the EEG or a burst of alpha activity of at least 3 seconds in duration, rather than causing behavioural wakefulness. In this study, sleepiness was measured repeatedly throughout the day with the MSLT, which has been shown to be a reliable measure of daytime sleepiness, and is systematically related to the amount of prior sleep (in sleep deprivation and sleep restriction studies) (Carskadon & Harvey, 1982; Carskadon, Harvey, & Dement, 1981; Roth, Roehrs, & Zorick, 1982). These studies demonstrated that sleep fragmentation, whether actually causing awakening or not, can result in increased EDS even when the "total sleep time" appears normal. Hence sleep fragmentation, which may be regarded as a kind of frequent sleep disruption, results in sleep deprivation in effect.

Results from Bonnet's studies (1985, 1986a) suggest that sleep continuity may be more integral to restoration of cognitive performance than "total sleep time" or specific sleep stage durations. In accordance with the sleep continuity theory (Bonnet, 1985, 1986a), the sleep process must continue undisturbed for a period of at least 10 minutes in order for sleep to be restorative. This theory is based on brain research findings that high sensory thresholds following sleep deprivation are instituted to maintain the continuity of sleep in order to allow sufficient time for effective protein synthesis (Adam, 1980; Oswald, 1980). Thus, it suggests that specific amounts of sleep stages are not important independent of sleep continuity.

Performances on psychomotor, vigilance, mental arithmetics tasks and daytime sleepiness have been shown to be a function of frequency and placement of sleep disruption (Bonnet, 1986a). It was found that arousals occurring at a rate of one per minute (sleep fragmentation) lead to daytime cognitive impairments associated with one night of sleep deprivation (Bonnet, 1986a). Bonnet, Downey, Wilms, and Dexter (1986) showed the number of arousing events and the periodic placement of these events are highly related to the severity of OSA. For example, patients with EDS rarely had a period of sleep as long as 10 minutes without an apnoea.

One night of sleep fragmentation, with sound pulses every two minutes, has been found to make normal subjects sleepier during the day, impairs their subjective assessment of mood, and decreases mental flexibility and sustained attention (Martin, Engleman, Deary, & Douglas, 1996). Furthermore, although there is more slow wave sleep (SWS) on the event-clustered night, similar numbers of sleep

fragmenting events produced similar daytime function whether the events were evenly spaced or clustered, supporting that sleep continuity is more important than the specific amount of sleep stages (Martin, Brander, Deary, & Douglas, 1999).

2.4 Sleep deprivation and neuropsychological function (The common denominator between shift workers and patients with OSAHS)

Sleep fragmentation diminishes tremendously the recuperative value of sleep (Levine, Roehrs, Stepanski, Zorick, & Roth, 1987) and results effectively in sleep deprivation as discussed previously. This occurs in patients with OSAHS despite the fact that total daily sleep time may be greatly increased due to excessive daytime somnolence in these patients (Downey & Bonnet, 1987). For shift workers, out-of-phase sleep is often fragmented too (Wegman et al., 1986). The disturbed sleep and the almost inevitable decrease in sleep duration due to different biopsychosocial reasons also amounts to a cumulative sleep loss or chronic sleep deprivation as discussed previously. Hence, significant sleep deprivation is a common denominator between shift workers and patients with OSAHS, albeit due to different pathophysiologies.

In general terms, excessive sleepiness is found to be associated with poor memory performance, poor concentration, and impaired learning and work performance, regardless of its etiology (Alapin et al., 2000; Rajaratnam & Arendt, 2000; Reimer & Flemons, 2003).

Basic cognitive functions traditionally found to be associated with sleep deprivation, such as alertness, reaction time, attention and vigilance (Dinges et al., 1997; Horne et al., 1983) can be important mediating factors leading to performance errors and hence accidents. For example, patients with OSA have more EEG monitored attention lapses and higher lane position variability on simulated driving tasks presumably due to delayed responses to lane drifts during lapses (Risser et al., 2000).

The underlying mechanisms through which sleep deprivation produces deficits in neurobehavioural and cognitive functioning have yet to be fully elucidated. One early explanation was termed a lapse hypothesis. Williams, Lubin, & Goodnow (1959) suggested that transient lapses in attention and performance occur following sleep deprivation, interspersed among periods of optimal performance and alertness. Others suggested a more global decrease in performance, such as a reduction in fastest reaction times on vigilance tasks (Dinges & Powell, 1989), and an increased variability in reaction times across tasks (Doran, Van Dongen, & Dinges, 2001). The

performance of fighter pilots on computerized cockpit simulation tasks assessing reaction time and vigilance and on a flight simulator was shown to deteriorate significantly during 37 hours of sleep deprivation (Caldwell, Caldwell, Brown, & Smith, 2004). In fact, one night of total sleep deprivation has been shown to affect reaction times and response accuracy to the same extent as having a blood alcohol concentration of .05% (Falleti, Maruff, Collie, Darby, & McStephen, 2003).

In the attention domain, significant deficits have been reported in vigilance (Blagrove, Alexander, & Horne, 1995; Caldwell et al., 2004; Orton & Gruzelier, 1989), sustained attention, attentional switching and short-term attention span (Frey, Badia, & Wright, 2004).

Sleep deprivation not only affects performances on monotonous and simple tasks, tasks which are short, stimulating and rely on accuracy rather than speed are also affected (Wilkinson, 1992). Performance on a number of tasks thought to be putatively subserved by the prefrontal cortex has been reported as significantly impaired following sleep loss, both total and chronic partial and the impairment was found to be reversible following recovery sleep (Doran et al., 2001; Mullaney, Kripke, Fleck, & Johnson, 1983; Harrison & Horne, 1998; Harrison, Horne, & Rothwell, 2000). That is, sleep loss has been found to impair certain types of executive functions such as supervisory control (Nilsson et al., 2005), problem solving, divergent thinking capacity (Horne, 1988; Linde & Bergstrom, 1992), temporal memory, verbal creativity, flexibility, response inhibition (Harrison & Horne, 1998; Harrison & Horne, 2000b) or inhibition of prepotent responses on a Go/No-Go task (Chuah, Venkatraman, Dinges, & Chee, 2006; Drummond, Paulus, & Tapert, 2006), and cognitive set shifting (Wimmer et al., 1992). Studies have shown that sleep deprivation is related to perseverations, working memory problems, increased distractibility and concern with irrelevancies (Harrison & Horne, 2000a).

Other higher order cognitive abilities such as logical reasoning have also been shown to be affected (Blagrove et al., 1995). Temporal memory, memory of when events occur, for visual stimuli (Harrison & Horne, 2000b) and verbal memory (Deary & Tait, 1987) were found to be impaired following sleep deprivation. However, performance on immediate memory recall and learning tasks are often dependant on attentional capacity as well as being mediated by executive function; hence deficits of the latter can adversely impact memory organization and retrieval, but not long-term storage (Harrison & Horne, 2000a, 2000b). Nevertheless, memory consolidation, or sleep-dependent learning and plasticity for skill performance are

found to be severely affected by sleep deprivation (Walker & Stickgold, 2005).

In addition to behavioural outputs of the prefrontal cortex demonstrating changes following sleep loss, brain imaging studies on sleep deprived subjects demonstrated decreased prefrontal activation associated with poorer performance on both arithmetic tasks involving symbolic working memory (Drummond & Brown, 2001; Drummond et al., 1999; Thomas et al., 2000) and verbal working memory tasks (Mu et al., 2005b). Sleep deprivation was also found to significantly reduce prefrontal metabolic activity with associated decrement in performance on executive function tasks (Thomas et al., 2000) and bias the person toward risky decision-making, especially with increasing age, with patterns resembling those of ventromedial prefrontal cortex lesions (Killgore et al., 2006). On the other hand, it has been reported that learning and divided attention tasks produced increased levels of prefrontal activation following sleep deprivation (Drummond & Brown, 2001), as well as in complex cognitive tasks, such as planning, relationship reasoning, and spatial working memory (Dagher, Owen, Boecker, & Brooks, 1999; Diwadkar, Carpenter, & Just, 2000; Dorrian, Rogers, Ryan, Szuba, & Dinges, 2002; Kroger et al., 2002; Mottaghy, Gangitano, Sparin, Krause, & Pascual-Leone, 2002). Moreover, a positive relationship between increased level of sleepiness and increased prefrontal activation has been reported. It is possible that this differential activation of prefrontal cortex may reflect task specific effects during sleep loss (Drummond et al., 2000) and compensatory effort to perform under sleep deprivation-induced sleepiness and fatigue. These alterations in prefrontal cortex dynamics following sleep deprivation are consistent with neurobehavioural studies showing deficits in attention, working memory and higher-order cognitive processes known to be mediated by the frontal lobes and various frontal reciprocal connections to brain regions, which are activated during tasks requiring integrated executive functioning (Nilsson et al., 2005).

There is evidence that sleep fragmentation in patients with OSA affects the frontal lobes of the brain by disrupting the normal restorative process of sleep (Beebe & Gozal, 2002). Based on functional neuroimaging and EEG findings, as well as on studies of the cognitive effects of sleep deprivation, several investigators have suggested that sleep is particularly important for restoring the prefrontal cortex functions (Dahl, 1996; Finelli, Borbely, & Achermann, 2001; Horne, 1993; Maquet, 1995). Notably, whereas the majority of other structures of the brain are active at some point during sleep, the prefrontal cortex displays reduced activity across all sleep stages. Furthermore, the prefrontal cortex appears functionally disconnected

during sleep from other regions with which it normally interacts during daytime hours (Braun et al., 1997, 1998; Hobson, Stickgold, & Pace-Scott 1998; Maquet, 2000). Dahl (1996) suggested that these findings may reflect a unique requirement for 'recalibration' of prefrontal cortex circuits without input interference from other brain regions. The prefrontal cortex is one of the most active brain regions while humans are awake, even during conscious rest, necessitating the greatest recovery during sleep; and sleep may be the only time when such restoration is possible (Binder et al., 1999; Harrison & Horne, 2000a). Finelli and colleagues (2001) using a quantitative EEG technique found that frontal regions are differentially sensitive to sleep deprivation and recovery sleep, and this effect appears to be related to time awake rather than circadian rhythmicity (Cajochen et al., 2001). In addition, by using magnetic resonance spectroscopy sensitive enough to study markers of neuronal integrity, it was revealed that neurochemical changes may be particularly prominent in the frontal lobes after sleep deprivation (Dorsey et al., 2000). Benington (2000) reviewed several hypotheses and concluded such restorative processes remain poorly understood at a cellular level. However, it is reasonable to assume that, these restorative processes require an extended period of sleep, and that disruption of sleep continuity can prevent homeostatic processes from taking place.

2.5 Hypoxemia experienced by patients with OSAHS

Benington (2000) suggested that limitation in tissue oxygen delivery (i.e., hypoxia) and decreases in intra- and extra-cellular pH (both hypoxia and hypercarbia) could also adversely affect sleep-related functions by creating a suboptimal environment for any number of cellular processes that have been implicated in restoration (e.g., mitochondrial integrity, protein synthesis, gene regulation). Bedard and colleagues (1991) reviewed research suggesting that synthesis of monoamines and acetylcholine may be disrupted by brief or intermittent hypoxemia.

David Gozal and his colleagues have been using experimentally-induced intermittent hypoxia in a rodent model of OSA to suggest potential mechanisms for neurobehavioural morbidity. Structural abnormalities were correlated with behavioural outcomes in an animal model of simulated sleep apnoea (Gozal, 2000; Gozal, Daniel, & Dohanich, 2001). Rats exposed to 2 weeks of intermittent hypoxia during sleep displayed poor maze learning and increased neuronal apoptosis in particular regions of the hippocampus and the overlying cortical region. Neuronal loss was particularly prominent among N-methyl-D-aspartate (NMDA) glutamate

receptor neurons. Row, Liu, Xu, Kheirandish, and Gozal (2003) demonstrated spatial learning deficits with the Morris water maze (Morris, 1984) and hippocampal ribonucleic acid (RNA) oxidant damage in a rodent model of sleep-disordered breathing, by exposure to intermittent hypoxia (IH), suggesting the episodic hypoxic-reoxygenation cycles of IH exposure is associated with increased oxidative stress, which is likely to play an important role in the behavioural impairments observed in patients with sleep-disordered breathing.

Li and colleagues (2004) demonstrated that IH selectively triggered one of the nitric oxide synthase (NOS) isoforms, inducible NOS (iNOS), which in turn led to excessive nitric oxide (NO) production and spatial learning deficits with the Morris water maze. Li and colleagues (2004) reported that IH exposures will also lead to substantial up-regulation of pro-inflammatory cytokines (Interleukin-1 beta, Tumor Necrosis Factor-alpha, and Interleukin-6) in the rat cortex. The putative mechanisms of neurotoxicity caused by excessive NO formation, include activation of glutamate receptors, especially the NMDA receptors, oxygen and glucose deprivation, protein nitrosylation, mitochrondrial dysfunction, and cortical neuronal cell death or apoptosis (Li et al., 2004). Xu and colleagues (2004) hypothesized that the oscillation of oxygen concentrations during chronic IH mimics the processes of ischemia-reoxygenation and could therefore increase cellular production of reactive oxygen species (ROS). Xu and colleagues (2004) demonstrated that long-term exposure of mice to intermittent hypoxia increased ROS production and oxidative stress propagation, which at least partially contribute to chronic IH-mediated cortical neuronal apoptosis. Together, IH during sleep has been shown to induce cortical neuronal apoptosis and spatial learning deficits on a water maze task in adult rats.

Payne, Goldbart, Gozal, and Schurr (2004) showed that exposures to IH during sleep can induce a diminished ability to express and sustain hippocampal long-term potentiation (LTP), which is correlated with spatial task learning deficits as well as programmed cell death in adult rats. In summary, increased oxidative stress (Row et al., 2003), up-regulation of pro-inflammatory cytokines (Li et al., 2004), and excessive nitric oxide levels, contribute to cortical and hippocampal neuronal apoptosis (Li et al., 2004; Xu et al., 2004) and reduced hippocampal LTP with associated spatial learning deficits (Payne et al., 2004). In addition, mice with genetic mutations that result in reduced free radicals or NO, or those who are given an anti-oxidant, showed attenuated apoptosis (Row et al., 2003; Li et al., 2004; Xu et al., 2004). For instance, Li and colleagues (2004) showed that IH-mediated neurobehavioural deficits on the water maze task were significantly attenuated in iNOS knockout mice, in which the

production of iNOS was inhibited by targeted deletion of iNOS gene.

Consistent with this model, there is accumulating evidence for increased levels of inflammatory markers in adults and children with OSA (Mills & Dimsdale, 2004; Larkin et al., 2005), as well as precursors of such inflammation, including increased sympathetic nervous system activation and decreased parasympathetic activity (Mills & Dimsdale, 2004; O'Brien & Gozal, 2005). Moreover, inflammatory cytokine markers correlate with daytime sleepiness and neurobehavioural dysfunction among adults (Mills & Dimsdale, 2004; Haensel et al., 2009) and children (Gozal et al., 2009) with OSA. Although these human studies have focused on peripheral inflammatory markers, the rodent findings suggest the occurrence of parallel processes in the central nervous system. In addition, peripheral inflammation has been implicated in vascular disease, which may have cerebrovascular consequences (Aloia et al., 2004).

Another potential mechanism of neuronal damage involves the neurotransmitter glutamate. During transient hypoxia, increased glutamate release occurs into the synaptic cleft, and can lead to overstimulation of excitatory glutamate receptors. These glutamate receptors, and more specifically excitatory NMDA receptors, have been extensively implicated in neuronal excitotoxicity and neurodegeneration (Englesen, 1986; Fung, 2000; Schousboe, Belhage, & Frandsen, 1997). Rats exposed to chemical hypoxia with carbon monoxide displayed an immediate and significant increase in glutamate release, followed days later by neuronal change that was particularly striking in the frontal cortex (Piantadosi, Zhang, Levin, Folz, & Schmeche, 1997).

Several brain structures and their associated neural systems have been held to be vulnerable to OSA. These include the prefrontal cortex (Beebe & Gozal, 2002), subcortical gray matter or basal ganglia (Aloia et al., 2004), and the hippocampus (Gozal et al., 2001). Aloia and colleagues (2001) found that patients with severe OSAHS had more subcortical white matter hyperintensities on brain magnetic resonance imaging (MRI) than those with minimal apnoea, and this was also negatively correlated with free recall performance on a word list. Also, an association was found between apnoea severity and small vessel ischemic brain disease (Aloia et al., 2001). There have been reports of scattered structural MRI changes in adults with OSAHS (Macey et al., 2002; Gale & Hopkins, 2004), but some studies have failed to replicate these findings (e.g., O'Donoghue et al., 2005). The inconsistency among structural MRI findings may be because the effects are subtle

and difficult to appreciate in the context of gross anatomical change.

Magnetic resonance spectroscopy study has found metabolic abnormalities in the left hippocampus similar to those seen in ischemic preconditioning, and this may reflect the differential susceptibility of these tissues to hypoxic damage in OSA. (Barlett et al., 2004). Other magnetic resonance spectra studies showed metabolic impairments in the frontal white matter (but not the prefrontal cortex or parietal white matter) of patients with OSA when compared to controls (Alchanatis et al., 2004; Kamba, Suto, Ohta, Inoue, & Matsuda, 1997; Kamba et al., 2001). Alchanatis and colleagues (2004) concluded that as frontal lobe white matter lesions are known to be associated with cognitive executive dysfunction, these findings may offer an explanation for the sometimes irreversible cognitive deficits, usually in the executive function domain, associated with OSA. Thus, cerebral metabolic changes occur in apparently normal brain tissue in patients with moderate to severe OSA. Some metabolic abnomalities suggest the presence of damage in frontal white matter, probably caused by repeated apnoeic episodes (Kamba et al., 1997). In contrast, functional MRI data suggest poor activation of dorsolateral prefrontal cortex in untreated adults with OSA when faced with a working memory task (Thomas, Rosen, Stern, Weiss, & Kwong, 2005).

2.6 Circadian misalignment or desynchronization in shift workers

One hypothetical mediating mechanism between circadian desynchronization or misalignment and cognitive dysfunction involves the impact of psychological stress on the brain via the hypothalamic-pituitary-adrenocortical (HPA) system with the increased secretion of cortisol (Lundberg, 2005). Briefly, stress causes the hypothalamus to release a corticotrophin releasing hormone (CRH) which stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH). ACTH causes the adrenal cortex to release cortisol into the blood circulation, activating the sympathetic nervous system. Negative feedback to the pituitary gland via a loop incorporating the hippocampus and amygdala via glucocorticoid receptors terminates the stress response. Chronic stress appears to cause down-regulation of glucocorticoid receptors, impairing the negative feedback mechanism, which results in over-activation of the HPA axis (Jameison & Dinan, 2001).

Disruptions of the sleep-wake cycle, such as sleep deprivation, night shift work and jet lag following rapid transmeridian flight, cause transient internal desynchronization of circadian rhythms (Winget, DeRoshia, Markley, & Holley, 1984).

Constant or prolonged sleep disruption, resulting in repeated disturbance of synchronization of the circadian system to the environment, can be considered as a physiological stressor (Winget et al., 1984).

Cognitive and neuroendocrine effects of chronic jet lag have been reported by Cho and colleagues (Cho, 2001; Cho et al., 2000). Cho and colleagues (2000) showed that flight attendants experiencing transmeridian flights, whereby crossing of several time zones results in desynchronization internal circadian rhythm from external light-dark cycle, had significantly higher average daily cortisol secretion (as measured by salivary cortisol level) than ground crew and cortisol elevation in female flight attendants, but not ground crew, was significantly correlated (r = -.78) with poorer visual working memory performance on visual delayed-match-to-sample tasks. This evidence supports the hypothesis that chronic circadian rhythm disruption resulting from repeated exposure to jet lag leads to significantly elevated cortisol levels and related neurocognitive deficits.

Cho (2001) compared temporal lobe volume (MRI scans corrected for head size), performance responses to an experimental visual spatial cognitive task and cortisol levels between two groups of female flight attendants, one had less than five days between transmeridian flights, whereas the other had more than 14 days in between, controlling for five working years and total flight exposure during this period. The results showed that the short recovery group, as compared to the long recovery group, had significantly reduced right temporal lobe volume, made more errors and were significantly slower on the visual-spatial task. There was also a strong and significant negative correlation between chronic elevation of cortisol levels and right temporal lobe atrophy (r = -.78) for the short recovery group only, suggesting a possible association between chronic jet lag induced stress and right temporal lobe atrophy, although longer periods between transmeridian flights may circumvent this effect.

Studies on the nature of circadian dysregulation of rotating night shift workers showed mixed results. For example, Lac and Chamoux (2003) demonstrated a significant increase in overall cortisol production while Zuzewicz, Kwarecki, and Waterhouse (2000) found lower cortisol level in night shift workers. Similarly, while Touitou and colleagues (1990) found dysregulation of the circadian markers of cortisol rhythm with no phase shift, others demonstrated phase shift (Goichot et al., 1998; Motohashi, 1992). To complicate matters, different shift systems (3 days work 2 days rest vs. 7 days work 5 days rest) appear to cause different effects to the

circadian markers of the cortisol rhythm (Lac & Chamoux, 2004). Moreover, Roden, Koller, Pirich, Vierhapper, and Waldhauser (1993) reported no differences in plasma cortisol rhythm characteristics (acrophase, amplitude, average secretion, and phase relationship with melatonin) between seven male controls and nine long-term, full-time, male night shift workers with high levels of work satisfaction. Overall, there is a general trend for cortisol rhythm dysregulation associated with shift work but the relationships between different circadian markers and different shift systems are complex. In addition, there seem to be large inter-individual differences in the tolerance of different shift schedules.

Notwithstanding this, it has become increasingly clear from research on HPA axis reactivity that chronically high or low levels of cortisol and problems with the up- or down-regulation of cortisol in response to stress are associated with difficulties in cognitive and behavioural self-regulation. The relation between cortisol and these brain functions generally follows an inverted U-shaped (Blair, Granger, & Razza, 2005). In children, moderate increase in cortisol followed by down-regulation of this increase, in mildly challenging situations, was positively associated with measures of executive function and self-regulation (Blair et al., 2005).

Wright, Hull, Hughes, Ronda, and Czeisler (2006) assessed learning in healthy patients who lived under shift-work conditions in a laboratory devoid of time cues. They compared improvements on the Mathematical Addition Test and the Digit Symbol Substitution Task between a synchronized group, where the normal relationship between sleep-wakefulness and internal circadian time was maintained, and a non-synchronized group mimicking the shift work condition, with both groups allowed to have 8 hours of scheduled sleep. Cognitive performance improved (i.e., learning) in the synchronized group, whereas learning was significantly impaired in the non-synchronized group. Hence, short-term circadian misalignment was found to be detrimental to learning in subjects who failed to adapt to their imposed schedule of sleep and wake, even though the total sleep time appears to be sufficient; in other words, proper alignment between sleep-wakefulness and internal circadian time is crucial for enhancement of cognitive performance (Wright et al., 2006).

In addition, alertness and cognitive processes may be especially impaired during the transition from day work to a series of night shifts, as many individuals will attempt to stay awake throughout the whole first day and night (Santhi, Horowitz, Duffy, & Czeisler, 2007). Acute circadian misalignment (and sleep deprivation to a lesser extent) associated with transition onto the first night shift was enough to significantly

affect the response times on tests of visual selective attention in a shift-work simulation study (Santhi et al., 2007).

Nevertheless, as mentioned previously, memory consolidation, learning, alertness and performance have been shown to be negatively affected by sleep deprivation, even in the absence of circadian misalignment (Dijk et al., 1992; Walker & Stickgold, 2005).

2.7 Neuropsychology of Obstructive Sleep Apnoea (OSA)

OSA can cause significant daytime behavioural and adaptive deficits. Functional impairments like sleepiness, impaired driving, increased risk of accidents, and decreased quality of life are common consequences of sleep apnoea (Engleman & Douglas, 2004; George & Smiley, 1999). Behavioural effects of OSA are often referred to as 'neurobehavioural' consequences because they are presumed to be directly related to brain function (Beebe, 2005). Neurobehavioural functioning is a broad term that includes several specific cognitive functions. Numerous studies have examined these specific cognitive functions and some have attempted to identify a "pattern" of cognitive dysfunction in OSA. Such patterns, as have been identified, are summarized below. Following that summary, theoretical models describing potential mechanisms involved in these relationships are discussed.

Cognition in OSA has been examined as both a unitary function (general intellectual functioning) and one divided into several specific domains (e.g., memory, attention, executive functioning, etc.).

2.7.1 General intellectual functioning

Global cognition or general intellectual functioning refers to the measure of an Intelligence Quotient (IQ) score, which is a standard score reflecting an individual's ability level at the time of testing in relation to the available age norms. Global cognition or "intelligence" is a unitary concept whereby a global IQ score is inferred from a multi-faceted testing instrument summarizing the average performance of the individual across various subtests. The Wechsler Adult Intelligence Scale-Revised (WAIS-R) is one of the most widely used instruments providing a Full Scale IQ score or general intelligence measure, which in turn can be subdivided into a Verbal IQ score and a Performance IQ score (Weschler, 1981).

In Aloia and colleagues' (2004) review, four out of seven group comparison studies using standardized neuropsychological measures found that global cognitive functioning was spared in OSA. In other words, OSA patients exhibit relatively few deficits in the global cognitive domain when compared to normal controls suggesting that cognitive impairment among OSA patients, if it exists, is not detectable on global measures. From another perspective, studies that limit themselves to global functioning would appear to lack a true appreciation of the various components of cognition that contribute to a global score, such that specific cognitive deficits can be masked. This masking effect may be present in Bedard, Montplaisir, Malo, Richer, & Rouleau' (1993) study in which the authors found no differences between untreated apnoea patients and controls on the WAIS-R Full Scale IQ and Verbal IQ, but reported a significantly lower WAIS-R Performance IQ in untreated apnoea patients. It is apparent that simply reporting a global score or Full Scale IQ score, which summarizes Verbal IQ score and Performance IQ score, would have masked significant changes in specific cognitive domains. Generally speaking, subtests relying on previously learned material or on verbal associations are more resistant to pathological processes or advancing age. Subtests requiring immediate memory, concentration, psychomotor speed, abstract concept formation or problem solving are vulnerable to such processes (Heaton, Baade, & Johnson, 1978).

Domain-specific hypotheses may remedy this problem. Domains can be delineated in several ways, but common domain names include executive functioning, attention, vigilance, visuospatial ability, constructional ability, psychomotor functioning, memory, and language. Each of these domains may also have subdomains that further break apart their complex nature and furthermore domains are not mutually exclusive in their functions (e.g., executive functioning and attention can overlap). For patients with OSA, the domains of cognitive functioning may be differentially affected.

2.7.2 Attentional function

EDS or hypersomnolence is one of the major consequences of OSA and has been associated with difficulty in maintaining adequate arousal to complete occupational and domestic activities (Ulfberg, Jonsson, & Edling, 1999). Therefore, difficulties concentrating and reduced sustained attention or vigilance are often reported; although the pathogenesis of attentional deficits in OSA remains unclear. Some attribute the attentional or concentration difficulties to hypoxemia (Findley et al., 1986; Greenberg, Watson, & Deptula, 1987; Presty, Barth, Surratt, Turkeimer, &

Findley, 1991), whereas, others relate them to daytime somnolence (Bedard, Montplaisir et al., 1991; Naegele et al., 1995).

The concept of attention is complex and multifaceted (Johnson & Dark, 1986). Several aspects of attention can be distinguished, including selective attention (or concentration), sustained attention (or vigilance) and divided attention as measured by dual tasks (Sohlberg & Mateer, 1989; van Zomeren & Brouwer, 1990).

Performances on the Digit Symbol Modality Test (Bedard et al., 1991), the Letter Cancellation Test (Bedard et al., 1991; Greenberg et al., 1987), auditory reaction time (Scheltens et al., 1991), the Paced Auditory Serial Additional Test (PASAT) (Engleman, Cheshire, Deary, & Douglas, 1993; Findley et al., 1986; Presty et al., 1991) have been found to be impaired and the impairment was interpreted in terms of attention and concentration deficits in OSA patients. However, the interpretation of what is being measured varies from one study to another. Limitations have been identified with established measures of attention, which may be contributing to these problems, namely, their multifactorial nature, poor ecological validity, and lack of a theoretical basis.

Most of these established measures, commonly employed by researchers to study a particular attentional function, were not originally designed with reference to any particular theory of attention (Sohlberg & Mateer, 1989). Many of these tests require upon the mental manipulation of complicated verbal or mathematical concepts, as well as making significant demands upon short-term memory (Sohlberg & Mateer, 1989). For example, although the Symbol Digit Modalities Test (SDMT; Smith, 1982) has been used as a test of divided attention (Ponsford & Kinsella, 1992), it also requires complex visual scanning and tracking abilities (Shum, McFarland, & Bain, 1990), in addition to motor speed and memory (Lezak, Howieson, & Loring, 2004). Similarly, the PASAT (Gronwall, 1977), often cited as a measure of divided attention (Kinsella, 1998; van Zomeren & Brouwer, 1994), relies heavily upon speed of information processing (Ponsford & Kinsella, 1992). Therefore, the multifactorial nature of many established tests of attention is a significant confounding problem in the interpretation of the results. The resulting variation in interpretation could lead to divergent conclusions.

Ecological validity refers to the ability of the assessment task to mimic the types of tasks that individuals are faced with in their everyday life and is particularly important in the rehabilitation context (Sbordone & Long, 1996). The failure of

established tests of attention to correlate either with the subjective reports of individuals or their carers has sometimes been attributed to the fact that many of these tests lack ecological validity (Kerns & Mateer, 1996).

Sloan and Ponsford (1995) stated that common measures of attention may not be sensitive enough to tap the various aspects of attention involved in everyday life. They argue that some attentional problems may only become apparent in more complex and less structured "real world" settings, and over longer periods of time, than are provided in the conventional assessment situation. Kerns and Mateer (1996) stated that "… psychometric assessment systematically reduces just those variables that challenge attentional resources and capacities in real life situations" (p.165). Ecologically valid tests that assess attention in more demanding situations, mimicking the more complex real life settings, are therefore needed, in order to capture specific attentional deficits that correlate with the reported everyday functional difficulties.

The choice of tests on attentional function will be explored further in a later section.

2.7.3 Vigilance

Much research has also been devoted to the problem of diminished vigilance levels and EDS suffered by OSA patients (Guilleminault, 1994). Vigilance is used to denote a state of readiness to detect and respond to changes in stimuli, which are difficult to detect, rare, or which occur at irregular intervals (Ballard, 1996; Cohen, 1993). Vigilance includes sustained attention, controlled attention, efficiency of information processing, and response time (Cohen, 1993). It is the most commonly assessed cognitive construct in OSA research and has been found to be the most consistently affected cognitive domain in apnoea patients, where six out of eight studies reviewed found impairments in the vigilance domain (Aloia et al., 2004). Vigilance tasks are long and tedious, usually lasting 30 minutes or more (Ballard, 1996). Performance tests, used to measure sustained attention in clinical settings, consist mainly of reaction time (RT) tests. The Continuous Performance Test (CPT) is one of these tests used to demonstrate deficits in sustained attention in relation to sleepiness in patients with OSA (Roehrs et al., 1995). The Psychomotor Vigilance Task (PVT) is a similar task used to study the effect of sleep restriction on neurobehavioural alertness while awake (Dinges et al., 1997). It was found that cumulative sleep restriction resulted in slowed reaction times and increased lapse frequency in PVT (Dinges et al., 1997). The Wilkinson Auditory Vigilance Test (Horne, Anderson, &

Wilkinson, 1983; Wilkinson & Houghton, 1975) and the Four Choice Reaction Time Test (FCRTT) (Wilkinson & Houghton, 1975) have also been used to demonstrate the manifest sleepiness of OSA patients.

On the one hand, both simple and choice reaction time tasks have been used to show that there is a strong relationship between a decrease in diurnal vigilance and nighttime sleep disruption in OSA patients (Guilleminault et al., 1988; Kramer, 1988). On the other hand, measures of hypoxemia have also been shown to predict lowered levels of daytime vigilance in moderate to severe OSA patients (Bedard et al., 1991; Roth et al., 1980). It is possible that the differential importance of each contributing factor to a particular neurocognitive deficit changes as the disease condition progresses in severity.

2.7.4 Executive function

Executive functioning refers to the ability to develop and sustain an organized, future-oriented, and flexible approach to problem situations (Eslinger, 1996; Goldberg, 2001). The executive functions allow individuals to adaptively use their basic skills (e.g., core language skills, visual-perceptual ability, and rote memory capacity) in complex and changing external environments (Eslinger, 1996; Goldberg, 2001). The functions of the frontal lobes probably include the ability to plan and coordinate willful action in the face of alternatives, to monitor and update action as necessary, and to suppress distracting materials, or to inhibit non-adaptive actions. While there is considerable agreement that "frontal lobes are the seat of the executive function", the measurement of executive function, as an indication of frontal lobe integrity, is far from simple (Rabbitt, 1997). The broad construct of executive functioning makes it difficult to accurately describe the deficits and to construct a model explaining causes of the impairment (Rabbitt, 1997). Examples of executive functioning include working memory, set shifting, perseveration, planning, abstract reasoning, and verbal fluency (Zillmer & Spiers, 2001). Even more, executive functions are in part supported by adequate attentional skills. Therefore, attentional problems could represent the root cause of executive dysfunction (Verstraeten & Cluydts, 2004).

Executive functioning, which includes processes involved in planning, initiation, execution of goal-oriented behaviour and mental flexibility, is another affected domain in OSA. Some argue that it is the most prominent form of cognitive impairment associated with untreated sleep-disordered breathing and that the

impairment of executive functioning extends to children with sleep apnoea as well as adults (Beebe & Gozal, 2002). Patients with OSA clearly perform consistently more poorly on tests tapping this broad construct when compared with matched controls (Bedard, Montplaisir, Richer, & Malo, 1991; Bedard et al., 1993; Feuerstein, Naegele, Pepin, & Levy, 1997; Naegele et al., 1995; Salorio, White, Piccirillo, & Uhles, 2002; Verstraeten, Cluydts, Verbraecken, & De Roeck, 1996). In more severe cases of OSA, Bedard and colleagues (1991) found a reduction in word fluency, mental flexibility and planning and sequential thinking compared to controls; and the size of deficits increased with the severity of the OSA. Naegele and colleagues (1995) reported that patients with OSA had a significantly decreased ability to initiate new mental processes and to inhibit automatic ones, in conjunction with a tendency to make perseverative errors. Rouleau, Decary, Chicoine, and Montplaisir (2002) found patients with OSA committed significantly more errors and took more time on the Maze Test of Weschler Intelligence Scale for Children-Revised (WISC-R) and they achieved fewer categories in the Wisconsin Card Sorting Test (WCST) and made more perseverative errors. These results extend the findings of the work of Bedard and colleagues (1991) who reported small and large deficits in the number of errors on the WISC-R Maze Test in individuals with moderate and severe OSA respectively. These findings were interpreted as showing dysfunction in planning and executive skills (Bedard et al., 1991; Rouleau et al., 2002).

A number of researchers have argued that memory and attention deficits found in patients with OSA are sleepiness related performance deficits whereas impairment on executive tasks represents persistent brain damage as a result of repeated hypoxemic episodes during sleep (Naegele et al., 1995; Naegele et al., 1998; Decary, Rouleau, & Montplaisir, 2000), with only slight improvement after treatment (Bedard et al., 1993; Montplaisir, Bedard, Richer, & Rouleau, 1992). Using logistic regression, Naeglele and colleagues (1995) found performance on the WCST (correct category shifts and total errors) to be predictive of severity of hypoxemia, and memory and attention tasks (digit span, visual span, and visual learning) to be predictive of severity of apnoeic events.

Several investigators have documented executive dysfunction in OSA and hypothesized that these findings allude to frontal lobe deficits associated with the disorder (Beebe, 2005; Beebe & Gozal, 2002; Jones & Harrison, 2001). Such a theory is supported by animal studies and neuroimaging (Beebe & Gozal, 2002; Beebe, 2005), but foundation functions like attention might also contribute to what is seen to be prominent executive dysfunction. Moreover, the cause of executive

dysfunction is often complex (Verstraeten & Cluydts, 2004).

2.7.5 Learning and Memory

Learning and memory are also impaired in patients with OSA. Learning and memory constitute a broad, complex domain that includes verbal memory, visual memory, short-term memory, and long-term memory. In Aloia and colleagues' (2004) review, 7 out of 11 studies reported poor "memory" performance in general, but only 2 of them (Feuerstein et al., 1997; Naegele et al., 1995) found primary learning impairments, while the remainder of the studies found deficits in free recall. Subjects displayed poor performances on immediate and delayed recall on verbal or visual episodic memory tests (Bedard et al., 1991; Berry, Webb, Block, Bauer, & Switzer, 1986; Block, Berry, & Webb, 1986; Ferini-Strambi et al., 2003; Findley et al., 1986; Salorio et al., 2002; Valencia-Flores, Bliwise, Guilleminault, Cilveti, & Clerk, 1996) and used semantic clustering and semantic cues less efficiently than controls do (Salorio et al., 2002).

Memory performance deficits can be attributed to initial learning, free recall, or forgetfulness, each of which has different implications (Aloia et al., 2004). Standard global tests of episodic memory measure performance in free recall, delayed recall, and recognition, and the subject is asked to remember as much information as possible. However, information encoding and information retrieval all significantly impact on memory test performance (Tulving & Pearlstone, 1966). Poor memory test results could therefore be the consequence of an attentional deficit, a failure to use an efficient memory strategy, an inability to appropriately process information, or a strategic memory retrieval deficit, all of which are contemporarily regarded as aspects of executive functioning. Attention and executive functioning, which are frontally mediated, contribute to impairments in "memory" test performance (Moscovitch et al., 2005).

Consequently, from a poor memory test result, one cannot conclusively determine whether patients have difficulty memorizing new information because of impaired encoding, impaired retrieval, or impaired maintenance or whether they forget more rapidly than controls do. Forced item encoding technique at the time of word presentation can increase the attention paid to the items to memorize whereas comparing the performance from cued and non-cued recall can differentiate poor strategic memory retrieval from poor memory maintenance (Buschke, 1984; Craik & Lockhart, 1972). The research by Salorio and colleagues (2002) represents an

attempt to untangle these processes. They reported that OSA-initiated executive-function deficits adversely impacted memory organization and retrieval, but not long-term storage. They speculated that OSA may disrupt the integration of processes mediated by frontal and distal regions of the brain. Naegele and colleagues (2006) showed that in spite of forced item encoding, patients with OSA showed poorer recall than controls, but they normalized their performance by cueing (i.e., they exhibited a retrieval deficit of memory), and their learning (intact maintenance) and recognition scores, as well as their forgetfulness rates, were not different from those of controls. Overall, the verbal episodic-memory performance pattern observed in OSA patients is consistent with isolated retrieval impairment, with no associated significant storage or consolidation deficit (Naegele et al., 1995, 2006; Salorio et al., 2002). This pattern of episodic-memory retrieval impairment is suggestive of prefrontal, subcortical, or both prefrontal and subcortical dysfunction (Lee, Robbins, & Owen, 2000; Moscovitch et al., 2005).

2.7.6 Working memory

Working memory is an important executive process used for temporary storage, active monitoring, updating, and manipulation of information (Baddeley, 1996). It plays a significant role in complex activities and is considered an integral component of executive functioning (Baddeley, 1996, 2002). Baddeley's working memory model was originally designed to replace the concept of a unitary short-term memory capacity, and comprised three components; the phonological loop, the visuo-spatial sketch-pad, and the central executive (Baddeley, 1986). According to this model, working memory consists of a limited capacity attentional system (central executive) and two subsidiary slave systems (phonological loop, visuo-spatial sketch-pad). Briefly, the functions of the central executive include selective attention, coordinating two or more concurrent activities, switching attention, and retrieval of information from long-term memory (Baddeley, 1996, 2002). The phonological loop temporarily maintains and manipulates speech-based information, while the visuo-spatial sketch-pad holds and manipulates visuo-spatial information. More recently, this model included a fourth component, an episodic buffer, which is controlled by the central executive, provides a workspace for the temporary storage of information and is capable of integrating information from the slave systems and long-term memory in order to create a unitary episodic event or representation (Baddeley, 2000, 2002).

The central executive offers a conceptual framework within which to describe

executive processes (Baddeley, 1996). According to Baddeley's model, the central executive has four primary functions (Baddeley, 1996, 2002). Firstly, the central executive selectively attends to one stream of information while ignoring irrelevant information and distractions. Selective attention impairments result in an inability to attend to targeted stimuli and maintain goal-directed behaviour due to actions being strongly influenced by distractions and intruding thoughts. Secondly, the central executive enables multiple tasks to be completed concurrently by coordinating adequate working memory resources across the various tasks. The third component of the central executive is the capacity to switch attention and response set within a task or situation that requires mental flexibility. This function is important for overriding habitual or stereotyped behaviour, or inhibition of prepotent responses, and impairment will result in rigid performance and perseverative behaviour. The fourth function is the selective and temporary activation of representations from long-term memory as it facilitates responsiveness to the demands of the environment.

While the central executive serves various functions, Baddeley believes further research is required to determine whether these multiple functions are components of a single coordinated system (i.e., unitary controller) or are a cluster of independent processes (Baddeley, 1996). While many of the central executive processes are associated with the prefrontal cortex (Baddeley, 2000; D'Esposito et al., 1995), Baddeley argues that his working memory model is principally a functional model that would exist and be useful even if there proved to be no simple mapping on to underlying neuroanatomy (Baddeley, 1996). The working memory model has been studied extensively and is considered a well-validated theoretical model. While the model accounts for some specific patterns of executive impairments, it is not inclusive of all executive impairments. For example, this working memory model neglects elements of executive functions such as goal setting, volition, reasoning, and planning.

Several researchers have reported significant working memory deficits in patients with OSA, commonly based on the interpretation of a deficient WAIS-R Digit Span test or Digit Span Backward test performance. Redline and colleagues (1997) used WAIS-R Digit Span Backward test to demonstrate working memory deficits in mildly affected individuals. This result further extends the work of Bedard and colleagues (1991) who reported small and large deficits in working memory in individuals with moderate and severe OSA respectively. Greenberg and colleagues (1987) showed that patients with OSA performed significantly worse on the Digit Span task than

healthy controls and patients with other disorders of excessive somnolence. There are a few studies reporting no working memory deficits using Digit Span Forward or Backward tests (Ferini-Strambi et al., 2003) or an experimental spatial working memory task (Lee, Strauss, Adams, & Redline, 1999).

From the viewpoint of Baddeley's (1986) theory of working memory, the forward digit span measures phonological working memory storage capacity, whereas the much more difficult backward digit span is supposed to measure the central executive functioning in addition to temporary memory storage capcity. Lehto (1996) and Morris and Jones (1990) have raised the possibility that patients with OSA may fail on Digit Span backward tests, not necessarily because of a deficit in the central executive, but because they already have difficulties in retaining the digits in working memory (phonological working memory storage capacity). However, the decline in the average digit forward span in patients with OSA relative to controls is small, such that the resulting forward span is still longer than the average digit backward span of controls (as shown for example in the results in Verstraeten, Cluydts, Pevernagie, and Hoffman's (2004) study). This suggests that the slightly reduced working memory capacity is unlikely to be the major limiting factor for the working memory central executive processes in the Digit Span backward performance in patients with OSA. Thus, it is generally valid to infer central executive deficits in monitoring and updating information from the findings of impaired WAIS-R Digit Span backward performance in patients with OSA compared to controls.

Indeed, in Naegele and colleagues' (1995) study, even though the reported backward digit span deficit was not controlled for the forward performance, which was also impaired, the effect size for Digit Span backward was larger than that associated with Digit Span forward. Hence, an interaction effect was evident, which supports the notion of a central executive deficit instead of a pure reduction in attentional capacity.

Naegele and colleagues (2006) found the most compelling evidence for cognitive dysfunction in OSA exists in working memory. The authors used a protocol derived from Baddeley's (1996) working memory model to precisely examine working memory in patients with OSA; that is, the self-ordering pointing paradigm spatial memory test from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Delis, Kramer, Kaplan, & Oben, 1987; Owen, Downes, Sahakian, Polkey, & Robbin, 1990), which has been well validated, and other tests requiring maintenance

and processing of information such as the Auditory Transformed Span (Fournet, Moreaud, Roulin, Naegele, & Pellat, 2000) and the PASAT (Gronwall, 1977). Using these tests, impairment of specific working memory capabilities were demonstrated despite normal short-term auditory and spatial spans (Naegele et al., 2006).

Felver-Grant and colleagues (2007) attempted to parse out the various cognitive functions underlying working memory to determine whether working memory deficits (2-Back Working Memory Task) were primarily the result of learning impairments and free recall impairments (Hopkins Verbal Learning Test-Revised; Shapiro, Benedict, Schretlen, & Brandt, 1999), motor dyscoordination and slowed motor speed (Grooved Pegboard test; Reitan & Wolfson, 1985), or selected executive dysfunction (set switching and divided attention in Trail Making Test part B; Reitan & Wolfson, 1985) by comparing any cognitive changes following 3 months continuous positive airway treatment as well as any interaction effect with high versus low treatment adherence. The 2-Back Working Memory Task is a verbal working memory task in which series of consonants are presented visually, one every 3000 milliseconds. In the 2-Back condition, subjects were told to respond with a "yes" only if the stimulus matched one presented 2 stimuli prior (Felver-Grant et al., 2007). Executive coordination, phonemic buffering, and subvocal phonemic rehearsal were required to successfully perform this task (Felver-Grant et al., 2007). Significant interaction effects between treatment time and adherence group were found in working memory tests (2-Back Working Memory Task and PASAT) only. Other potential subordinate cognitive processes, although all being significantly correlated with the working memory task (2-Back Working Memory Task), demonstrated neither main effect nor interaction effect. This study concluded that the impairments were more commonly seen on complete tests of working memory than on any specific cognitive sub-function. This suggests that this construct may be quite sensitive to the consequences of OSA.

In a functional imaging study, Thomas and colleagues (2005) showed that, on a 2-Back Verbal Working Memory Task, working memory speed in patients with OSA was significantly slower than in healthy controls, and a group average map showed the absence of dorsolateral prefrontal activation, regardless of nocturnal hypoxia. Overall, these findings support the notion of an executive dysfunction in OSA.

2.7.7 Procedural memory

Implicit, or non-declarative, memory is a type of memory that does not enter into

the contents of consciousness (Zillmer & Spiers, 2001). One type of implicit memory is procedural memory, which is a form of learning that cannot be verbalized or is very difficult to verbalize (Markowitz & Jensen, 1999). It refers to the gradual acquisition and maintenance of motor skills and procedures (Decary et al., 2000). It represents the 'how to' of a memory task and though procedural memory is embedded through practice, the skill becomes virtually automatic over time, that is, implicit memory of motor sequences (Markowitz & Jensen, 1999). Decary and colleagues (2000) hypothesized that procedural memory deficits may exist in patients with OSA based on the findings of a deficient acquisition of a complex visuomotor task (Mirror Tracing Task; MTT) in their patients group as compared to controls. Rouleau and colleagues (2002) identified a subgroup of patients with OSA who showed marked difficulties in the initial acquisition of the MTT, and although their performance remained deficient during the training trials, they did improve significantly across trials. Moreover, with additional practice, their performance gradually became indistinguishable from that of healthy controls. A similar pattern was observed in the patients with OSA in a study by Neagele and colleagues (2006). They exhibited poor MTT performance, but progressed significantly from one trial to the next despite remaining consistently below the level of performance of matched controls. Overall, this pattern of result was interpreted as representing impaired behavioural adjustment, which may be related to an inhibition deficit of an overlearned motor response consistent with the notion of executive dysfunction in patients with OSA rather than a primary procedural learning deficit (Rouleau et al., 2002; Neagele et al., 2006).

2.7.8 Psychomotor performance and Motor coordination

Psychomotor performance is a domain that has been assessed less frequently in OSA. However, most studies show patients with OSA to be impaired in psychomotor performance relative to controls (see Aloia et al., 2004 for review). Specifically, OSA patients perform relatively poorer on tests of fine motor coordination (e.g., Purdue Pegboard Test) (Bedard et al., 1991, 1993; Greenberg et al., 1987; Verstraeten et al, 1997), but they perform as well as controls on tests of motor speed only (e.g., Finger Tapping) (Knight et al., 1987; Lojander, Kajaste, Maasilta, & Partinen, 1999; Roehrs et al., 1995; Verstraeten et al., 1997). Overall, there has been relatively little discussion of this psychomotor domain as a primary source of impairment. One explanation for psychomotor difficulties is excessive sleepiness associated with OSA patients (Telakivi, et al., 1988), but this does not account for the discrepancy between tests for fine motor skills and motor speed.

2.7.9 Meta-analysis and implication for the present study – focusing on attentional and executive functioning, and motor coordination

Beebe, Groesz, Wells, Nichols and McGee (2003) used meta-analytic techniques on twenty five neuropsychological effect studies on untreated OSA, generating two complementary sets of effect sizes: (1) a control-referenced data set (comparison of OSA patients to within-study healthy controls) and (2) a norm-referenced data set (comparison of OSA patients to published normative data). Their data did not support a model of generalized neurologic dysfunction, as intelligence and basic verbal and visual-perceptual abilities were found to be resilient to the effects of OSA, whereas vigilance (attention), executive functions, and motor coordination were found to be moderately to markedly negatively affected. Specifically, the domain of executive functioning displayed a moderate to large effect size (.53 in norm-referenced analyses, .73 in control-referenced analyses). The domain of vigilance displayed a very large effect size (1.40 in control-referenced analyses, with no norm-referenced analysis available); however, it should be cautioned to attend to the psychometric aspects of the vigilance tasks due to the minimal normative data available for most of these tasks (Riccio, Reynolds, & Lowe, 2001). Within the control-referenced data set, tests of visual and motor ability displayed moderate to large effect sizes, ranging from .68 to 1.21. In contrast, the effect sizes were generally much smaller and insignificant in the norm-referenced data sets. Post hoc exploration for the source of variability across studies suggested OSA markedly affected fine-motor coordination and drawing but had much less effect on simple motor speed or visual perception.

In the memory functioning domains, the effects of OSA on long-term verbal and visual memory functioning and short-term visual memory were mixed depending on whether the study was a control-referenced or norm-referenced comparison, whereas that on short-term verbal memory was statistically insignificant in both sets of comparison. While the control-referenced data set suggested moderate impairments in both short- and long-term visual memory (d = .56 and .55), the norm-referenced data set yielded small and insignificant effect sizes in both visual memory domains (d < .14). Moreover, both data sets suggested that the impact of OSA on short-term verbal memory was small and insignificant (d < .29). However, whereas the norm-referenced data set indicated moderately impaired long-term verbal memory (d = .53), the control-referenced data set yielded small and insignificant long-term verbal memory effects (d = .27).

Guided by this result, the current study uses a control-referenced and norm-referenced design to explore in detail the subcomponents of attention and executive functions, as well as motor coordination, with the aim of outlining and comparing the cognitive profiles of patients with OSA and shift workers.

The next section will discuss the potential mechanisms and models for OSA, providing further justifications for a focus on attentional/executive functioning, and motor coordination in the current study.

2.8 Potential mechanisms for neurobehavioural dysfunction in OSA

The theoretical models discussed below propose certain mechanisms that may be involved in the relationship between OSA and cognition.

2.8.1 Executive dysfunction model

Beebe and Gozal (2002) posited that OSA is accompanied by significant daytime cognitive and behavioural deficits that extend beyond the effects of sleepiness. The model proposes that sleep disruption (i.e., sleep fragmentation) and blood gas abnormalities (i.e., hypoxemia) prevent sleep-related restorative processes and further induce chemical and structural central nervous system cellular injury. Together, hypoxemia and sleep fragmentation lead to dysfunction of the prefrontal cortex, manifested behaviourally as executive dysfunction (Beebe & Gozal, 2002). The authors used sleep deprivation studies showing a strong relationship to executive functions to provide evidence for their model (e.g., Finelli et al., 2001; Harrison & Horne, 1998; Harrison et al., 2000a). The executive model was one of the first models to take a neurofunctional approach to explaining the cognitive dysfunction seen in OSA. The model also employed both basic and clinical studies as evidence.

Beebe (2005) further developed his heuristic model of the mechanisms underlying cognitive dysfunction in OSA. He summarized those mechanisms that interact with the vulnerable brain regions from the recent advances in the field of OSA research, highlighting specifically the hippocampus (Gozal et al., 2001), the prefrontal cortex (Beebe & Gozal, 2002), subcortical grey matter (Aloia et al., 2004), and white matter (Aloia et al., 2004). The inclusion of the subcortical grey and white matter reflects an appreciation for the potential involvement of the small vessels of the brain (Aloia

et al., 2004; Caine & Watson, 2000). He also hypothesized that the effects of sleep fragmentation and hypoxemia interact in a synergistic manner. Experimentally-induced intermittent hypoxia in a rodent model of OSA and a sleep-deprived rodent model were used to investigate how the mechanism of hypoxemia and sleep fragmentation each impacted on neurobehavioural functions at the systemic and/or cellular level.

Beebe also attended to the possibility that findings in studies of the potential mechanisms of cognitive dysfunction are dependent in part on task demands including skills being assessed, assessment timing, and the amount of environmental support provided (Beebe, 2005). Because the office testing setting often provides considerable structure and support, it is important to get input from informants on the patient's daily functioning to elicit information about emotional and behavioural regulation (Gioia, Isquith, Guy, & Kenwothy, 2000). This addition shows an appreciation for the complexity of executive dysfunction and attentional deficits as multifactorial and the importance of ecological validity in tests for executive and attention functions.

Beebe's heuristic model also provides a more complete framework to better capture the wide variation in neurobehavioural outcome seen by practicing clinicians (Beebe, 2005). The model included risk and resilience factors which are potential moderators of morbidity that may alter the nature or severity of neurobehavioural deficits resulting from OSA. For example, in accordance with the "cognitive reserve" principle, which states that individuals with highly functioning brains or cognitive strategies (high premorbid cognitive ability) are less vulnerable to cognitive decline due to the impact of brain injury or disease (Stern, 2002), individuals with high intelligence scores appear to be at less risk for OSA-related attention deficits (Alchanatis et al., 2005). Also, a functional MRI experiment found that healthy adults who showed little to no decline in working memory performance after sleep deprivation displayed greater activation of relevant brain systems while rested than did those whose working memory skills degraded with sleep deprivation (Mu et al., 2005a), suggesting that attentional-controlling and central executive systems are more effective in sleep deprivation-resilient individuals than in sleep deprivation-vulnerable individuals.

2.8.2 Attentional deficits model

Another proposed model is the attentional model. Verstraeten and Cluydts (2004) have made a case that higher-order cognitive dysfunction in OSA can be explained by the impairment of basic attentional processes and slowed mental processing.

The authors proposed a theoretical model of neurocognitive functioning marked by the hierarchical ordering of cognitive processes such that impairment of more basic attentional and lower-level cognitive processes can lead to the appearance of higher-order cognitive dysfunction. To distinguish the influence of 'lower-level' alertness on 'higher-level' executive attention, relevant theoretical concepts (Mesulam, 1981, 1990; Posner & Peterson, 1990; Posner, 1992; Posner & DiGirolamo, 1998; Posner & Raichle, 1994), and an integrated model of arousal, attention, and executive function (LaBerge's triangular circuit theory of attention; LaBerge, 1995, 1997, 2000) were presented. Sleep apnoea patients' cognitive performance is characterized by attentional capacity and vigilance deficits and time-on-task decrements. Although some studies have suggested executive attentional dysfunction, pervasive effects of sleep-dependent arousal on higher cognitive function were not fully taken in account in the sleep apnoea literature. Based on the hierarchical model of executive control of attention (Verstraeten & Cluydts, 2004), they made the case that performance on executive attention tasks in patients with OSA needs careful analysis and interpretation, given that potentially profound effects of sleep disruption on arousal, basic processing speed, and attentional ability. The conclusion of their paper is that investigators should consider developing studies that allow them to systematically control for attentional functions in the assessment of higher-order cognitive ability.

Briefly, the hierarchical model of executive control of attention (Verstraeten & Cluydts, 2004) is that, based on the theories of arousal, attention, and executive control, an underlying level of alertness is in the loop of higher-order (executive) attentional processes. Empirical studies on the waking neural substrates of attention after sleep deprivation were provided as evidence. For example, thalamic deactivation has been found after 24 to 35 hours of sleep deprivation and was related to objective and subjective sleepiness (Thomas et al., 2000), vigilance performance decrements (Thomas et al., 2000; Wu et al., 1991), and serial subtraction decreases (Thomas et al., 2000; Drummond et al., 1999). These sleep deprivation studies also demonstrated significant decreases of brain activity in

prefrontal and posterior parietal cortices, which is in line with results showing activations within a right lateralized fronto-parietal-thalamic-brainstem network during alertness and sustained attention (Kinomura, Larsson, Gulyas, & Roland, 1996; Sturm et al., 1999). The one lacking component of this work is the provision of data to support any specific mechanisms related to sleep fragmentation or hypoxemia.

2.8.3 Microvascular theory

The microvascular theory as a model for cognitive dysfunction in OSA was first put forth by Aloia and colleagues in 2004, owing in large part to the work of Somers and colleagues (Lanfranchi & Somers, 2001). Aloia and colleagues (2004) culled mechanisms of dysfunction from the cardiovascular literature and proposed that since cardiovascular dysfunction was a well-supported consequence of OSA it was reasonable that vascular compromise might also exist in the brain. The Lanfranchi and Somers (2001) model suggests that the hypoxemia seen in OSA results in a number of autonomic, humoral, and neuroendocrine responses that can lead to vasculopathy. Together, this cascade of responses in OSA, involving an increase in sympathetic vasoconstriction together with a decrease in vascular protective mechanisms, results in profound, and possibly lasting, changes to the structure and function of blood vessels. In addition, small vessels may be more susceptible to hypertension in general as well as to these mechanisms of vasculopathy.

The literature on hypoxia (Caine & Watson, 2000) indicates that hypoxemia would preferentially affect regions of the brain that were metabolically active during the event and fed by small vessels. Damage to the small vessels may result in a predictable pattern of cognitive dysfunction associated with small vessel brain disease. The pattern would involve deficits in motor speed and coordination, executive function, memory impairment, and some problems with attention and mental processing speed. After a review of the literature, Aloia and colleagues (2004) argued that this pattern of cognitive dysfunction was indeed present in OSA and may represent microvascular disease.

Empirical evidence suggesting an association between apnoea severity and small vessel ischemic brain disease (Aloia et al., 2001; Colrain, Bliwise, DeCarli, & Carmelli, 2002) were provided. Colrain and colleagues (2002) demonstrated a relationship between severity of subcortical white matter hyperintensities and level of hypoxemia in 41 identical twin pairs. The presence of these hyperintensities with the subcortical grey and deep white matter suggests the involvement of endothelial

damage of small blood vessels in these regions, where vascular hypoperfusion is more common. Aloia and colleagues (2001) found that severe OSA had more subcortical white matter hyperintensities on brain MRI than had cases with minimal apnoea; moreover, there was a trend towards a negative association between subcortical hyperintensities and free recall of a word list. Consistent with these findings, Kamba and colleagues (1997, 2001) used magnetic resonance spectroscopy to show lower cerebral metabolism in the white matter, but not in the cortex, in participants with moderate to severe OSA compared with participants with mild OSA; and this relationship was independent of age.

Since the publication of this review, several studies have been published both to support and to refute this model. One supportive study identified a subgroup of OSA patients with cognitive dysfunction that corresponded to a pattern seen in Multiple Infarct Dementia (MID). Antonelli Incalzi and colleagues compared older individuals with sleep apnoea to patients with either Alzheimer's Disorder or MID on a battery of neuropsychological tests (Antonelli Incalzi et al., 2004). This study suggested that the cognitive profile of apnoea is most like that seen in MID. They related this finding to the probable involvement of similar subcortical brain regions in apnoea, a relationship that is consistent with the microvascular theory of OSA (Aloia et al., 2004; Lanfranchi & Somers, 2001).

One primary limitation of the model was that it did not attend strongly to the differential effects of sleep fragmentation and hypoxemia. The model is promising in that it is parsimonious and incorporates a known mechanism of dysfunction in OSA, vascular compromise, into the cognitive realm. Further research, however, is needed to defend, refute, or expand the model and to relate its effects to complaints of fatigue and sleepiness.

2.9 Rationale behind the choice of neuropsychological sub-functions studied

2.9.1 Posner and Peterson's (1990) model of attention

The major concern with established measures of "attention" is that the majority of them are not based on any particular theory of attention (Sohlberg & Mateer, 1989), as evidenced by the fact that one measure can be regarded as a test of selective attention by one authority but also as a test of sustained attention by another (Shum et al., 1990).

One of the reasons might be that there has been no well-validated and comprehensive attentional model available for the development of attentional tests until Posner and Peterson (1990) proposed their model of attention, based on findings of neuroimaging and lesion studies (Posner, Cohen, & Rafal, 1982; Posner, Inhoff, Friedrich & Cohen, 1987; Posner, Walker, Friedrich, Rafal, 1984). Indeed, Positron Emission Tomography Scan (PET) studies have provided the strongest support that attention is fractionated into different supramodal systems; and that such systems have distinct neuro-anatomical bases. Posner and Peterson (1990) have argued that attention consists of at least three separate systems: (1) a selection system responsible for selecting relevant stimuli and inhibiting irrelevant ones; (2) a vigilance system responsible for maintaining readiness to respond; and (3) an orientation system responsible for engaging, moving and disengaging attention.

2.9.2 A theory-based test of attention with ecological validity

For the present study, the Test of Everyday Attention (TEA) was selected as the major tool for a number of reasons. Notably, it attempts to address the major weaknesses of the abovementioned established tests of attention; namely their multifactorial nature, their poor ecological validity, and their lack of any theoretical basis (Bate, Mathias, & Crawford, 2001).

The TEA is one of the few tests based on an established theory of attention that also satisfies ecological validity. The development of the TEA (Robertson, Ridgeway, & Nimmo-Smith, 1994) leans heavily on Posner and Peterson's (1990) model of attention, while attempting to engage the interest of the subject by using relatively familiar materials, such as maps, telephone directories, and hotel elevators, that approximate everyday activities, thus meeting requirements for ecological validity.

The TEA embeds its subtests in the format of mock holiday activities using materials that simulate real-life tasks. This is an asset to clinicians and patients because a major factor predicting satisfaction with neuropsychological assessment is the perceived relevance of the tests (Bennett-Levy, Klein-Boonschate, Batchelor, McCarter, & Walton, 1994). Furthermore, profile analysis is possible using tables developed by Crawford, Sommerville, & Robertson (1997).

The TEA attempts to measure the first two aspects of Posner and Peterson's (1990) attentional systems, namely, the selective system and the vigilance system, which correspond to the selective attention factor and the sustained attention factor

respectively. It also attempts to measure different aspects of the selection system, including attentional switching and divided attention (Roberston et al., 1994). This is in accordance with the theoretical postulate that attention is fractionated into different supramodal systems, which have distinct neuro-anatomical bases. Robertson and colleagues (1994) have highlighted the importance of including dual task conditions to measure divided attention, suggesting that such conditions have the potential to unmask attentional deficits that would otherwise go undetected, and are highly sensitive in clinical populations. Overall, the test-retest coefficients of subtests are also substantially high (Strauss, Sherman, & Spreen, 2006). On these grounds, the current study employed the TEA to investigate the subcomponents of attention and executive function.

2.9.3 Latent variables of traditional executive function tasks

Many executive function tasks are plagued with "task impurity" problems, so that they have low test-retest or within-subject reliability, reflecting the fact that executive functions rely on non-executive cognitive abilities as they are after all "coordinators" and also suggesting that the use of multiple strategies may be confounding the results. To mitigate these problems, Miyake et al. (2000) adopted a unique statistical approach known as latent variable analysis or structural equation modeling. This approach allows one to test a small number of hidden variables which are thought to be responsible for the variation seen across a number of manifest variables.

Miyake et al. (2000) examined putative executive function measures (WCST, Tower of Hanoi (TOH), Random number generation (RNG), operation span, dual tasking) (N=137, college students) with Confirmatory Factor Analysis (CFA). This analysis indicated there are three moderately correlated, but discriminable factors underlying these putative executive function measures – (1) mental set shifting ('Shifting'), (2) information updating and monitoring ('Updating'), and (3) inhibition of prepotent responses ('Inhibition'). They concluded that set-shifting, updating, and inhibition of prepotent responses are the three latent variables underlying complex "frontal lobe" or executive function tasks. The first latent variable of executive function is the 'Shifting' sub-function, which refers to the ability to switch attention back and forth between multiple responses, either in a dual task paradigm or in a task requiring different responses under different conditions. The second 'Updating' sub-function refers to the monitoring and coding of incoming information for relevancy, and then updating Working Memory representations with more relevant

information. Finally, the 'Inhibition' sub-function refers to the deliberate suppression of dominant or prepotent responses.

Structural Equation Modeling (Miyake et al., 2000) indicated these three factors contribute differentially to each of the complex executive function measures. The 'Set Shifting' factor contributed most to the WCST performance, the 'Inhibition' factor contributed most to TOH, and both the 'Inhibition' and 'Updating' factors contributed to RNG. The 'Updating' factor also contributed to operation span scores.

2.9.4 Rationale behind the selection of attentional and executive function measures

2.9.4.1 Measuring Attentional functioning

As discussed, attention can be fractionated into different supramodal systems which have distinct neuro-anatomical bases. To date, several aspects of attention can be distinguished and have been investigated using traditional tests of attention in the clinical literature. They include selective attention (or concentration), sustained attention (or vigilance) and divided attention as measured by dual tasks (Sohlberg & Mateer, 1989; van Zomeren & Brouwer, 1990). The current study followed this classification, while using instead a well normed, theory based test battery for attention, which also strives for enhanced ecological validity and minimization of the multifactorial problems. Hence, it is reasonable to expect there is not much overlapping with the subcomponents of executive function.

These constructs not only provide continuity in comparison with other research, but are also readily appreciated by the general population and can be translated into practical situations or rehabilitation goals. To recapitulate, the current study will investigate selective attention, sustained attention, and divided attention by using the corresponding subtests from the well-validated and theory-based TEA (Roberston et al., 1994). Visual selective attention will be measured by the Map Search subtest and the Telephone Search subtest; while the auditory selective attention will be measured by the Elevator with Distraction subtest of TEA. Sustained attention will be measured by the Lottery subtest of TEA. Divided attention will be measured by the Telephone Search While Counting (Dual Task) of TEA.

By comparing the results of a principle component analysis and correlational analysis

on TEA subtests and other conventional attentional and executive functions tests in three studies (Roberston et al., 1994; Robertson, Ward, Ridgeway, & Nimmo-Smith, 1996; Chan, Hoosain, & Lee, 2002; Bate et al., 2001), it is found that the Map Search and Telephone Search subtests are consistently associated with a Visual Selective Attention factor; the Lottery subtest is consistently associated with a Sustained Attention factor (or Vigilance); the Telephone Search while Counting (dual task decrement) is associated with a Divided Attention factor. Visual Elevator (number correct) (Roberston et al., 1996) and (time) (Chan et al., 2002), Elevator Counting with Reversal and Elevator Counting with Distraction (Bate et al., 2001) are associated with Attentional Control/Switching factor, which was classified as a Set Shifting component of executive function in the present study.

Details of individual subtests can be found in the methodology section.

2.9.4.2 Measuring Executive Functions

Verstraetan and Cluydts (2004), holding a hierarchical view on cognitive functions, have argued for designing studies that systematically control for "lower-order" functions in the assessment of presumed "higher-order" executive functions. However, Elliot (2003) stated that while the prefrontal cortex plays a key monitoring role in executive functioning, other brain areas are also involved. There is an emerging view that executive function is mediated by a dynamic and flexible modulation of neuronal interactions, and this modulation is task-dependent and condition specific, involving a distributed network. In this connectivist view (Royall et al, 2002), executive functions supervise and therefore also rely on non-executive cognitive abilities. In this regard, controlling for a "lower-order" function may be arbitrary from the connectivist's perspective. It is likely that once the variance of the so called non-executive abilities are statistically controlled for, what the executive tests set out to measure may be masked or lost.

Being aware of the "impurity" problems of traditional executive function tasks, the current study attempted to explore the latent variables of executive function by choosing the most validated test(s) for each latent variable.

The set-shifting sub-function was measured by the two subtests of TEA, Visual Elevator and (Auditory) Elevator Counting with Reversal, validated by confirmatory factor analyses (Bate et al., 2001; Chan et al., 2002; Roberston et al., 1996) as measuring the attentional switching factor, an alternative term for set-shifting.

The updating abilities are considered to be essential to working memory (Friedman et al., 2006). To investigate the updating sub-function of executive function, the Verbal Working Memory and Symbolic Working Memory subtests from the Wide Range Assessment of Memory and Learning – Second Edition (WRAML-2; Sheslow & Adams, 2003) were selected, taking advantage of the exceptionally wide age norms. The most commonly used working memory task in clinical research is arguably the Digit Span Backward test. The Symbolic Working Memory subtest resembles the Digit Span Backward test but involves reordering of numbers and letters according to numerical and alphabetical order. Verbal working memory is rarely studied in clinical populations. It is interesting to explore whether there are any differential deficits between the verbal and symbolic working memory function in our sample of patients with OSA and shift workers, as it certainly bears functional significance in daily life.

Finally, to study the third executive component, inhibition of prepotent responses, the well normed Golden version of the classical Stroop Interference task (Golden, 1978) was chosen.

2.9.5 Maze learning test to specifically explore the effect of intermittent hypoxia hypothesis and to capture other aspects of executive functions

Finally, because Row and colleagues (2003) demonstrated spatial learning deficits in the Morris water maze (Morris, 1984) in a rodent model of sleep-disordered breathing, by exposure to IH, it was considered worthwhile to compare performances on a maze learning task, such as Austin Maze, between patients with OSA and shift workers, since only the former are affected by hypoxemia. The current study included the Austin Maze, which is a spatial learning task based upon Milner's earlier work examining maze learning following brain lesions (Milner, 1965). The Austin Maze is a complex spatial learning task, which was originally promoted as a measure of planning, error utilization and behavioural regulation. It was found that patients with frontal lobe lesions performed poorly on this test (Milner, 1965; Walsh & Darby, 1994). Crowe and colleagues (1999) found that the Austin Maze measures visuospatial abilities and visuospatial memory in healthy populations. Hence, it is likely that these abilities are the major determinants of performance among cognitively intact individuals, because small amount of inter-individual variations in executive functioning are unlikely to affect the maze learning process significantly.

On the other hand, the complexity of the task could be expected to unveil executive dysfunction in the clinical populations, whereby too many executive errors would produce confusion which in turn would inhibit effective learning. As such, impairments in executive control abilities will interfere with the cumulative learning process, thereby overshadowing the overall performance on complex maze learning in the clinical populations.

2.9.6 Overall goals of the current study as a function of the choice of neuropsychological sub-functions and their corresponding tests

In the literature, clinical studies often select a few cognitive tests and, based on the results generated, comment on the possible deficits in certain cognitive domains. However, what each of the individual traditional tests is measuring is often not well validated by factor analysis and many of them are likely to be multifactorial, sometimes resulting in the one test being used by different authors to draw conclusions about different functional domains without any clear theoretical backup. The conclusions so drawn are therefore often at a relatively general level, lacking the much needed refinement in concept.

The current study adopted a top-down theory-driven approach by firstly identifying the key sub-functions of attention and executive function, based on a careful review of the relevant models and theories. Wherever possible, tests used to measure each sub-function have been validated by CFAs. The rest of the chosen tests are consistently used by researchers measuring the same construct. The overall outcome would be laying out a matrix of tests, with each test neatly representing one of the sub-functions of attention and executive function, and these sub-functions although not totally independent of one another are nevertheless clearly separable based on the contemporary theories. By doing so, it hoped that the current operationalization can achieve a fair comparison between the measured attentional and executive sub-functions without the need to control for “lower-order” attentional functions as advocated by Verstraetan and Cluydts (2004).

In summary, the current study measured selective attention, sustained attention, divdided attention, shifting, verbal and symbolic working memory, inhibition, and other executive functions including planning, error utilization, and behavioural regulation in healthy controls, shift workers and patients with OSA.

The goals are three fold: First, to compare the profiles of attention and executive

functions between patients with OSA and shift workers, aiming to shed light on the contribution of different pathophysiologies in each condition; second, to clarify any deficits in the attention and executive function domains at a subcomponent level; and third, by putting the sub-functions from each domain squarely against each other, the present study aims to contribute to the debate about the existence of executive dysfunction in the two clinical populations.

2.10 Rationale for the current study

Shift work has been associated with the experience of driver sleepiness. OSA is another condition associated with a significantly increased frequency of falling asleep while driving and increased risk of RTAs. Although sleepiness while driving is thought to be an important cause of accidents, recent evidence suggests that actually falling asleep is much less likely to be the causal event than making attentional and judgment errors. There is evidence suggesting that perceived sleepiness, the ESS score, and the objective sleepiness measured in the MSLT are poor predictors of the accident rate in sleep apnoea patients. Generally speaking, ESS was not correlated with driving simulator performance in OSA patients.

On the other hand, adult OSA is also associated with occupational and social failures related to poor planning, disorganization, diminished judgment, rigid thinking, poor motivation, and affective lability. Childhood OSA is associated with school failure and behaviours reminiscent of attention-deficit/hyperactivity disorder (ADHD). These neuropsychological deficits cannot be subsumed under the term sleepiness, as some research revealed that neuropsychological deficits correlate better with polysomnographic sleep data than with self-reported or objectively measured sleepiness. It has been demonstrated that such deficits may persist despite treatment-related resolution of daytime sleepiness. Based on this evidence, it can be reasoned that neuropsychological deficits of OSA are important mediators leading to occupational and social failures as well as increased driving risk, independent of daytime sleepiness.

If sleep disorders are frequently associated with accidents, and occupational and social failures, but daytime sleepiness does not provide a satisfactory explanation, it could be that factors such as sleep fragmentation and hypoxemia in OSA and sleep deprivation secondary to sleep cycle disruption in shift work may underlie both daytime sleepiness and cognitive impairment. In addition, it is the latter which may be the major cause of performance and judgment errors, and which in turn may

mediate the higher accident rate and other occupational and social failures described. Hence, it is crucial to have a better understanding of these mediating neurocognitive factors. This constitutes the first aim of the current study.

2.10.1 Aim 1

The current study uses a control-referenced and norm-referenced design to explore in detail the subcomponents of attention/executive functions and motor coordination of patients with OSA and shift workers with an aim to outline and compare the profiles of any cognitive impairment between these groups.

Furthermore, the study design allows the establishment of an unambiguous matching of individual subcomponents of cognitive deficits in the clinical populations with one or more validated standardized tests. These tests come with reliable norm references and are relatively easy to administer in a clinical setting. This will also facilitate future research about how each of these subcomponents of cognitive deficits may play the mediating role in increased automobile accidents and other occupational/social impairments in patients with OSA and shift workers.

Only patients with OSA suffer nocturnal intermittent hypoxemia, but both patients with OSA and shift-workers are affected by sleep deprivation, though of varying magnitudes and different underlying causes, which are sleep fragmentation and disruption of circadian cycle/chronic partial sleep losses respectively. Hence, it warrants a detailed comparison of the different aspects of attention and executive functions between the two groups, leading to the second and third aims of the study.

2.10.2 Aim 2

The current study aims to provide insights into the differential contributions of chronic sleep fragmentation and hypoxemia to neuropsychological impairment in OSA by comparing and contrasting the characteristic neuropsychological profiles resulting from the single factor of sleep deprivation (secondary to chronic disruption of the sleep cycle) in shift workers versus that resulting from the compounding effect of sleep deprivation (resulting from sleep fragmentation) and intermittent hypoxemia in patients with OSA.

2.10.3 Aim 3

From the literature review, there are three models attempting to explain the neurocognitive deficits in OSA, with emphases on (1) prefrontal cortex dysfunction and executive dysfunction, (2) deficits in attentional control, and (3) microvascular changes in subcortical brain structures. Since the measures in the present study cover all the relevant constructs presented in each model, it provides an opportunity to evaluate the explanatory power of these models in relation to the OSA sample population of the present study.

Neurocognitive testing is common in studies involving OSA. The cognitive sequelae of the disorder have been repeatedly discussed, but are not always consistent across studies (e.g., Aloia et al., 2004; Engleman, Kingshott, Martin, & Douglas, 2000; Sateia, 2003). Some inconsistencies may be associated with the heterogeneity of the samples, while others may be the result of the different tests utilized in the studies. Too few studies utilize the same cognitive tests to draw any definitive conclusions as to the degree or pattern of cognitive deficits in OSA. This, in turn, limits the potential use of neuropsychological assessment in clinical setting to inform medical decisions.

However, like the medical consequences of OSA, daytime neuropsychological deficits should also be considered when making medical decisions. In addition to diminishing immediate quality of life, the neuropsychological effects of OSA can have long-term impacts by the accumulation of scholastic, occupational, and relationship problems. It follows that there is a demand for a neuropsychological battery designed to directly assess attention/vigilance, executive functions and motor functioning in an efficient way in clinical setting such that pre- and post-treatment assessment can be done to determine the degree of improvement of the cognitive impairment implicated in quality of life and safety to drive of patients.

In view of this, the fourth aim of the current study is as follows.

2.10.4 Aim 4

The present research aims to develop a clinically efficient neuropsychological test battery that simultaneously examines the theoretically discrete components of attention, executive and working memory functions, as well as fine motor control. Also, all tests are standardized with reliable norm references. They are easy to administer in a clinical setting; and many of them also meet the requirements for ecological validity.

This test battery has the potential to facilitate the comparison of results across research literature and the sharing of clinical data; moreover, it permits the testing of moderator effects in meta-analysis. The differential effects of treatment on discrete components of attention, executive and working memory sub-functions can be systematically monitored across the treatment period. This information is potentially important in health education as it is directly related to patients' well-being and occupational and social adjustment. Patients should benefit from the easy communication of these sub-functions for informed medical decisions.

2.11 Research design

The present research is a norm-referenced and matched control study of the subcomponents of attention and executive function in patients with OSA and shift workers using a neuropsychological test battery, in which the majority of the tests have well established validity, reliability and standardized norms. The aim of this study is to clarify the profile of cognitive deficits in the attention and executive function domains at a subcomponent level for each clinical group; and by putting the discrete sub-functions from each domain squarely against each other, we aim to contribute to the debate about the existence of executive dysfunction in these two clinical populations and the comparison of the existing pathophysiological models for OSA.

Furthermore, while both shift workers and patients with OSA suffer from various degree of sleep deprivation, the latter also suffer from IH or hypoxemia during sleep (see Figure 1).

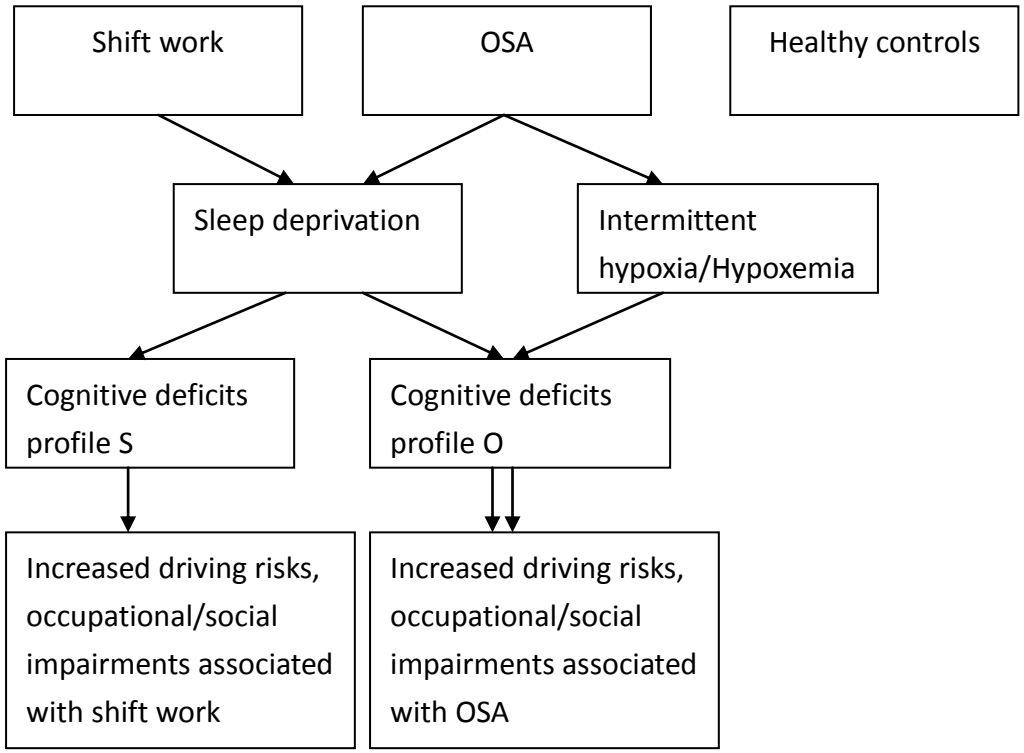


Figure 1. A highly simplified representation showing the relationships among the pathophysiological mechanisms, the cognitive deficits profiles and the functional impairments in the participant groups.

It was assumed that the additive and/or synergistic effect of these two pathophysiological mechanisms (intermittent hypoxemia and sleep deprivation due to sleep fragmentation) operates in any of the cognitive dysfunctions seen in patients with OSA; while only sleep deprivation effects may be shown in our sample of shift workers, as the circadian misalignment in shift workers appears to be not the major pathophysiological factor independent of chronic sleep loss and the heterogeneity of the shift work schedules was not controlled for in the present study.

Hence, by comparing and contrasting the profiles of attention and executive functions between patients with OSA and shift workers, the present study aims to shed light on the relative contribution of different pathophysiologies, sleep deprivation and intermittent hypoxemia, to the cognitive deficits in OSA.

2.11.1 Hypothesis 1

Sleep deprivation studies have demonstrated deficits in sustained attention/vigilance, selective or focused attention/concentration, and divided attention. IH or hypoxemia in rodent model of OSA was shown to result in neurotoxicity, and hypoxemia may also be implicated in microvascular changes in the brain often associated with problems of attention. While both shift workers and patients with OSA suffer from various degrees of sleep deprivation, the latter also suffer from intermittent hypoxia or hypoxemia during sleep.

It was assumed that the additive and/or synergistic effect of these two pathophysiological mechanisms (intermittent hypoxemia and sleep deprivation due to sleep fragmentation) operates in any of the cognitive dysfunctions seen in patients with OSA; while only sleep deprivation effects may be shown in our sample of shift workers, as the circadian misalignment in shift workers appears to be not the major pathophysiological factor independent of chronic sleep loss and the heterogeneity of the shift work schedules was not controlled for in the present study.

Hence, it was hypothesized that shift workers as group will show a significant reduction in some of the attentional sub-functions compared to healthy controls, and that patients with OSA will exhibit a more pervasive pattern of attentional dysfunction as measured by the attentional tests, in terms of the number of subdomains affected and the level of severity, compared to shift workers.

2.11.1.1 Hypothesis 1a

It was hypothesized that shift workers would perform more poorly on some of the tests of attention subdomains, including sustained attention, selective attention, or divided attention, than healthy control participants.

Operationalization

Shift workers will perform significantly poorer than healthy controls on one or more of the attentional measures: Visual Selective Attention (Map Search subtest, Telephone Search subtest), Auditory Selective Attention (Elevator Counting with Distraction), Sustained Attention (Lottery subtest), and Divided Attention (Telephone Search While Counting subtest).

2.11.1.2 Hypothesis 1b

It was hypothesized that patients with OSA would perform more poorly on some of the tests of attention subdomains, including sustained attention, selective attention, or divided attention, than shift workers and healthy control participants.

Operationalization

Patients with OSA will perform significantly poorer than shift workers and healthy controls on one or more of the attentional measures: Visual Selective Attention (Map Search subtest, Telephone Search subtest), Auditory Selective Attention (Elevator Counting with Distraction), Sustained Attention (Lottery subtest), and Divided Attention (Telephone Search While Counting subtest).

2.11.1.3 Hypothesis 1c

It was hypothesized that patients with OSA would have a more pervasive pattern of poor performance on tests of attentional subdomains than shift workers, i.e., patients with OSA would demonstrate poor performance in more attention subdomains than shift workers, and in some of those domains that shift workers showed poor performance, patients with OSA will perform even more poorly.

Operationalization

Compared to shift workers, patients with OSA will perform significantly more poorly than healthy controls on more attentional measures: Visual Selective Attention (Map Search subtest, Telephone Search subtest), Auditory Selective Attention (Elevator Counting with Distraction), Sustained Attention (Lottery subtest), and Divided Attention (Telephone Search While Counting subtest).

Among those attentional measures whereon shift workers showed reduced performance compared to healthy controls, on one or more of them, patients with OSA will have significantly poorer performance than shift workers.

2.11.2 Hypothesis 2

Sleep deprivation studies have demonstrated deficits in set shifting, symbolic and verbal working memory, and inhibition of prepotent responses. IH or hypoxemia in a rodent model of OSA has been shown to result in neurotoxicity, and hypoxemia may also be implicated in microvascular changes in the brain, specifically in the prefrontal cortex, subcortical gray matter and basal ganglia, often associated with executive dysfunction.

While both shift workers and patients with OSA suffer from various degrees of sleep deprivation, the latter also suffer from IH or hypoxemia during sleep.

It was assumed that the additive and/or synergistic effect of these two pathophysiological mechanisms (sleep deprivation due to sleep fragmentation and intermittent hypoxemia) operates in any of the cognitive dysfunctions seen in patients with OSA; while only sleep deprivation effects may be shown in our sample of shift workers, as the circadian misalignment in shift workers appears to be not the major pathophysiological factor independent of chronic sleep loss and the heterogeneity of the shift work schedules was not controlled for in the present study.

Hence, it was hypothesized that shift workers as a group will show a significant reduction in some of the executive sub-functions compared to healthy controls, and that patients with OSA will exhibit a more pervasive pattern of executive dysfunction, among set shifting, verbal and symbolic working memory, inhibition of prepotent responses, planning, error utilization, and behavioural regulation, in terms of the number of subdomains affected and the level of severity, compared to shift workers.

2.11.2.1 Hypothesis 2a

It was hypothesized that shift workers would perform more poorly on some of the tests of executive function subdomains, including set shifting, verbal and symbolic working memory, inhibition of prepotent responses, planning, error utilization and behavioural regulation, than healthy control participants.

Operationalization

Shift workers will perform significantly poorer than healthy controls on one or more

of the executive measures: Set Shifting (Visual Elevator subtest accuracy and timing scores, Elevator Counting with Reversal subtest), Working Memory (Verbal Working Memory subtest, Symbolic Working Memory subtest), Inhibition of Prepotent Responses (Stroop Test Interference score), and Planning, Error Utilization and Behavioural Inhibition (Austin Maze total number of errors at 10th trial and total time at 10th trial).

2.11.2.2 Hypothesis 2b

It was hypothesized that patients with OSA would perform more poorly on some of the tests of executive function subdomains, including set shifting, verbal and symbolic working memory, inhibition of prepotent responses, planning, error utilization and behavioural regulation, than shift workers and healthy control participants.

Operationalization

Patients with OSA will perform significantly more poorly than shift workers and healthy controls on one or more of the executive function measures: Set Shifting (Visual Elevator subtest accuracy and timing scores, Elevator Counting with Reversal subtest), Working Memory (Verbal Working Memory subtest, Symbolic Working Memory subtest), Inhibition of Prepotent Responses (Stroop Test Interference score), and Planning, Error Utilization and Behavioural Inhibition (Austin Maze total number of errors at 10th trial and total time at 10th trial).

2.11.2.3 Hypothesis 2c

It was hypothesized that patients with OSA would have a more pervasive pattern of poor performance in tests of executive function subdomains than shift workers, i.e., patients with OSA would have poor performance in more executive function subdomains than shift workers.

Operationalization

Compared to shift workers, patients with OSA will perform significantly more poorly than healthy controls on more executive function measures: Set Shifting (Visual Elevator subtest accuracy and timing scores, Elevator Counting with Reversal subtest), Working Memory (Verbal Working Memory subtest, Symbolic Working Memory

subtest), Inhibition of Prepotent Responses (Stroop Test Interference score), and Planning, Error Utilization and Behavioural Inhibition (Austin Maze total number of errors at 10th trial and total time at 10th trial).

Among those executive function measures that shift workers showed reduced performance compared to healthy controls, on one or more of them, patients with OSA will have a significantly poorer performance than shift workers.

2.11.3 Hypothesis 3

Based on a review of the relevant models and theories of the sub-functions of attention and executive function, we have identified discrete and validated constructs within the attentional and executive domains. The majority of these discrete subdomains are matched with theory based tests validated by confirmatory factor analyses as measuring that particular construct. The rest of the tests are consistently used by researchers measuring the same construct. It was hypothesized that the overall outcome would be the laying out of a matrix of tests, with each test neatly representing one of the sub-functions of attention and executive function, and these sub-functions although not totally independent of one another are clearly separable based on the contemporary theories.

That is, it was hypothesized that attentional function and executive function measured in a theory driven design are separable constructs and they are not in a simple hierarchical relationship (i.e. attention as lower level cognitive function in relation to executive functions); hence, attentional dysfunction and executive dysfunction, if identified, can be dissociated from one another in either shift workers or patients with OSA.

Operationalization

In either shift workers or patients with OSA, a pattern of dissociation between attentional dysfunction and executive dysfunction will be observed, that is, either a pattern that many executive sub-functions will be reduced, sparing many attentional sub-functions, or a reversed pattern that many attentional sub-functions will be reduced, sparing many executive sub-functions.

2.11.4 Hypothesis 4

Microvascular theory (Aloia et al., 2004; Lanfranchi & Somers, 2001) described microvascular changes in the brain in the prefrontal cortex, subcortical gray matter and basal ganglia in patients with OSA, and posited that the cognitive profile of OSA would resemble that seen in Multiple-Infarct Dementia. Because of the involvement of the subcortical brain structures and the associated frontostriatal pathways, this model predicts a pattern of executive dysfunction associated with motor incoordination (Anderson, Northam, Hendy, & Wrennall, 2001). Moreover, Row and colleagues (2003) demonstrated spatial learning deficits in a maze learning task in a rodent model of sleep-disordered breathing, by exposure to IH. In shift workers, there is no theoretical reason to predict a similar pattern of cognitive deficits.

It was hypothesized that patients with OSA will display a more pervasive pattern of executive dysfunction, involving motor incoordination as well as deficits in other executive subdomains (including planning, error utilization and behavioural inhibition), and these effects will be manifested as impaired performance on complex spatial learning task, such as maze learning. The Austin Maze is a complex spatial learning task considered sensitive to deficits in Planning, Error Utilization and Behavioural Inhibition, as well as Motor Coordination.

<u>Operationalization</u>

Patients with OSA will demonstrate significantly poorer performance than shift workers and healthy controls on Austin Maze Learning Test (Austin Maze total number of errors at 10^{th} trial and total time at 10^{th} trial). There would be no significant difference between shift workers and healthy controls on Austin Maze learning test.

CHAPTER THREE: METHOD

3.1 Participants

The participants were 15 men and women with moderate to severe untreated OSA, 15 men and women on rotating or night shift work and 15 control men and women. The control participants were closely matched to the OSA and shift work groups by age. The control group participants were screened to exclude individuals with OSA, chronic sleepiness, respiratory disorders and/or a history of major neuropathology and shift work. Shift workers were be screened to exclude those with OSA, respiratory disorders or a history of neurological disorders. Obstructive sleep apnoea participants were recruited via Austin Health Sleep clinics by via Participant Information Statement with contract details (see Appendix 2). Shift-workers and control participants were recruited from the Melbourne Metropolitan area via advertising in local papers, the Austin Health newsletter and Trade Union publications (see Appendix 1). Volunteers who responded to the advertisements were mailed a Participant Information Statement with contact (see Appendix 2). Potential participants were subsequently contacted by telephone and those who agree to participate after reading the Participant Information Sheets were enrolled in the study after they completed the Informed Consent Forms (see Appendix 2).

Inclusion Criteria

All participants were required to be 18-year-old or older, with a current driving licence.

OSA participants were diagnosed with polysomnogram by respiratory physicians to have moderate to severe OSA diagnosis (AHI > 20/hr and ESS > 8).

Shift work participants were required to be current night shift workers or rotating shift workers, of at least 3 years' duration. They were required to have at least one normal night sleep prior the day of participation.

All participants were required not to participate in testing immediately after work to avoid fatigue.

Exclusion Criteria

People with other conditions that may affect driving or neurocognitive performance were excluded, including chronic neurological illness or significant medical co-morbidity, chronic psychiatric illness, visual acuity problems not correctable with glasses, regular use of sedating medication, inability to give informed consent, and inability to speak or write English.

Shift workers and control participants were screened for sleep disorders and excessive sleepiness. Control participants were excluded if they had a high ESS score (> 10) or a high MAPI (> 0.5), while shift workers were excluded only if they had high MAPI (> 0.5).

3.2 Research design and procedure

The study utilized a case control design with three groups; control participants, obstructive sleep apnoea patients and shift workers. All participants were asked to attend for two sessions at the sleep laboratory at the Austin Hospital, approximately two weeks apart. All participants were required not to participate in testing immediately after work to avoid fatigue. They were requested to avoid coffee and tea on the day of testing. The testing time was restricted to late afternoon at about 3:30pm to control for the variations in circadian rhythm. Half past three in the afternoon is known to be associated with the highest reaction time during the circadian rhythm cycle (Smolensky & Lamberg, 2000).

An initial consultation with the participants was arranged to obtain informed consent after an explanation of the Participant Information Statement was given and any questions participants had were answered. Participants were then screened for exclusion criteria via completing a demographic and health questionnaire, the Maislin Apnoea Prediction Questionnaire (Maislin et al., 1995), and the ESS (Johns, 1991). The completion of a sleep diary was also discussed. Some potential participants were excluded on the basis of not meeting the baseline eligibility criteria. Doubtful cases (e.g., high level of sleepiness in the control group or occurrence any of the symptoms including snoring, gasping or struggling for breath in the shift workers or control group) were requested to do an overnight polysomnography at the Austin Health Sleep Unit to rule out undetected OSA. All OSA participants had previously undergone a polysomnographic sleep study and a diagnosis of moderate to severe obstructive sleep apnoea (AHI > 20/hr and ESS > 8) had been established and verified

by a respiratory physician.

Participants spent approximately three hours undertaking neuropsychology tasks in the afternoon as outlined in detail below (see Table 1). Short breaks were scheduled every 30 to 45 minutes between tests. To avoid fatigue, extra breaking times were allowed on request. At the end of the session, participants were administered the Karolinska Sleepiness Scale (KSS) (Akerstedt & Gillberg, 1990) to assess subjective sleepiness and alertness at that point in time. Participants were reminded that another researcher would arrange another day to complete the driving simulator performance and PVT (the results of the second session are not reported in this present research thesis).

Table 1. Summary of cognitive testing conditions.

Subject Groups: ***Assessments:***	**OSA**	**Shift Worker**	**Control**
Neuropsychology tests order			
1. Stroop Colour Word Test	X	X	X
2. WRAML-2-Verbal and Symbolic Working Memory Tests	X	X	X
3. Test of Everyday Attention	X	X	X
4. Austin Maze	X	X	X

3.3 Measures

3.3.1 Participant Information Statement (Plain Language Statement)

This statement was written to explain the aims of the research, the requirements of participation and the possible risks of participating in the research (see Appendix 2).

3.3.2 Consent Form

The consent form was an adapted version of the Austin and Repatriation Medical Centre standard consent form for participation in psychological/medical research (see Appendix 2).

3.3.3 Demographics questionnaire, screening tools, and sleep diary

The demographic questionnaire consisted questions designed to elicit information about age, height, weight, occupation, shift work history, driving history, and medical history relevant to the exclusion and inclusion criteria (see Appendix 3 and 4).

Screening tools include the Maislin Apnoea Prediction Questionnaire (Maislin et al., 1995) (see Appendix 5), and the ESS (Johns, 1991) (see Appendix 6).

A two-week sleep diary is used to record working time, sleep pattern and times of going to bed and waking up, day naps, number of nocturnal awakening, and it also allowed for the calculation of total sleep time per night and time taken to fall asleep. The sleep diary was primarily used as a screening tool to confirm the shift work pattern (see Appendix 8).

3.3.3.1 Maislin Apnoea Prediction Questionnaire

The Maislin Apnoea Prediction Questionnaire (Maislin et al., 1995) is a self-report rating scale consisting of three questions about sleep-disordered breathing and 10 questions about other symptoms of excessive daytime sleepiness (see Appendix 5). Participants are asked to consider whether during the last month they have experienced, or have been told that they showed symptoms of sleep apnoea. Reponses are recorded on a 6-point rating scale (0 = never, 1 = rarely/less than once a week, 2 = 1-2 times a week, 3 = 3-4 times a week, 4 = 5-7 times a week, 5 = don't know). The Index-1 represents a symptom frequency index of apnoea. It was computed by averaging the values for the frequency of the first three questions, which are about loud snoring, breathing cessation, and snorting and gasping. By substituting the value of Index-1, age, gender, and body mass index (BMI) into a multiple logistic regression formula, a multivariable apnoea risk index, MAPI, can be calculated. This MAPI predicts apnoea risk using a probability score between 0 and 1, with 0 representing low risk and 1 representing high risk. Control participants and shift workers with MAPI greater than 0.5 were excluded from the current study.

Test-retest correlations (retest after 2 weeks) for the MAPI are high (r = .92). Measures of the predictive ability of Index-1 (endorsement of apnoea items compared to clinical diagnosis of sleep apnoea) showed that the prevalence of clinically diagnosable sleep apnoea ranged from model sample (n= 321) from 20% of

patients with Index-1 value of < 1, to 74% of patients with Index-1 value of 4 (having highly endorsed all sleep apnoea items) (Maislin et al., 1995).

3.3.3.2 Epworth Sleepiness Scale (ESS)

ESS (Johns, 1991, 1992) is a self-reported measure of chronic daytime sleepiness and was used to identify participants who may have been experiencing disordered sleep (see Appendix 6). Participants were required to rate their self-perceived likelihood of falling asleep or dozing off in eight everyday situations. Such situations include sitting and reading, watching television, sitting in a cinema, as a passenger in a car. Participants responded to items on a 4-point rating scale (0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing). Possible scores ranged from 0 to 24, with higher scores reflecting more disordered sleep. Scores of above 16 are considered indicative of a probable sleep-related disorder. This scale is used a screen for insomnia, sleep apnoea and narcolepsy. A score between 0 and 10 is considered to be in normal range (Johns & Hocking, 1997), thus control participants with an ESS score greater than 10 were excluded from the current study.

The ESS has a high internal consistency and test-retest reliability, and can be considered as a simple and reliable method for measuring persistent daytime sleepiness in adults (Johns, 1992). Johns (1992) found a Pearson's *r* correlation coefficient of .82 in a group of healthy participants when tested and re-tested five months later. Cronbach's alpha results were .88 for a patient sample with various sleep disorders and .73 for a control sample.

3.3.3.3 Karolinska Sleepiness Scale (KSS)

KSS (Akerstedt & Gillberg, 1990) is a single item scale used to measure subjective sleepiness at a point in time (see Appendix 7). Participants were required to place a cross next to a number that best described how sleepy they felt at the time they completed the KSS. The numbers ranged from 1 = extremely alert, 3 = alert, 5 = neither alert nor sleepy, 7 = sleepy but no difficulty remaining awake, to 9 = extremely sleepy fighting sleep, with even items having a scale value but no verbal label. Possible scores ranged from 1 to 9. Higher scores represented higher subjective sleepiness. The KSS is highly correlated with EEG and electrooculography (EOG) measures of sleepiness and therefore has high validity (Akerstedt & Gilberg, 1990). This scale was found to be highly positively correlated with a visual analogue

scale of sleepiness and the Accumulated Time Sleepiness Scale (Gillberg, Kecklund, & Akerstedt, 1994), which suggests good concurrent validity.

3.3.4 Stroop Colour and Word Test

The Stroop Colour and Word Test (Golden, 1978; Chafetz &Matthews, 2004) has been used to tap Prepotent Response Inhibition, including the study that derived the latent variables of executive function (e.g., Miyake et al., 2000; Vendrell et al., 1995). The Stroop task is sometimes classified as a Resistance-to-Interference task (e.g., Nigg, 2000), it differs from a simple focus attention task in that the response that must be avoided is dominant (MacLeod, 1991), whereas other tests use simple distractors. One has to inhibit the prepotent response triggered by distracters, and focus on a less compelling aspect of the stimulus.

In Golden's (1978) version of Stroop colour-word test, 45 seconds are given to read each page of colour words (red, green, blue) (W) printed in black ink, colour hues (C) printed as 'XXXX's, and colour hues printed as competing colour words (CW) (e.g., 'red' printed in blue ink). Golden's (1978) asserted that the time to read a CW item is an additive function of the time to read a word plus the time to name a colour. The addition of the time to read a word (45/W) and the time to name a colour (45/C) gives the formula of (W x C)/(W + C) for the number of predicted CW items completed in 45 seconds.

Chafetz and Matthews (2004) have questioned the theoretical model underlying Golden's interference score. The Stroop effect in neuropsychology has not been about addition, but about inhibition or how well a person can suppress a habitual response in favour of an unusual one (Spreen & Strauss, 1991). Consistent with this notion, Chafetz and Matthews (2004) proposed a different interference score based on the notion that the time to read a CW item reflects the time to suppress the reading of a word, the dominant response, plus the time to name a colour. Chafetz and Matthews (2004) considered that the simple act of word reading alone would involve some hypothetical amount of word suppression, modeled by the formula (216-W) (i.e., 216, the uninhibited maximal value obtained by 5 standard deviations from the mean of 108 in Golden's (1978) data, minus the actual word reading value). Adding the time to *suppress* reading a word (45/(216-W)) plus the time to name a colour (45/C) gives the formula: (((216-W) x C)/((216-W)+C)) for the number of predicted CW items completed in 45 seconds. To obtain the new interference score values, the new predicted CW score is derived from the actual (age-corrected) W and

C scores, and then subtracted from the obtained CW score to give a difference score. When the difference is 0, a *T* score of 50 is given (Golden, 1978). Negative difference scores, giving rise to smaller *T* scores, reflect a performance that is worse than predicted, with interpretation as to the person's relative ability to suppress word reading in favour of colour naming. The primary difference between the old Golden's (1978) and the new Chafetz and Matthews' (2004) systems is that rising W scores lead to rising interference scores in the new system and falling scores in the old. In the new system, rising W values are associated with lower predicted CW values, thus a mid-range actual CW leads to higher interference scores. It is exactly the opposite in the old system. The theoretical underpinning of the new system is straightforward; a person with a greater facility for the linguistic process of wording reading, that is, a fast word reader, should have more difficulty suppressing word reading in order to name the colour, and hence obtain a lower predicted CW value to account for this. The resulting new Interference score would therefore reflect the *extra* amount of difficulty suppressing a habitual response in favour of an unusual one due to interference, taking into account the relative abilities in linguistic facility or processing speed.

The present study used the new Chafetz and Matthews' (2004) formula to calculate the Interference score, to preclude the possibility that a slow processing speed due to excessive sleepiness *per se* would lower the speed of word reading (W) and colour reading (C), resulting in a lower predicted CW score using the old Golden's (1978) formula and therefore a better Interference score, that is, insensitive to any genuine inhibition deficits (see Appendix 9).

3.3.5 Wide Range Assessment of Memory and Learning – Second Edition (WRAML-2)

The Verbal Working Memory and Symbolic Working Memory subtests were selected from the WRAML-2 (Sheslow & Adams, 2003).

3.3.5.1 Verbal Working Memory

The participant listens to a list of words composed of animal names and objects and then repeats the list, placing all the animal names first and reordering them according to their size (i.e., from small to large), followed by all the nonanimal words in any order; in the second part of the test, the participant must repeat both sets of stimuli in order of size (i.e., animal first and then objects, both from small to large)

(see Appendix 10).

3.3.5.2 Symbolic Working Memory

The examiner dictates a number series (e.g., “8-2-4”), and the examinee reproduces the series in correct numerical order (e.g., “2-4-8’) by pointing to numbers on a card; in the second part of the test, the examinee hears a random number-letter series (e.g., “3-B-1-A”) which must then be reproduced by pointing on a number-letter card, with the numbers in correct numerical order first, followed by the letters in alphabetical order (e.g., “1-3-A-B”) (see Appendix 11).

Based on a sample of 79 healthy adults, the WRAML-2 Working Memory Index comprising only Verbal Working Memory and Symbolic Working Memory subtests was found to be highly correlated with the Weschler Memory Scale-Third Edition (WMS-III) and Weschler Adult Intelligence Scale-Third Edition (WAIS-III) Working Memory Indices (r = 0.6 and 0.67 respectively) (Sheslow & Adams, 2003). The WRAML-2 Attention/Concentration Index is highly correlated with WMS-III and WAIS-III Working Memory Indices (r = 0.65 and 0.69 respectively) and WRAML-2 Working Memory and Attention/Concentration Indices are highly correlated (r = 0.67). However, confirmatory factor analysis of all the WRAML-2 core subtests and Working Memory subtests (N = 1200) yielded a Four-Factor solution (Visual Memory, Verbal Memory, Attention/Concentration, and Working Memory) with all goodness-of-fit measures being higher than the .95 cutoff and root mean square error of approximation (RMSEA) equal to .058 (Sheslow & Adams, 2003). In accordance to Kline’s (1998) good measurement models, all the factor loadings are moderate to high (convergent validity), ranging from .56 to .79, and the correlations are not too high (< .85) (discriminant validity), ranging from .48 to .80. There are approximately 64 %, 30%, and 34% variance of ability variables measured by the Working Memory factor overlapping with those measured by Verbal Memory, Visual Memory, and Attention/Concentration factors respectively. Overall, these suggest adequate discriminant validity among the four dimensions and imply that the scores from the four factors can be interpreted in isolation as separate constructs.

3.3.6 The Test of Everyday Attention (TEA)

The following subtests were selected from the TEA (Robertson et al., 1994).

3.3.6.1 Map Search

This is a test of visual selective attention in which participants are required to search for designated symbols of one type on a coloured map for a 2-minute period. The score is the number of symbols found within a 2-minute period (maximum possible score is 80), representing the efficiency with which stimuli can be filtered to detect the relevant information and reject or inhibit the irrelevant or distracting information (see Appendix 12).

3.3.6.2 Telephone Search

This is a visual selective attention task in which participants must look for 4 types of designated key symbol pairs and ignore other symbols, while searching entries in a simulated classified telephone directory. The score is calculated by dividing the total time taken by the number of symbols detected. Lower values represent a superior performance or an efficient visual selective attention in detecting several types of targeted information while rejecting similar but irrelevant information. This task may also draw upon visual working memory holding the 4 types of target symbols in mind for comparison (see Appendix 13).

3.3.6.3 Elevator Counting with Distraction

This task, in addition to involving auditory selective attention, also draws upon auditory-verbal working memory. Participants have to count the same pitched tones while ignoring the interspersed high pitch tones which have been introduced as distracters. The score indicates the number of strings counted correctly, giving scores ranging from 0 to 10, representing the efficacy in filtering off auditory distractions (see Appendix 14).

3.3.6.4 Lottery

In this subtest, which is considered to be a measure of sustained attention, the subject listens to a series of numbers presented by a tape recorder (see Appendix 15).

All numbers are in sets of three and are preceded by two letters. Participants are instructed to write down the two letters preceding all numbers that end in 55. These are considered 'winning' numbers. There are 10 'winning' numbers randomly included during the 10-minute presentation. The participants score is the number of correctly recorded numbers (maximum = 10). This subtest was found to have a significant relationship to a traditional sustained attention measure, PASAT, in the factor analysis of Bate and colleagues (2004) study. The former can be considered as a purer measure of sustained attention as it does not require mathematical ability or working memory as does the PASAT.

3.3.6.5 Telephone Search while Counting (Dual Task)

While this task loaded on the sustained attention factor in the factor analysis of Robertson and colleagues (1994) study, it is also considered a measure of divided attention (Chan et al., 2002). In this task, the subject must again search the telephone directory while simultaneously counting strings of tones presented by a tape recorder. This subtest yields a 'dual task decrement' score which is calculated by subtracting the time per target score of the previous subtest from the time per target score on the current subtest, which has been weighted for accuracy of tone counting. Lower and negative values represent a superior performance on this task. Essentially, by using the dual task decrement score, the previous Telephone Search subtest serves as the 'motor control task' for the dual task subtest, by which individual variation in processing speed or psychomotor speed has been controlled for as advocated by Verstraeten and Cluydts (2004) (see Appendix 16).

3.3.6.6 Visual Elevator

This subtest is considered to be a measure of (visual) attentional switching. Participants are asked to count a series of drawings of elevator doors that are presented in rows on the pages of presentation booklet. The task is self-paced. The drawings of the elevator doors are interspersed with large up- and down-pointing arrows, indicating that the direction of counting should change in line with the arrow (i.e., counting up or down). Two separate scores are derived from this subtest: the first score represents the number of visual strings counted correctly (maximum score = 10) inversely related to the mental errors elicited during attentional switching, while the second score is a timing score calculated by dividing the total time taken for the correct items by the total number of switches for the correct items by the total number of switches for the correct items, indicating the

efficiency of attentional switching. Lower values represent a superior performance to higher values on this timing score (see Appendix 17).

In the factor analysis of Robertson and colleagues (1994) study, the Visual Elevator subtest was found to have a significant relationship with the WCST (Berg, 1948; Heaton, Chelune, Talley, Kay, & Curtiss, 1981, 1993; Nelson, 1976), originally developed as a test of 'flexible thinking' and now widely used as a measure of executive function. However, WCST is a somewhat complex measure in which the subject must work out a rule, use feedback and remember previous responses, in addition to switching from one strategy to another. Visual Elevator reduces the demands for all but the last of these capacities (Manly et al., 1999), hence can be considered as a purer measure of mental flexibility or set-shifting, one of the three key components of executive function (Miyake et al., 2000).

3.3.6.7 Auditory Elevator with Reversal

This task is a measure of (auditory) attentional switching and is presented at a fixed speed on audio tape. Participants are required to count string of 'medium' pitched tones. Interspersed with these 'medium' pitched tones are both high and low tones (indicating the subject must switch to counting up or down respectively). The score represents the number of strings of tones counted correctly (maximum = 10) (see Appendix 18).

3.3.7 Austin Maze (Milner, 1965; Tucker, Kinsella, Gawith, & Harrison, 1987; Walsh & Darby, 1994)

The Austin Maze is an electric push-button maze based on Milner's (1965) Spatial Maze Learning Test (see Appendix 19). In the basic administration of the test, the participant is required to learn the path through the maze using a trial-and-error approach, following rules restricting direction of movement (no diagonal moves) and response to errors (if an error, indicated by a red light and a buzzer, is made, the participant must return to the last correct button position and then continue), until reaching the criterion of two errorless trials. In the current study, administration was limited to 10 trials as previous research (Bowden et al., 1992) showed a high correlation between errors to criterion and errors over 10 trials in both normal (r = .89) and clinical populations (r = .94). Raw scores for total errors over 10 trials and total time taken over 10 trials (seconds) were used in all data analysis.

The Austin Maze, a complex spatial learning task, has been considered as a measure of planning, error utilization and behavioural regulation in frontal lobe patients, and used as a means of assessing executive functioning in clinical settings (Milner, 1965; Walsh & Darby 1994). On the other hand, it is considered as a test of spatial ability, visuospatial learning, and to some extent, working memory based on healthy adult population study (Crowe et al., 1999).

CHAPTER FOUR: RESULTS

4.1 Statistical analysis

Raw data from all questionnaires and neuropsychological tests were entered into the Statistical Package for Social Sciences (SPSS) data file. Descriptive statistics were computed to ensure that all data were in the specified ranges, and that there were no missing values. The data were found to be within the specified range and there were no missing values.

Demographic variables and subjective sleepiness scales were analysed using One-Way Analysis of Variance (ANOVA). The One-Way ANOVA is suitable to compare means of each measure, entered as a dependent variable, among independent groups (control participants, shift workers, and patients with OSA), which were entered as the fixed factor. Post hoc Tukey HSD tests ($p < .05$) were conducted to assess where exactly each of these means was different from each other when ANOVA *F*-tests were found significant.

Participants' performance on neuropsychology tests were analysed using single factor multivariate analyses of variance (MANOVA). The between-subjects fixed factor was participant Group (control participants, shift workers, and patients with OSA). The post hoc Tukey HSD tests ($p < .05$) were conducted to compare the means between each pair of groups when there were significant differences on any variables using MANOVA univariate *F*-tests. Bivariate correlation analyses were conducted on all the dependent variables of neuropsychological measures on the whole data set to check for the multicollinearity and singularity assumptions. Bivariate correlation analyses were conducted seperarately on each group data sets of patients with OSA, shift workers and controls in order to investigate the relationships between various measured neuropsychological functions and Austin Maze 10^{th}-Trial Total Error within different groups.

4.2 Data screening

The data were screened in accordance with criteria recommended by Tabachnick and Fidell (2001).

Sample Size

With 15 cases for each participant group and no missing data on all dependent measures, there were more cases than dependent variables in every cell, ensuring sufficient power.

Normality of sampling distribution

Based on visual inspection of histograms, evaluation of skewness and kurtosis values, and Shapiro-Wilk statistic values of $p > .05$, a few measures displayed non-normal distributions, namely the Elevator Counting with Distraction Scaled Score (all groups), the Lottery Scaled Score (Controls, patients with OSA), the Stroop Interference Chafetz T Score (patients with OSA), the Austin Maze 10^{th}-Trial Total Errors (all groups), the Austin Maze 10^{th}-Trial Total Time (patients with OSA). Performances on the Stroop test and Austin Maze were skewed in the direction expected for each condition. The distributions for the performance on Elevator Counting with Distraction, and Lottery were also judged to be reasonable.

For all analyses, the sample size was sufficient to produce 20 degrees of freedom for error in the univariate case ensuring the robustness of the test (in combination with equal sample sizes across groups and use of two-tailed tests) in regards to multivariate normality.

Outliers

One outlier was detected for the variable, the Austin Maze 10^{th}-Trial Total Errors, through inspection of box plot. In accordance with Tabachnick and Fidell's (2001) criterion, these outlier data points were given a raw score one unit above or below the next most extreme case, depending on the direction of the outlying value. In this case, a raw score of one unit above the next highest case was used for transformation. This procedure was successful in abating the influence of the outlying case on multivariate analysis.

Mahalanobis distance (χ^2 = 34.53, *df* = 13, *p* < .001; Tabachnick & Fidell, 2001) was used to test for the presence of multivariate outliers. With the application of a criterion of *p* < .001, no multivariate outliers were detected in the present sample. The maximum Mahalanobis distance was 17.16 for controls, 20.55 for shift workers, and 25.58 for patients with OSA.

Homogeneity of the variance-covariance matrices

Box's Test of Equality of Covariance Matrices (Box's *M* test) and Levene's Test of Equality of Error Variances were used to test the assumption of homogeneity of the variance-covariance matrices. The Box's *M* test was not significant at *p* < .05. Levene's tests on three variables including Elevator Counting with Distraction Scaled Score, the Austin Maze 10th-Trial Total Errors, and the Austin Maze 10th-Trial Total Time were significant at *p* < .05. Hence the assumption of homogeneity for MANOVA was not strongly violated. In addition, given that sample sizes are equal across groups, the robustness of significance tests is expected.

Linearity

An analysis of all the residuals and normality probability (P-P) was performed to test the assumptions of normality, linearity and homoscedasticity. The data did not violate the assumptions of linearity according to inspection of bivariate scatterplots; no curvilinearity was detected.

Multicollinearity and singularity

An absence of multicollinearity and singularity was demonstrated through correlation of the dependent variables, using Pearson's product-moment correlations. All the dependent variables are mildly to moderately correlated, all being less than .711 and none being near zero.

4.3 Data analysis

4.3.1 Demographic variables, BMI, MAPI, and subjective sleepiness scales

Means, standard deviations and ranges for demographic variables, BMI, MAPI and reported subjective sleepiness for patients with OSA, shift workers, and control participants are shown in Table 2. One-way ANOVAs were conducted to assess any differences on these variables among the groups, with their *F* and *p* values tabulated. Levene's Test was used to test the assumption of homogeneity of variances. Where the assumption of equal variances was met, the *F*-test was used, and where it was violated, adjustment was made by reporting the Welch *F*-ratio (Tabachnick & Fidell, 2001).

Table 2 shows that on one-way ANOVAs there was no significant difference between patients with OSA, shift workers, and control participants on their age and height. Fifteen patients with moderate to severe OSA, 13 men and 2 women, aged between 34 and 58 (*M* = 46.20, *SD* = 8.15), fifteen shift workers, 9 men and 6 women, aged between 25 and 49 (*M* = 42.13, *SD* = 8.33), and fifteen healthy controls, 6 men and 9 women, aged between 25 and 69 (*M* = 46.80, *SD* = 13.48) participated in the study. There were significantly more men in the OSA patient group (13 men out of 15) than in control group (6 men out of 15) but this was not so in the shift workers group (9 men out of 15). The height of patients with OSA ranged from 165 to 191 cm (*M* = 175.20, *SD* = 7.89); that of shift workers ranged from 160 to 176 cm (*M* = 171.33, *SD* = 4.08); and that of controls ranged from 157 to 194 cm (*M* = 169.60, *SD* = 10.55).

In comparison to control participants and shift workers, patients with OSA weighed significantly more and had a significantly higher BMI. The weight of patients with OSA (*M* = 106.40, *SD* = 22.70, range from 70 to 157kg) was significantly greater than that of shift workers (*M* = 72.83, *SD* = 11.96, range from 55 to 92kg) and controls (*M* = 66.87, *SD* = 15.51, range from 51 to 106 kg). The BMI of patients with OSA (*M* = 34.54, *SD* = 6.23, range from 23.66 to 44.9kg/m^2) was significantly greater than that of shift workers (*M* = 24.87, *SD* = 4.27, range from 17.96 to 30.42kg/m^2) and controls (*M* = 22.74, *SD* = 3.26, range from 19.20 to 30.97kg/m^2).

Patients with OSA obtained a significantly higher MAPI (*M* = .696, *SD* = .130, range from .422 to .835) than both shift workers (*M* = .179, *SD* = .103, range from .012 to .384) and controls (*M* = .119, *SD* = .119, range from .021 to .458). Patients with

OSA also reported significantly higher subjective sleepiness scores. Their ESS score (*M* = 13.13, *SD* = 4.69, range from 9 to 22) was significantly higher than both shift workers (*M* = 7.66, *SD* = 3.68, range from 3 to 14) and controls (*M* = 5.00, *SD* = 3.27, range from 0 to 9). Patients with OSA's KSS score (*M* = 5.27, *SD* = 1.28) was significantly higher than control participants (*M* = 4.00, *SD* = 1.25) but not significantly different from shift workers (*M* = 4.07, *SD* = 1.71).

Table 2. Means, standard deviations, and ranges for demographic variables, Body Mass Index, Maislin Apnoea Prediction Index, and subjective sleepiness scales.

	Control (N=15)		**Shift worker (N=15)**		**Patients with OSA (N=15)**			
	Mean (SD)*	**Range**	**Mean (SD)***	**Range**	**Mean (SD)***	**Range**	***F***	***p***
Age	46.80(13.48)	25-69	42.13(8.33)	25-49	46.20(8.15)	34-58	.913	.409
Weight (kg)	$66.87(15.51)_a$	51-106	$72.83(11.96)_b$	55-92	$106.40(22.70)_{ab}$	70-157	22.740	.0005
Height (cm)	169.60(10.55)	157-194	171.33(4.08)	160-176	175.20(7.89)	165-191	1.944	.156
Body Mass Index (kg/m^2)	$22.01(3.19)_a$	19.20-30.97	$24.87(4.27)_b$	17.96-30.42	$34.54(6.23)_{ab}$	23.66-44.9	25.686	.0005
Maislin Apnoea Prediction Index	$.119(.119)_a$	.021-.458	$.179(.103)_b$	.012-.384	$.696(.130)_{ab}$	.422-.835	108.56	.0005
Epworth Sleepiness Scale Score	$5.00(3.27)_a$	0-9	$7.66(3.68)_b$	3-14	$13.13(4.69)_{ab}$	9-22	16.738	.0005
Karolinska Sleepiness Scale	$4.00(1.25)_a$	1-6	4.07(1.71)	1-7	$5.27(1.28)_a$	3-7	3.728	.032

*Post hoc comparison of means - Tukey HSD test:
Means with common subscripts are significantly ($p < .05$) different from one another.

Demographics questionnaires were reviewed. It was found that all shift worker participants recruited had been doing shift work continuously for at least three years preceding the testing date. Review of the sleep diaries confirmed that all shift workers were currently doing shift work, with either night shifts or rotating shifts shown in the past two-week working time.

4.3.2 Neuropsychological measures

Control-referenced comparison

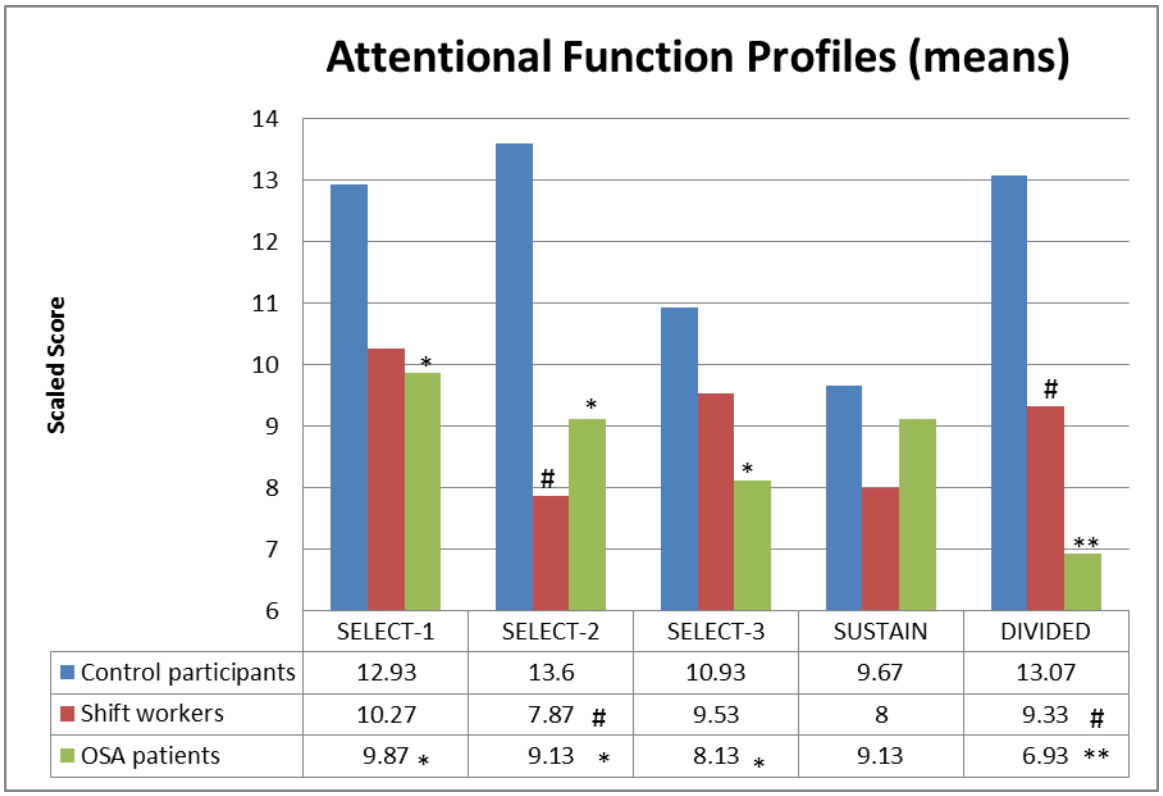
Analyses of participants' performance on neuropsychology tests were conducted using SPSS single factor MANOVA. The between-subjects fixed factor was participant Group (control participants, shift workers, and patients with OSA). A single factor MANOVA was performed to test whether there was any significant main effect for the participant Group factor on thirteen dependent variables: Map Search 2-min Scaled Score, Telephone Search Time Scaled Score, Elevator Counting with Distraction Scaled Score, Lottery Scaled Score, Telephone Search while Counting (Dual Task Decrement), Visual Elevator Accuracy Scaled Score, Visual Elevator Time Scaled Score, Elevator Counting with Reversal Scaled Score, Verbal Working Memory Scaled Score, Symbolic Working Memory Scaled Score, Stroop Interference Chafetz *T* Score, Austin Maze 10^{th}-Trial Total Errors, and Austin Maze 10^{th}-Trial Total Time.

There was a significant main effect for the participant Group factor, *Wilks' λ* = .088, $F(26, 60) = 5.466$, $p = .0005$, *Partial* $\eta^2 = .703$, Observed Power = 1.0. *Partial* η^2 values range from 0 to 1, with larger values representing larger effect sizes (Cohen, 1988). Table 3 presents the inferential statistics of the univariate analyses, showing the *F* and *p* values, effect size (*Partial* η^2) and Observed Power using $\alpha = .05$.

Comparison of the neuropsychological profilesof attentional function, executive function and Austin Maze performance for each participant group were represented in Figures 2, 3 and 4. Performance of each participant group shown in these figures was compared in details in Section 4.3.3 to follow, under individual variables. Discussion of results shown in Figure 2 can be found in pages 77, to 85; Figure 3 in pages 87 to 97; and Figure 4 in pages 97 and 102. Further discussion of the profiles can be found in Chapter Four: Discussion of results.

Table 3. Univariate analyses of variance for neuropsychology tests performance, with participant Group as independent variable.

Measures	*Sum of Squares*	*df*	*Mean Square*	*F*	*p*	*Partial* η^2	*Observed Power*
Map Search 2-min Scaled Score	83.378	2	41.689	3.729	.032	.151	.651
Telephone Search Time Scaled Score	272.133	2	136.067	11.543	.0005	.355	.990
Elevator Counting with Distraction Scaled Score	58.800	2	29.400	3.565	.037	.145	.630
Lottery Scaled Score	21.733	2	10.867	1.300	.283	.058	.266
Telephone Search while Counting - Dual Task Decrement Scaled Score	286.578	2	143.289	21.402	.0005	.505	1.000
Visual Elevator Accuracy Scaled Score	57.911	2	28.956	5.017	.011	.193	.787
Visual Elevator Time Scaled Score	37.911	2	18.956	3.580	.037	.146	.632
Elevator Counting with Reversal Scaled Score	139.600	2	69.800	9.798	.0005	.318	.976
Verbal Working Memory Scaled Score	146.978	2	73.489	11.546	.0005	.355	.990
Symbolic Working Memory Scaled Score	107.244	2	53.622	11.86	.0005	.361	.992
Stroop Interference Chafetz T Score	1434.711	2	717.356	10.743	.0005	.338	.985
Austin Maze 10^{th}-Trial Total Errors	63774.044	2	31887.002	7.754	.001	.270	.935
Austin Maze 10^{th}-Trial Total Time	518353.911	2	259176.956	5.388	.008	.204	.816



	SELECT-1	SELECT-2	SELECT-3	SUSTAIN	DIVIDED
Control participants	12.93	13.6	10.93	9.67	13.07
Shift workers	10.27	7.87 #	9.53	8	9.33 #
OSA patients	9.87 *	9.13 *	8.13 *	9.13	6.93 **

Figure 2. Comparison of attentional function profiles for each participant group.

Means of neuropsychological measures for attentional functions were shown, with SELECT stands for Selective Attention, SUSTAIN for Sustained Attention, and DIVIDED for Divided Attention. The key for the corresponding neuropsychological measures as follows: SELECT-1: Map Search 2-min Scaled Score; SELECT-2: Telephone Search Scaled Score; SELECT-3: Elevator Counting with Distraction Scaled Score; SUSTAIN: Lottery; DIVIDED: Telephone Search while Counting Dual Task Decrement Scaled Score.
**and # denote significant differences from controls; ** denotes significant difference between patients with OSA and shift workers as well as from controls.*

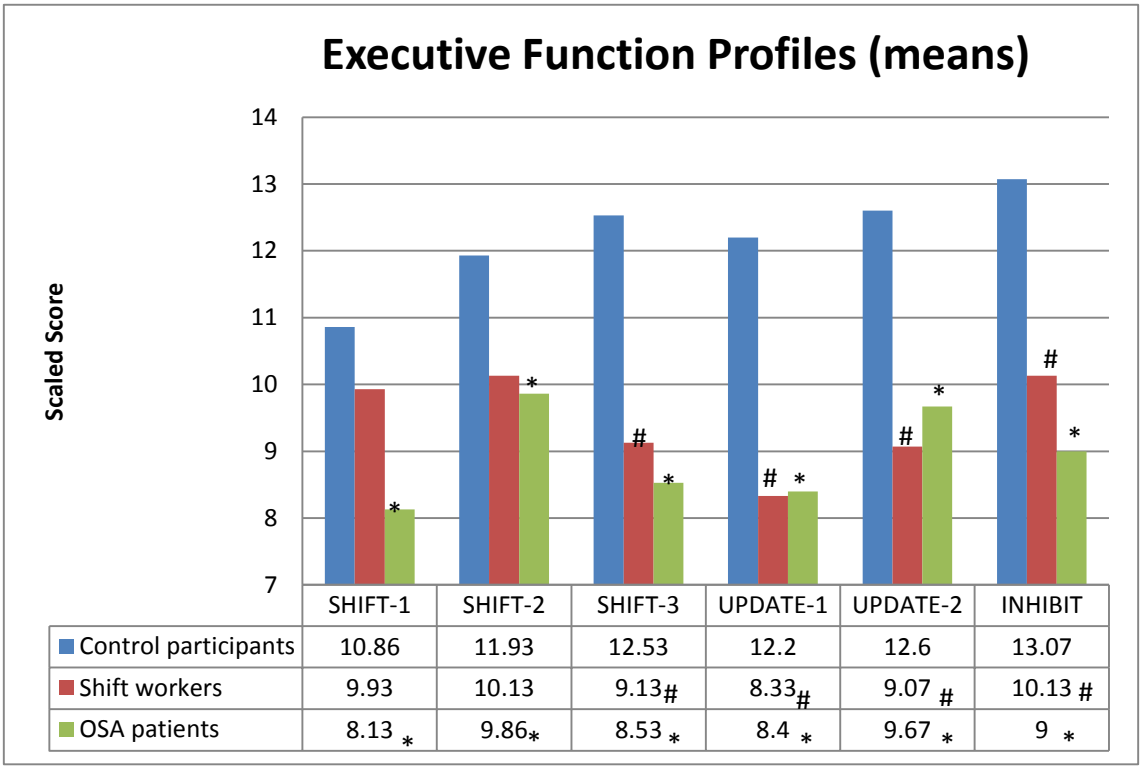


Figure 3. Comparison of executive function profiles for each participant group.

Means of neuropsychological measures for executive functions were shown, with SHIFT stands for Set-shifting, UPDATE for Updating (Working Memory), and INHIBIT for Inhibition of prepotent responses. The key for the corresponding neuropsychological measures as follows: SHIFT-1: Visual Elevator Accuracy Scaled Score; SHIFT-2: Visual Elevator Time Scaled Score; SHIFT-3: Elevator Counting with Reversal Scaled Score; UPDATE-1: Verbal Working Memory Scaled Score; UPDATE-2: Symbolic Working Memory Scaled Score; INHIBIT: Stroop Interference Chafetz Scaled Score.
**and # denote significant differences from controls.*

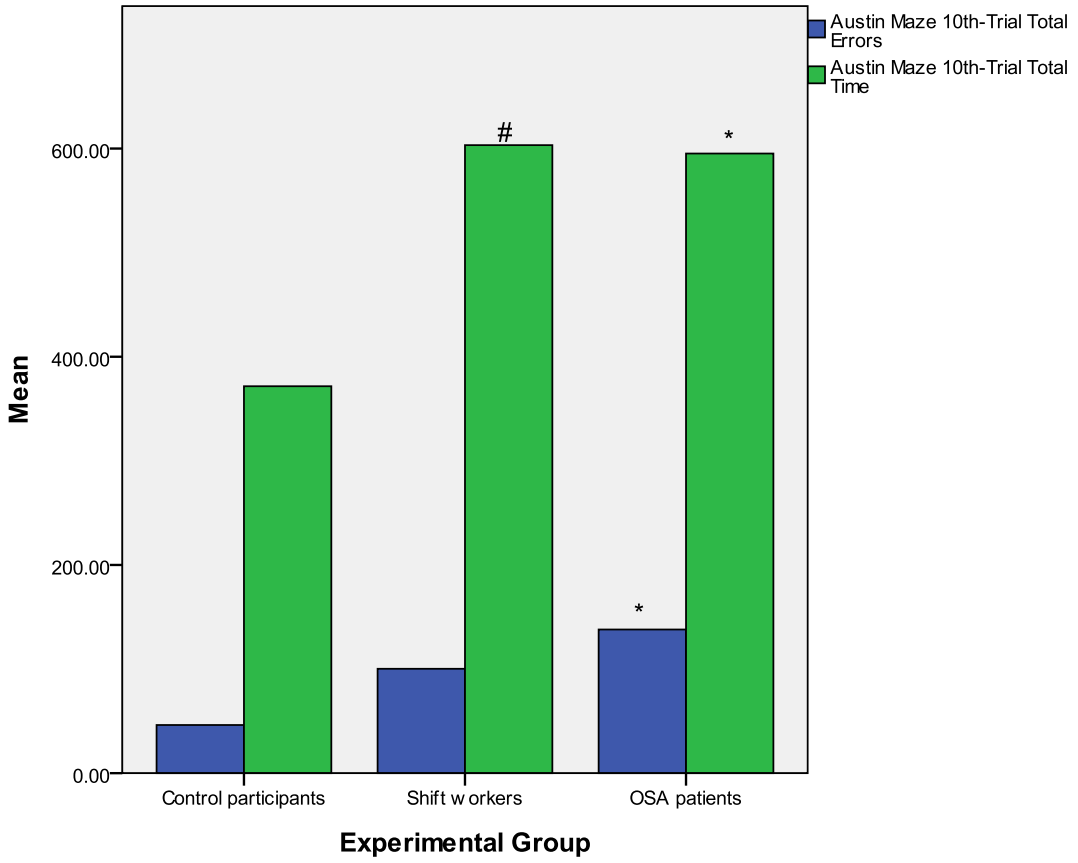


Figure 4. Comparison of performances on Austin Maze for each participant group.

Means of the total number of errors and total time (seconds) at the 10th learning trial were shown. **and # denote significant differences from controls.*

Norm-referenced comparison

The normative data sets of the standardized tests allow the calculation of standard scores, that is, the raw data are converted into standard measurement units for the performance of a standardization sample where there is an assumption of data being normally distributed in the population (Lezak et al., 2004). Thus, these data are commonly transformed into standardized scores for comparability across individuals in clinical settings and across studies in research. Common standardized scores include Weschler IQ score and scaled score and *T*-score. Wechsler series IQ scores are deviation IQ with a mean *(M)* of 100 and standard deviation *(SD)* of 15, and the subtest scaled scores have a mean of 10 and a *SD* of 3 (Lezak et al., 2004). The TEA and WRAML-2 present their subtest scaled scores with a mean of 10 and a *SD* of 3. The Golden version Stroop Test uses *T*-scores with a mean of 50 and a *SD* of 10. Standardized scores can be converted among themselves (e.g., from *T*-score to scaled score) and into a non-standard score such as percentile, but not necessarily in reverse when the normalization assumption is violated. For example, Austin Maze

culmulative errors scores can be expressed as percentiles only as they were positively skewed in the normative population. Percentiles were arranged so that lower ranks correspond to higher error scores, that is poorer performances on the maze (Bowden et al., 1992).

The current study presented the data of cognitive measures in standardized scaled scores for the TEA and WRAML-2 subtests, in standardized *T*-score for the Stroop Interference score, and in raw scores for Austin Maze. All these measures were analyzed using either ANOVA or MANOVA techniques for control-referenced comparison. In addition, direct interpretation of standardized data was presented, as this gives the relative position of the mean performance of patients with OSA and shift workers on each measure compared with their age-related peers. In other words, generalized conclusions about the relative performance of the clinical groups on these neurocognitive measures in relation to the general population can be made, assuming the normative samples of the respective tests are representative of the general population. Therefore, two sets of comparisons were undertaken, namely control-referenced comparisons using inferential statistical analyses and norm-referenced comparisons. In norm-referenced comparisons, standardized scaled scores were directly interpreted in order to analyse the relative performance of the two clinical groups with reference to the normative sample populations. For the standardized scaled scores, 'an average range' comprises scaled scores ranging from 8 to below 12 and scaled scores below 9 may be considered as 'at the lower end of the average range; 'a low average range' comprises scaled scores ranging from 6 to below 8 and scaled scores below 7 may be interpreted as 'in the borderline impaired range' or 'below average' because it is one standard deviation below the sample population mean. The results of norm-referenced comparisons can be directly referred to figure 2 and figure 3, in which the standardized scaled scores were used for the vertical axes of the profile comparisons. Discussion of control-referenced and norm-referenced comparisons can be found in Chapter Four: Discussion of results.

4.3.2.1 Map Search 2-min Scaled Score

- *Visual selective attention measure*

Univariate analysis showed that there was a significant main effect for the participant groups on Map Search 2-min Scaled Score, $F(2, 44) = 3.73$, $p = .032$, *partial* $\eta^2 = .151$, observed power = .651 (see Table 3). Comparisons of means, using the post hoc Tukey HSD test ($p = .05$), indicated a significant difference between the control group and the OSA patient group ($p < .05$) only (see Table 4). Figure 2 and 5 showed that the OSA patients group ($M = 9.87$, $SD = 3.31$) performed significantly more poorly than the control participants group ($M = 12.93$, $SD = 3.58$) on Map Search 2-min, measuring the efficacy of visual selective attention in filtering off irrelevant or distracting visual information and detect the relevant. There was a trend of reduced visual selective attention performance in the Shift worker group ($M = 10.27$, $SD = 3.13$), although it was not significantly different from either the control participant group or the OSA patient group.

Table 4. Post hoc comparison of means of Map Search 2-min Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Map Search 2-min	**N**	**Mean (*SD*)***	**N**	**Mean (*SD*)**	**N**	**Mean (*SD*)***
Scaled Score	15	$12.93\ (3.58)_a$	15	10.27 (3.13)	15	$9.87\ (3.31)_a$

*(Means with common subscripts are significantly ($p < .05$) different from one another.)

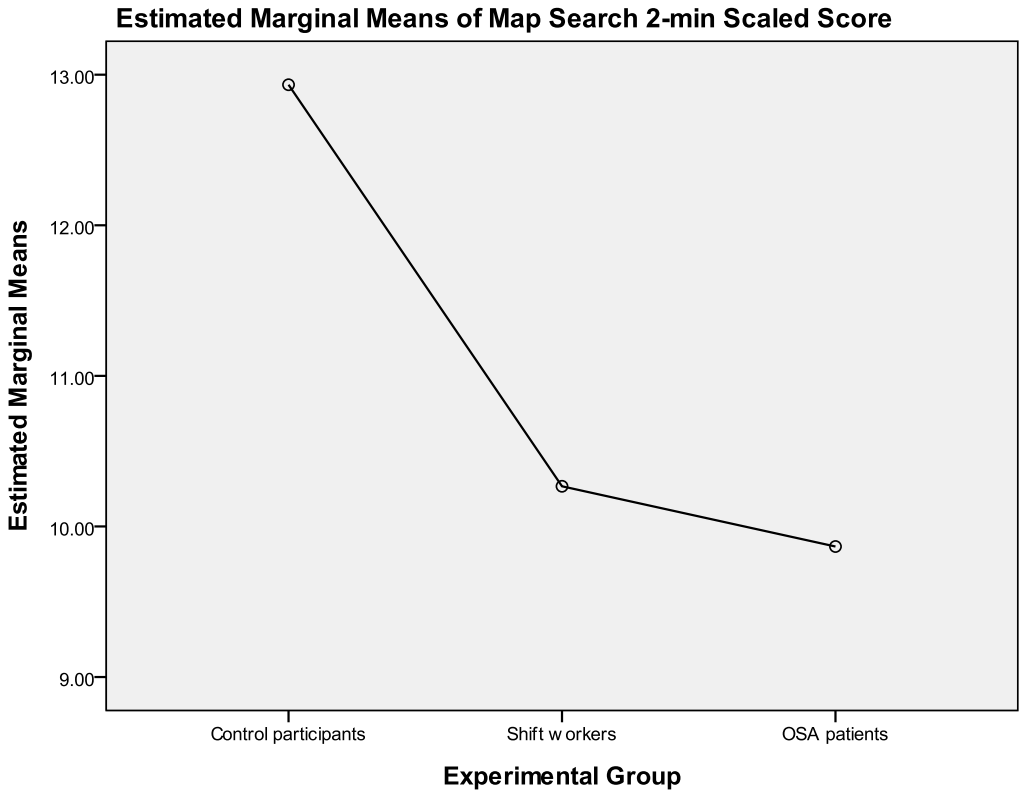


Figure 5. Means for Map Search 2-min Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.2 Telephone Search Time Scaled Score

- *Visual selective attention measure*

Univariate analysis showed that there was a significant main effect for the participant groups on the Telephone Search Time Scaled Score, $F(2, 44) = 11.54$, $p = .0005$, *partial* $\eta^2 = .355$, observed power = .990 (see Table 3). Comparisons of means using the post hoc Tukey HSD test indicated significant difference between the control group and the OSA patient group as well as between the control group and the Shift worker group ($p < .01$) (see Table 5). Figure 2 and 6 showed that both the OSA patient group ($M = 9.13$, $SD = 3.00$) and the Shift workers group ($M = 7.87$, $SD = 3.44$) performed significantly more poorly than the control participants group ($M = 13.60$, $SD = 3.81$) on Telephone Search Time, which predominantly measures how efficient the visual selective attention in detecting several types of targeted information while rejecting similar but irrelevant information. In addition, there was no significant difference in performance between the OSA patient group and the Shift worker group.

Table 5. Post hoc comparison of means of Telephone Search Time Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Telephone Search Time	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *
Scaled Score	15	$13.60\ (3.81)_{bc}$	15	$7.87\ (3.44)_{a}$	15	$9.13\ (3.00)_{b}$

*(Means with common subscripts are significantly ($p < .01$) different from one another.)

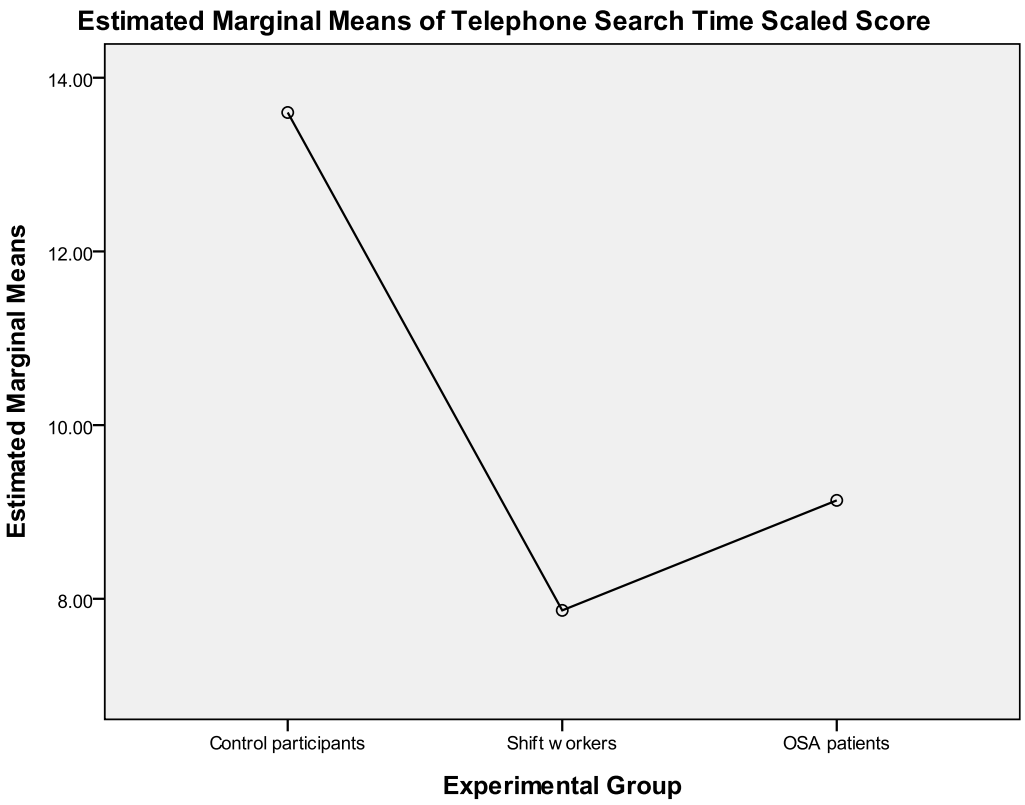


Figure 6. Means for Telephone Search Time Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.3 Elevator Counting with Distraction Scaled Score

- *Auditory selective attention measure*

Univariate analysis showed that there was a significant main effect for the participant groups on the Elevator Counting with Distraction Scaled Score, $F(2, 44) = 3.57$, $p = .037$, *partial* $\eta^2 = .145$, observed power = .630 (see Table 3). Tukey HSD test post hoc comparisons of means indicated significant difference between the control group and the OSA patient group ($p < .05$) only (see Table 6). Figure 2 and 7 showed that the OSA patient group ($M = 8.13$, $SD = 3.27$) performed significantly more poorly than control participant group ($M = 10.93$, $SD = 1.98$) on Elevator Counting with Distraction, measuring the efficacy of auditory selective attention in filtering off auditory distractions and the reliability of auditory working memory. The auditory selective attention performance in the Shift worker group ($M = 9.53$, $SD = 3.18$) was not significantly different from either the control participant group or the OSA patient group, although there was a trend suggesting their performance lay midway between that of the control participant group and that of the OSA patient group.

Table 6. Post hoc comparison of means of Elevator Counting with Distraction Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Elevator Counting with	**N**	**Mean (*SD*)***	**N**	**Mean (*SD*)**	**N**	**Mean (*SD*)***
Distraction Scaled Score	15	$10.93(1.98)_d$	15	9.53 (3.18)	15	$8.13\ (3.27)_d$

*(Means with common subscripts are significantly ($p < .05$) different from one another.)

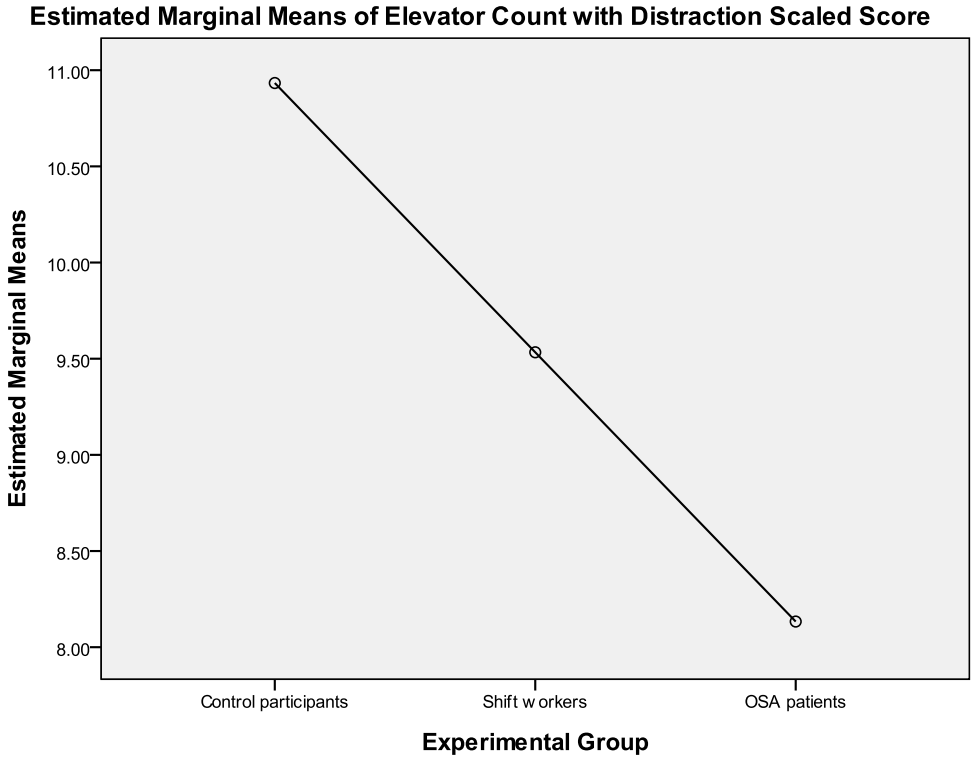


Figure 7. Means for Elevator Counting with Distraction Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.4 Lottery Scaled Score

- *Sustained attention measure*

Univariate analysis showed that there was no significant main effect for the participant groups on the Lottery Scaled Score, $F(2, 44) = 1.30$, $p = .283$, *partial* $\eta^2 = .058$, observed power = .266 (see Table 3). Figure 2 and 8 showed that the Shift worker group ($M = 8.00$, $SD = 3.40$) performed relatively more poorly than the OSA patient group ($M = 9.13$, $SD = 2.70$) which in turn performed slightly more poorly than the control group ($M = 9.67$, $SD = 2.50$), however, none of these pairs of Scaled Score means reached a statistical significant difference at $p = .05$ level on post hoc comparisons using the Tukey HSD test. The results suggested that there were no significant differences in sustained attention ability as measured by the Lottery test among the OSA patient group, the Shift worker group and the control participant group.

Table 7. Post hoc comparison of means of Lottery Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Lottery Scaled Score	**N**	**Mean (*SD*)**	**N**	**Mean (*SD*)**	**N**	**Mean (*SD*)**
	15	9.67(2.50)	15	8.00 (3.40)	15	9.13 (2.70)

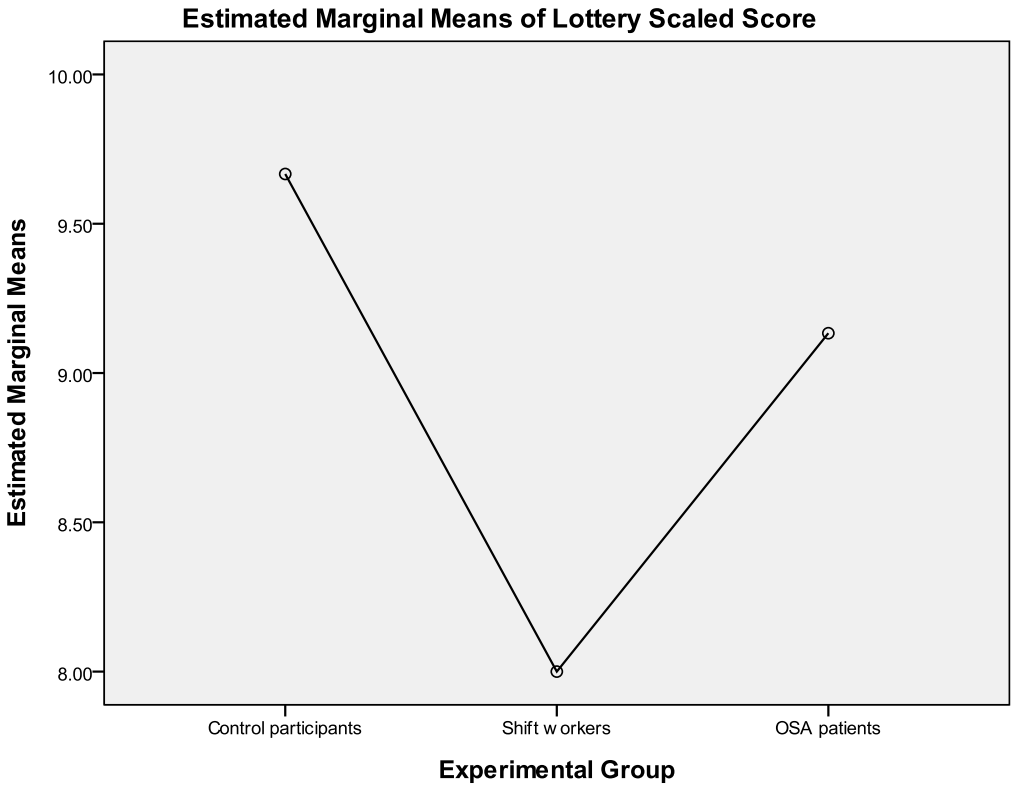


Figure 8. Means for Lottery Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.5 Telephone Search while Counting Dual Task Decrement Scaled Score

- *Divided attention measure*

Univariate analysis showed that there was a significant main effect for the participant groups on the Telephone Search while Counting Dual Task Decrement Scaled Score, $F(2, 44) = 21.40$, $p = .0005$, *partial* $\eta^2 = .505$, observed power = 1.000 (see Table 3). Post hoc comparisons of means using the Tukey HSD test indicated significant difference between the control group and the OSA patients group as well as the Shift worker group ($p < .01$), and also significant difference between the OSA patient group and Shift worker group ($p < .05$) (see Table 8). Figure 2 and 9 showed that the OSA patient group ($M = 6.93$, $SD = 2.43$) performed significantly more poorly than the Shift worker group ($M = 9.33$, $SD = 2.53$), and both performed significantly more poorly than the control participant group ($M = 13.07$, $SD = 2.79$) on Telephone Search while Counting Dual Task Decrement, which predominantly measures the ability to efficiently divide attention between a visual spatial task and an auditory task.

Table 8. Post hoc comparison of means of Telephone Search while Counting Dual Task Decrement Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Telephone Search while Counting Dual Task Decrement Scaled Score	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *	**N**	**Mean *(SD)*** *
	15	$13.07\ (2.79)_{ef}$	15	$9.33\ (2.52)_{fg}$	15	$6.93\ (2.43)_{eg}$

* (Means with common subscripts are significantly different from one another, while subscripts a or b indicates $p < .01$ and subscript c indicates $p < .05$)

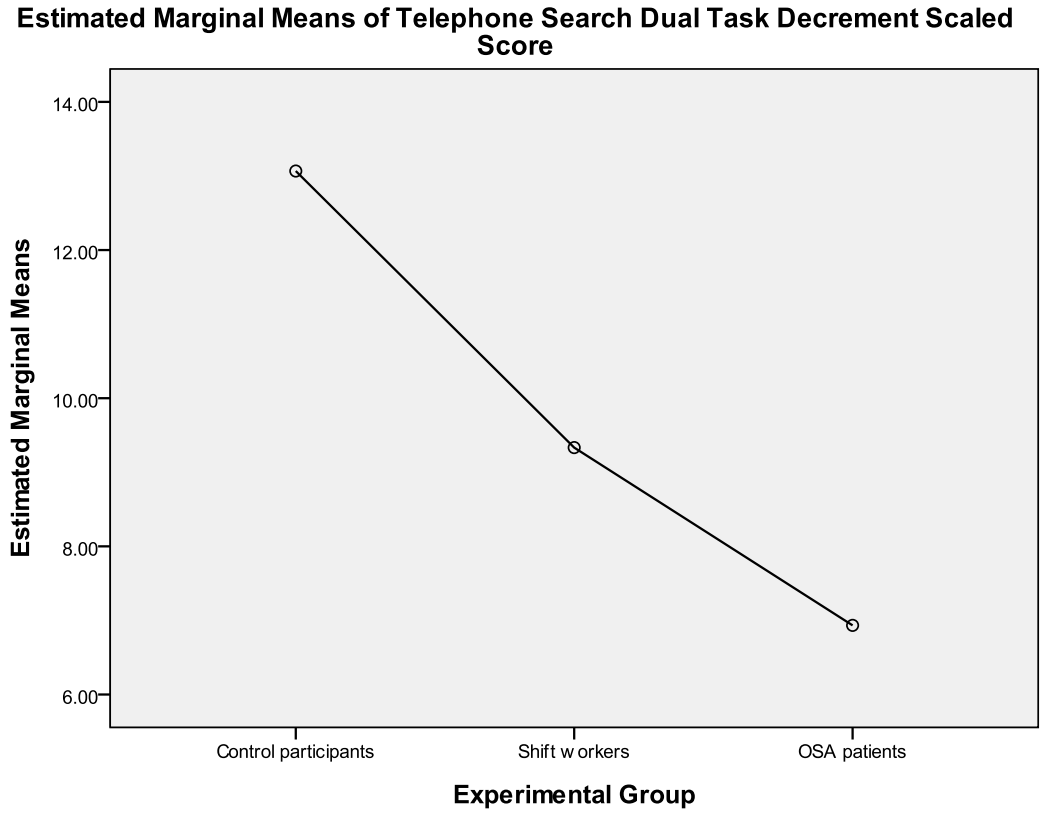


Figure 9. Means for Telephone Search while Counting Dual Task Decrement Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.6 Visual Elevator Accuracy Scaled Score

- *Visual set-shifting measure (reliability)*

Univariate analysis showed that there was a significant main effect for the participant groups on the Visual Elevator Accuracy Scaled Score, $F(2, 44) = 5.02$, $p = .011$, *partial* $\eta^2 = .193$, observed power = .787 (see Table 3). Post hoc comparisons of means using the Tukey HSD test indicated significant difference between the control group and the OSA patient group ($p < .01$) only (see Table 9). Figure 3 and 10 showed that both the OSA patient group ($M = 8.13$, $SD = 2.26$) performed significantly poorer than the control participant group ($M = 10.86$, $SD = 1.96$) on Visual Elevator Accuracy, measuring the efficiency of the complex mental control of shifting/mental flexibility and the reliability of working memory during mental switching. The Shift worker group's ($M = 9.93$, $SD = 2.89$) mean accuracy in visual set-shifting/mental flexibility and reliability of working memory during mental switching was similar to that of the control participants group. There was a trend of a more reliable visual set-shifting performance in the Shift worker group than in the OSA patient group, although Shift worker group performance was not significantly different from either the control group or the OSA patient group.

Table 9. Post hoc comparison of means of Visual Elevator Accuracy Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Visual Elevator	**N**	**Mean (*SD*)***	**N**	**Mean (*SD*)**	**N**	**Mean (*SD*)***
Accuracy Scaled Score	15	$10.86\ (1.96)_h$	15	9.93 (2.89)	15	$8.13\ (2.26)_h$

*(Means with common subscripts are significantly ($p < .05$) different from one another.)

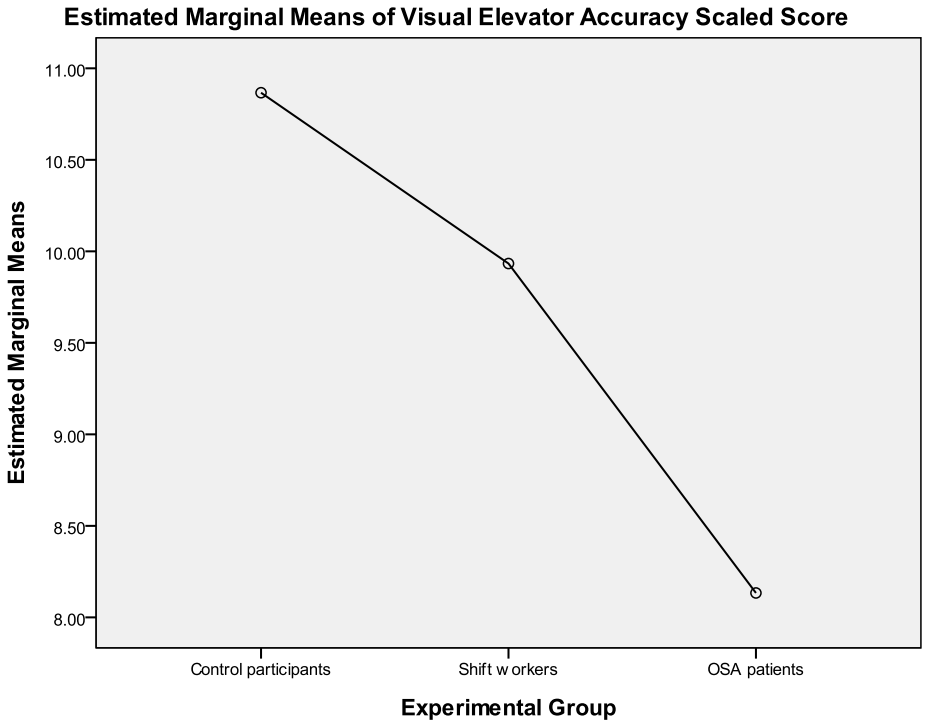


Figure 10. Means for Visual Elevator Accuracy Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.7 Visual Elevator Time Scaled Score

- *Visual set-shifting measure (efficiency)*

Univariate analysis showed that there was a significant main effect for the participant groups on the Visual Elevator Time Scaled Score, $F(2, 44) = 3.58$, $p = .037$, *partial* $\eta^2 = .146$, observed power = .632 (see Table 3). Post hoc Tukey HSD test comparison of means indicated significant difference between the control group and the OSA patient group ($p < .05$) only (see Table 10). Figure 3 and 11 showed that the OSA patient group ($M = 9.86$, $SD = 2.29$) performed significantly more poorly than the control participant group ($M = 11.93$, $SD = 2.05$) on Visual Elevator Time measuring the efficiency of the complex mental control of shifting/mental flexibility and working memory during switching. There was a trend of reduced efficiency in visual set-shifting performance in the Shift worker group ($M = 10.13$, $SD = 2.53$), although it was not significantly different from either the control participant group or the OSA patient group.

Table 10. Post hoc comparison of means of Visual Elevator Time Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Visual Elevator Time	**N**	**Mean (*SD*)***	**N**	**Mean (*SD*)**	**N**	**Mean (*SD*)***
Scaled Score	15	$11.93\ (2.05)_i$	15	10.13 (2.53)	15	$9.86\ (2.29)_i$

*(Means with common subscripts are significantly ($p < .05$) different from one another.)

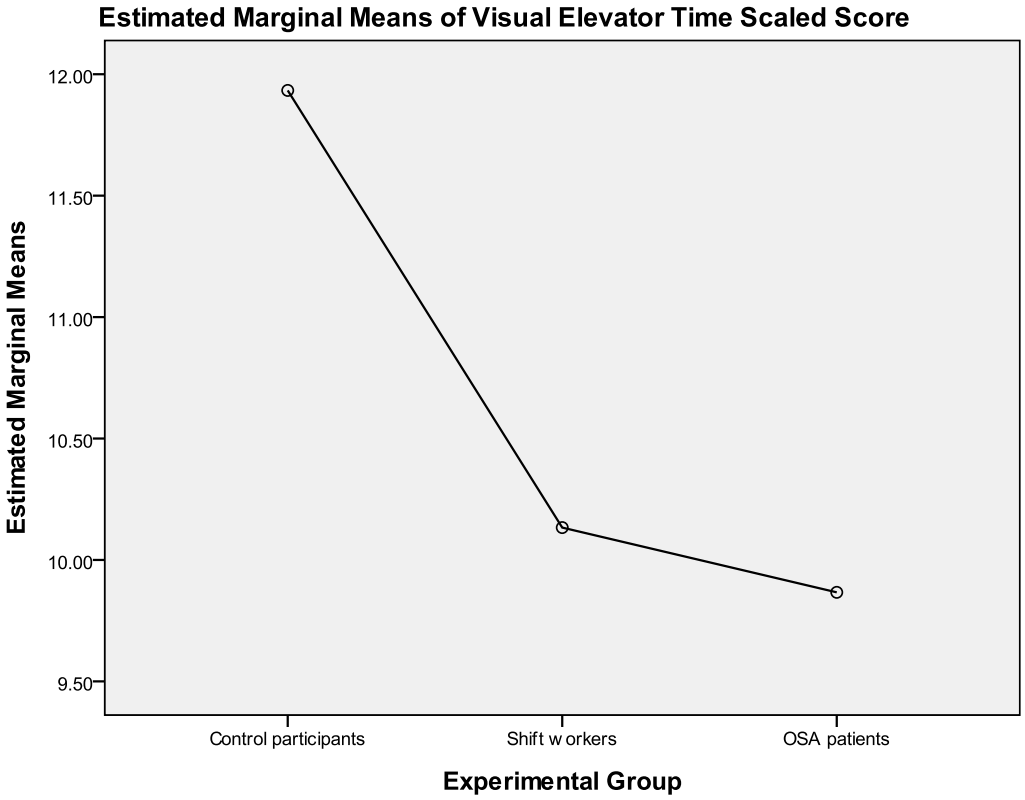


Figure 11. Means for Visual Elevator Time Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.8 Elevator Counting with Reversal Scaled Score

- *Auditory set-shifting measure*

Univariate analysis showed that there was a significant main effect for the participant groups on the Elevator Counting with Reversal Scaled Score, $F(2, 44) = 9.80$, $p = .0005$, *partial* $\eta^2 = .318$, observed power = .976 (see Table 3). Comparisons of means, using the post hoc Tukey HSD test ($p = .05$), indicated significant difference between the control group and the OSA patient group as well as between the control group and the Shift worker group ($p < .01$) (see Table 11). Figure 3 and 12 showed that both the OSA patient group ($M = 8.53$, $SD = 2.74$) and the Shift worker group ($M = 9.13$, $SD = 2.72$) performed significantly more poorly than the control participant group ($M = 12.53$, $SD = 2.53$) on Elevator Counting with Reversal, measuring predominantly the efficacy in auditory attentional switching/mental flexibility and the reliability of working memory during switching. In addition, there was no significant difference in auditory set-shifting performance between the OSA patient group and the Shift worker group.

Table 11. Post hoc comparison of means of Elevator Counting with Reversal Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Elevator Counting with	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *
Reversal Scaled Score	15	$12.53\ (2.53)_{jk}$	15	$9.13\ (2.72)_{k}$	15	$8.53\ (2.74)_{j}$

*(Means with common subscripts are significantly ($p < .01$) different from one another.)

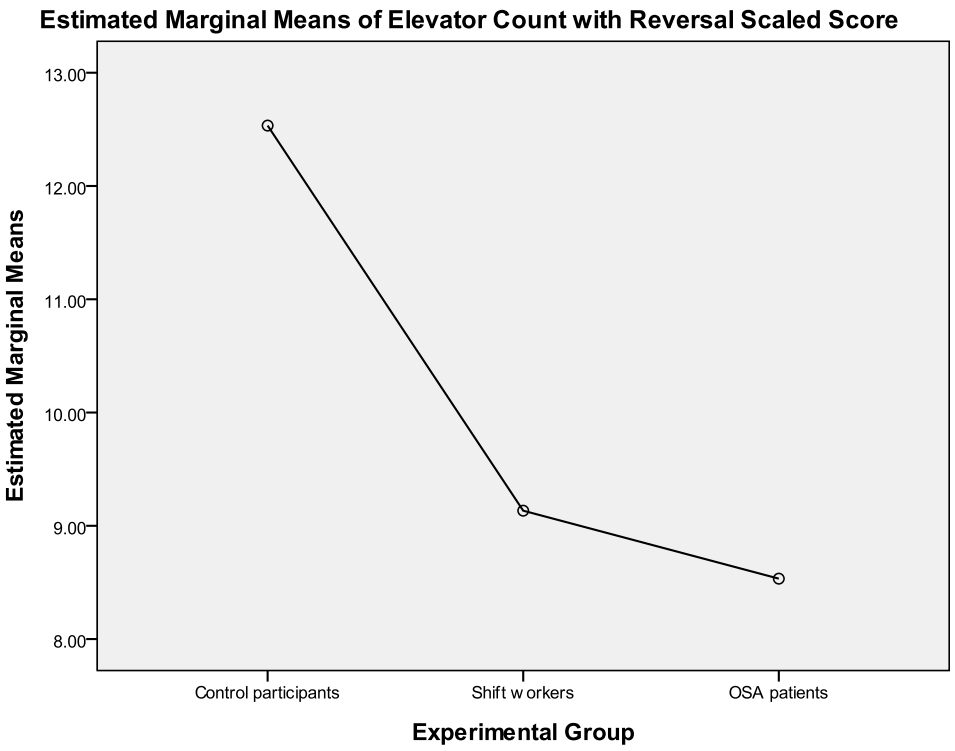


Figure 12. Means for Elevator Counting with Reversal Scaled Score for patients with OSA, shift worker, and controls.

4.3.2.9 Verbal Working Memory Scaled Score

- *Updating of verbal information measure*

Univariate analysis showed that there was a significant main effect for the participant groups on the Verbal Working Memory Scaled Score, $F(2, 44) = 11.55$, $p = .0005$, *partial* $\eta^2 = .355$, observed power = .990 (see Table 3). Comparisons of means using the post hoc Tukey HSD test indicated significant difference between the control group and the OSA patient group as well as between the control group and the Shift worker group ($p < .01$) (see Table 12). Figure 3 and 13 showed that both the OSA patient group ($M = 8.40$, $SD = 2.87$) and the Shift worker group ($M = 8.33$, $SD = 2.23$) performed significantly poorer than the control participant group ($M = 12.20$, $SD = 2.42$) on Verbal Working Memory test, measuring the updating ability on verbal information. In addition, there was no significant difference in Verbal Working Memory performance or verbal updating ability between the OSA patient group and the Shift worker group.

Table 12. Post hoc comparison of means of Verbal Working Memory Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Verbal Working	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *
Memory Scaled Score	15	$12.20\ (2.42)_{lm}$	15	$8.33\ (2.23)_{l}$	15	$8.40\ (2.87)_{m}$

*(Means with common subscripts are significantly ($p < .01$) different from one another.)

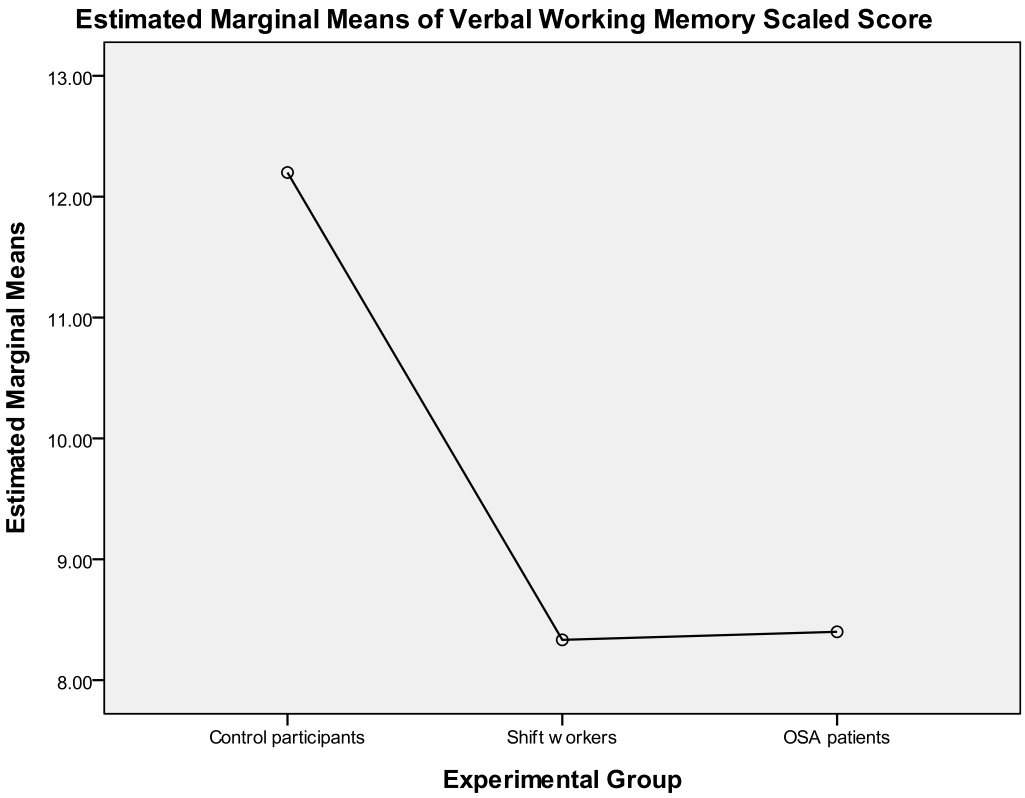


Figure 13. Means for Verbal Working Memory Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.10 Symbolic Working Memory Scaled Score

- *Updating of symbolic information measure*

Univariate analysis showed that there was a significant main effect for the participant groups on the Symbolic Working Memory Scaled Score, $F(2, 44) = 11.86$, $p = .0005$, *partial* $\eta^2 = .361$, observed power = .992 (see Table 3). Comparisons of means using the post hoc Tukey HSD test indicated significant difference between the control group and the OSA patient group as well as between the control group and the Shift worker group ($p < .01$) (see Table 13). Figure 3 and 14 showed that both the OSA patient group ($M = 9.67$, $SD = 2.47$) and the Shift workers group ($M = 9.07$, $SD = 2.05$) performed significantly poorer than the control participants group ($M = 12.60$, $SD = 1.80$) on Symbolic Working Memory test, measuring the updating ability on symbolic information. In addition, there was no significant difference in performance in Symbolic Working Memory or symbolic updating ability between the OSA patient group and the Shift worker group.

Table 13. Post hoc comparison of means of Symbolic Working Memory Scaled Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Symbolic Working	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)** *
Memory Scaled Score	15	$12.60\ (1.80)_{no}$	15	$9.07\ (2.05)_{n}$	15	$9.67\ (2.47)_{o}$

*(Means with common subscripts are significantly ($p < .01$) different from one another.)

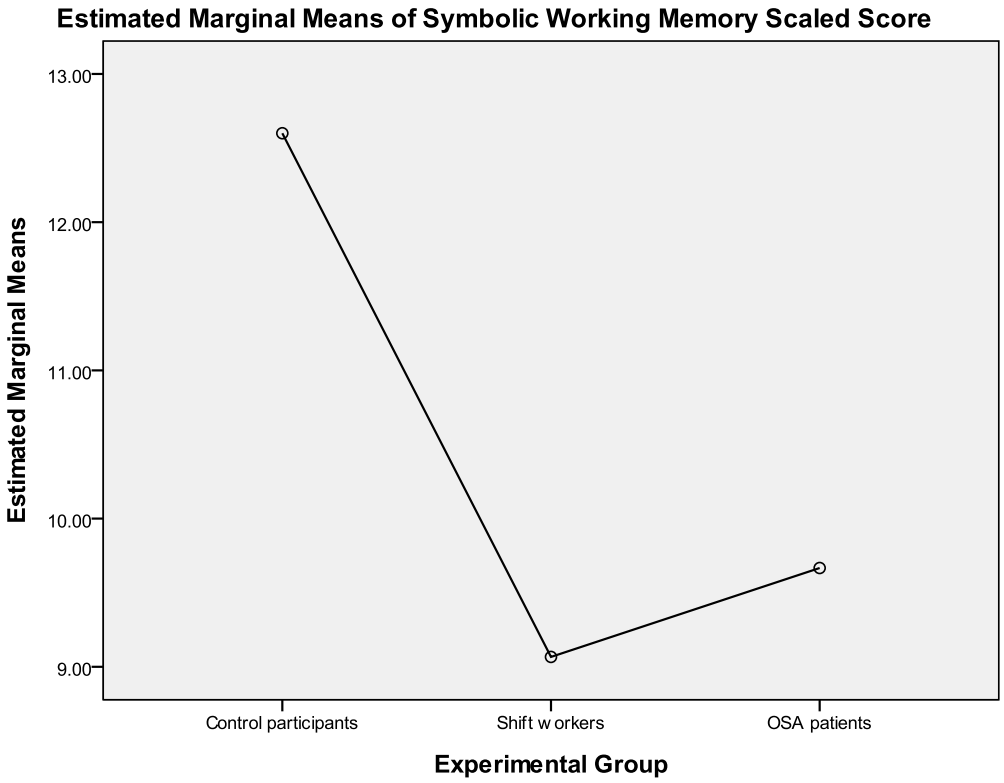


Figure 14. Means for Symbolic Working Memory Scaled Score for patients with OSA, shift workers, and controls.

4.3.2.11 Stroop Interference Chafetz T Score

- *Inhibition of prepotent responses measure*

Univariate analysis showed that there was a significant main effect for the participant groups on the Stroop Interference Chafetz *T* Score, $F(2, 44) = 10.74$, $p = .0005$, *partial* $\eta^2 = .338$, observed power = .985 (see Table 3). Comparisons of means using the post hoc Tukey HSD test indicated significant difference between the control group and the OSA patient group as well as between the control group and the Shift worker group ($p < .01$) (see Table 14). Figure 3 and 15 showed that both the OSA patient group ($M = 46.80$, $SD = 7.57$) and the Shift worker group ($M = 50.53$, $SD = 8.09$) were significantly worse than the control participant group ($M = 60.20$, $SD = 8.81$) on Stroop Interference Chafetz T score, indicating that both the OSA patients group and the Shift worker group were significantly poorer in inhibiting prepotent responses than the control participant group. However, the OSA patient group did not demonstrate significantly worse ability inhibiting prepotent responses in the Stroop test than the Shift worker group.

Table 14. Post hoc comparison of means of Stroop Interference Chafetz T Score - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Stroop Interference	**N**	**Mean (*SD*)** *	**N**	**Mean *(SD)*** *	**N**	**Mean (*SD*)** *
Chafetz T Score	15	$60.20\ (8.81)_{pq}$	15	$50.53\ (8.09)_{q}$	15	$46.80\ (7.57)_{p}$
[Scaled Score]		$13.07\ (2.69)_{rs}$		$10.13\ (2.53)_{s}$		$9.00\ (2.14)_{r}$

*(Means with common subscripts are significantly ($p < .01$) different from one another.)

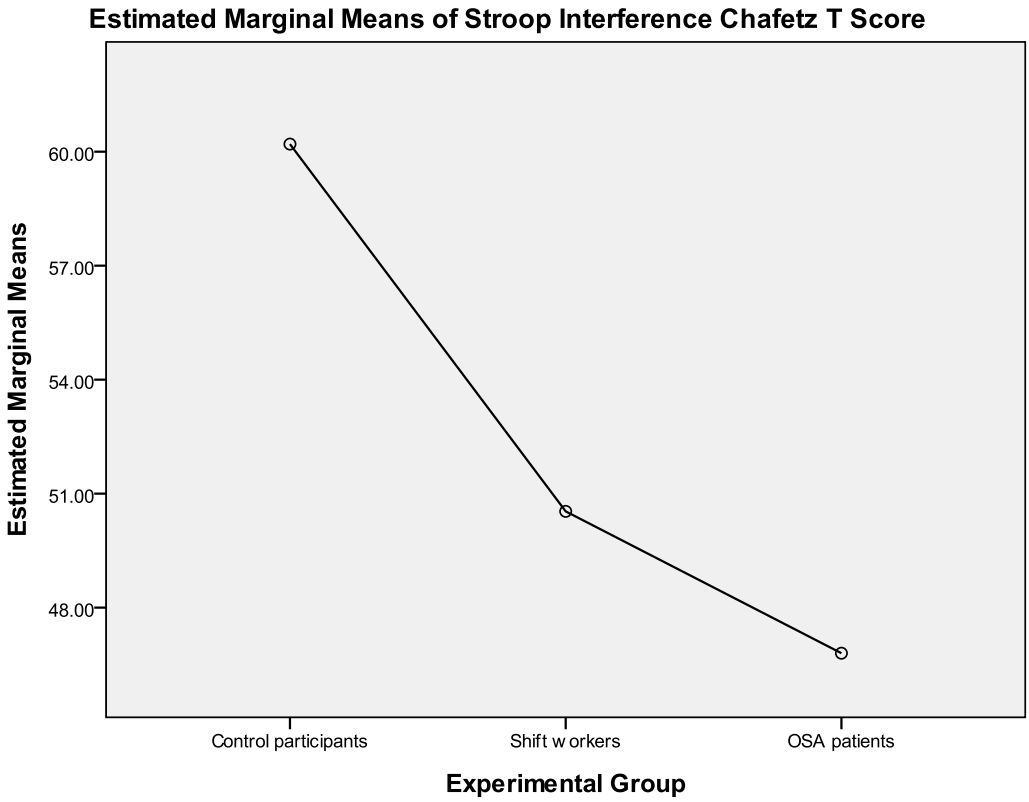


Figure 15. Means for Stroop Interference Chafetz *T* Score for patients with OSA, shift workers, and controls.

4.3.2.12 Austin Maze 10th-Trial Total Errors

- *Complex spatial learning measure – Planning, Error utilization, Behavioural regulation (reliability)*

Univariate analysis showed that there was a significant main effect for the participant groups on the Austin Maze 10th-Trial Total Errors, $F(2, 44) = 7.754$, $p = .001$, partial $\eta^2 = .270$, observed power = .935 (see Table 3). Comparisons of means using the post hoc Tukey HSD test indicated significant difference between the control group and the OSA patient group ($p < .05$) only (see Table 15). Figure 4 and 16 showed that there was a general increasing trend in the mean number of errors committed on Austin Maze path learning across the control group ($M = 46.27$, $SD = 26.43$), the Shift worker group ($M = 100.27$, $SD = 67.39$), and the OSA patients group ($M = 138.00$, $SD = 84.24$). However, only the difference in the mean number of Total Errors between the OSA patient group and the controls reached statistical significance ($p < .001$), indicating that the OSA patient group committed significantly more errors across the first ten trials of path learning than did the controls. There was a trend suggesting the reliability of complex spatial learning as well as planning, error utilization, behavioural regulation in the Shift worker group was better than the OSA patient group but poorer than the controls, although the differences were not significant.

Table 15. Post hoc comparison of means of Austin Maze 10th-Trial Total Errors - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Austin Maze 10th-Trial	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)**	**N**	**Mean (*SD*)** *
Total Errors	15	$46.27\ (26.43)_t$	15	100.27 (67.39)	15	$138.00\ (84.24)_t$

*(Means with common subscripts are significantly ($p < .001$) different from one another.)

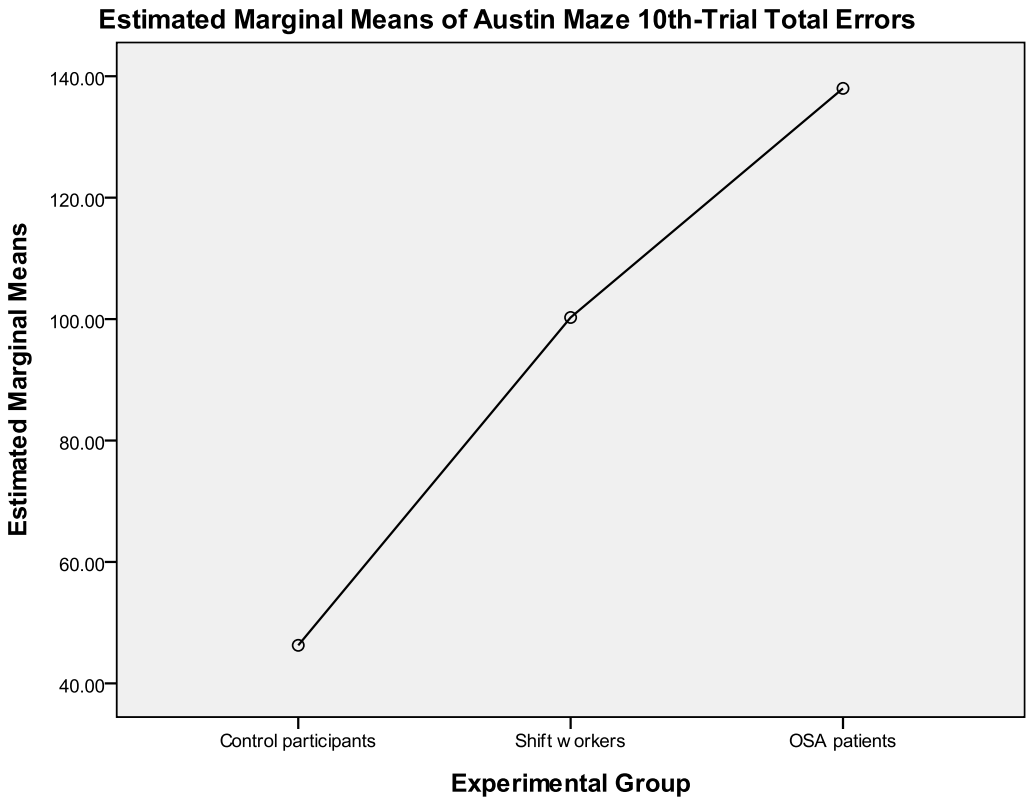


Figure 16. Means for Austin Maze 10th-Trial Total Errors for patients with OSA, shift workers, and controls.

4.3.2.13 The differential relationships between various measured neuropsychological functions and Austin Maze 10th-Trial Total Error across different groups

Bivariate correlation analyses were conducted seperarately on the data sets of patients with OSA, shift workers and controls in order to investigate the relationships between various measured neuropsychological functions and Austin Maze error performance across different groups.

In the present study, for the patients with OSA group, the cumulative errors to trial 10 of Austin Maze was moderately correlated with poor performance on Telephone Search Time (r = -.597, p < .05), Visual Elevator Time (r = -.384, p = .157), Lottery (r = -.532, p < .05), Verbal Working Memory (r = -.407, p = .132), and Stroop Interference Chafetz *T* Score (r = -.515, p < .05). By contrast, none of the cognitive performance or sleepiness scores in the shift workers group showed significant strong relationship with Austin Maze cumulative errors. Similarly, for the control participants group, apart from a moderate negative correlation with Map Search (r = -.495, p < .1), no other significant relationship with the other cognitive performance or sleepiness scores was found.

4.3.2.14 Austin Maze 10th-Trial Total Time

- *Complex spatial learning – Planning, Error utilization, Behavioural regulation (efficiency)*

Univariate analysis showed that there was a significant main effect for the participant groups on the Austin Maze 10th-Trial Total Time, $F(2, 44) = 5.388$, $p = .008$, partial $\eta^2 = .204$, observed power = .816 (see Table 3). Comparisons of means using the post hoc Tukey HSD test indicated significant difference between the control group and the Shift worker group as well as between the control group and the OSA patient group (see Table 16). Figure 4 and 17 showed the means of the total time spent on learning the Austin Maze path in the Shift worker group ($M = 603.27$, $SD = 221.48$) and the OSA patients group ($M = 595.20$, $SD = 273.51$) were both significantly larger than that in the control participants group ($M = 371.67$, $SD = 142.96$). While both the OSA patient group and the Shift worker group spent statistically more time on the first 10 learning trials than the control participants group ($p < .05$), there were no significant differences between the OSA patient group and the Shift worker group on this performance measure, suggesting their efficiencies in complex visual learning as well as planning, error utilization, behavioural regulation were as poor.

Table 16. Post hoc comparison of means of Austin Maze 10th-Trial Total Time - Tukey HSD test

Measure	**Control participants**		**Shift workers**		**OSA patients**	
Austin Maze	**N**	**Mean (*SD*)** *	**N**	**Mean (*SD*)***	**N**	**Mean (*SD*)** *
10th-Trial Total Time	15	371.67 (142.96)$_{uv}$	15	603.27 (221.48)$_{v}$	15	595.20 (273.51)$_{u}$

*(Means with common subscripts are significantly ($p < .05$) different from one another.)

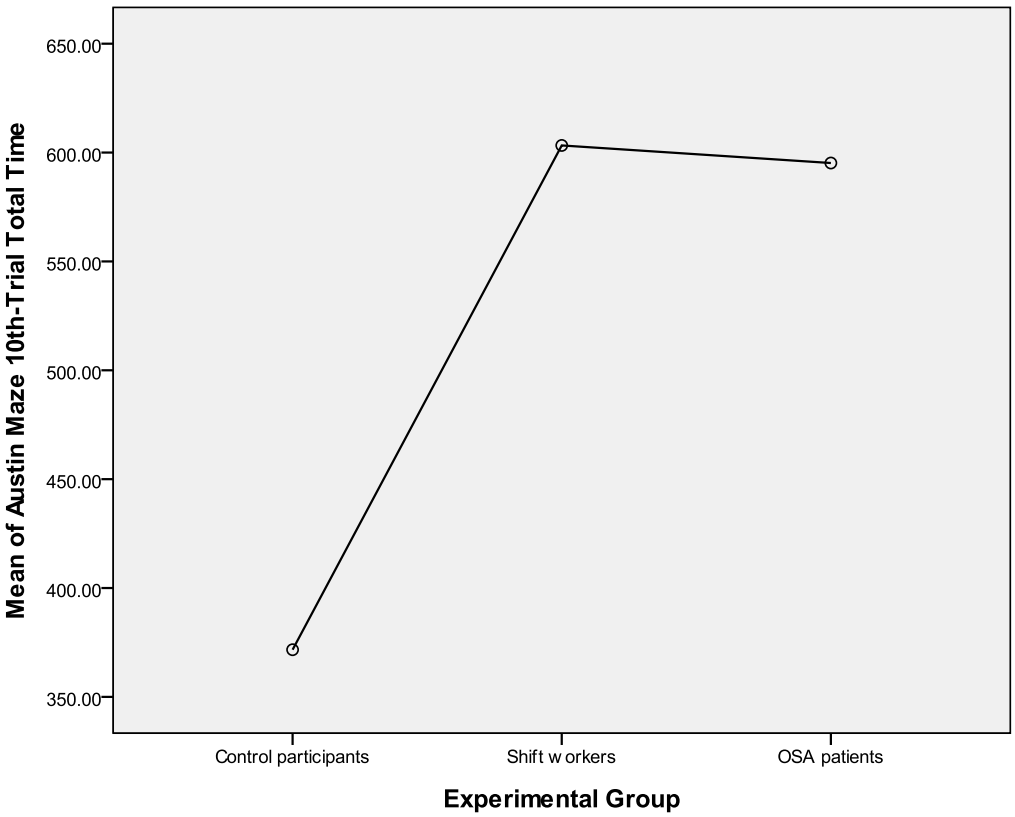


Figure 17. Means for Austin Maze 10th-Trial Total Time for patients with OSA, shift workers, and controls.

CHAPTER FIVE: DISCUSSION OF RESULTS

5.1 Selective Attention

Map Search, Telephone Search, and Elevator Counting with Distraction

The Map Search and Telephone Search subtest of TEA are visual selective attention tasks (Bates et al., 2001; Chan et al., 2002; Robertson et al., 1996) based on principle component analyses, involving visual search for predetermined targets against competing and irrelevant foils. Both tests require active inhibition of these competing distractors and selective activation of the target representation (Robertson et al., 1996). Though time plays a part in the derived scores of both of these tests, other tests where time plays an equally important role do not load on the same factors, ruling out the possibility that these subtests are simply sampling speed of processing (Robertson et al., 1996). The Map Search subtest requires that subjects search for as many designated symbols of one type as they can on a coloured map for a 2-minute period in any way they like; whereas the Telephone Search subtest not only requires subjects to look for 4 types of designated key symbol pairs and ignore other very similar symbol pairs as they search through searching entries one by one and column by column in a simulated classified telephone directory but also asks them to go back and continue searching the columns where they have failed to discover all the targets. As a result, if a subject finds relatively few of the targets when he reaches the end, he will end up spending more time going back, hence a poor score may suggest impulsive completion (Manly, Robertson, Anderson, & Nimmo-Smith, 1999). Mastery of the Telephone Search subtest requires mental comparison of the symbol pairs being read with all 4 designated key symbols held in the mind (i.e., working memory). That is, the person needs to keep the objective in mind, know the rules, recall the goal representation in order to 'discover' the targets. To meet these demands of the Telephone Search task, subjects may have to rely on an on-line memory store such as working memory (Goldman-Rakic, 1988; Baddeley, Bressi, Della Salla, Logie, & Spinnler, 1991; Petrides, 1994).

The Elevator Counting with Distraction subtest, which measures the ability to count one type of tone, while ignoring irrelevant, higher-frequency tones, is designed to be an auditory selective attention task (Robertson et al., 1996).

The current study found that, in control-referenced analyses, patients with OSA were

impaired in all three selective attention measures, both visual and auditory; whereas shift workers showed deficient performance only in one of the visual selective attention measures, i.e., the Telephone Search subtest, but no significantly poorer performance in another visual selective attention measure, i.e., Map Search subtest, and the auditory selective attention measure, i.e., Elevator Counting with Distraction.

The performance of shift workers might appear conflicting if individual subtests were considered in isolation. Because there was one intact selective attention performance from each modality, visual and auditory, we can conclude that shift workers did not show any general selective attention impairment. The less-than-expected level of performance of shift workers on Telephone Search can be attributed to their impulsivity in finishing the task resulting in the need to spend more time going back to search for the remaining targets, and/or poor working memory in holding all the 4 types of template pairs resulting in missing one type of symbol. Poor impulse control and working memory can be considered within the realm of executive dysfunction, which will be discussed in further details. Alternatively, the current result can be interpreted as evidence of mild deficits in visual selective attention in shift workers was only revealed in complex attentional task.

Using standardized scores and thereby comparing the group performances with those of the normative population, a mildly reduced visual selective attention ('low average range') was demonstrated only in a complex visual attention task (Telephone Search subtest) but not in simple visual attention task (Map Search subtest) in shift workers. A mild reduction in auditory selective attention ('low average range') was evident in patients with OSA only.

The mild reduction in selective attention on standardized scaled scores in both groups and that the lack of any significant difference between the two groups in control-referenced analysis suggest that intermittent hypoxemia may not contribute significantly independent of sleep fragmentation to selective attention deficiency in patients with OSA, and sleep deprivation is likely to be the primary factor.

The present findings are consistent with a recent experiment on the effects of sleep deprivation on attentional lapses during performance on a visual selective attention task (Chee et al., 2008). Chee and colleagues (2008) found reduced activation in the frontoparietal regions during attention lapses in addition to decreased mean activation in these regions after sleep deprivation. Relative to lapse after a normal

night's sleep, attention lapses during sleep deprivation were associated with the expected reduction in activity in frontal and parietal control, but also a marked reduction in visual sensory cortex activation and thalamic activation. Despite these differences, the fastest responses after normal sleep and after sleep deprivation elicited comparable frontoparietal activation. The authors concluded that performing a visual selective attention task while sleep deprived involved periods of apparently normal neural activation interleaved with periods of depressed cognitive control, visual perceptual functions and arousal. These findings also support the state instability hypothesis by providing evidence that neural changes are occurring rapidly and frequently in the brain when sleep-deprived individuals are attempting to maintain goal-directed behaviour in the presence of elevated homeostatic sleep drive.

5.2 Sustained Attention or Vigilance

Lottery

The Lottery subtest of TEA is designed to measure the ability to self-sustain attention in the absence of external manipulators of attention such as novelty, where mock lottery numbers have to be monitored for rare targets ending in a particular number pair (Robertson et al., 1996). On studying a group of patients who had sustained severe traumatic brain injury (TBI), subdivided into early (< 1 year post injury) and late phase of recovery (> 2 years post injury), with matched controls on the TEA, Bate and colleagues (2004) found significantly deficient performances on the Lottery subtest in the early recovery group only; while overall, this subtest was significantly related to traditional sustained attention measures, PASAT, in the factor analysis, confirming its utility as an ecologically valid test of sustained attention in differentiating early and late TBI on the partial recovery of attentional function.

In the present control referenced analysis, there were no significant differences in performance on Lottery subtest between OSA patients, shift workers, and control participants. Using standardized scores and thereby comparing the group performances with those of the normative population, a mildly reduced sustained attention as measured by Lottery subtest ('low average range') was demonstrated in shift workers.

This indicates that while patients with OSA or shiftworkers are likely to show deficient performances on the PVT as in Dinges and colleagues' (1997) study or on

the CPT (Roehrs et al., 1995), they may perform adequately in another sustained attention measure, the Lottery subtest of TEA. Both PVT and CPT are clinical instruments commonly used to study slowed reaction times and increased lapse frequency associated with cumulative sleep restriction; while the Lottery test is a neuropsychological test designed to measure the sustained attention construct in Posner and Peterson's (1990) model of attention. In other words, patients with OSA and shift workers are likely to have a deficient sustained attention capacity characterized by slow reaction times and increased attention lapses, but generally remain fairly able to detect infrequent meaningful information which they are anticipating in a monotonous auditory continuous performance task lasting for 10 minutes. Hence, one may be unable to respond quickly to meaningless signals or even miss the target, but remain able to notice meaningful auditory information in a speech deliberately attended to. This is a form of preparatory attention recognized by LaBerge (2000) as reflected in everyday attention in real world settings. It should be noted that the Lottery test lasts for about 10 minutes, and it remains uncertain whether patients with OSA and shift workers are able to sustain attention for a longer time, for example 30 minutes, in order to pick out important information they are anticipating.

The current results suggest that patients with OSA and shift workers, if motivated, have the ability to sustain their attention briefly and pick out meaningful auditory information even in a monotonous environment; however, this does not contradict the general findings of poor vigilance affecting the response time and errors in activities demanding long period of sustained attention such as driving in highway.

The relatively minor reduction in sustained attention on standardized scaled scores in shift workers ('low average range') and patients with OSA ('lower end of the average range') and the lack of any significant difference between the two groups in control-referenced analysis suggest that intermittent hypoxemia may not contribute significantly independent of sleep fragmentation to sustained attention deficiency in patients with OSA, and sleep deprivation is likely to be the primary factor.

5.3 Divided Attention

Telephone Search while Counting (Dual Task Decrement)

While selective attention requires attention focused on one source or kind of information to the exclusion others, divided attention require attention to be divided

or shared between two or more sources or kinds of information, or two or more mental operations/behavioural responses, although subjects are still highly selective when doing dual tasks (Davies, Jones, & Taylor, 1984; Solberg & Mateer, 1989). Divided attention deficits may result from a limited capacity of the system for controlling processing, dividing itself between two sources of information or two kinds of responses when carrying out two tasks or two elements of unfamiliar skill simultaneously (van Zomeren & Brouwer, 1994). Apart from processing capacity, individual performance on a divided attention task is determined by the efficiency of allocating or time-sharing of attentional resources among separable processes and switching attention between subtasks that cannot be executed simultaneously (van Zomeren & Brouwer, 1994). In the Telephone Search Dual Task subtest, simultaneous performance of two tasks would be likely to draw on the ability to switch attention from one to the other, as well as sustaining attention on each task successively (Robertson et al., 1996). In the Telephone Search Dual Task subtest, the subjects must search the telephone directory while simultaneously counting strings of tones presented by a tape recorder and the subtest yields a 'dual task decrement' score by subtracting the time per target score of the previous Telephone Search subtest from the current subtest. By doing so, the ability of the subjects to divide their attention would be less confounded with the differential selective attention ability and motor speed, both of which have contributed to the performance of simple Telephone Search task. This means that, the Telephone Search Dual Task Decrement score can be reasonably interpreted in terms of the efficacy of divided attention, controlled for other factors like selective attention and motor speed. On principle component analyses, this Dual Task Decrement score was found to be loaded on the divided attention factor by Bates and colleagues (2001) and Chan and colleagues (2002) and sustained attention factor by Robertson and colleagues (1996).

In the current study, both patients with OSA and shift workers were found to have significant divided attention deficits, as compared to control participants. In addition, the severity of divided attention deficits in patients with OSA was significantly worse than that of shift workers. Few traditional neuropsychology tests are formally classified as divided attention, but the SDMT (Smith, 1982) has been used as a test of divided attention (Ponsford & Kinsella, 1992) and the PASAT (Gronwall, 1977), is often cited as a measure of divided attention (Kinsella, 1998; van Zomeren & Brouwer, 1994), although other cognitive processes are also involved in these tasks and have not been controlled for (Robertson et al., 1996). The present results are consistent with available research findings in that OSA patients are found

to have impaired performances on the PASAT (Findley et al., 1986; Presty et al., 1991; Englement et al., 1993), and the Digit Symbol task (Bedard et al., 1991), a task similar to SDMT, which has also been cited as a measure of divided attention by van Zomeren & Brouwer (1994).

Reduced capacity for divided attention undoubtedly results in significant impairment in daily life. In many common activities, we are required to divide our attention among several subtasks such as listening to the radio while making dinner or driving while talking to apassenger (Solberg & Mateer, 1989). The current finding that patients with OSA revealed impaired divided attention on a neuropsychology test is consistent with the findings from driving simulator studies in patients with OSA.

George, Boudreau, & Smiley (1996) found that patients with OSA when compared with control participants performed substantially worse on a Divided Attention Driving Test (DADT) comprising both a tracking task controlled by a steering wheel and a secondary visual search task. Moreover, the mean difference between the two groups on this dual task was greater than on a simple visual search measure, indicating that patients with OSA were more impaired on tasks requiring the ability to divide attention (George et al., 1996). While driving, the participant is required to process complex visual, tactile and auditory information including visual search tasks like scanning for pedestrians, other vehicles, traffic signs and lights in order to produce a well-coordinated motor output of vehicle control, and leep the vehicle within the lane (i.e., tracking) (George et al., 1996). Driving, involving speed and lane control as well as the monitoring of these tasks, is therefore a divided attention task (George, 2004). Indeed, as a group, patients with OSA have a higher risk of having motor vehicle crashes (George, Nickerson, Hanly, Millar, & Kryger, 1987).

The current results also suggest that despite a relatively intact basic attention function in shift workers, they can have substantially reduced ability to divide attention in multitasking conditions, albeit less severe than OSA patients. This might have contributed to the increased work and road-related accident rate found in shift workers (Adam-Guppy & Guppy, 2003; Akerstedt, 2003; Folkard & Tucker, 2003; Knauth & Hornberger, 2003; Shen et al., 2006). Relatively normal behaviour in simple daily activities might provide a false impression of shift workers so that they seem to have an adequate capacity to cope quite well in multitasking situations. Consequently, it may appear unnecessary to take any precautions on daily multitasking tasks, such as driving, which place strong demand on divided attention; as such shift workers may put themselves into high risk situations inadvertently.

Using standardized scores and thereby comparing the group performances with those of the normative population, divided attention ability was in 'the borderline impaired range' in patients with OSA only and that patients with OSA performed significantly more poorly than shift workers in control-referenced analysis. As sleep deprivation is a common factor between OSA patients and shift workers, our findings support that the notion that intermittent hypoxemia is more important than sleep deprivation in contributing to the divided attention deficits in patients with OSA in comparison to the relatively minor reduction in divided attention abilities in shift workers; nevertheless, sleep deprivation may have compounded on this detrimental effect.

5.4 Set-Shifting or Attentional Switching

Visual Elevator and (Auditory) Elevator Counting with Reversal

Both the Visual Elevator and (Auditory) Elevator Counting with Reversal subtests require the frequent shifting of direction of counting backward and forward in single digits (Robertson et al., 1996). In the Visual Elevator subtest, participants count up and down as they follow a series of visually presented 'floors' in the elevator and arrows to indicate the direction of counting. This reversal task is a measure of attentional switching, and hence of cognitive flexibility, and is self-paced. Apart from an accuracy score (number of correct count), there is also a time-per-switch measure derived from this test (Robertson et al., 1996). In the (Auditory) Elevator Counting with Reversal subtest, the scenario is the same as the Visual Elevator subtest, except that the 'floor' and the direction of counting are signaled by low, medium and high pitched tones, and they are presented at a fixed speed on audio tape with the number of correct counts as the accuracy measure (Robertson et al., 1996). A widely used measure of executive function is WCST (Berg, 1948; Heaton et al., 1981, 1993; Nelson, 1976), originally developed as a test of 'flexible thinking'. The WCST is a somewhat complicated measure in which subject must work out a rule, use feedback and remember previous responses, in addition to switching from one strategy to another. The Visual Elevator subtest of TEA, which shows a significant relationship to the WCST (Robertson et al., 1996) and loaded on attentional switching factor on confirmatory factor analysis (Chan et al., 2002), reduced the demands for all but the last of these capacities, i.e., attentional switching or cognitive flexibility in executive functioning (Manly et al., 1999). The Auditory Elevator with Reversal subtest was loaded on auditory working memory factor in Robertson and colleagues'

(1996) analysis and attentional switching in Bate and colleagues' (2001) analysis. It is likely that both tasks mainly measure cognitive flexibility or the efficiency of attentional switching but also rely on the efficacy and reliability of a working memory store when shifting of attention is required.

Notably, flexible shifting between mental sets and attending to changes in stimulation or feedback, as required in the WCST, while being regarded as "frontal functions" or core subprocesses of executive functions (Miyake et a.l, 2000), are also considered integral to "supervisory attentional control" processes in Shallice's (1982) model (van Zomeren & Brouwer, 1994).

In the current study, patients with OSA demonstrated deficient performances on the Visual Elevator subtest, both on Accuracy score and Time-per-switch score, and on Elevator Counting with Reversal, as compared to control participants. These results indicated that OSA patients are impaired in their attentional switching or mental shifting resulting in a significant reduction in the accuracy and efficiency in mental processes, introducing errors into working memory. Mental flexibility or shifting is generally grouped under the term "executive functions", and breakdown in this and other executive functions are generally associated with prefrontal lesions (Fuster, 1996; Stuss & Benson, 1986) and can also be due to subcortical brain lesions (Goldberg & Bilder, 1987; Lezak et al., 2004). The current findings are consistent with previous research on different aspects of executive dysfunction found in patients with OSA. For example, increasingly abnormal breathing and oxygenation during sleep in heavy snorers has been found to be related to obtaining fewer categories on the WCST (Block et al., 1986). OSA patients were found to commit significantly more perseverative errors on the WCST, suggesting deficits in set-shifting subprocesses of executive function (Lee et al., 1999). Using a modified version of the WCST, Naegele and colleagues (1995) reported that errors on this task are predictive of the deleterious effects of severe hypoxemia on cognitive performance of patients with OSA.

Compared to control participants, shift workers recorded significantly more errors on Elevator Counting with Reversal subtest. On the Visual Elevator subtest, shift workers did not committed significantly more errors than controls and there was a trend of larger time-per-switch measures albeit not statistically significant. However, none of the three set-shifting measures of shift workers was significantly different from that of patients with OSA.

These results indicated that there is some reduction in the efficiency of attention switching or set-shifting, sometimes making the process slower than expected; in most circumstances, this will not result in significantly more errors unless the task also places high demands on selective attention, as in the case of Auditory Elevator Counting with Reversal where distinguishing the three types of tones requires a high level of concentration.

Our finding of reduced efficiency in set-shifting ability in shift workers as compared to controls suggests sleep deprivation may have detrimental effects on mental flexibility. This notion is supported by the results of Harrison and Horne's (1999) sleep deprivation study using an applied problem-solving game, Masterplanner (Saunders, 1989), involving changing reinforcement contingencies and scores for perseverative errors similar to the WCST, hence considered as a measure of set-shifting. Among the sleep-deprived subjects, a key dissociation was found between the impaired performance on Masterplanner, rigid thinking with increased perseverative errors and marked difficulty in appreciating an update situation, against the unaffected performance on a convergent reasoning task that did not require set-shifting (Harrison & Horne, 1999).

Using standardized scores and thereby comparing the group performances with those of the normative population, a mildly reduced set-shifting ability ('lower end of the average range') was demonstrated on accuracy of visual and auditory set-shifting tasks in patients with OSA. By contrast, shift workers performance on visual and auditory set-shifting tasks was in 'the average range' on standardized scaled score. As sleep deprivation is a common factor between patients with OSA and shift workers, our findings support the notion that intermittent hypoxemia is more important than sleep deprivation in contributing to the set-shifting deficits in patients with OSA in comparison to the relatively minor reduction in divided attention abilities in shift workers; nevertheless, sleep deprivation may have compounded this detrimental effect.

5.5 Updating – Working Memory

Verbal Working Memory and Symbolic Working Memory

In the current study, both OSA patients and shift workers were found to have deficient performances on both Verbal and Symbolic Working Memory subtests of WRAML-2, compared to control participants. This is consistent with previous

research on the working memory ability of patients with OSA.

Working memory speed in OSA was significantly slower than in healthy subjects, and a group average map showed an absence of dorsolateral prefrontal activation, regardless of nocturnal hypoxia (Thomas et al., 2005). Even after treatment, resolution of subjective sleepiness contrasted with no significant change in behavioural performance, persistent lack of prefrontal activation, and partial recovery of posterior partial activation (Thomas et al., 2005). These findings suggest that working memory may be impaired in OSA and that this impairment is associated with disproportionate impairment of function in the dorsolateral prefrontal cortex (Thomas et al., 2005). By comparing the working memory task performance and activation maps between the hypoxic and nonhypoxic groups (using 90% minimum arterial oxygenation desaturation cutcoff), the authors concluded that nocturnal hypoxia may not be a necessary determinant of cognitive dysfunction, and sleep fragmentation may be sufficient (Thomas et al., 2005).

This hypothesis is supported by a finding that moderate sleep loss compromises the function of neural circuits critical to attentional allocation during working memory tasks, resulting in responses became slower, more variable, and more error prone even when an effort is made to maintain wakefulness and performance (Smith, McEvoy, & Gevins, 2002).

In our control referenced analysis, there was no significant difference in the mean Verbal and Symbolic Working Memory performance between OSA patients and shift workers. Using standardized scores and thereby comparing the group performances with those of the normative population, a mildly reduced verbal working memory ('lower end of the average range') was demonstrated in both patients with OSA and shift workers. As sleep deprivation is a common factor between patients with OSA and shift workers, our findings can be interpreted as supporting to the notion that sleep deprivation is more important than intermittent hypoxemia in contributing to working memory deficits, because a similar pattern of working memory deficiency was observed in both the shift workers and patients with OSA.

The current results are also consistent with a recent functional imaging study of working memory following normal sleep and after 24 and 35 hours of sleep deprivation, showing correlations of fronto-parietal activation with inter-individual difference in working memory performance (Chee et al., 2006). Specifically, activation of the left parietal and left frontal regions after normal sleep was

negatively correlated with performance accuracy decline from normal sleep to 24 hours of sleep deprivation thus differentiating persons who maintained working memory performance following sleep deprivation from those who were vulnerable to its effects (Chee et al., 2006).

5.6 Inhibition of Prepotent Responses

Stroop Interference

Prepotent responses generally have immediate survival benefit or have been previously met with a favourable risk-to-benefit ratio, making them 'default' responses that would occur within behavioural inhibition (Beebe & Gozal, 2002). Behavioural inhibition, as one of the executive functions defined by Barkley (1997) refers to three interrelated processes: (1) inhibition of the initial prepotent response of an event; (2) stopping of an ongoing response, which thereby permits a delay in the decision to respond; (3) the protection of this period of delay and the self-directed responses that occur within it from the disruption by competing events and response (interference control) (p.67). One laboratory measure of behavioural inhibition is the Stroop Colour-Word Interference Task, which requires test-takers to inhibit the prepotent response of word-reading to name the nonmatching colours in which a series of words are printed (Golden, 1978).

In the current study, both patients with OSA and shift workers were found to have a deficient Stroop Interference scores in comparison with the controls, suggesting a deficit in inhibition of (interfering) dominant responses, after accounting for processing speed and visual selective attention as reflected by the performance in neutral conditions on the Stroop task.

These results are consistent with previous research on the Stroop Colour Word Test as a measure of prepotent response inhibition of OSA patients. Naegele and colleagues (1995) reported prolonged time to complete the incongruent condition, Stroop Colour-Word Test, relative to the congruent conditions in patients with moderate to severe apnoea. Ferini-Strambi colleagues (2003) reported that performance on Stroop Colour-Word Test was significantly poorer in patients with OSA than in controls.

In the present study, there was no significant difference in Stroop Interference score between OSA patients and shift workers. Since both groups are affected by sleep

deprivation, it is possible that sleep deprivation is an important factor in behavioural inhibition, one of the core components of executive dysfunction. These results are consistent with sleep deprivation studies which have suggested that sleep deprivation results in the loss of ability to suppress a prepotent response. For instance, a range of executive functions that rely on inhibition are found to be adversely affected by sleep deprivation, resulting in impaired decision making (Harrison & Horn, 2000a) and deficient error detection (Nilsson et al., 2005; Tsai, Young, Hsieh, & Lee, 2005). On functional magnetic resonance imaging (fMRI), Chuah and colleagues (2006) found that regardless of the extent of change in inhibitory efficiency, 24-hour sleep deprivation lowered Go/No-Go sustained, task-related activation of the ventral and anterior prefrontal cortex bilaterally. Similar to the Stroop Colour-Word Test, the Go/No-Go task demands suppression of prepotent responses to avoid commission of errors. Successful response inhibition has been shown to activate the right inferior lateral prefrontal cortex (Konishi, Nakajima, Uchida, Sekibara & Miyashita, 1998; Garavan, Ross, & Stein, 1999) while ongoing error monitoring has been associated with the anterior cingulate cortex and medial frontal gyrus (Garavan, Ross, Kaufman, & Stein, 2003). These regions are considered to be crucial for the higher-order, cognitive control of behaviour, with anterior cingulated being important for conflict monitoring (Carter et al., 1998; Braver, Barch, Gray, Molfese, & Snyder, 2001) and the inferior frontal cortex for sustained attentional control (Braver, Reynolds, & Donaldson, 2003; Egner & Hirsch, 2005) as well as the suppression of irrelevant responses (Aron, Robbins, & Poldrack, 2004).

Nevertheless, Ferini-Strambi and colleagues (2003) revealed that the impairments in prepotent response inhibition, as demonstrated in untreated patients with OSA, was not reversed after 15-day and 4-month continuous positive airway pressure (CPAP) treatment. Based on these results, the authors suggests that deficits in inhibition of prepotent responses could be related to an irreversible, chronic hypoxemic damage, particularly affecting the frontal lobes, which are considered to be the crucial substrate of executive functions (Ferini-Strambi et al., 2003).

This interpretation is consistent with our findings that on standardized scaled scores the ability to inhibit prepotent responses was in 'the lower end of the average range' for patients with OSA, whereas shift workers demonstrated an average ability as compared to the normative sample population. Considering that only patients with OSA but not shift workers are affected by chronic hypoxemic change, our study provides support to the notion that intermittent hypoxemia is more important than

sleep deprivation in contributing to the prepotent reponses inhibition deficiency in patients with OSA, although sleep deprivation may have compounded this detrimental effect. Accordingly, intermittent hypoxemia causes neuronal damage particularly affecting the prefrontal cortex and basal ganglia (Beebe & Gozal, 2002; Beebe, 2005), and response inhibition is dependent on the right inferior lateral prefrontal cortex (Konishi et al., 1998; Garavan et al., 1999).

5.7 Complex Spatial Learning - Planning, Error Utilization, and Behavioural Regulation

Austin Maze

To recapitulate, the Austin Maze is a spatial learning task that is based upon Milner's earlier work examining maze learning following brain lesions (Milner, 1965). It comprises a 10 x 10 array of identical buttons within which is embedded a secret pathway that leads from the "start" (bottom left hand corner) to the "finish" (top right hand corner). The respondent's task is to learn the pathway, initially via trial and error but eventually by learning the maze and avoiding touching blocks off the path. Feedback is provided after each block is touched to indicate whether the response was correct or incorrect. Typically the criterion for success is judged as 3 consecutive error-free trials, as used in the current study.

The Austin Maze represents a complex spatial learning task, which was originally promoted as a measure of planning, error utilization and regulation based on findings that patients with frontal lobe lesions do poorly (Milner, 1965; Walsh & Darby, 1994). It has been suggested that the most valuable use of Austin Maze is in relation to the study of patients' error utilization; where patients with frontal lobe damage have difficulty eradicating errors from their performance: thus even if one error-free trial is attained, this performance is unlikely to be maintained (Walsh & Darby, 1994).

Crowe and colleagues (1999) used tasks of executive functioning, visuospatial memory and working memory to investigate the cognitive determinants of Austin Maze performance on a group of healthy undergraduate students. Based on the results from healthy undergraduate students, Crowe and colleagues (1999) suggested that the Austin Maze might measure visual-spatial ability in early trials when the individual is orienting themselves to the path and visual-spatial memory in later trials when consolidation of the details of the path assumes primary

importance (Crowe et al., 1999). Auditory working memory also accounted for a small but significant amount of variance; although its contribution to the overall performance may overlap with visuo-spatial memory (i.e., auditory working memory also contributes to visuospatial abilities, which in turn contribute to the overall performance) (Crowe et al., 1999). In contrast, no association between conventional measures of executive function (such as the WCST or the Tower of London (TOL)) was found in healthy adults (Crowe et al., 1999). It should be noted that no visuospatial working memory task was included in this study, precluding the possibility of this important of executive function component as a candidate contributing to maze performance. Also, there is a paucity of research on clinical populations that provides an examination of the role of different kinds of cognitive impairments following neurological damage or other pathophysiological processes in Austin Maze performance.

In the present study, when compared to the control participants, the patients with OSA showed deficits in their ability to learn the secret path in the Austin Maze committing significantly more errors and taking more time across the first ten trials of path learning than did the control participants. On the other hand, the shift workers, despite spending significantly more time across the first ten trials than the control participants, the cumulative errors to trial 10 was more than that of the control participants but fewer than that of the OSA patients, neither of the differences were statistical significant. Based on Bowden and colleagues' (1992) correlation study between errors to criterion and errors over 10 trials in both normal (r = .89) and clinical populations (r = .94), the performance of the OSA patients in the present study can be extrapolated to infer an impaired ability to learn this complex spatial path and a failure to eliminate errors across trials in order to reach the error-free criterion, while the shift workers may take somewhat longer time to reach the criterion, they neither committed significantly more errors nor used more trials to reach the criterion as compared to the control participants.

Results of the current study indicate a deficit in OSA patients' ability to utilize information from a particular behaviour in order to modify the next performance, which may be referred to as "error utilization". For example, it was common to observe participants in the OSA patients group showing poor abilities to regulate their error-making behaviour (e.g., failure to try a new direction when blocked but going back the same route repeatedly, or failure to inhibit a habitual error-making turn thereby making overshooting move in an impulsive manner, etc.) or devising various strategies (e.g., failure to initiate verbal mediation strategy by counting the

steps to know where to make turns, or failure to use an obvious method visualizing the secret route as a map to guide the learning, but simply making turns only after being blocked as if hoping that one will somehow habituate with the route after making numerous errors, etc.) to decrease the numbers of errors as learning trials proceeded. Our observation echoes with Bedard and colleagues' (1991) findings that OSA patients made significantly more impulsive errors than control on tests of maze completion, and often impulsively moved into 'blind alleys', even after exhortations not to do so.

In the present study, for the OSA patients group, the cumulative errors to trial 10 of Austin Maze was moderately correlated with poor performance on Telephone Search Time, Visual Elevator Time, Lottery, Verbal Working Memory, and Stroop Interference Chafetz *T* Score. By contrast, none of the cognitive performance or sleepiness scores in the shift workers group showed significant strong relationship with Austin Maze cumulative errors. Similarly, for the control participants group, apart from a moderate negative correlation with Map Search, no other significant relationship with the other cognitive performance or sleepiness scores was found. It can be deduced that deficits in visual selective attention, complex mental control of attentional shifting, reliability of working memory during shifting, sustained attention, and verbal working memory may contribute to the impaired Austin Maze performance in OSA clinical patients. In summary, multiple impairments in executive functioning (attentional shifting/mental flexibility and verbal working memory) together with other attentional deficits (visual selective attention and sustained attention) may account for the observed error utilization deficit phenomenon, and hence the extremely poor Austin Maze cumulative error scores in OSA patients.

This pattern of results supports that notion that the Austin Maze is a measure of planning, error utilization, and behavioural regulation in clinical groups where the frontostriatal pathway may be affected, causing executive functioning deficits. This is by no means contradicting Crowe and colleagues' (1999) report that Austin Maze is a test of spatial ability, visuospatial learning, and to some extent, working memory for the healthy adult population. These abilities are likely to make a fundamental contribution to the maze learning process. For the healthy adult population, especially the undergraduate sample, it is not too difficult to find a new direction when blocked, to be aware of a habitual error and correct it, to visualize the path, or to use a counting strategy. Ceiling effect may be implicated when the WCST and the TOL were used to measure executive functioning in the healthy adult population.

Moreover, relatively mild variability in executive functioning in healthy population is unlikely to prevent them from regulating their error-making behaviour or devising various learning strategies, hence this will not be the limiting factor in the Austin Maze performance, and rather visuospatial abilities will make the major contribution in such circumstances. Moreover, a few deficits in the repertoire of executive sub-functions may not be enough to result in significant deficits in planning, error utilization and behavioural regulation to impede the learning process. Indeed, despite the fact that the shift workers group in the present study did exhibit some attentional and working memory deficits, they appear insignificant in the complex spatial learning process; or because participants can use various combination of strategies to learn the maze, weaknesses in certain abilities can be effectively compensated by other intact abilities as long as the cognitive deficits are not pervasive, as in shift workers. In summary, the notion that Austin Maze is not a sensitive measure of executive functioning in healthy or subclinical population is supported by two findings. First, shift workers in the present study did not show deficits in mastering Austin Maze and made no more errors although they took longer time, compared to the control participants; second, the Austin Maze performance in shift workers and control participants did not correlate well with other attentional or executive performances.

That shift workers in the present study spent significantly more time but did not commit more errors than the control participants during the maze learning process suggested that despite some attentional/executive deficits found in the shift workers group, they were not pervasive, as a result, individual shift workers were able to recruit some compensating mechanism to help accomplish the criterion, although by doing so the efficiency was compromised. Moreover, the cumulative time to trial 10 of Austin Maze was moderately correlated with ESS (r = -.472, p < .1) in shift workers. This is consistent with previous research reporting reduced work rates and longer task completion time in sleep deprived partipants (Blagrove et al., 1995; Chmiel, Totterdell, & Folkard, 1995).

Current findings suggest Austin Maze can be used to as a measure of planning, error utilization, and behavioural regulation in clinical groups characterized by executive dysfunction. Mastery of the maze requires simultaneous monitoring of performance and comparison of the correct and incorrect choices made on the current as well as previous trials (i.e., divided attention and working memory). That is, the person needs to keep the objective in mind, know the rules, recall previous errors in order to avoid them in future, and remember the correct coordinates of the

hidden path learned from previous trials (i.e., set maintenance, strategic recall, and mental control). To meet these demands the maze taker may have to rely on an on-line memory store such as working memory (Crowe et al., 1999), and many other executive functioning such as mental flexibility in order to try alternative direction when getting stuck. Working memory circumvents the need for direct stimulation to drive behaviour; instead behaviour can be guided by representations of the outside world (Goldman-Rakic, 1995). In Austin Maze learning, working memory may be recruited to circumvent the need to change direction only after red light and buzzer is on to indicate error has been committed; but rather whether to push a button or not can be guided by topographic memory or visual-spatial memory of the hidden path gradually learned from previous trials. Kimberg and Farah (1993) propose that the frontal lobes are involved in maintaining the connections between working memory associations, such as those that represent goals, information in the environment, and stored declarative knowledge.

Procedural memory has been examined in research studies using a variety of tasks, such as pursuit motor learning, mirror writing and maze learning (Butters, Salmon, Heindel, & Granholm, 1988; Bylsma, Brandt, & Strauss, 1990; Milner, 1965). For example, Bylsma and colleagues (1990) used a push-button maze learning task to assess procedural memory in Huntington's patients. The stylus maze task in Milner's (1965) study, which was similar to the Austin Maze used in the current study, can also be interpreted as a procedural learning problem since it required repeated tracing of a constant path until the most direct route from the starting point to the ending point had been mastered. Hence, at a certain point after repeated learning trials, performance would be less likely to be affected by minor visuospatial learning deficits than by difficulty in remembering the correct sequence of turns by an implicit learning system. The current study revealed deficits in maze learning in the OSA group. However, it was observed in some patients, that they did not progress significantly from one trial to the next. In these severe cases, provision of more learning trials appeared to be not beneficial, and the trend suggested an error-free perfect trial was unlikely to be achieved. These results, when examined within the framework of a procedural learning deficit, are somewhat inconsistent with previous research. For example, in the studies of Rouleau and colleagues (2002) and Neagle and colleagues (2006), although patients with OSA also showed poor MTT performance, they generally progressed significantly from one trial to the next despite remaining consistently below the level of performance of matched controls. On the contrary, many of the patients with OSA in our study actually regressed in their performance committing more errors after several trials.

This discrepancy in findings suggests that the Austin Maze may be a more sensitive measure of behaviour adjustment deficit than MTT in patients with OSA. Indeed, a more parsimonious explanation for the impaired acquisition of MTT found in subjects with OSA in the study of Decary and colleagues (2000) would be that this complex visuomotor learning task generates higher cognitive demands uncovering their difficulty employing an efficient strategy for completing such task. In other words, the significant executive function impairments may have overshadowed any learning experience in more severe clinical cases.

In addition, it was suggested that poor fine motor skills made it difficult for patients with OSA to create new sensorimotor coordination in a visuomotor-skill-learning task, MTT (Naegele, et al., 2006). Patients with OSA in Naegele and colleagues (2006) study progressed significantly from one trial to the next, but remained consistently below the performance level of controls; hence, it was interpreted as an impaired behavioural adjustment rather than difficulty retaining the newly created sensorimotor coordination or a procedural learning deficit. Also, Rouleau and colleagues (2002) found that only a subgroup of patients with OSA showed deficits in initial skill adaptation in the visuomotor-skill-learning task, where numerous nonprogressive tracing occurred. Rouleau and colleagues (2002) argued that patients with OSA did not show a procedural learning deficit per se, but a frontal dysfunction.

On the one hand, Chouinard, Rouleau, and Richer (1998) found that, compared to temporal lobe excision and control subjects, frontal lobe patients had more frequent oscillation episodes leading to an increase in tracing time and a MTT initial adaptation deficit. On the other hand, Naegele et al. (2006) argued that a fine motor-skill coordination deficit and MTT impairment is suggestive of an early dysfunction of subcortical brain structures, in particular the striatum, a major structure of basal ganglia; moreover, these regions are particularly sensitive to severe hypoxemia. These two hypotheses are not necessarily contradictory as it is now known that frontostriatal pathway contributes to both executive functioning and motor coordination (Anderson et al., 2001).

In fact, with damage to the basal ganglia, cognitive flexibility, the ability to generate and shift ideas and responses, which is considered to be one of the major components of executive functioning, is also reduced (Lezak et al., 2004). While researchers once believed that the sole activity of the basal ganglia is to regulate voluntary movements, specifically related to planning and initiating motor behaviour

(Zillmer & Spiers, 2001), the basal ganglia have also been implicated in the learning of cognitive skills and procedural memory (Saint-Cyr, Taylor, & Lange, 1988). It has been suggested that movement reinforces memory by providing an anchor or external stimulus to match the internal stimulus (Markowitz & Jenson, 1999). Given that the basal ganglia are linked to the frontal cortex via the frontostriatal pathway, the frontal lobes may also play a role in the acquisition of procedural skills. Since the basal ganglia are among brain structures that are most vulnerable to hypoxemia as experience in patients with OSA and that slowing of EEG in frontal regions has been identified in patients with OSA (Svanborg & Gilleminault, 1996), these patients may have an attenuated capacity for procedural learning and executive functioning and difficulties employing efficient strategies to complete high cognitive demands intrinsically embedded in the complex procedural learning task (Decary et al., 2000).

To conclude, procedural memory is not deficient in shift workers, suggesting errors are not due to executive or motor skills deficits associated with the frontostriatal pathway. Results do not support the presence of pervasive executive functioning deficits in shift workers that are severe enough to impede complex procedural learning.

CHAPTER SIX: GENERAL DISCUSSION

6.1 More pervasive and severe attentional function impairments in patients with OSA relative to shift workers, both in control-referenced comparison and norm-referenced comparison.

In comparison with controls, shift workers demonstrated a clear deficiency in one attentional sub-function, namely is divided attention. Results also suggested that they might exhibit some deficits in visual selective attention, as demonstrated by the impaired performance on the Telephone Search subtest, and a trend of poor performance on the Map Search subtest. Nevertheless, the fact that variable performance was observed across the three tests considered to be measuring the same selective attention subdomain suggested that shift workers are likely to have intact or only slightly reduced selective attention; rather some other factors may be operating on the poorly performed test. Indeed, on the complex selective attention task Telephone Search subtest, it was common to observe in the shift workers a tendency to quickly scan through the telephone directory, thus trading off accuracy for speed, suggesting impulsive test behaviour. They often failed to circle one of the four types of targeted symbols suggesting unreliable working memory functioning.

Patients with OSA showed impairments in two attentional sub-functions namely selective attention and divided attention, in comparison to healthy controls. The reduced selective attention in patients with OSA was shown to cover both visual and auditory domains. In support of the hypothesis that an additive and/or synergistic effect of two pathophysiological factors, sleep deprivation and intermittent hypoxia, operating in OSA outweighs a single factor, sleep deprivation, in shift work, the deficits found in attentional functioning were found to be more pervasive in patients with OSA than in shift workers in the current study; nevertheless, sustained attention was spared in both participant groups. Notably, patients with OSA demonstrated a higher level of impairment in divided attention than shift workers. Therefore, the hypothesis that the level of severity in attentional function deficits in patients with OSA is higher than that in shift workers is partially supported, in line with the additive and or/synergistic hypothesis.

In comparison with the normative population of the standardized attentional tests, shift workers showed mildly reduced performances on the complex selective attention task (‘low average range’ in standardized scaled score); on the other hand,

patients with OSA showed mildly reduced performance on auditory selective attention task ('low average range' in standardized scaled score), and a significant 'borderline impairment' on divided attention task (more than one standard deviation below the sample population mean, i.e., 'below average' in standardized scaled score).

Hence, a more pervasive and severe pattern of attentional function impairments was found in patients with OSA relative to shift workers, both in control-referenced comparison and norm-referenced comparison.

6.2 More pervasive and severe executive dysfunction in patients with OSA relative to shift workers, both in control-referenced comparison and norm-referenced comparison, affecting complex spatial learning.

In comparison with controls, shift workers demonstrated clear deficiencies on two of the three executive sub-functions, namely verbal and symbolic working memory and the ability to inhibit prepotent responses; although set-shifting ability in complex tasks such as Elevator Counting with Reversal was also reduced; whereas in comparison with controls, patients with OSA showed significant impairments in set-shifting, working memory and inhibition of prepotent responses, the three latent variables of executive function. Furthermore, in comparison with controls, patients with OSA showed reduced accuracy and efficiency in planning, error utilization and behavioural inhibition, resulting in an increased number of errors committed and total time spent at the 10^{th} trial of Austin Maze learning and therefore many of patients had a difficulty learning the maze or failed to eliminate all the errors in reasonable time. On the contrary, shift workers showed reduced efficiency in these abilities with accuracy being spared, as shown by an intact ability attaining the Austin Maze learning criterion with no significant increase in the number of errors, although they spent a significantly longer time on each trial. Overall, the hypothesis that an additive and/or synergistic effect of two pathophysiological factors in OSA outweighs the effect of sleep deprivation only in shift work would result in a more pervasive and more severe executive dysfunction is generally supported.

In comparison with the normative population of the standardized tests measuring executive sub-functions, shift workers showed mildly reduced performances on verbal working memory task ('low average range' in standardized scaled score) only; on the other hand, patients with OSA showed mildly reduced performance on visual and auditory set-shifting tasks, verbal working memory task, and prepotent response

inhibition task ('low average range' in standardized scaled score).

Hence, a more pervasive and severe pattern of executive function impairments was found in patients with OSA relative to shift workers, both in control-referenced comparison and norm-referenced comparison. There is evidence that the executive dysfunction shown in patients with OSA had impacted on complex spatial learning.

6.3 The measured attentional and executive sub-functions are separable constructs and are not in a simple hierarchical relationship.

The hypothesis that attentional functions and executive functions are separate constructs and they are not in a simple hierarchical relationship (i.e., attention as lower-order cognitive function in relation to executive functions) is supported.

In shift workers, performances on all the tests requiring verbal and symbolic working memory and prepotent response inhibition as well as on a test loaded on set-shifting were reduced as compared to controls, suggesting at least two of the three executive sub-functions were affected. On the contrary, a smaller number of attentional sub-functions were deficient as compared to controls. The performance of shift workers was reduced on only two tests measuring complex visual selective attention and divided attention.

Similarly, in patients with OSA, performance on all executive measures, and all but one attention measures, sustained attention, were reduced as compared to controls. Therefore, dissociations of deficits in attentional sub-functions against executive sub-functions were observed in patients with OSA and in shift workers.

Using Pearson's product-moment correlations, all neuropsychological measures were found to be mildly to moderately correlated to each others, all being less than .711. Therefore, the hypothesis that attentional and executive sub-functions measured in the present theory driven design are clearly separable and yet related constructs.

In other words, the attentional and executive sub-functions measured in the present theory-driven design and standardized test batteries are discrete and separable constructs. The dissociation of deficits identified in attentional domain against executive function domain did not support a simple hierarchical relationship between the attentional and the executive dysfunction in patients with OSA and shift workers. This also lends support to the existence of executive dysfunction in additional to

attentional deficiency in the two clinical populations.

6.4 Summary of control-referenced analyses.

In comparison to controls, shift workers demonstrated significant reductions in the abilities of complex visual selective attention, divided attention, auditory set-shifting, verbal and symbolic working memory, and inhibition of prepotent responses, as well as a reduced spatial learning efficiency.

In comparison to controls, patients with OSA demonstrated significant reductions in the abilities of visual and auditory selective attention, divided attention, visual and auditory set-shifting, verbal and symbolic working memory, and inhibition of prepotent responses, as well as an impaired spatial learning due to poor planning, error utilization, behavioural inhibition and possible poor motor coordination.

6.5 A pattern of predominant attentional deficiency in shift workers and a dual pattern of attentional deficiency and pervasive executive dysfunction in patients with OSA in norm-referenced analysis.

Compared to the normative sample population, shift workers demonstrated a pattern of attentional deficiency characterized by a mild visual selective inattention on complex visual task and a mild reduction in sustained attention, as well as a trend of mild verbal working memory deficiency.

Compared with the normative sample population, patients with OSA demonstrated a dual pattern of attentional deficiency characterized by a mild auditory selective inattention, a trend of reduced sustained attention and impaired divided attention, together with pervasive executive dysfunction characterized by a trend of mild deficits in visual and auditory set-shifting abilities, a trend of mild verbal working memory deficiency and a trend of mildly reduced ability to inhibit prepotent responses.

6.6 Sleep deprivation and intermittent hypoxemia.

As sleep deprivation is a common factor between shift workers and patients with OSA, and that only the latter are affected by intermittent hypoxemia, by comparing the neuropsychological profiles of the two groups in standardized scaled score, it can be deduced that sleep deprivation may be the more important contributing factor to the selective inattention, the trend of reduced sustained attention, and the reduced verbal working memory in patients with OSA; whereas intermittent hypoxemia may be the more important contributing factor to the deficits in divided attention, and the trends of mildly reduced visual and auditory set-shifting abilities and inhibiton of prepotent responses.

Furthermore, based on the incremental deficiencies in the divided attention and set-shifting sub-functions evident in the comparative control-referenced analysis between shift workers and patients with OSA, it is possible that sleep deprivation and intermittent hypoxemia may contribute additively/synergistically to these two neuropsychological sub-functions of patients with OSA.

6.7 Austin Maze results support the notion that the pathophysiology of OSA involves subcortical brain structures and the associated frontostriatal pathways.

Patients with OSA demonstrated significantly more errors than shift workers and healthy controls on Austin Maze and there was no significant difference between shift workers and healthy controls on this accuracy measure. Interestingly, total time spent at the 10^{th} trial for shift workers and patients with OSA were found to significantly greater than that for controls, and there was no significant difference between shift workers and patients with OSA on this efficiency measure. Since the total numbers of errors at the 10^{th} trial has been shown to be highly correlated with the trial to criterion (Bowen et al., 1992), we can conclude that shift workers were able to learn complex spatial information as accurately as controls but more time was required suggesting a poorer learning efficiency. This can be explained by the cognitive profile of shift workers, mildly reduced attentional functioning and verbal working memory, but other executive functions and divided attention ability spared on the standardized score scale. Since more effort and motivation was required to compensate for the attentional lapses, shift workers generally took a longer time to contemplate each move in the Austin Maze. Despite taking longer time, shift

workers committed no more errors than controls during the learning process and the learned material accumulated across trials as well as controls, producing a good learning slope. This cognitive profile of shift workers is consistent with attentional deficits which have impacted on the efficiency of information encoding, whereas executive functionings as well as learning and memory functions remain generally intact. Moreover, no problem of motor coordination or psychomotor function was evident in shift workers.

On the other hand, significant problems with planning, error utilization, and behavioural regulation were demonstrated in patients with OSA resulting in impaired performances on both the accuracy and efficiency in the learning of complex spatial information. From the total errors committed at the 10^{th} trial, it can be predicted that many of the patients with OSA would not be able to reach the perfect learning criterion, three consecutive error-free trials. Motor incoordination and psychomotor dysfunction were observed in some of the patients who performed poorly on this task.

The present results suggest that the deficits associated with shift workers are generally attentional in nature with only a mild involvement of executive functioning. The major contributing factor is sleep deprivation.

Moreover, these results generally support the notion that the pathophysiology of OSA involves subcortical brain structures and the associated frontostriatal pathways, and the model which predicts a pattern of executive dysfunction associated with motor incoordination. The major contributing factor to this is likely to be intermittent hypoxemia, although sleep deprivation might contribute additively or synergistically to the pathophysiology. Furthermore, sleep deprivation per se can result in attention deficiency similar to the pattern of shift workers, and this will overlay on the executive and motor dysfunctions.

6.8 The relative merits of the three OSA models.

Regarding the relative merits of the models of OSA, the Executive dysfunction model (Beebe, 2005; Beebe & Gozal, 2002) and the Microvascular theory (Aloia et al., 2004; Lanfranchi & Somers, 2001) are supported by the results of the current study. Although a pure Attentional deficits model (Verstraeten & Cluydts, 2004) is not supported, the current study demonstrated a number of attentional deficits including attentional control in OSA, consistent with the attentional systems described in the

model. Therefore, the three models appear to be complementary to each others with different emphases describing the executive, attentional and motor coordination deficits in OSA.

6.9 Strengths and weaknesses.

To date, this was the first comparative study on the neuropsychological profiles of shift workers and patients with OSA using standardized tests with norm reference. The advantage of using standardized tests is that it allows easy replication and comparison of results in both clinical settings and research studies. In this way, clinicians may benefit from repeating the neuropsychological testing on patients pre- and post-treatment as well as during follow-up consultations in order to monitor the change in the cognitive sequelae of OSA, important for informed medical decisions such as advice on fitness to drive or to work in situations with high decision-making demands.

For researchers, the current study exemplifies how a neuropsychological comparative study using standardized tests may serve as an experimental paradigm allowing detailed contrast of the differences in cognitive sub-functions between clinical groups that share a common pathophysiological factor, so that enriched information about the linking of each factor with various neurocognitive deficits can be deduced. Since shift workers are mainly affected by sleep deprivation while patients with OSA are affected by both sleep deprivation due to sleep fragmentation and intermittent hypoxemia, by comparing and contrasting the neuropsychological profiles, we can deduce the differential contribution of each pathophysiological factor to individual neurocognitive deficits.

In terms of construct validity, each of the attentional and executive sub-functions investigated are substantiated by theory-based models and are neatly matched with one or more standardized subtests, which are also developed in accordance with a theory and ecological validity.

Partipicants were carefully recruited, and precautions were taken to avoid overlapping between shift work and control conditions with unidentified OSA. All patients with OSA had undergone a polysomnographic sleep study in order to qualify for the diagnostic criteria specified by the AASM. Moreover, a clinical diagnosis had been established and verified by a respiratory physician in each participant case. All shift workers and controls were screened by MAPI to exclude potentially unidentified

sleep apnoeic cases. All shift worker participants recruited have been doing shift work continuously for at least three years preceding the testing date, allowing the long-term effects of shift work to precipitate.

The age was closely matched among patients with OSA, shift workers and controls, and there were no significant differences on these variables across the groups. Although it was desirable for patients with OSA to be matched to shift workers and control participants by gender and weight, close matching of these variables was very difficult if not impossible in practice due to recruitment difficulty and that patients with OSA are more common in male with obesity as a predisposing factor. Therefore, patients with OSA tended to have a higher than average BMI.

The aim of the present study was to investigate the long-term effects of the interested conditions, rather than the temporary tiredness associated with fatique after work or acute sleep deprivation after a night shift. To achieve this, all participants were required not to participate in testing immediately after work to avoid fatigue after long working hours and to avoid coffee and tea on the day of testing. Special instructions were given to shift workers to allow at least one full night sleep before participating in the neuropsychology tests and they were not allowed to participate in the testing session immediately after work or a night shift. To control the effect of the variations in circadian rhythm among individual participants, the testing time was fixed at around 3:30pm.

With these precautions, there was no significant difference between shift workers and controls on the subjective state of sleepiness as measured by KSS, suggesting that the neuropsychological deficiencies identified in the current study is unlikely to be a result of fatigue or excessive daytime sleepiness. Although patients with OSA were significantly sleepier than controls as measured by KSS, the absolute difference was small. While a higher level of sleepiness in patients with OSA is expected, measures have been taken to minimize the effect of fatigue, including allowance of breaking times on request, and the testing time was chosen to be at about 3:30pm known to be associated with the highest reaction time during the circadian rhythm cycle (Smolensky & Lamberg, 2000). Overall, optimal performances on neuropsychological tests were expected in each partipant group.

6.10 Conclusions and implications on clinical practice and future research.

The study was the first to compare the neuropsychological profiles between patients with OSA and shift workers, using a control-referenced and norm-referenced design. With reference to the normative populations, the effects of sleep deprivation on the neuropsychological functions of shift workers are generally attentional in nature with only a mild involvement of verbal working memory; whereas in patients with OSA, in addition to the attentional deficiencies expected from the sleep deprivation component of the disorder, a pervasive pattern of mild executive dysfunctions and a possible motor coordination deficiency, which further impact on complex spatial learning, was demonstrated, likely to be associated with intermittent hypoxemia by inference. This also supports the notion that the pathophysiology of OSA involves the frontostriatal pathway including the vulnerable subcortical brain structures as proposed by the Executive dysfunction model (Beebe, 2005; Beebe & Gozal, 2002) and the Microvascular theory (Aloia et al., 2004; Lanfranchi & Somers, 2001).

In comparison to controls, patients with OSA demonstrated significant reductions in the abilities of visual and auditory selective attention, divided attention, visual and auditory set-shifting, verbal and symbolic working memory, and inhibition of prepotent responses, as well as an impaired spatial learning due to poor planning, error utilization, behavioural inhibition and possible poor motor coordination. Although many of these are in the lower end of the average range to low average range on the standardized norm, divided attention and complex spatial learning were in the impaired range. These results suggest that OSA can produce a pervasive pattern of neurocognitive dysfunction involving attention, executive function, complex spatial learning, motor coordination, and other aspects of higher cognitive functions. The reduction of individual neuropsychological function may be mild, but the pervasive nature of the deficiencies in OSA implies that compensatory mechanisms to cope with a neurobehavioural demand may not be available; as such, performance and judgmental errors may be difficult to avoid. These pervasive cognitive dysfunctions are likely to serve as the mediating factors underpinning the social and occupational impairments as well as increased risk of road traffic accidents associated with patients with OSA.

In comparison to controls, shift workers demonstrated significant reductions in the abilities of complex visual selective attention, divided attention, auditory set-shifting, verbal and symbolic working memory, and inhibition of prepotent responses, as well

as a reduced spatial learning efficiency. Although most of these are in the lower end of the average range to low average range on the standardized norms, these results suggest that shift work can potentially result in a reduction in various aspects of neurocognitive function to suboptimal levels of the individuals, providing a cognitive base explaining the social and occupational impairments as well as increased risk of road traffic accidents associated with shift workers.

In this study, the functional impairment in shift workers was significant enough to be presented as a similar profile as patients with OSA, albeit somewhat less pervasive and less severe. The results indicated the potential hazard of shift work as functional impairment as patients with OSA. Although daytime traffic accident was not contributed by the excessive daytime sleepiness of patients with OSA and shift workers, the functional impairment was a fact which should be considered seriously. Heavy health toll should be considered in all potential shift workers, and it is recommended to send out warning and precaution to shift workers and medical personnel.

Future research could be directed to establishing the relationship between the neuropsychological subcomponents and specific functional impairments such as driving simulator performance and other decision-making paradigms, both before and after treatment. This could further our understanding of the cognitive causes for reported social and occupational impairments. Moreover, the degree of performance improvement on repeatable neuropsychological measures, which potentially predict the level of functional impairments, can potentially serve as objective indicators for the effects of CPAP treatments. Furthermore, since these objective indicators of neuropsychological functions are expected to have high ecological validity and are expressed in standardized scores allowing comparison of individual performance with his or her age-related peers, monitoring of these objective cognitive measures may generate valuable information to supplement the subjective reported improvement following treatment. This is important for clinical decisions such as assessment of driving risks.

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Appendix 1: Recruitment Advertisement

Ever wondered about the effects of obstructive sleep apnoea and/or rotating shift work on your health?

Participants wanted for research study

It will come as no surprise to the many people who work rotating shifts that *shift work* is associated with a variety of adverse consequences. Shift work, like jet lag, disrupts circadian rhythms and affects sleep patterns. It can negatively affect work performance and efficiency, health, and family and social relationships. In the short-term adverse effects may include sleep disturbances, psychosomatic disorders and cardiovascular diseases. More recent evidence has suggested that mood and cognitive functions (such as memory and attention) may also be affected by prolonged disruptions to the sleep-wake cycle. People with *obstructive sleep apnoea (OSA)* also report similar adverse consequences. OSA is associated with problems in daytime functioning, including excessive sleepiness, cognitive deficits, psychological impairment, various medical conditions (such as hypertension and cardiovascular disease) and a greater risk of road traffic accidents.

Victoria University, School of Psychology in conjunction with the Sleep Disorders Unit at the Austin Hospital is conducting a study looking at the nature and extent of mood, thinking and performance impairments in shift workers and people with obstructive sleep apnoea, and invites people between the ages of 18 and 65 years to participate. We are seeking people who are currently employed in rotating shift-work and have been for at least three years. Control participants who are currently not working or have not worked rotating shifts may also be eligible to participate in the study. The study involves neuropsychological assessment, a series of questionnaires about how you have been feeling lately, a driving simulation task, and a reaction time task. Participation requires attendance at the Austin Hospital in Heidelberg. People with chronic medical or psychiatric disorders or recent stressful life events are not eligible to participate.

Please contact Jacen Lee (04## ### ###; xxx@gmail.com) for additional information about participating in this study.

Appendix 2: Participant Information Statement and Informed Consent Form

PARTICIPANT INFORMATION FORM
(shiftwork participants)

AN INVESTIGATION OF AFFECTIVE AND NEUROPSYCHOLOGICAL FUNCTIONING AND DRIVING SIMULATOR PERFORMANCE IN SHIFT WORKERS AND PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

Principal Researcher: Dr Gerard Kennedy

Associate Researchers: Dr Mark Howard, Dr Maree Barnes

Student Researcher: Jacen Lee

You are invited to take part in this research project designed to investigate mood, thinking and driving performance in shift workers and people with obstructive sleep apnoea. This is a student research project for a Doctor of Psychology (Clinical Neuropsychology) (Jacen Lee).

This Participant Information Form contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information Form carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this. We cannot guarantee or promise that you will receive any benefits from this project. You will not be paid for your participation in this project.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project. Participation is entirely voluntary. You may withdraw from the project for any reason and at any time without prejudice and without giving any reason.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Austin Health Human Research Ethics Committee.

PURPOSE OF THE STUDY

This project is designed to investigate the nature and extent of mood, cognitive and

performance impairments in patients with obstructive sleep apnoea and shift-workers compared to people without obstructive sleep apnoea and who do not do shift work (control group). Sleep may be disrupted in patients with sleep apnoea as well as shift-workers, and this can lead to impaired performance at work or while driving a vehicle, which can increase the risk of accidental injury. This study aims to evaluate the effect of these conditions on mood and cognitive function. In particular, we are looking at driving ability, attention, reaction time and higher thinking functions. In this study a number of tasks that measure thinking processes, performance on a computer-based driving task and questionnaires will be used to assess these thinking functions and mood. It is also aimed to relate impairments to estimates of accident risk.

WHAT WILL THIS PROJECT INVOLVE?

Your participation in the study will involve two separate sessions at the Austin Hospital.

1. During the first session any questions you or your family members may have will be answered, and the study will be fully explained to you. If you agree to participate, you will be asked to sign the Consent Form and will also have an opportunity to practice on some of the equipment that will be used in the study. This session will take about one hour to complete.
2. On the day of the second session, you will be requested not to consume any caffeine or stimulant medication until completion of the study. You will be asked to arrive after dinner at approximately 3.00pm and the session will finish at around 7.00pm. During this session, you will be asked to participate in a series of tasks to assess memory and concentration and to complete a series of questionnaires about how you have been feeling lately and about your mood. After completing these questionnaires, your performance on a driving simulator task and a reaction time task will be assessed. A series of questionnaires designed to help assess levels of sleepiness will then be administered. This session will take approximately four hours to complete.
3. You will then stay for an overnight sleep study (see below)
4. At 6am the following morning you will go home.

WHAT DOES THE OVERNIGHT SLEEP STUDY INVOLVE?

The overnight sleep study takes place in the sleep laboratory.

When you arrive you will be shown to your private room. Bathroom facilities are

shared. There is a small lounge/television room for your use, and microwave / fridge facilities are available. Bring night attire, toiletries, something to read and you are welcome to bring your own pillow. You should bring all your own medication and take any medication as you would normally. Since caffeine is a stimulant, you are asked to refrain from drinking coffee, tea or coke from 7am on the morning of the overnight study. If you wish, you may bring non-caffeinated drinks with you to the hospital. Alcohol should also be avoided all day on the day of this study.

The sleep technician is a trained scientist or nurse who is experienced in this area. After you complete the tests for the research study, he/she will explain the equipment and procedures to you, then will attach several electrodes to your head, face, chest and legs to monitor your heart and the activity of your brain, your eyes, and the muscles of your face and legs. You will also have 2 bands strapped around your chest and abdomen to monitor your breathing, an airflow detector attached to your nose and mouth and an oxygen sensor attached to a finger. This may sound very uncomfortable and restrictive, but you are able to walk around, read, watch television, eat and drink. You will be asked to go to bed at around 10-11pm, and the electrodes will be plugged in to a board at the head of your bed. There is an infra-red camera in your room which allows the technician to see you during the night.

ARE THERE LIKELY TO BE ANY SIDE-EFFECTS OR RISKS?

No significant physical or psychological risks are anticipated in the proposed study. The main inconvenience will be the time commitment involved.

BENEFITS

There may be no direct benefit to you for participating in this study.

COSTS

There is no cost for being in this study. Travel costs will be reimbursed on production of a receipt.

WHAT WILL HAPPEN TO MY RESULTS?

At the end of the study you will receive a copy of your results and these will be explained to you by one of the researchers. The results of the study may be published, but your identity will not be revealed, nor will your results be shared with anyone else for any other purpose. Participant records may be inspected by authorised persons for the purpose of data audit (e.g. members of the Austin Health Human Research Ethics Committee), but no other people will be authorised to access them. The records dealing with this study will be kept in safe storage for 7 years,

and will then be shredded.

CONFIDENTIALITY

Your confidentiality will be respected at all times. Participation is entirely voluntary. You may withdraw from the project for any reason and at any time without prejudice and without giving any reason. At all stages of the study, you will be encouraged to ask questions.

CONTACTS AND SUPPORT

For the duration of the study the supervisors will be Dr. Gerard Kennedy and Dr. Mark Howard. If you have any questions concerning the nature of the research or your rights as a participant, please contact:

Dr Gerard Kennedy XXXX XXXX After Hours: XX XXXX XXXX
Dr Mark Howard XXXX XXXX

If you wish to contact someone, independent of the study, about ethical issues or your rights, you may contact Mr Andrew Crowden, Chairperson Austin Health Human Research Ethics Committee, phone XXXX XXXX.

Austin Health

Version: 2 A

Date: 02 /03 / 2007

Consent Form to Participate in Research

An investigation of affective and neuropsychological functioning and driving simulator performance in shift workers and patients with obstructive sleep apnoea (control and shift work participants)

I, ...have been invited to participate in the above study which is being conducted under the direction of Dr. Gerard Kennedy and Dr Mark Howard.

I understand that while the study will be under their supervision, other relevant and appropriate persons may assist or act on their behalf.

- My consent is based on the understanding that the study involves the procedures as explained on page 2 of this document.
- This is **not** a drug trial.

The study may involve the following risks, inconvenience and discomforts which have been explained to me and which are listed on page 2 of this document

I have read this 'Participant Information and Consent Form' and understand the general purposes, methods and demands of the study. All of my questions have been answered to my satisfaction.

I understand that the project may not be of direct benefit to me.

I can withdraw or be withdrawn by the Principal Investigator from this study at any time, without prejudicing my further management.

I consent to the publishing of results from this study provided my identity is not revealed.

I hereby voluntarily consent and offer to take part in this study.

Signature (Participant)	Date:	Time:
Witness to signature	Date:	Time:
Signature (Investigator)	Date:	Time:

PARTICIPANT INFORMATION FORM
(sleep apnoea participants)

AN INVESTIGATION OF AFFECTIVE AND NEUROPSYCHOLOGICAL FUNCTIONING AND DRIVING SIMULATOR PERFORMANCE IN SHIFT WORKERS AND PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA

Principal Researcher: Dr Gerard Kennedy

Associate Researchers: Dr Mark Howard, Dr Maree Barnes

Student Researcher: Jacen Lee

You are invited to take part in this research project designed to investigate mood, thinking and driving performance in shift workers and people with obstructive sleep apnoea. This is a student research project for a Doctor of Psychology (Clinical Neuropsychology) (Jacen Lee).

This Participant Information Form contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information Form carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this. We cannot guarantee or promise that you will receive any benefits from this project. You will not be paid for your participation in this project.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project. Participation is entirely voluntary. You may withdraw from the project for any reason and at any time without prejudice and without giving any reason.

You will be given a copy of the Participant Information and Consent Form to keep as a record.

This project will be carried out according to the *National Statement on Ethical Conduct in Research Involving Humans* (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Austin Health Human Research Ethics Committee.

PURPOSE OF THE STUDY

This project is designed to investigate the nature and extent of mood, cognitive and

performance impairments in patients with obstructive sleep apnoea and shift-workers compared to people without obstructive sleep apnoea and who do not do shift work (control group). Sleep may be disrupted in patients with sleep apnoea as well as shift-workers, and this can lead to impaired performance at work or while driving a vehicle, which can increase the risk of accidental injury. This study aims to evaluate the effect of these conditions on mood and cognitive function. In particular, we are looking at driving ability, attention, reaction time and higher thinking functions. In this study a number of tasks that measure thinking processes, performance on a computer-based driving task and questionnaires will be used to assess these thinking functions and mood. It is also aimed to relate impairments to estimates of accident risk.

WHAT WILL THIS PROJECT INVOLVE?

Your participation in the study will involve two separate sessions at the Austin Hospital.

1. During the first session any questions you or your family members may have will be answered, and the study will be fully explained to you. If you agree to participate, you will be asked to sign the Consent Form and will also have an opportunity to practice on some of the equipment that will be used in the study. This session will take about one hour to complete.
2. On the day of the second session, you will be requested not to consume any caffeine or stimulant medication until completion of the study. You will be asked to arrive after dinner at approximately 3.00pm and the session will finish at around 7.00pm. During this session, you will be asked to participate in a series of tasks to assess memory and concentration and to complete a series of questionnaires about how you have been feeling lately and about your mood. After completing these questionnaires, your performance on a driving simulator task and a reaction time task will be assessed. A series of questionnaires designed to help assess levels of sleepiness will then be administered. This session will take approximately four hours to complete.

ARE THERE LIKELY TO BE ANY SIDE-EFFECTS OR RISKS?

No significant physical or psychological risks are anticipated in the proposed study. The main inconvenience will be the time commitment involved.

BENEFITS

There may be no direct benefit to you for participating in this study.

COSTS

There is no cost for being in this study. Travel costs will be reimbursed on production of a receipt.

WHAT WILL HAPPEN TO MY RESULTS?

At the end of the study you will receive a copy of your results and these will be explained to you by one of the researchers. The results of the study may be published, but your identity will not be revealed, nor will your results be shared with anyone else for any other purpose. Participant records may be inspected by authorised persons for the purpose of data audit (e.g. members of the Austin Health Human Research Ethics Committee), but no other people will be authorised to access them. The records dealing with this study will be kept in safe storage for 7 years, and will then be shredded.

CONFIDENTIALITY

Your confidentiality will be respected at all times. Participation is entirely voluntary. You may withdraw from the project for any reason and at any time without prejudice and without giving any reason. At all stages of the study, you will be encouraged to ask questions.

CONTACTS AND SUPPORT

For the duration of the study the supervisors will be Dr. Gerard Kennedy and Dr. Mark Howard. If you have any questions concerning the nature of the research or your rights as a participant, please contact:

Dr Gerard Kennedy XXXX XXXX After Hours: XX XXXX XXXX
Dr Mark Howard XXXX XXXX

If you wish to contact someone, independent of the study, about ethical issues or your rights, you may contact Mr Andrew Crowden, Chairperson Austin Health Human Research Ethics Committee, phone XXXX XXXX.

Austin Health

Version: 2 B

Date: 02 /03 / 2007

Consent Form to Participate in Research

An investigation of affective and neuropsychological functioning and driving simulator performance in shift workers and patients with obstructive sleep apnoea (sleep apnoea participants)

I, ...have been invited to participate in the above study which is being conducted under the direction of Dr. Gerard Kennedy and Dr Mark Howard.

I understand that while the study will be under their supervision, other relevant and appropriate persons may assist or act on their behalf.

- My consent is based on the understanding that the study involves the procedures as explained on page 2 of this document.
- This is **not** a drug trial.

The study may involve the following risks, inconvenience and discomforts which have been explained to me and which are listed on page 2 of this document

I have read this 'Participant Information and Consent Form' and understand the general purposes, methods and demands of the study. All of my questions have been answered to my satisfaction.

I understand that the project may not be of direct benefit to me.

I can withdraw or be withdrawn by the Principal Investigator from this study at any time, without prejudicing my further management.

I consent to the publishing of results from this study provided my identity is not revealed.

I hereby voluntarily consent and offer to take part in this study.

Signature (Participant)	Date:	Time:
Witness to signature	Date:	Time:
Signature (Investigator)	Date:	Time:

Appendix 3: Demographics Questionnaire

Demographic Information

	ID	G	No.
		O/S/N	

1. What is your age? _____ _
_

2. What is your sex? 1 Male 2 Female

3. What is your weight? _____

4. What is your height? _____

5. What language do you speak at home? _____If not English, how many percentage of the time do you speak English at home? _____%

6. What is your current occupation? _____(NOTE: Also mark the most representative occupation before if you have worked in several major occupations)
(Please also <u>tick</u> one of the categories listed below to indicate your answer)

____ (1) Unskilled: e.g. farm labour, food service, janitor, house cleaner, factory work
____ (2) Skilled work: e.g. technician, carpenter, hairdresser, seamstress, plumber, electrician, auto repair
____ (3) White collar (office) work: e.g. clerk, salesperson, secretary, small business
____ (4) Professional: e.g. doctor, lawyer, teacher, business
____ (5) Not currently working (check one below & mark also your most representative occupation before:)
____ (6) Unemployed
____ (7) Retired
____ (8) Homemaker
____ (9) Student **____Others: _____**

7. What is the highest level of education you have completed?

Total number of years of education: _____

(Please <u>tick</u> one of the categories listed below to indicate your answer)

____ (1) None; 0 years
____ (2) 1-3 years (some primary school)
____ (3) 4-6 years (completed primary school)
____ (4) 7-9 years (some secondary school)
____ (5) 10-12 years (completed secondary school)
____ (6) Some college; no degree
____ (7) College degree
____ (8) Graduate or professional education

8. Are you a smoker? Yes_____ No_____
If Yes, how many cigarettes do you smoke per day?_____
How many years have you been smoking? _____

9. Do you drink alcohol? Yes____ No_____
If Yes, How many standard drinks would you have in a normal week? _____
(1 standard drink equals one pot beer, one glass wine, one 30ml shot spirits or liqueur)
How long have you been drinking at this level?_____

10. Have you ever lost consciousness as a result of being struck in the head? If so, please describe the circumstances:
_____
_____

11. Do you have a diagnosed neurological condition (stroke, epilepsy, brain tumour, or others)?_____

12. Do you have a diagnosed psychiatric condition (depression, schizophrenia, or others)? _____

13. Please list any medications you regularly take and the condition for which you take them, excluding common pain killers such as Panadol"
_____
_____

14. In the past year, have you experienced an extremely stressful life event, such as the death of an immediate family member or friend, a life threatening event, a divorce etc?_____

Appendix 4: Driving Information Questionnaire

Driving Information

We want to ask you some questions about driving.

For The Following Questions Put A Cross In One Or More Boxes

1. Do you drive at work? Yes ☐ No ☐
2. How long have you been doing shift work in total?
   Never ☐ or Year ☐ Months ☐
3. How long since you did any shift work ?
   N/A ☐ or Year ☐ Months ☐
4. Which shifts do you work?
   days ☐ afternoons ☐ nights ☐
5. Do you rotate shifts?
   yes ☐ no ☐
6. Where do you drive?
   metropolitan ☐ country ☐ interstate ☐

For The Following Questions Write The Appropriate Number In The Box

7. How many hours is your longest shift? ☐
8. How many days do you work per week? ☐
9. How many hours do you work per week? ☐
10. How many hours do you drive per week?
    at work ☐ not work related ☐
11. How many kilometers do you drive each year?
    at work ☐ 000 km not work related ☐ 000 km
12. How many hours of sleep do you have each night or day?
    on work days ☐ on days off ☐
13. How many glasses of alcohol do you normally have each day?
    on work days ☐ on days off ☐
14. How many cups do you have each day of the following beverages?
    tea ☐ coffee ☐ cola ☐

Most drivers have had an accident at some time. We would like to ask you about any accidents in the last three years.

Include any accident where someone was injured, the police were called or a vehicle was damaged and required repair

15. Have you had any motor vehicle accidents in the last 3 years?

Tick Yes ☐ No ☐

(Put a number in each box opposite)

Number of accidents involving another vehicle:
at work ☐ non work related ☐

Number of accidents with no other vehicle involved:
at work ☐ non work related ☐

1. What is your: height ☐

   weight ☐

2. What is your age in years? ☐

3. Gender (put a cross in one box)
   male ☐ female ☐

Appendix 5: Maislin Apnoea Prediction Questionnaire

Now we would like to ask you some questions about your sleep

During the last month, have you had, or have you been told about the following symptoms: (show the frequency by putting a cross in one box)

Symptoms:	(0) Never	(1) Rarely, less than once a	(2) 1-2 times a week	(3) 3-4 times a week	(4) 5-7 times a week	(5) Don't know
1. snorting or gasping	☐	☐	☐	☐	☐	☐
2. loud snoring	☐	☐	☐	☐	☐	☐
3. breathing stops, choke or struggle for breath	☐	☐	☐	☐	☐	☐
4. falling asleep when at work or school	☐	☐	☐	☐	☐	☐
5. falling asleep when driving	☐	☐	☐	☐	☐	☐
6. excessive sleepiness during the day	☐	☐	☐	☐	☐	☐

---

1. How long have you had the above 6 symptoms to an extent that affects your normal daily functioning? No. of Years _____ No. of Months _____

2. Have you even been diagnosed to have obstructive sleep apnoea?
   Yes ☐ No ☐

   If yes, when was the diagnosis made? _____

   Any treatment received? (Please specify) _____

Appendix 6: Epworth Sleepiness Scale

EPWORTH SLEEPINESS SCALE (ESS)

The following questions refer to sleepiness or the tendency to doze off when relaxed.

How likely are you to doze off or fall asleep in the situations described in the box below, in contrast to just feeling tired? This refers to your usual way of life in recent times. If you haven't done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose the **most appropriate** number for each situation:

0 = would **never** doze
1 = **slight** chance of dozing
2 = **moderate** chance of dozing
3 = **high** chance of dozing

Situation	**Chance of Dozing**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g., a theatre or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch without alcohol	
In a car, while stopped for a few minutes in traffic	

Total Score =

Appendix 7: Karolinska Sleepiness Scale

KAROLINSKA SLEEPINESS SCALE (KSS)

	ID	G	No.
		O/S/N	

The following is a 9 point scale to describe sleepiness. Put a cross in the box next to the point that describes how *sleepy* you feel *right now*

1. ☐ Extremely alert
2. ☐
3. ☐ Alert
4. ☐
5. ☐ Neither alert nor sleepy
6. ☐
7. ☐ Sleepy - but no difficulty remaining awake
8. ☐
9. ☐ Extremely sleepy - fighting sleep

Appendix 8: Sleep Diary

Code number:_____ **Please complete this diary of your sleep and work habits for two weeks prior to your sleep study**

Each Morning Complete The Following (see example below):

1. Write in the day and date
2. With an arrow pointing down mark the time you got into bed last night
3. With a plain line mark the time you think you fell asleep and woke up in the morning
4. With plain lines, mark times when you woke up and went back to sleep during the night
5. With an arrow pointing up mark when you got out of bed
6. With plain lines mark any naps you have during the day
7. With an X mark hours that you were at work
8. With an A and a number mark the number of glasses of alcohol you had during the day

	Day	Date	8	pm 9	pm 10	pm 11	pm 12	pm 1	am 2	am 3	am 4	am 5	am 6	am 7	am 8	am 9	am 10	am 11	am no	on 1	pm 2	pm 3	pm 4	pm 5	pm 6	pm 7	pm 8	pm
1																												
2																												
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13																												
14																												

E X A M P L E ***E X A M P L E***

Mon	1/02/1995			↓	I	*sleep*	I	I	*sleep*	I	↑	X	X	X	X	X	X	X	X	X	A 1	I	*nap* I				

	ID	G	No.
8		O/S/N	

Appendix 9: Stroop Colour and Word Test Instructions

Stroop Colour and Word Test Instructions

MATERIALS: *STOP WATCH, TEST BOOKLET, EXAMINER RECORD FORM, AND PENCIL.*

Instructions for the Word Page

After the subject has been given the test booklet, the following instructions are read: **"This is a test of how fast you can read the words on this page. After I say begin, you are to read down the columns starting with the first one** *(point to the left-most column)* **until you complete it** *(run hand down the left-most column)* **and then continue without stopping down the remaining columns in order** *(run your hand down the second column, then the third, fourth and fifth columns)***. If you finish all the columns before I say "Stop," then return to the first column and begin again** *(point to the first column)***. Remember, do not stop reading until I tell you to "Stop" and read out loud as quickly as you can. If you make a mistake, I will say "No" to you. Correct your error and continue without stopping. Are there any questions?"** *Instructions may be repeated or paraphrased as often as necessary so that the subject understands what is to be done. Then continue:* **"Ready? ... Then begin."** *As the subject says the first response (whether right or wrong), start timing. After 45 seconds, say:* **"Stop. Circle the item you are on. If you finished the entire page and began again, put a one by your circle. Turn to the next page."**

Instructions for the Colour Page

The instructions for the Colour page are identical, except the first sentence reads: **"This is a test of how fast you can name the colours on this page."** *If the subject generally understands the instructions for the Word page, the remaining instructions can be given briefly:* **"You will complete this page just as you did the previous page, starting with this first column. Remember to name the colours out loud as quickly as you can".** *If the subject has had any trouble following the instructions, they should be repeated in their entirety. As with the first page, the subject should be allowed 45 seconds.*

Instructions for the Colour-Word Page

At the beginning of the Colour-Word page, the following instructions should be used: **"This Word page is like the page you just finished. I want you to name the colour of the ink the words are printed in, ignoring the word that is printed for each item. For example,** *[point to the first item of the first column],* **this is the first item: what would you say?"** *If the subject is correct, go on with the instructions, if incorrect, say:* **"No. That is the word that is spelled here. I want you to name the colour of the ink the word is printed in. Now,** *(pointing to the same item)* **what would you say to this item? That's correct** *(point to second item)***. What would the response be to this item?"** *If correct, proceed; if incorrect, repeat above as many as necessary until the subject understands or it becomes clear that it is impossible to go on. Continue with the statement:* **"Good. You will do this page just like the others, starting with the first column** *[pointing]* **and then going on to as many columns as you can. Remember, if you make a mistake, just correct it and go on. Are there any questions?"** *(As with the other two pages, the instructions can be repeated or paraphrased as often as necessary.)* **"Then begin."** *(Time for 45 seconds, then say:)* **"Stop. Circle the item you are on."**

Appendix 10: Verbal Working Memory Test Instructions

Verbal Working Memory Test Instructions

MATERIALS: *EXAMINER FORM*

Instructions for Level B

Item B-1

Say: **I am going to say some words. Some are animals and some are not. After I say the words, I will ask you to tell me all the animals, but tell me the smallest animal first, then the next in size and so forth to the biggest.** *(pause)* **Then I will ask you to tell me the words that are not animals, in any order. So, if I said bear, care, cat, when I asked you for the animals you would say cat, bear.** *(pause)* **Then when I asked you to tell me the words that were not animals, you would say car.** *(pause)* **So, when I ask for the animals, you would say the animals from smallest to largest – cat and then bear – and then, when I ask for the words that are not animals you would say car. Any questions?** (If so, clarify the procedure as necessary). **Let's begin: rope, dolphin, frog. Tell me all the animals in order of size. Now tell me the non-animals.** If the Participant responds correctly, proceed to Item B-2.

If the Participant responds incorrectly or seems clearly unsure how to respond, say: **I said "rope, dolphin, frog", so you should say all the animal in order of size. First you should say the smallest animal, "frog", and then the next larger one, "dolphin". When I ask you to say any words that are not animals, you should say "rope".** *(pause)* Readminister the item. ***(Let's try it again. Remember when I ask you for the animals, you tell me all of the animals from smallest to biggest. Then all the words that are not animals. Try this one again: rope, dolphin, frog.)*** Repeat this procedure as many times as necessary for the Participant to successfully complete both parts of the item. Additional instruction on this item is permissible. However, the responses are numbered and the item scored based on the Participant's *first* response. Proceed to Item B-2.

Item B-2 and subsequent items: **Here's the next one. Remember when I ask for all the animals, you tell me the animals from smallest to largest, and then, when I ask, tell me the words that are not animals in any order: calf, turtle, ball. Tell me the animals in order of size.** *(pause)* **Now tell me the non-animals.** Give no additional help on this or subsequent items. Once the Participant understands the task, introduce subsequent items with an alert like, **Here's the next one.** Continue

administrating items until the Discontinue Rule is satisfied or all items within the level are administered. Once Level B is completed, proceed to Level C.

Instruction for Level C

Say: **You are doing fine. Now we are going to change things a little. This time after I say the words, I will ask you for all the animals, in order of size, and then I will ask you to tell me the other things in order of their size. That is, when I ask, first tell me the animals from smallest to largest and next I will ask for the other things from smallest to largest. Any questions?** (If so, clarify the procedure as necessary.) **Let's begin.** Administer Item C-1 and all subsequent Level C items unless the Discontinue Rule is satisfied. Introduce subsequent items with an alert like, Here's the next one. Provide no training with any Level C items.

On rare occasions, the Participant may remark about the variability in size of some animal or object. (e.g., "some refrigerators are small.") Say something like, **"think of the most usual size."** Do not debate sizes of animals or objects; simply move on to the next item.

Appendix 11: Symbolic Working Memory Test Instructions

Symbolic Working Memory Test Instructions

MATERIALS: *SYMBOLIC WORKING MEMORY STIMULUS CARD, AND EXAMINER FORM*

Instructions for Level A

Say, **I am going to say some numbers in mixed up order. When I'm done, I am going to show you a card with numbers on it. Using the card, point to all the numbers that I said, but point them out in the correct numerical order. Let's try one.** Say, **4, 1**. Immediately display the Number Stimulus Card on which numbers from 1 – 8 are appropriately ordered. Encourage the Participant to point out his/her response.

If the Participant is correct, say, **Good**, and proceed to the next item. If the Participant is incorrect, say, **That's not quite right. I said 4, 1, so you would point to 1, 4 in the correct order** (Examiner should point to 1, 4 to demonstrate). If the Participant verbalizes while pointing, indicate that it is not necessary to say the numbers while pointing to them. Remove the Number Stimulus Card. Proceed to the second training item (T-2).

Say, **Let's try another one. Remember, when I'm done saying the numbers in a mixed up order, you point them out in the correct order. Ready? Try this: 3, 2.** Immediately display the Number Stimulus Card. Encourage the Participant to respond. If the Participant is correct, say, Good, and proceed to the next item. If the Participant is incorrect, say, **That's not quite right. I said 3, 2, so you would point to 2, and then 3, their correct order** (Examiner should point to 2, 3 to demonstrate). Teaching the training items is permitted to ensure that the Participant understands the task. Proceed to Item A-1. No further help is permitted.

Read each number sequence at a rate of one number per second. The Examiner's voice should drop slightly when reciting the last number of an item to signal the end of that sequence. ***Remove the Number Stimulus Card before administering each number sequence.*** When each sequence is complete, immediately present the card to the Participant. Continue to administer all items sequentially until the Participant fails 3 items in a row for Level A. Proceed to Level B.

Instructions for Level B

Say, **This time I'm going to say some numbers and letters in a mixed up order. When I'm done, I am going to show you a card with numbers and letters on it.** (Display the Number-Alphabet Stimulus Card on which numbers from 1-8 and letters A-J are correctly ordered). Say, **Using the card, point to all the numbers and letters that I said, but point them out in the correct numerical and alphabetical orders.** Remove the card. Say, **Point to the numbers in correct order first and then point to the letters in correct order. Let's try one.** Say, **5, B, 2**. Immediately display the Number-Alphabet Stimulus Card. Encourage the Participant to point out his/her response.

If the Participant is correct, say, **Good**, and proceed to the next training item (T-2). If the Participant is incorrect, say, **That's not quite right**. **I said 5, B, 2, so you would point to 2, 5 in the correct order and then to letter B** (Examiner should point to 2, 5, B to demonstrate). If the Participant verbalizes while pointing, indicate that it is not necessary the numbers while pointing to them. Remove the Number-Alphabet Stimulus Card.

Say, **Let's try another one. Remember, when I'm done saying the numbers and letters in a mixed up order, you point them out in the correct order. Numbers first, then letters in the correct order. Ready? Try this: 3, B, A, 2.** (Immediately display the Number-Alphabet Stimulus Card.) Encourage the Participant to respond. If the Participant is correct, say, **Good**, and proceed with Level B. If the Participant is incorrect, say, **That's not quite right. I said 3, B, A, 2, so you would point to the numbers first: 2, 3 in correct order** (Examiner should point to 2, 3 to demonstrate) **and then the letters A, B in the correct order** (Examine should point to A, B to demonstrate). Teaching the practice items is permitted to ensure that the Participant understands the task. Proceed to Item B-1. No further help is permitted.

Read each number-letter sequence at a rate of one per second. ***Remove the Number-Alphabet Stimulus Card before administering each number-letter sequence.*** After each sequence is read, immediately present the card to the Participant. Continue to administer all items sequentially until the Participant fails 3 items in a row on Level B.

Appendix 12: Map Search Test Instructions

Map Search Test Instructions

MATERIALS: *CUEBOOK, COLOURED MAP, COLOURED PEN, EXAMINER FORM, STOPWATCH*

Instructions for Map Search

Say: **The symbol here (show symbol from cuebook) shows where restaurants can be found in the Philadelphia area. There are many symbols like this on the map.**

(Point to one at left side of map. Also, indicate to subjects that the symbols are found all over the map, left and right, top and bottom. Check that the subject can see the symbol clearly.)

Turn the map over so the subject cannot scan it while you give further instructions.

Say: **Let's say you are with a family member or a friend. They are driving while want to you are navigating. You want to know where restaurants are located in case you decide to stop for a meal. What I would like you to do is to look at the map for two minutes and circle as many symbols as you can. I will stop you once when a minute has gone by to ask you to swap pens. OK?**

When the subject indicate that they have understood (reiterate the instructions if they have not) turn the map over to reveal the symbols, give them a red pen and begin timing. After one minute, ask the subject to change pens and hand them a blue pen. At the end of two minutes ask the subject to stop.

If the subject feels that they have completed the task before the two minute time limit, or if they assume that they have done so by reaching the right hand edge of the map, ask them to continue searching for any symbols which they might have missed until the end of the time limit.

Appendix 13: Telephone Search Test Instructions

Telephone Search Test Instructions

MATERIALS: *CUEBOOK, TELEPHONE DIRECTORY PAGE, COLOURED PEN, EXAMINER FORM, STOPWATCH*

Instructions for Telephone Search

Say: **In this exercise, you should imagine that you are using a telephone directory to look up various services while you are on your trip.**

Here we have the yellow pages you would see in a telephone directory, in this case it lists plumbers.

(Place the cuebook and directory pages before the subject.)
Say: **Imagine that during your vacation, you are staying in a house belonging to a friend of yours. You are going to be there for a few weeks. Your friend is away and not reachable on the telephone. Image that the sink in the kitchen starts to leak badly each time you use it. You want to reach a plumber. You have been advised to consider only using plumbers who have the same two symbols before the number. Let's say that means that their work is especially guaranteed. That way you go about that is by looking through the yellow pages for any two symbols (two squares, two stars, two circles, or two crosses).**

(Point to the appropriate symbol on the cue sheet.)
Say: **Just circle the two symbols when they are the same. Work as quickly but also as accurately as you can to find all the double symbols quickly. Let me know the moment you finish working through the four columns. When you reach the bottom, put a cross in the box, here, and put your pen down. We don't want you to go back and check after you have reached the bottom right-hand corner. OK?**

When the subject fully understands and is ready, say **'begin'** and start your stopwatch. When the subject indicates they have found all the targets, note the time. Do not give prompts to find more of the double symbols. Discontinue the task after four minutes.

If you see that the subject has reached the bottom of the fourth column and they have not put a cross in the box, cue them to do so by saying:
When you have reached the bottom, put a cross in the box.

Appendix 14: Elevator Counting with Distraction Test Instructions

Elevator Counting with Distraction Test Instructions

MATERIALS: *AUDIO-TAPE, EXAMINER FORM*

Instructions for Elevator Counting with Distraction

(Forward the audio-tape to the Elevator Counting subtest.)
Say: **Imagine that you are in an elevator in your hotel. The visual floor indicator light that should show you what floor you are on is not working. You need to know which floor you are at, so you can get off to go to your room. The elevator is only going up. You are helped by the fact that as the elevator passes each floor, a tone sounds. So by counting the tones you can work out which floor the elevator is at. Tell me how many floors you count, or in other words which floor you have reached when the tones stop, and when the voice on the tape says 'how many?'. You will notice that the time the elevator takes to move up from floor to floor may vary.**

Play the first example, counting with the subject, and, if they are right, say:
That's right, you would be on the third floor.

If they are wrong, rewind the tape and play it again, continuing to do so until you are sure that the subject understands the subtest and can do the first example.

Then forward the audio-tape to the Elevator Counting with Distraction, say: **This time you will hear the same elevator tone but now there are also higher pitched tones as well as the lower tones you are listening for. Try to ignore the high pitched tones and count the other tones to tell which floor you are on as in the last exercise.**

Let's try two practice trials to make sure you can tell the elevator tone indicator from the higher tone, remembering that you are to ignore the high tone and try not to count it.

The first tone you will hear in each string is always the low tone.

Play the first example, counting with the subject, and, if they are right, say:
That's right, you would be on the third floor.

If they are wrong, rewind the tape and play it again, continuing to do so until you are sure that the subject understands the subtest and can do the first example. Then go on to the second example.

Say: **Let's have another practice.**

Let the subject count for the second practice, and if they get it right, go on to the subtest. If they get it wrong, then return to the beginning and count with them, continuing until they get the right answer on their own.

Say: **Now, I would like you to do the same thing, with another series of elevator tones.**

Press the pause button to restart the tape, *reminding the subject to wait for the end of the string of tones to give their answer, in response to the command on tape 'How many?'*

Appendix 15: Lottery Test Instructions

Lottery Test Instructions

MATERIALS: *CUEBOOK, AUDIO-TAPE, EXAMINER FORM, PAPER, PENCIL*

Instructions for Lottery

Say: **While you are on your trip, you become interested in the state lottey. You buy lottery tickets every week while you are out shopping. In this task, I want you to imagine you have some lottery tickets, that you need to check against winning numbers. The winning numbers are played on the radio. Imagine that you are listening to a long list of lottery numbers on the radio. Examples of lottery numbers might be WD389 or ZX638, i.e., two letters, followed by three numbers. All your tickets end in 55 so you must listen for all the tickets that end in 55. When you hear a ticket ending in this number, write down the first two letters of the ticket. So, if you hear SD355, you will write SD. To remind you, the number you are listening for is displayed here. Here is a piece of paper for you to write on. OK?**

(Point to the cue book, which shows 55)
Say: **The radio programme goes on for quite a long time. Your number is not going to be mentioned very often. Try your best to listen for your number over the fairly long radio broadcast. Let's listen to the beginning of the radio programme to make certain you are clear about what you have to do.**

Play the audio-tape to the point when the first lottery number ending in 55 is mentioned. Note that the subject has heard the series and has recorded the correct letters. If they subject fails to write the letters, remind them that they will hear two letters and three numbers and when the last two numbers are 55 they are to write down the letters. Restart the tape until they successfully respond to the first number.

Appendix 16: Telephone Search while Counting (Dual Task) Test Instructions

Telephone Search while Counting (Dual Task) Test Instructions

MATERIALS: *CUEBOOK, COLOURED MAP, AUDIO-TAPE, TELEPHONE DIRECTORY PAGE, COLOURED PEN, STOPWATCH, EXAMINER FORM*

Instructions for Telephone Search while Counting (Dual Task)

Say: **Now you will search through a different set of yellow pages for the same double symbols as in the last subtest. But this time, I want you to do a second and equally important task at the same time – counting a number of series of tones which are very easy to count on their own, but which are more difficult to count when searching in the telephone directory at the same time.**

On this telephone search task, imagine that you are interested in finding out which restaurants are in the area you are staying. You have been told that the restaurants there are most recommended are those that have the double symbols.

Say: **Now let's play a sample of what you will hear on the tape.**

Start the audio-tape. Count the first (practice) series with the subject.

Say: **So you will be looking for the same double symbols as before and marking them as quickly and as accurately as possible. As soon as you have finished marking them, cross this box in the lower right hand corner, as you did before.**

At the same time as you are circling the double symbols, listen for the tones and when you hear that the series has come to an end, tell me how many there were right away.

Remember to tell me as soon as you have finished marking the symbols and put a cross in the box *(point to box),* **even if you are in the middle of counting. Remember to give equal importance to the telephone and counting tasks. OK?**

Press the pause button on the tape after the first example when the voice says 'OK, let's start…'. The tape is now in the correct position to start the task.

Say: **Get ready, and when the voice says 'ready', please start both tasks, remembering to put equal effort into both, and not forgetting to count each string**

of tones and to say out loud the answer each time the voice on the tape says 'how many?'.

Score each string (i.e., between each '*ready*' and '*how many*') on the tape as to whether it was attempted, and if it was, whether it was right or wrong. Continue scoring the tones *just* until the person has finished marking the symbols, even if a tone-string is on-going. Then switch off the tape, while simultaneously noting the time taken to complete the telephone task.

Appendix 17: Visual Elevator Test Instructions

Visual ElevatorTest Instructions

MATERIALS: *CUEBOOK, STOPWATCH, EXAMINER FORM*

Instructions for Visual Elevator

Say: **Try to imagine that during your trip, you decided to stay in a large hotel, many stories high. While you are staying there, you find that the indicator in the elevator that tells you what floor you are on is not working properly.**

(Show the subject the first visual elevator example page.)
Say: **Look at this series of pictures. As you can see, each one shows an elevator. Every so often there is a large arrow, like this one. An arrow pointing down means that the elevator is going down, so you need to reverse count. An arrow pointing up means the elevator is going up. What I want you to do is count out the floors. Say 'up' and 'down' when you come to the large arrows, as this avoids counting them. I will point at each one in turn as you say the number. Remember the big arrows are not floors, they only tell you which way the elevator is going. So, in this first example, you would say – *one-two-down-one-up-two*. Now you try.**

Repeat as often as necessary until the person has comprehended the task. Do not proceed with the subtest until you are sure that the subject has performed both practice items correctly on his or her own.

Say: **OK? Now you try the next example.**

Continue to explain the procedure using the next practice example. The correct answers to the examples are Example 1 = 2 and Example 2 = 4. *Emphasize to the subject that the rows go left to right then right to left and so on.*

Say: **Now try and do the same with next set of pictures. Work as quickly and accurately as you can. Count out loud as you move along the elevators.**

Note the subject's performance on the scoring sheet, indicating whether the final number was right or wrong. Time each item and mark the time taken on the scoring sheet.

Appendix 18: Elevator Counting with Reversal Test Instructions

Elevator Counting with Reversal Test Instructions

MATERIALS: *CUEBOOK, AUDIO-TAPE, STOPWATCH, EXAMINER FORM*

Instructions for Elevator Counting with Reversal

Say: **Now we're going to try something similar but a bit more complicated. Look again at what you did here.**

(Point to the first example of the Visual Elevator subtest.)
Say: **Remember how the big arrows tell you whether the elevator is going up or down? Now we are going to try an auditory (sound) version of this. This time, imagine that as the elevator goes up, it may stop briefly at a floor and then it might go down. You know whether the elevator is going up or down by the sounds. There are three types of sound – the normal, middle-pitched one corresponds to a 'floor' and is the equivalent of one of the elevator doors in the Visual Elevator task. The second tone is a high-pitched one, which means 'up' and is equivalent to the large upward-pointing arrow in the Visual Elevator task. The third tone is a low-pitched tone which means 'down' and is equivalent to the large downward-pointing arrow in the Visual Elevator task.**

To summarize, the middle tone is the floor to be counted, the high tone means the elevator has stopped and is going to go up (so this tone is not counted); and the low tone means the elevator has stopped and is going to go down (again this tone is not to be counted). OK?

Referring to the Visual Elevator subtest already carried out, make sure the subject has grasped that the idea is exactly the same as for that task, except that high and low tones replace the up and down arrows.

Say: **To begin with, listen to this example, which I will count out loud to give you the idea.**

Play the tape and say: **One-two-up-three-four-down-three-two – so the answer is 2.**

I want you just to tell me the floor that you end up on. It helps to say 'up' and 'down' to yourself when you hear the high and low tones.

Now try this second example. Remember that it is not necessary to count out loud, and that what we are interested in is what floor you have arrived at when the voice on the tape asks 'which floor?'

Play the practice audio-tape.
The second example is as follows:
Tone, tone, high-tone, tone
(the answer is three by counting 'one-two-(up)-three').

In the third example you hear:
Tone, tone, tone, tone, low-tone, tone
(the answer is three by counting 'one-two-three-four-(down)-three').

Go through the example as many times as is necessary to ensure that the subject comprehends the task before starting the test items that are introduced on the tape by the words *'OK, now try these…'*.

Do not proceed with the subtest until you are sure that the subject has performed both practice items correctly on his or her own.

Appendix 19: Austin Maze Test Instructions

Austin Maze Test Instructions

MATERIALS: *AUSTIN MAZE, EXAMINER FORM*

Instructions for Austin Maze

Say: **This is a learning task in which you are required to find the pathway which leads from the start (marked 's') to finish (marked 'F'). The way to find the path is to press one button at a time, if it is on the path the green light will show, if it is off the path the red light will show. The rules are 1) you can only move one button at time, no jumping buttons – and 2) you can move up or down, to the left or the right but not diagonally. To help you to keep your bearings if you step off the path and get a red light, go back to the last button that was on the path and press it before you try a different direction. On your first turn see if you can find your way to the finish. Then have more turns because the aim of the test is to see how many turns you need to learn the pathway and to remember where it is.**

Remember that the aim is to see how many trials you need to learn the pathway, the fewer the better. When you can remember it and you can run along path without making any mistakes, you are to do 3 perfect trials in a row to show that you have the idea. (You have 10 trials; try to get to zero errors in a row) Do you have any questions? If not, you can begin.