Obstructive sleep apnoea and cognitive impairment in older adults

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the project is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and, ethics procedures and guidelines have been followed.

V Vien Lee

4th June 2019
“Oh, the terrible struggle that I have had against sleep so often of late; the pain of the sleeplessness, or the pain of the fear of sleep, and with such unknown horror as it has for me! How blessed are some people, whose lives have no fears, no dreads; to whom sleep is a blessing that comes nightly, and brings nothing but sweet dreams.”

—Bram Stoker, *Dracula*
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This thesis contains three study chapters written as papers in preparation for publication. Accordingly, each study chapter has been written as a self-contained paper, and thus each has its own abstract, introduction, methods, results and discussion.

The chapters are preceded by an introduction to the research project and a chapter describing the overall methods and materials used in this thesis. At the end, they are followed by a general discussion that draws together the key outcomes and findings of the collective research.
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<th>Full Form</th>
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<tbody>
<tr>
<td>AASM</td>
<td>American Academy of Sleep Medicine</td>
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<tr>
<td>Aβ</td>
<td>Beta Amyloid</td>
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<td>AD</td>
<td>Alzheimer’s Disease</td>
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<td>ADNI</td>
<td>Alzheimer's Disease Neuroimaging Initiative</td>
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<td>AHI</td>
<td>Apnoea-Hypopnea Index</td>
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<td>AI</td>
<td>Arousal Index</td>
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<tr>
<td>AIBL</td>
<td>Australian Imaging, Biomarkers and Lifestyle Study of Ageing</td>
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<tr>
<td>AM</td>
<td>Autobiographical Memory</td>
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<td>AMI</td>
<td>Autobiographical Memory Interview</td>
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<td>AMT</td>
<td>Autobiographical Memory Test</td>
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<td>ANOVA</td>
<td>One-way Analysis of Variance</td>
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<td>APOE</td>
<td>Apolipoprotein E</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BVRT</td>
<td>Benton Visual Retention Test</td>
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<tr>
<td>CDAMS</td>
<td>Cognitive, Dementia and Memory Service</td>
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<tr>
<td>CES-D</td>
<td>Centre of Epidemiological Studies Depression Scale</td>
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<tr>
<td>CO₂</td>
<td>Carbon Dioxide</td>
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<td>COMM</td>
<td>CPAP for OSA and MCI study</td>
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<td>COSAD</td>
<td>CPAP for OSA and Depression study</td>
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<tr>
<td>CPAP</td>
<td>Continuous Positive Airway Pressure</td>
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<td>CPT</td>
<td>Continuous Performance Tests</td>
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<td>Digit Span</td>
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<td>ECG</td>
<td>Electrocardigram</td>
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<td>EMG</td>
<td>Electromyogram</td>
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<td>EMT</td>
<td>Emotional Memory Test</td>
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<td>EOG</td>
<td>Electrooculogram</td>
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<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>HC</td>
<td>Healthy Controls</td>
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<td>hr</td>
<td>hour</td>
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<td>HREC</td>
<td>Human Research Ethics Committee</td>
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<td>HSD</td>
<td>Honestly Significant Difference</td>
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<td>LM</td>
<td>Logical Memory</td>
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<td>MAPI</td>
<td>Multivariable Apnea Prediction Index</td>
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<td>MCI</td>
<td>Mild Cognitive Impairment</td>
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<td>MEQ</td>
<td>Morningness-Eveningness Questionnaire</td>
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<td>MMSE</td>
<td>Mini Mental State Examination</td>
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mPFC  Medial Prefrontal Cortex
N1    Stage 1
N2    Stage 2
N3    Stage 3
ODI   Oxygen Desaturation Index
OSA   Obstructive Sleep Apnoea
PSG   Polysomnography
PSQI  Pittsburgh Sleep Quality Index
PVT   Psychomotor Vigilance Test
RCFT  Rey-Osterrieth Complex Figure Test
RDI   Respiratory Disturbance Index
REM   Rapid Eye Movement
SaO₂  Oxygen Saturation
SD    Standard Deviation
SWA   Slow Wave Activity
SWS   Slow Wave Sleep
TMT   Trail Making Test
TST   Total Sleep Time
WAIS  Wechsler Adult Intelligence Scale
WASO  Wake After Sleep Onset
WCST  Wisconsin Card Sorting Test
WMS   Wechsler Memory Scale
Abstract

Obstructive sleep apnoea (OSA) has been linked to several neuropsychological deficits, such as attention and executive functioning deficits, and memory impairment. Recently, OSA has been identified as a risk factor for the development of mild cognitive impairment (MCI)/dementia. Given the reported association between OSA and cognitive decline, identifying the potential mechanisms can have important implications for early detection and risk assessment. Identification of cognitive areas affected by OSA is also important as it allows the possibility of an intervention that targets the sleep-related factors that may be contributing towards the development of cognitive impairment. The broad aim of this thesis was to examine the relationship between cognition and obstructive sleep apnoea in older adults with and without comorbid MCI.

The first study of the thesis consists of two parts and both aimed to investigate specific autobiographical memory impairment in OSA patients. While our previous study (Lee, Trinder & Jackson, 2016) reported impairment in specific autobiographical memory recall in OSA patients, we also reported that age may be a potential confounding factor. Accordingly, the first aim was to expand our previous work and investigate if there is an age-related effect on specific autobiographical memory impairment in OSA patients. Specific autobiographical memory performance was compared between four groups: (i) 20 young healthy controls (<50 years); (ii) 20 young OSA patients (<50 years); (iii) 19 older healthy controls (≥50 years); and (iv) 18 older OSA patients (≥50 years). Results indicated that all OSA patients performed significantly worse than healthy controls and young OSA patients are as impaired as older OSA patients in specific autobiographical memory recall.

Secondly, specific autobiographical memory impairment has been reported in OSA and MCI patients independently. Given the high comorbidity between OSA and MCI patients, it is yet unknown if this specific autobiographical memory impairment observed in individuals with clinically significant cognitive decline can be attributed to sleep apnoea. Accordingly, the second part of this study aimed to assess specific autobiographical memory performance in patients with comorbid OSA and MCI in comparison to OSA with no significantly cognitive impairment and healthy controls. In this part, specific autobiographical memory performance was compared
between three groups (i) 18 OSA patients with comorbid MCI; (ii) 19 age-matched OSA patients; and (iii) 19 aged-matched healthy controls. The results revealed that OSA patients without clinically significant cognitive impairment performed as poorly as OSA patients with MCI in specific autobiographical memory recall.

Following on from the first study, the second study continued the investigation of cognitive impairment in patients with comorbid OSA and MCI. The majority of studies that examined cognitive impairment in patients with comorbid OSA and MCI/dementia have mainly focused on global cognition. Given the known impairments of different cognitive domains in OSA patients, limited studies have examined the relationship between specific cognitive domains and sleep apnoea in patients with comorbid OSA and MCI. Accordingly, the second study aimed to examine the relationship between sleep apnoea severity and cognitive performance in patients with comorbid OSA and MCI. To examine the potential underlying mechanisms of this relationship, this portion of the thesis was also interested in exploring the relationship between cognitive performance and the different aspects of sleep apnoea, including intermittent hypoxia, sleep fragmentation, sleep architecture and subjective sleep measures. Also, the study compared cognitive performance and mood between MCI patients with and without OSA in a subset of cognitive domains.

Eighteen OSA patients with MCI completed a neuropsychological test-battery including measures of global cognition, verbal memory, visual memory, working memory, processing speed and attention, and executive function. Results indicated that higher sleep apnoea severity was significantly associated with poorer global cognition and working memory. Further analyses showed that cognitive performance was significantly linked with measures of intermittent hypoxia and percentage of time spent in slow wave sleep (SWS) but not measures of sleep fragmentation, subjective daytime sleepiness and subjective sleep quality. Finally, the between group comparison demonstrated that MCI patients with OSA had significantly more anxiety symptoms, and poorer processing speed when compared to MCI patients without OSA, or with age-matched healthy controls.

Finally, study three aimed to investigate the efficacy of three months of CPAP therapy on cognitive performance and mood in patients with comorbid OSA and MCI. Recent findings from Osorio and colleagues (2015) reported that individuals at an earlier stage of cognitive
impairment may benefit the most from CPAP use, and that CPAP therapy has the potential to slow down the age of onset in MCI patients. While several CPAP trial studies have been conducted with patients with Alzheimer’s disease, limited studies have examined the effects of CPAP therapy on cognitive performance and mood in MCI patients. In this study, eight OSA patients with MCI received three months of CPAP therapy. Prior to starting CPAP and again after three months of treatment, participants completed a 90-minute neuropsychological test battery, and a set of mood and sleep questionnaires. The results indicated that three months of CPAP therapy in this patient population have the potential to improve daytime sleepiness, global cognitive, logical memory and specific autobiographical memory.
Chapter 1

General introduction

1.1 Obstructive Sleep Apnoea

1.1.1 Epidemiology, Clinical Features and Diagnosis

OSA is a clinically recognised sleep disorder characterised by repeated episodes of complete or partial cessation of airflow, known as apnoeas and hypopnoeas respectively, during sleep due to an obstructed airway. As a result of the continual apnoeas and hypopnoeas, OSA patients experience arousals from sleep and decrease in blood oxygen saturation levels (Aloia et al., 2004). This recurrent cycle of apnoeas and central nervous system arousals contribute towards the two significant consequences of OSA – intermittent hypoxia and sleep fragmentation (Shamsuzzaman, Gersh & Somers, 2003). Moreover, due to the patients’ fragmented sleeping patterns, OSA is commonly accompanied by excessive daytime sleepiness (Caples, Gami & Somers, 2005).

OSA is the most common sleep-related breathing disorder with a population prevalence range of 9% to 38% in the general adult population (Senaratna et al., 2017). Nevertheless, the prevalence of undiagnosed OSA is still relatively high. It has been estimated that up to 9% of adults from Western countries suffer from undiagnosed OSA (Simpson et al., 2013; Young, Peppard & Gottlieb, 2002). In studies examining the prevalence of undiagnosed OSA in surgical patients, up to 27.5% of patients have been screened to be at high risk of OSA, with 86% of high-risk patients having confirmed OSA after an overnight polysomnography (PSG; Finkel et al., 2009; Sharma et al., 2006). Furthermore, the incidence of OSA has been shown to increase steadily with age, independent of other risk factors such as obesity (Franklin & Lindberg, 2014). It has been observed that the prevalence of OSA in individuals above 65 years is approximately 3 times higher than those in middle age (Young et al., 2002). Prevalence in older individuals have been reported to be as high as 84% (Senaratna et al., 2017).
The standard diagnostic test conducted for OSA is an overnight PSG, which includes either an in-laboratory or unattended at-home testing. An overnight PSG includes electroencephalogram, electrooculogram, electromyogram, thoracic and respiratory belts, oronasal thermal airflow sensor and oximetry to simultaneously record overnight brain activity, respiratory functions, and blood oxygen levels (Punjabi, 2008). From the PSG recordings, sleep-related apnoeas and hypopnoeas can be identified. Based on the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (American Academy of Sleep Medicine, 2007), apnoea is defined by a drop in the peak signal excursion of at least 90% of pre-event baseline for 10 seconds or more. On the other hand, hypopnoea is defined as a reduction in oronasal airflow by at least 30% for 10 seconds or more, followed by either a ≥3% arterial oxygen desaturation or an arousal from sleep. Collectively, both apnoeas and hypopnoeas have been utilised to categorise sleep apnoea severity. The apnoea-hypopnoea index (AHI) reflects the number of apnoea and hypopnoea episodes per hour of sleep. An AHI of 5 to 15 indicates mild sleep apnoea, 16 to 30 indicates moderate sleep apnoea and more than 30 indicates severe sleep apnoea (Epstein et al., 2009).

1.1.2 Treatment for OSA

Depending on the severity of OSA, patients may be advised on various appropriate treatment options, including lifestyle changes, CPAP therapy, oral appliances and surgery. For instance, lifestyle changes such as weight management, increased physical activity and avoiding alcohol prior to sleep have been shown to reduce the frequency of apnoea episodes in mild to moderate OSA patients (Araghi et al., 2013; Foster et al. 2009; Scanlan, Roebuck, Little, Redman & Naughton, 2000). In mild-moderate OSA patients, the use of an oral appliance to hold the lower jaw in a protruded position during sleep has been reported to be effective in reducing AHI and daytime sleepiness (Barnes et al. 2004). Although lifestyle changes and oral appliances can be effective for less severe patients, CPAP therapy is often the preferred and recommended treatment for moderate-to-severe patients (American Academy of Sleep Medicine, 2009).

CPAP consists of a flow generator that delivers mild air pressure to the patient during sleep through a nasal or oro-nasal mask to prevent the pharyngeal airway from collapsing (Giles et al.,
Randomised controlled trials of CPAP in OSA patients have reported significant improvements in objective sleep measures such as AHI, arousal index and rate of oxygen desaturation of at least 4% (Barnes et al., 2004; Monasterio et al. 2001; Weaver & Chasens, 2007). These findings were supported by a Cochrane Review (2008) which also reported similar improvements in AHI. Furthermore, a comparison between the CPAP and oral appliances in the review (2008) revealed CPAP to be significantly more effective in reducing AHI and improving sleep efficiency and minimum oxygen saturation.

Besides objective sleep measures, CPAP therapy has also been shown to improve subjective sleepiness, daytime functioning, memory and mood in OSA patients (Hobzova et al., 2017; Giles et al. 2008, Ferini-Strambi et al., 2003; Zimmerman et al., 2006). Following 15 days to one year of CPAP usage, studies have reported significant reductions in daytime somnolence and depressive symptoms, and improvements in sustained attention, verbal delayed memory recall, psychomotor and executive functioning, and quality of life (Antic et al., 2011; Ferini-Strambi et al., 2003; Kawahara et al., 2005; Pecotic et al., 2019; Schwartz & Karatinos, 2007; Zimmerman et al., 2006).

1.2 OSA and cognitive impairment

Besides the direct physiological consequences, OSA has been linked to several neuropsychological deficits, such as attention and executive functioning deficits, and memory impairment (Aloia et al, 2005; Knoepke & Aloia, 2009; Peppard, Szklo-Coxr, Hla & Young, 2006). Studies examining memory impairment in OSA patients have demonstrated impairments in short-term verbal, visual and long-term semantic memory (Ferini-Strambi et al., 2003; Naegele et al., 2006; Jackson et al., 2011).

1.2.1 Attention/vigilance

Attention/vigilance performance has generally been linked to sleep, with individuals displaying poorer attentional performance following sleep deprivation (Doran, Van Dongen, & Dinges, 2001), poor sleep quality (Gobin, Banks, Fins & Tartar, 2015) and sleep fragmentation (see Stepanski, 2002 for review). Tests including the Psychomotor Vigilance Test (PVT), Trail
Making Test A (TMT A; Armitage, 1946) and Continuous Performance Tests (CPT) have been utilised to measure sustained attention. Divided attention, another aspect of attention, has also been studied in OSA patients and is often measured by a driving stimulator (Turkington, Sircar, Allgar & Elliott, 2001; Vakulin et al., 2011).

1.2.1.1 Attention/vigilance deficits in OSA patients

Most of the literature in OSA patients reports attentional deficits (Aloia, Arnedt, Davis, Riggs & Byrd, 2004; Beebe, Groesz, Wells, Nichols & McGee, 2003; Canessa et al., 2011; D’Rozario et al., 2018; Gagnon et al., 2014; Luz et al., 2016; Mazza et al., 2005; Kim, Dinges & Young, 2006; Sforza, Haba-Rubio, Bilbao, Rochat & Ibanez, 2004; Tanno et al., 2017). While the magnitude of attentional impairment may vary among individuals, studies have reported a significant deficit in divided, selective and sustained attention in OSA patients when compared to healthy controls (Luz et al., 2016; Mazza et al., 2005; Sforza, Haba-Rubio, Bilbao, Rochat & Ibanez, 2004). Deficits in attention have been reported as poorer accuracy (i.e., lapses or false response) and slower processing speed (i.e., longer reaction time). The findings on accuracy and processing speed have been mixed, with some studies indicating that accuracy rather than speed is compromised in OSA patients (Mazza et al., 2005; Sforza, Haba-Rubio, Bilbao, Rochat & Ibanez, 2004), some reporting impaired reaction time (Ayalon, Ancoli-Israel, Allison, McKenna & Drummond, 2009) and some observing deficits in both accuracy and speed (Luz et al., 2016; Mathieu et al., 2008).

In support of attentional deficits observed in OSA patients, neuroimaging studies have showed impairment in brain areas typically involved in attention (Canessa et al., 2011; Ayalon, Ancoli-Israel, Allison, McKenna & Drummond, 2009). For example, Ayalon and colleagues (2009) reported decreased activation in cingulate, frontal and parietal regions during a sustained attention task in OSA patients when compared to healthy controls.

Age has been shown to influence attentional performance, with older OSA patients (50+ years) presenting longer mean reaction time and more lapses (Mathieu et al., 2008). A large community-based study of 611 individuals revealed that sleep-disordered breathing was only
linked to impaired psychomotor vigilance in older individuals, aged 65 to 74 years, but not in those younger than 65 years of age (Kim, Dinges & Young, 2007).

1.2.1.2 Effect of CPAP therapy on attention/vigilance

A review of studies that measured cognitive performance pre- and post-CPAP reported that the majority (11 out of 17) of CPAP treatment studies indicated significant improvement in attention/vigilance (Aloia et al., 2004). One study reported notable improvements in attention and concentration following two consecutive CPAP titration nights (Valencia-Flores, Bliwise, Guilleminault, Citveti & Clerk, 1996). Furthermore, impaired attentional performance in OSA patients has been shown to revert to a level comparable to healthy controls following 15 days of CPAP therapy (Ferini-Strambi et al., 2003). Consistently, another meta-analysis (Kylstra, Aaronson, Hofman & Schmand, 2013) of thirteen CPAP treatment studies reported a small, significant treatment effect on attention, and more recent studies (Deering, Liu, Zamora, Hamilton & Stepnowsky, 2017; Hobzova et al., 2017) in severe OSA patients reported significant improvements in attentional performance following one to six months of CPAP therapy.

1.2.2 Executive function

Several studies have reported executive functioning deficits in patients with OSA (see Olaithe & Bucks, 2013 and Saunamäki & Jehkonen, 2007 for reviews). Executive functioning encompasses neuropsychological processes that involve cognitive flexibility, problem-solving and response maintenance (Alvarez & Emory, 2006). Tests including the Wisconsin Card Sorting Tests (WCST; Heaton, Chelune, Talley, Kay & Curtiss, 1993), Trail Making Test B (TMT B; Armitage, 1946) and Stroop colour and word test (Golden & Freshwater, 1978) have been used to measure executive functioning.

1.2.2.1 Executive function impairment in OSA patients

Most of the literature describing OSA patients reports executive dysfunction (Aloia, Arnedt, Davis, Rigg & Byrd, 2004; Beebe, Groesz, Wells, Nichols, McGee, 2003; Ju et al., 2012; Krysta,

A meta-analysis by Olaithe and Bucks (2013) divided executive function into five sub-domains: (i) shifting (e.g., WCST, TMT B); (ii) updating (e.g., N-back tasks, Digit Span backwards); (iii) inhibition (e.g., Stroop task, Go No-go task); (iv) generativity (e.g., verbal fluency tasks); and (v) fluid reasoning (e.g., Mazes, Ravens progressive matrices). From 35 studies examined, 21 compared executive functioning performance between untreated OSA patients and healthy controls, and OSA patients were reported to be impaired in all five subcomponents.

Nevertheless, it is unclear if there is a relationship between disease severity and executive dysfunction, with both reviews cited above unable to examine the link due to homogeneity of patient groups and insufficient studies reporting the effects of mild-moderate OSA patients on executive function performance. Olaithe and Bucks (2013) divided the samples into severe (AHI 30-50) and very severe (AHI 51+) but reported no significant effect. In another review by Aloia, Arnedt, Davis, Riggs & Byrd (2004), five out of eleven studies examined reported a link between executive function and OSA severity, as measured by respiratory disturbance index (RDI) or hypoxemia.

On the other hand, a more recent meta-analysis in older adults (Cross et al., 2017) reported no significant association between OSA and executive dysfunction in older adults. While Cross et al. (2017) reported a small but significant association between OSA and overall neuropsychological performance, only memory and processing speed domains were significantly linked with OSA in healthy older adults.

1.2.2 Effect of CPAP therapy on executive function

Multiple studies and extensive reviews have examined the impact of CPAP therapy on executive functioning following CPAP treatment lasting from one week to one year (Aloia, Arnedt, Davis,
Riggs & Byrd, 2004; Dalmases et al., 2015; Kang, Yoon, Lee & Kim, 2016; Li, Shen, Wang, Chang & Jan, 2017; Olaithe & Bucks, 2013; Saunamäki & Jehkonen, 2007). All have reported promising findings. For example, Olaithe and Bucks (2013) conducted a meta-analysis of 19 studies and reported small to medium effect size improvements in all five domains of executive function (see above regarding domains) after CPAP therapy (mean months of CPAP treatment = 2.89; mean hours CPAP usage per night = 5.34 hours). After dividing studies into short (0-5 months) and long term (5+ months) CPAP use, all effects remained significant and length of CPAP treatment did not moderate the effects found. Saunamäki and Jehkonen (2007) indicated that CPAP treatment significantly improved cognitive flexibility and speed, and planning but not working memory.

1.2.3 Verbal memory

Aspects of verbal memory that have been examined in studies include learning, immediate recall, delayed recall and recognition. Verbal memory is often measured by tasks such as the Hopkins Verbal Learning Test (Benedict, Schretlen & Brandt, 1997), Logical Memory from WMS and the Rey Auditory Verbal Learning Test (Lezak, 1995). The majority of studies that examined verbal memory in OSA patients reported significant impairment in this cognitive domain (Naegele et al., 2011; Stranks & Crowe, 2016; Torelli et al., 2011; Twigg et al., 2010, see Wallace & Bucks, 2013 for review).

1.2.3.1 Sleep clinic studies

Twigg and colleagues (2010) examined various aspects of memory (e.g., semantic memory, verbal episodic memory, visual episodic memory, working memory) in 60 OSA patients and 60 healthy controls. In this study, verbal episodic memory was measured using the Logical Memory task obtained from the Wechsler Memory Scale (WMS) III. When compared to healthy controls, OSA patients had significantly poorer immediate and delayed recall scores. Following this, linear regression models indicated no significant relationship between verbal episodic memory and disease severity, as measured by AHI and subjective sleepiness, as measured by the Epworth Sleepiness Scale (ESS), suggesting that individuals with mild and severe OSA may be equally impaired. It should also be noted that while OSA patients performed significantly poorer on the
free recall tasks, no difference was observed for the recognition task. This was similarly observed by Naegele and colleagues (2011) who reported a deficit in delayed verbal recall but intact learning and recognition performance, suggesting that verbal memory deficit observed in OSA patients may be due to a retrieval impairment rather than the inability to encode or consolidate information.

A comprehensive meta-analysis (see Wallace and Bucks, 2013 for review) examined 21 studies that have compared verbal episodic memory recall in OSA patients to healthy controls/norms and reported that OSA patients performed significantly poorer in all aspects of verbal episodic memory (i.e., immediate recall, delayed recall, learning and recognition) in comparison to healthy controls. Contrary to the theory of verbal impairment due to retrieval, Wallace and Bucks (2013) proposed that OSA patients have trouble encoding, potentially due to attention or executive function deficits – both domains that are linked to the prefrontal cortex.

Earlier meta-analyses (Fulda and Schulz, 2001; Beebe, Groesz, Wells, Nichols & McGee, 2003) reported mixed findings, with both reporting small and limited effect of OSA on verbal memory. As suggested by Wallace and Bucks (2013), the difference in findings may reflect the larger sample studies that have examined verbal memory in OSA patients over the last 10 years. Furthermore, it is also possible that newer verbal memory tests used in later studies are more sensitive and better able to differentiate the different aspects of verbal memory.

1.2.3.2 Community-based studies

Findings from large community-based studies have been mixed. Hrubos-Strøm and colleagues (2012) examined 290 individuals with high risk of developing OSA (mean AHI=7.7), based on their responses to the Berlin Questionnaire. Compared to available norms for the Rey Auditory Verbal Learning task, the group performed about 1.3 standard deviations below normal mean and verbal memory performance was reported to be independently related to average oxygen saturation. Given the relatively young sample population (mean age=48.2 years) at high-risk of developing OSA, the findings capture a picture of early verbal memory decline in individuals who are developing OSA or who have recently developed OSA.
On the other hand, a 15-year longitudinal study (Lutsey et al., 2016) following 966 older individuals (mean age=61.3 years), that examined verbal memory using a Delayed Word Recall task, reported no significant association between the severity of OSA, and decline in verbal learning and memory.

1.2.3.3 Effect of CPAP therapy on verbal memory

Studies that have examined the impact of CPAP therapy ranging from three to six months on verbal memory have reported improvements in verbal memory performance (Antic et al., 2011; Borak, Cieślicki, Koziej, Matuszewski & Zienliński, 1996; Canessa et al., 2011; Crawford-Achour et al., 2015; Montplaisir, Bédard, Richer & Rouleau, 1992; Zimmerman, Arnedt, Stanchina, Millman & Aloia, 2006).

Borak and colleagues (1996) reported significant improvement in verbal memory performance, as measured by Rey’s 15-item memory test, after 3 months of CPAP usage. No further improvement in verbal memory was observed after one year. This may be due to a ceiling effect as the same level of verbal memory performance was maintained after 12 months. Nevertheless, it is unclear if patients have attained normalisation or partial reversibility and are unable to improve further due to permanent impairment.

Verbal memory impairment in OSA patients has been shown to return to a clinically normal range or are comparable to healthy controls after 3 months of optimal and consistent use of CPAP (Antic et al., 2011; Zimmerman et al., 2006), suggesting that it is possible to normalise verbal memory from CPAP usage. Nevertheless, it should be noted in Antic et al.’s (2011) study, verbal memory impairment in a proportion of patients remained impaired and not normalised after 3 months despite adequate and continual CPAP use. There are also studies that have reported no improvement in verbal memory performance after CPAP therapy (Bédard, Montplaisir, Malo, Richer & Rouleau, 1993; Ferini-Strambi et al., 2003; Jackson, McEvoy, Banks & Barnes, 2018; Naegle et al., 1998). It is possible that normalisation of cognitive performance following CPAP therapy is dependent on the severity of sleep apnoea. For example, a recent study (Jackson, McEvoy, Banks & Barnes, 2018) reported that mild-moderate OSA patients (mean AHI = 21.3 ±1.4) did not return to the functional level of healthy controls.
following three months of CPAP therapy while another study (Crawford-Achour et al., 2015) that examined more severe OSA patients (mean AHI = 49.0 ±15.4) reported significant improvements in verbal memory.

1.2.4 Visual memory

Similar to verbal memory, studies examining visual memory in OSA patients typically test both immediate and delayed recall. Tests that have been used to measure visual memory include the Benton Visual Retention Test (BVRT; Sivan, 1992), Rey-Osterrieth Complex Figure Test (RCFT, Meyers & Meyers, 1995) and Figural Memory from WMS. Findings on visual memory performance in patients with OSA have been inconsistent (see Beebe, Groesz, Wells, Nichols & McGee, 2003; Fulda and Schulz, 2001; Wallace & Bucks, 2013 for reviews).

1.2.4.2 Visual memory impairment in OSA patients

Studies examining verbal memory impairment in OSA patients have been mixed, with some studies reporting immediate recall deficits (Bédard et al., 1991) or delayed recall deficits (Berry et al., 1990; see Olaithe, Bucks, Hillman & Eastwood, 2018 for review) or no significant visual memory impairment (Phillips, Berry, Schmitt, Harbinson & Lipke-Molby, 1994; Twigg et al., 2010).

Within Beebe and colleagues’ (2003) meta-analysis, there was inconsistency in the significance of visual memory deficits when compared to healthy controls and normative data. Control-referenced data indicated a significant deficit in both immediate and delayed visual memory with a moderate effect size, whereas norm-referenced data showed small and non-significant effect sizes in both aspects of visual memory. While the dataset for normative data was larger than for healthy controls, it should be noted that healthy controls are more rigorously screened for sleep disorders whereas normative data are likely to include individuals with undiagnosed sleep disorders.

Wallace and Bucks (2013) further examined the visual memory domain by distinguishing visuospatial memory tasks from visual memory tasks. Visual tasks include tests that require an
individual to recall visual information (e.g., recalling a picture; WMS Figural Recall) while visuo-spatial tasks evaluate the ability of an individual to recall information with both visual and spatial elements (e.g., drawing a diagram; BVRT, RCFT, WMS Figural Memory). Similar to Beebe et al., (2003), OSA patients were reported to be significantly impaired in immediate and delayed visuo-spatial recall when compared to healthy controls. Nevertheless, this was not observed in immediate visual recall.

1.2.4.2 Effect of CPAP therapy on visual memory

The findings on the effects of CPAP therapy on visual memory in OSA patients are equivocal. For instance, a study examining 125 mild OSA patients (59 on conservative treatment and 66 on CPAP therapy) reported significant visual memory improvements after 3 months of CPAP usage compared to those without (Monasterio et al., 2001). Improvements in long-term memory visual learning and visuo-spatial memory were also observed in CPAP studies ranging from three to six months (Monasterio et al., 2001; Naegele, et al., 1998).

On the other hand, studies examining four to eight weeks of CPAP therapy in patients with mild to severe OSA reported no significant improvement in visual memory (Barnes et al., 2002; Engleman, Martin, Deary & Douglas, 1997; Engleman et al., 1998; Joyeux-Faure et al., 2016). It is possible that four to eight weeks of CPAP therapy is not sufficient to observe any notable improvement and long-term continual use may be more beneficial.

1.2.5 Working memory

Working memory allows for the temporary storage, processing and manipulation of information (Baddeley, 1992). Tests including the WAIS Digit Span (Backwards and Sequencing), Paced Auditory Serial Addition Test (PASAT) and the N-Back task have been used to measure working memory.
1.2.5.1 Working memory impairment in OSA patients

Most studies that examined working memory reported that OSA patients displayed notably poorer maintenance and processing of information simultaneously (D’Rozario et al., 2018; Dalmases et al., 2015; Naegele et al., 2011; Sharma et al., 2010; Thomas, Rosen, Stern, Weiss & Kwong, 2005; Prilipko et al., 2011). For example, a functional imaging study reported that severe OSA patients had significantly poorer accuracy and performance speed in the 2-back test when compared to healthy controls (Thomas, Rosen, Stern, Weiss & Kwong, 2005). Furthermore, the neuroimaging findings showed that OSA patients had significantly impaired dorsolateral prefrontal activation when completing the working memory task, suggesting an involvement of the prefrontal regions in the working memory deficit observed in OSA patients. Nevertheless, some studies have reported no difference in working memory performance between OSA patients and healthy controls (Sforza et al., 2010; Twigg et al., 2010).

Several variables have been reported to influence working memory performance in OSA patients. For example, the presence of the Apolipoprotein E (APOE) e4 allele in OSA patients was linked to poorer spatial working memory (Cosentino et al., 2008). Obesity also appears to play a role in working memory in OSA patients, with a recent study reporting decreased working memory performance in obese OSA patients (BMI ≥ 30) compared to those with a BMI of below 30 (Shen, Kung, Chang, Hong & Wang, 2018).

1.2.5.2 Effect of CPAP therapy on working memory

Findings on the effects of CPAP therapy on working memory in OSA patients have been mainly negative with most studies indicating no effect of CPAP therapy, ranging from one week to four months, on working memory performance (Bardwell, Ancoli-Israel, Berry & Dimsdale, 2001; Dalmases et al., 2015; Ferini-Strambi et al., 2003; Joyeux-Faure et al., 2016; Lee et al., 2011; Monasterio et al., 2001; Naegele et al., 1998). Furthermore, a functional MRI study showed a persistent lack of prefrontal activation in OSA patients when performing a working memory task after eight weeks of CPAP therapy (Thomas, Rosen, Stern, Weiss & Kwong, 2005). While Thomas et al. (2005) reported a significant decrease in daytime sleepiness and improved sleep quality after eight weeks of CPAP, it is possible that a longer period of CPAP therapy is required.
to observe neurological changes. For instance, a three-month CPAP study reported significant improvement on multiple cognitive tests, including the Digit Span (Backward) scores, and these were associated with grey matter volume increases in the hippocampus, the medial orbitofrontal cortex and rostral portion of the right superior frontal gyrus (Canessa et al., 2011).

1.2.6 Autobiographical memory

While there is substantial evidence that memory is affected in OSA patients, the consistency of findings varies between the different aspects of memory. Nevertheless, one aspect of memory that has yet to be fully examined in OSA patients is autobiographical memory.

Autobiographical memory can be defined as “memory for events of one’s life” (Conway & Rubin, 1993, p. 103), and has generally been conceptualised into two categories: personal semantic information, and personal episodic information. Personal semantic information is often linked to a sense of ‘knowing’ or familiarity of the self, such as knowing where one was born, while recalling personal episodic information requires recollection of a particular event that one has experienced in the past (Holland & Kensinger, 2010). Both aspects of autobiographical memory are important as they play significant roles in the construction of an individual’s identity (Wilson and Ross, 2003). Particularly, episodic autobiographical memory, allows individuals to recall experiences from the past with detail and specificity. The current study is interested in examining autobiographical memory overgenerality which refers to the inability to recall specific episodic autobiographical memories.

1.2.6.1 Autobiographical memory overgenerality

The overgeneral memory phenomenon was first recognised by Williams and Broadbent (1986) who examined the episodic component of autobiographical memory in suicidal individuals. During retrieval of memories to positive and negative cue words, it was noted that patients had difficulties recalling specific memories, which was required by the task. Correspondingly, the findings indicated that depressed individuals with suicidal behaviours were more inclined to retrieve more overgeneral autobiographical memories than healthy controls when given an emotional cue word. One of the possible explanations of this phenomenon can be described by
the affect-regulation hypothesis. It is possible that individuals learn to retrieve negative memories in a less specific way to reduce negative affect experiences during recall (Raes, Hermans, de Decker, Eelen & Williams, 2003).

The retrieval of a specific autobiographical memory can be described as a memory of a single event that occurred at a particular time and place, with a time span of less than a day. Accordingly, a general memory that reflects repeated activities (categoric memory) or a memory that describes an event that lasted longer than a day (extended memory) would be categorised as an overgeneral autobiographical memory (Williams, 2005). Most studies have since used the Autobiographical Memory Test (AMT) developed by Williams and Broadbent (1986) to elicit specific autobiographical memory, and congruent findings have been consistently replicated in individuals with depression (Kuyken & Dalgleish, 1995; Goddard, Dritschel and Burton, 1996; Brewin, Watson, McCarthy, Hyman & Dayson, 1998; Scott, Stanton, Garland & Ferrier, 2000; Kaney, Bowen-Jones & Bentall, 1999; Wessel, Meeren, Peeters, Arntz & Merkelbach, 2001). Besides individuals with depression, overgeneral autobiographical memories has also been observed in other clinical populations including post-traumatic stress disorder (McNally, Litz, Prassas, Shin & Weathers, 1994), postnatal depression (Croll & Bryant, 2000), obsessive-compulsive disorder (Wilhelm, McNally, Baer & Florin, 2011), acute stress disorder (Harvey, Bryant & Dang, 1998) and most recently, mild cognitive impairment (MCI; Donix et al., 2010; Meléndez, Escudero, Satorres & Pitarque, 2019).

The ability to recall specific autobiographical memories is important as it has been linked to problem-solving performance (Evans, Williams, O’Loughlin & Howells, 1992; Sidley, Whitaker, Calam & Wells, 1997; Pollock & Williams, 2001), imageability of future events (Williams et al., 1996), working memory (Birch & Davidson, 2010) and the course of depression (Brittlebank, Scott, Williams & Ferrier, 1993; Dalgleish, Spinks, Yiend & Kyuken, 2001; Gibbs & Rude, 2004; Kuyken & Dalgleish, 2011; Liu et al., 2016; Mackinger et al., 2004; Peeters et al., 2002). For instance, Brittlebank, Scott, Williams and Ferrier (1993) assessed 22 patients with major depressive disorder for seven months and reported that overgeneral memory recall at baseline was significantly correlated with poorer recovery from depression, with the baseline
autobiographical memory scores accounting for 33% of the variance in depression scores seven months later.

1.2.6.2 Autobiographical memory overgenerality in OSA patients

The hippocampus has been implicated in the retrieval of autobiographical memory, with patients with hippocampal damage reported to exhibit autobiographical memory impairment (Addis, Moscovitch & McAndrews, 2007; Gilboa et al., 2006). Given that neuroimaging studies in OSA patients have observed volumetric changes in the hippocampal region (Macey et al., 2002; Morrell et al., 2003), autobiographical memory in OSA patients warrants more attention.

As overgeneral autobiographical memory has generally been linked with depression, the majority of studies examining autobiographical memory recall in a clinical OSA population have mainly focused on its relationship with depression (e.g., Mackinger & Svaldi, 2004; Svaldi & Mackinger, 2003). In the first study, Svaldi and Mackinger (2003) were interested in investigating the predictive quality of specific autobiographical memory recall for the course of depression of OSA patients after undergoing treatment for OSA. A sample of 54 OSA patients completed the AMT task at baseline and were followed up after approximately six to nine weeks of CPAP therapy. During the follow-up session, participants completed the Beck Depression Inventory (BDI) to assess depressive symptoms. Firstly, the study reported that participants reported significantly lower depressive symptoms following CPAP therapy. Secondly, hierarchical regression analyses revealed that those who recalled more specific positive autobiographical memories showed better recovery from depression after receiving CPAP therapy.

In the second study, Mackinger and Svaldi (2004) examined the same sample of 54 OSA patients as used in their previous paper (Svaldi and Mackinger, 2003). In this study, participants were divided into two groups based on their vulnerability to depression (i.e., incidence of a depressive disorder prior to onset of OSA) and the authors were interested in the predictive power of autobiographical memory overgenerality on two different aspects of depression: (i) cognitive-affective and (ii) somatic. Similar to the first study, hierarchical regression analyses were
conducted and the findings revealed that specific autobiographical memory recall to positive cue words predicted the cognitive-affective, but not somatic, symptoms of depression.

More recently, we examined the recall of specific autobiographical memory in OSA patients symptomatic and asymptomatic of depressive symptoms and reported no distinction between both groups in specific autobiographical memory recall, suggesting that autobiographical memory overgenerality can be observed in patients with OSA regardless of the severity of depressive symptoms (Lee, Trinder & Jackson, 2016). Consistent with these findings, another study by our research group reported that OSA patients recalled significantly more overgeneral memories when compared to healthy controls, and no difference in AM recall was observed between participants with high and low depressive symptoms (Delhikar et al., 2019). Delhikar and colleagues (2019) utilised the Autobiographical Memory Interview (AMI), which is a semi-structured interview that assesses episodic and personal semantic AM recall from childhood, early adult life and recent life, and reported that OSA patients had notably poorer semantic AM recall of their early adult life when compared to healthy controls.

In Lee, Trinder and Jackson (2016), there was a significant difference in age between the groups (i.e., controls, OSA patients asymptomatic for depressive symptoms and OSA patients symptomatic for depressive symptoms). After an analysis of a subset of the younger participants (aged 25 to 49 years), the difference between the controls and OSA patients asymptomatic for depression did not reach statistical significance ($p=0.09$). It is possible that younger OSA patients have had the disease for a shorter period of time, and thus they may not have developed cognitive impairments seen in older OSA patients. Alternatively, younger OSA patients may have higher ‘cognitive reserve’ which allows greater cognitive functioning despite the burden of OSA. Accordingly, it is possible that specific autobiographical memory impairment may be more prominent in older OSA adults.

### 1.3 Possible mechanisms

While the nature of the link between OSA and cognitive impairment remains a matter for speculation, the prevailing view is that the cognitive deficits observed in OSA patients are due to the effects of intermittent hypoxia and sleep fragmentation on brain function.
1.3.1 Hypoxia

Measures of nocturnal hypoxia in OSA patients include the oxygen desaturation index (ODI), percentage of sleep time with oxygen saturation (SaO₂) below 90%, and sleep time in apnoea or hypopnoea with ≥3%.

1.3.1.1 Nocturnal hypoxia associated with cognitive impairment in OSA patients

Intermittent hypoxia in OSA patients has been reported to be linked with global cognition (Yaffe et al., 2011), memory (Findley et al., 1986), working memory (Champod et al., 2013), executive function (Ferini-Strambi et al., 2003) and attention (Montplaisir, Bédard, Richer & Rouleau, 1992). For instance, a cross-sectional study showed that OSA patients with hypoxia had significantly poorer memory and attentional performance than age-matched non-hypoxemic OSA patients. Furthermore, overall cognitive impairment was significantly correlated with the degree of hypoxia and not sleep fragmentation (Findley et al., 1986).

The vulnerability of the brain to intermittent hypoxia, as reported in animal (Gozal, Row, Schurr & Gozal, 2001; Veasey et al., 2004; Xu et al., 2004; Zhang et al., 2018) and human studies (Gale & Hopkins, 2004), had led to speculation that neural cell loss associated with recurrent hypoxia may underlie the cognitive impairment observed in OSA patients. For example, a quantitative MRI study (Gale & Hopskins, 2004) showed that both OSA patients and individuals with post-carbon monoxide poisoning displayed similar hippocampal atrophy. While individuals from both groups have similarly been exposed to hypoxic-related injury, only the memory test scores (RCFT, RAVL) from the OSA group was significantly correlated with hippocampal volume. The difference in memory impairment observed in both groups may be attributed to the varying frequency and length of hypoxia (i.e., intermittent hypoxia compared to a single but longer duration of hypoxia).

In support of this, neuroimaging studies in OSA patients have revealed significant degenerative changes in several brain regions including the hippocampus, parietal cortex and prefrontal cortex (Canessa et al., 2011; Castronovo et al., 2014; Kim et al., 2016; Macey et al., 2002; Morrell et al., 2003; Shi et al., 2017; Torelli et al., 2011; Yaouhi et al., 2009). Following 3 months of CPAP
therapy, Canessa and colleagues (2011) reported significant increases in grey-matter volume in hippocampal and frontal regions, accompanied by notable improvement in memory, attention and executive-functioning performance. In line, Castronovo and colleagues (2014) reported significant reversal in white matter abnormalities in OSA patient after 12 months of consistent and compliant CPAP usage. Furthermore, these changes in white matter were accompanied with significant improvements in neurocognitive performance. However, it should be noted that neuroimaging deficits observed in OSA patients may not be solely attributed to intermittent hypoxia as sleep fragmentation has also been shown to impair neurological functioning in animal models (Guzman-Marin, Bashir, Suntova, Szumusia & McGinty, 2007; Tartar et al., 2006).

1.3.1.2 Nocturnal hypoxia associated with cognitive impairment in older adults

Large longitudinal community-based studies of older individuals (65+ years) have reported a significant link between hypoxia and cognitive functioning (Blackwell et al., 2015; Saint Martin, Sforza, Roche, Barthélemy & Thomas-Anterion, 2015; Yaffe et al., 2011). For example, Yaffe and colleagues (2011) noted that two indices of hypoxia (ODI $\geq$ 15 and high percentage of total sleep time [7%] in apnoea/hypopnoea) were significantly associated with an increased risk of developing MCI or dementia in women with OSA, while no notable link was found for sleep fragmentation, as measured by arousal index. Similarly, Blackwell et al. (2015) reported that higher ODI levels were significantly associated with greater decline in global cognition with a 0.36-point decline in the Modified Mini Mental State Examination (MMSE) score per year for each 5-unit increase in ODI. Furthermore, those with $\geq$1% sleep time with SaO$_2$ <90% had 1.7 times greater decline per year in the Modified MMSE score than those with <1% sleep time with oxygen saturation <90%.

Another study by Saint Martin and colleagues (2015) demonstrated that three measures of hypoxia (% sleep time with oxygen saturation <90%, mean oxygen saturation and ODI 4%) were significantly related to the decline in attentional performance across 8 years. Changes in executive function scores were also significantly related to minimal oxygen desaturation value.
1.3.2 Sleep fragmentation

Measures of sleep fragmentation in OSA patients include the arousal index, defined as frequency of arousals per hour of sleep, and wake after sleep onset (WASO), defined as the amount of wakefulness that occur after sleep onset.

1.3.2.1 Sleep fragmentation associated with cognitive impairment in OSA patients

Sleep fragmentation in OSA patients has been linked to deficits in attention (Ayalon, Ancoli-Israel, Allison, McKenna & Drummond, 2009, Conradt et al., 1998), spatial and temporal memory (Daurat, Foret, Bret-Dibat, Fureix & Tiberge, 2008), and procedural memory (Djonlagic, Saboisky, Carusona, Stickgold & Malhotra, 2012). For instance, Ayalon and colleagues (2009) reported that the arousal index, but not desaturation index, in OSA patients was significantly associated with slower reaction time during a sustained attention task, with those with an arousal index of less than 30 performed comparably to healthy controls. Furthermore, a higher arousal index was significantly linked to decreased brain activation in several regions including areas involved in response selection and attention, motor response, and decision making.

Sleep fragmentation has been proposed to impair cognitive functioning via (i) excessive daytime sleepiness; and (ii) disruption of sleep's restorative process (Beebe & Gozal, 2002; Bucks, Olaite & Eastwood, 2012). While not all OSA patients experience excessive daytime sleepiness, it is a commonly reported symptom of OSA (Chervin, 2000; Franklin & Lindberg, 2015; Seneviratne & Puvanendran, 2004). In an Asian population, up to 87.2% of OSA patients demonstrated excessive daytime sleepiness with total arousal, sleep efficiency and severity of snoring being significant predictors of excessive daytime sleepiness (Seneviratne & Puvanendran, 2004). Similarly, measures of sleep fragmentation significantly predicted both objective and subjective daytime sleepiness in OSA patients (Bennett, Langford, Stradling & Davies, 1998). Correspondingly, increased daytime sleepiness in OSA patients has been linked to poorer cognitive performance, including executive functioning (Naismith, Winter,
Gotsopoulos, Hickie & Cistulli, 2004) and driving performance (Dinges, 1998; Howard et al., 2004).

Sleep plays an important role in learning and memory consolidation (see Stickgold & Walker, 2007; Walker & Stickgold, 2004 for review). Experimental sleep deprivation and sleep fragmentation studies have reported similar neurocognitive deficits to those seen in OSA patients, including impaired sustained attention, delayed visual memory and working memory (Bonnet, 1993; see Fulda & Schulz, 2003 for review). Similar findings have been reported in animal studies (McCoy et al., 2007; Ward et al., 2009). In OSA patients, studies have reported significant impairments in overnight memory consolidation when compared to control groups (Landry, Anderson, Andrewartha, Sasse & Conduit, 2014; Landry, O'Driscoll, Hamilton & Conduit, 2016). For example, healthy controls showed a 15.3% improvement in the sequential finger tapping task following sleep. On the other hand, despite exhibiting a similar learning curve to controls during the pre-sleep practice session, untreated OSA patients showed a notable lack of improvement following sleep (1.78%; Landry, Anderson, Andrewartha, Sasse & Conduit, 2014). Memory consolidation has been shown to improve following compliant CPAP use of at least six weeks (Landry, O'Driscoll, Hamilton & Conduit, 2016).

1.3.2.2 Sleep fragmentation associated with cognitive impairment in older adults

The majority of community-based studies that have examined the relationship between arousal index and cognitive performance in older individuals have reported no significant association (Cohen-Zion et al., 2004; Lutsey et al., 2016; Yaffe et al., 2011). One longitudinal study reported a significant link between change in memory performance and respiratory autonomic arousal index, but noted that the lack of significant decline in memory over the 7.8 years of the study precludes valid interpretation of the model (Saint Martin et al., 2015).

Nevertheless, a longitudinal study that followed 737 older adults for up to six years identified sleep fragmentation, as measured by actigraphy, to be a risk factor for further cognitive decline and Alzheimer’s disease (AD; Lim, Kowgier, Yu, Buchman & Bennett, 2013). While the study did not specifically examine OSA patients, Lim and colleagues (2013) demonstrated that sleep
fragmentation does play an important role in cognitive decline and neurodegeneration in older adults.

1.3.3 Summary

The contributions of recurrent hypoxia and sleep fragmentation to the development of cognitive impairment in patients with OSA remain unclear. Nevertheless, accumulating evidence in the literature suggest that both intermittent hypoxia and sleep fragmentation play roles and contribute differently to the cognitive deficits observed in OSA patients.

1.4 OSA and mood disturbances

Both depressive and anxiety symptoms are commonly observed in OSA patients. Given that both anxiety and depression in OSA patients have been significantly associated with a lower quality of life (Akashiba et al., 2002; Lee, Han & Ryu, 2015), it remains an important topic of research in the sleep apnoea population.

1.4.1 OSA and depressive symptoms

One of the most significant comorbidities recognised in OSA patients is depression, with rates of clinically significant depressive symptoms being as high as 35% in older adults (Acker et al., 2017; Garbarino et al., 2018; Jackson et al., 2019; Schröder & O’Hara, 2005). A prevalence study that reviewed 4,060,504 individuals from the Veterans Health Administration database revealed that 21.8% of OSA patients were diagnosed with a depressive disorder, compared to only 9.43% of those without OSA (Sharafkhaneh, Giray, Richardson, Young & Hirshkowitz, 2005). Nevertheless, the underlying mechanism between depression and OSA is still unclear. While some correlational studies have demonstrated a significant positive relationship between depression scores and OSA severity (Aloia et al., 2005; Edwards et al., 2015), others have reported no relationship (Asghari et al., 2012, see Harris, Glozier, Ratnavadivel & Grunstein, 2009 for review). Instead of OSA severity, studies have also reported links between depressive symptoms in OSA patients with excessive daytime sleepiness (Ishman, Cavey, Mettel & Gourin, 2010) and daytime alertness (Sforza, de Saint Hilaire, Pelissolo, Rochat & Ibanez, 2002).
A longitudinal study revealed that individuals who developed a sleep-related breathing disorder during the 4-year study period were approximately 80% more likely to develop depression compared to those who did not (Peppard, Szklo-Cose, Hla & Young, 2006).

1.4.2 OSA and anxiety symptoms

While anxiety has not been as extensively studied as depression in the OSA population, reviews that examined anxiety in OSA patients reported a prevalence rate of 12%-50% (Garbarino et al., 2018; Shapiro, 2012). Shapiro (2014) observed that 34 out of the 36 studies examined reported anxiety to be present in the OSA sample population. Similar to findings on the association between OSA and depression, the link between anxiety symptoms and OSA severity is inconsistent, with some studies reporting a link (Lehto et al., 2013) and others not (Asghari et al., 2012; Lee, Han & Ryu, 2015). Anxiety in OSA patients has also been associated with poorer subjective sleep quality (Macey, Woo, Kumar, Cross & Harper, 2010) and excessive daytime sleepiness (Lee, Han, Ryu, 2015).

1.4.3 Effect of CPAP therapy on anxiety and depressive symptoms

Findings on the effect of CPAP therapy on mood have been varied (see Schröder & O’Hara, 2005 for review). A review examining seven studies that investigated the effect of CPAP on depression and anxiety symptoms reported mixed findings (Sánchez, Martínez, Miró, Bardwell & Buela-Casal, 2009). For instance, a four-week CPAP trial study in mild OSA patients (Engleman et al., 1999) reported a significant improvement in depressive symptoms, as measured by the HADS, and a trend for improvement in the HADS anxiety scores. This is consistent with more recent CPAP studies that have reported significant improvement in depressive and anxiety symptoms following three to six months of CPAP therapy (Edwards et al., 2015; Li et al., 2016). On the other hand, Barnes and colleagues (2002) reported no significant benefit of CPAP on mood scores after 4 months, as measured by the Profile of Mood States and Beck Depression Inventory, over a placebo pill.

Similarly, another systematic review (Saunamäki & Jehkonen, 2007) examined the effect of CPAP therapy, with a treatment time ranging from three months to two years, on depression and
anxiety in patients with OSA and reported mixed findings. Four of the seven studies examined reported significantly lower depressive symptoms after CPAP use, while the other three found no change. Two out of four studies reported significantly reduced anxiety symptoms after CPAP therapy. A more recent meta-analysis (Gupta, Simpson & Lyons, 2016) reported a moderate effect of CPAP on depressive and anxiety symptoms, however CPAP was not more effective at reducing these symptoms compared to sham CPAP.

While both depression and anxiety have generally been linked with OSA, the nature of their relationship, and the impact of CPAP therapy on depression and anxiety, are unclear. The nature of the relationship may be complicated by the presence of overlapping symptoms and comorbidities between OSA and depression. These symptoms include daytime sleepiness, fatigue, poor concentration, irritability, psychomotor retardation and weight gain (Ejaz, Khawaja, Bhatia & Hurwitz, et al., 2011). Furthermore, other confounding variables such as gender, obesity, cardiovascular disease, and excessive daytime sleepiness can influence the relationship (Aloia et al., 2005; BaHammam et al., 2015). For example, in men, OSA severity was significantly associated with the somatic symptoms of depression, independent of obesity. On the other hand, obesity was significantly associated with the cognitive symptoms of depression, independent of apnoea severity in women with OSA (Aloia et al., 2005). Given the variability in the aetiology and manifestation of depression and anxiety, it is possible that only a subset of OSA patients with depression and/or anxiety benefit psychologically from CPAP therapy.

### 1.5 Obstructive sleep apnoea and mild cognitive impairment

As discussed above, OSA has generally been linked to cognitive impairment in the literature. Correspondingly, recent studies have begun questioning whether a link also exist between OSA and cognitive decline in older adults; specifically, whether OSA contributes to MCI and dementia. As it is possible to treat OSA, and as some studies discussed above have reported partial reversibility in cognitive deficits, it is important to address OSA as a risk factor for cognitive decline and to investigate the potential for treatment of OSA to reduce cognitive impairment or decline in patients with MCI/dementia.
1.5.1 Mild cognitive impairment

Subjective memory complaints and poorer memory performance are common among older individuals, and many seek advice about their memory difficulties from their primary care provider. While general mental decline has been linked with normal ageing (Braver et al., 2001) there is a group of individuals who experience considerably greater cognitive decline than expected for their age and education level, but do not meet the clinical criteria of dementia. This intermediate stage has been termed MCI. It is estimated that between 3% and 25% of individuals over 65 years of age have MCI (Gauthier et al., 2006; Petersen et al., 2018).

The recommended and most widely used diagnostic criteria for MCI includes: (i) subjective memory complaint (reported by patient or informant or observed by clinician); (ii) objective impairment of one or more cognitive domains relative to age; (iii) preservation of independence of functional abilities; and (iv) no presence of dementia (Petersen, 2004; Tangalos & Petersen, 2018). Although not every individual with MCI progresses to dementia, clinical studies have revealed that a high number of MCI patients with memory impairment do go on to develop Alzheimer’s disease at a rate between 8% to 15% per year (Petersen, 2004; Petersen, 2016). For example, a 10-year longitudinal study following 64 patients with amnestic MCI reported that almost half of the group have developed dementia by the 10-year follow up session (Visser et al., 2006). Another longitudinal study that followed 93 patients with amnestic MCI reported a conversion rate of 34% to AD within 6 years (Annerbo, Wahlund & Lökk, 2006).

1.5.2 Impact of sleep disturbance on cognition in MCI patients

Sleep disturbances are often observed in MCI patients (prevalence rate of 14-59%), and are one of the most prevalent neuropsychiatric symptoms reported by these individuals (see Beaulieu-Bonneau & Hudon, 2009 for review; Lyketsos et al., 2002). Given the high rate of sleep complaints in MCI patients, and the known effects of poor sleep on cognition and daily functioning (see Miller, Wright, Hough & Cappuccio, 2014; Walker, 2009 for reviews), studies have examined the impact of sleep disturbances on cognitive functioning in patients with MCI.
Sleep disturbances in MCI patients have generally been linked with cognitive deficits (Hita-Yañez, Atienza, Gil-Neciga & Cantero, 2012; Naismith et al., 2010; Westerberg et al., 2010; Westerberg et al., 2012). For example, Naismith and colleagues (2010) revealed that increased WASO in non-amnestic MCI patients was significantly linked with reduced attention and executive functioning, and more arousals were notably associated with poorer nonverbal learning and problem solving. Besides objective sleep indices, subjective sleep variables may also play a role in contributing towards cognitive deficits in MCI patients. Examining amnestic MCI patients, Westerberg and colleagues (2010) revealed an association between both poorer subjective and objective sleep variables, and poorer declarative memory recall performance.

1.5.3 Mood disturbances in patients with MCI/dementia

Mood disturbances including depressive and anxiety symptoms are commonly reported in patients with MCI/dementia (Lyketsos et al., 1997; Seignourel, Kunik, Snow, Wilson & Stanley, 2008).

Depressive symptoms are one of the most common and earliest neuropsychiatric symptoms reported, and it is estimated that up to 32% of patients with MCI and 49% of patients with AD suffer from minor or major depression (Craig et al., 2005; Ismail et al., 2017; Lee & Lyketsos, 2003; Lyketsos et al. 1997). For some patients, depression may be a relapse of a pre-existing major depressive disorder but for others, the depressive symptoms are new and have developed following the onset of AD (Lyketsos et al., 1997). Interestingly, studies have suggested that pre-existing depressive symptoms may be linked to the risk of developing AD. For example, a seven-year longitudinal study following 821 elderly individuals with no clinical diagnosis of dementia revealed that for each additional depressive symptom, as measured by the Centre of Epidemiological Studies Depression Scale (CES-D), the risk of developing AD increases by about 20% (Wilson et al., 2002). Another study that examined MCI patients over the course of three years reported that a notable 85% of depressed MCI patients converted to dementia while only 32% of non-depressed MCI patients developed dementia (Modrego & Ferrández, 2004).

Anxiety symptoms have been reported in 8% to 71% of patients with dementia (see Seignourel, Kunik, Snow, Wilson & Stanley, 2008 for review). In MCI patients, a large international multi-
centre study consisting of 1,010 individuals with MCI reported a high prevalence of anxiety with almost 45% of the cohort reporting anxiety symptoms (Feldman, 2004). Furthermore, anxiety along with depression have been demonstrated to be significantly more prevalent in MCI patients compared to healthy ageing controls (Geda et al., 2008; Mirza et al., 2017).

1.5.4 Comorbidity between OSA and MCI/AD

Clinically significant sleep disorders are also commonly reported in MCI/AD patients (Bombois, Derambure, Pasquier & Monaca, 2010; Emamian et al., 2016; Guarnieri et al., 2012). In a sample of 431 MCI/dementia patients, sleep disordered breathing (SDB), a broader category which includes snoring and the different variations of sleep apnoea, was reported to be the most frequent sleep disorder present with almost 60% of the patients reporting SDB (Guarnieri et al., 2012). Another study reported that up to 84.6% of MCI patients were diagnosed with OSA (Bombois, Derambure, Pasquier & Monaca, 2010). While it should be noted that the latter study had a smaller sample size of 65 MCI patients, studies reporting prevalence have consistently demonstrated that OSA is highly prevalent in MCI/dementia patients.

OSA is prevalent in individuals with dementia (Bombois, Derambure, Pasquier & Monaca, 2010; Guarnieri et al., 2012) and conversely, cognitive impairment is prevalent in OSA patients (discussed above). Currently, the directionality of the relationship is speculative but studies have suggested that OSA may predispose individuals to clinically significant cognitive decline (Bliwise, 2002; Leng et al., 2017; Yaffe et al., 2011). It has been suggested that the link between sleep apnoea severity and risk for AD may be mediated by an increase in amyloid deposition (Sharma et al., 2018). Beta-amyloid (Aβ) is a 37 to 49 amino acid residue peptide that is the primary component of amyloid plaques, one of the pathological characteristics of AD (Chen et al., 2017). For example, a longitudinal study reported that OSA severity was significantly associated with increased amyloid burden over two years (Sharma et al., 2018). This was similarly reported in MCI patients in whom higher OSA severity was linked with greater brain Aβ deposition globally and regionally in the precuneus (Spira et al., 2014). Nevertheless, the underlying mechanisms by which OSA may contribute to these neuropathological changes is unclear.
One possible pathway mechanism involves the effect of intermittent hypoxia on neurodegeneration through oxidative stress and altered protein processing (Pan & Kastin, 2014). Animal studies have previously demonstrated increased expression of oxidative stress response markers and Aβ generation following prolonged exposure to intermittent hypoxia, which has been linked with neurocognitive dysfunction and cortical neuronal apoptosis (Row, Liu, Xu, Kheirandish & Gozal, 2003; Shiota et al., 2013; Xu et al., 2004; Zhang et al., 2007). A recent human neuroimaging study of older OSA adults at risk for dementia revealed oxygen desaturation to be significantly associated with reduced cortical thickness in both left and right temporal lobes (Cross et al., 2018), areas that have been reported to be affected in the early stages of AD (Chan et al., 2001; Killiany et al., 1993; Wolk et al., 2017). Furthermore, reduced thickness in the bilateral lobes were notably associated with poorer encoding on a verbal memory task (Cross et al., 2018).

Besides intermittent hypoxia, sleep disturbances resulting from sleep fragmentation may also be a contributing factor to neurodegeneration in OSA patients. Sleep has been argued to have a restorative function and has been shown in animal models to facilitate clearance of neurotoxic waste products, including Aβ (Xie et al., 2013). Accordingly, animal studies that have implemented chronic sleep restriction in mice have demonstrated increased Aβ plaque formation (Kang et al., 2009). Amyloid deposition in preclinical stages of AD has been similarly linked to poorer sleep quality in human studies (Ju et al., 2013).

Nevertheless, not all OSA patients experience clinically significant cognitive decline. OSA and AD share overlapping symptoms (e.g., daytime sleepiness, decreased cognitive function, mood changes), as well as similar risk factors and comorbid conditions such as the presence of APOE e4 allele, depression, and cardiovascular and cerebrovascular disease (Gottlieb et al., 2004; Luchsinger & Mayeux, 2004; Ownby et al., 2006; Young, Skatrud, Peppard, 2013). It is also possible that the presence of these shared risk factors/comorbidities place a subset of OSA patients at a higher risk of developing AD. For example, more severe sleep apnoea was significantly linked to poorer global cognition, verbal memory, attention and executive function performance in OSA patients with the APOE e4 allele but this relationship was not observed in those without the allele (Johnson et al., 2017; Nikodemova, Finn, Mignot, Salzieder & Peppard,
While recent meta-analysis indicated no significant link between the presence of APOE e4 and incidence of OSA (Lu, Wu, Jin, Peng & Ling, 2016; Uyrum et al., 2015), the presence of APOE e4 may increase the susceptibility of OSA patients to further cognitive decline (Baril et al., 2018).

While there are studies that have linked OSA with AD, the exact mechanism is not entirely known. Given the shared risk factors and that studies have demonstrated the involvement of both intermittent hypoxia and sleep fragmentation in neurodegeneration, the link between OSA and clinically significant cognitive decline may be underpinned by a multifaceted mechanism.

1.5.5 Cognitive impairment in patients with comorbid OSA and MCI/dementia

While limited studies have examined cognitive impairment in patients with comorbid OSA and MCI, community-based studies that have investigated this relationship have linked cognitive decline in these individuals to certain aspects of OSA, such as sleep apnoea severity, intermittent hypoxia and sleep quality (Kim, Lee, Lee, Jhoo & Woo, 2011; Yaffe et al., 2011)

1.5.5.1 General cognition

Longitudinal studies have linked comorbid OSA to faster cognitive decline in MCI/dementia (Lutsey et al., 2018; Yaffe et al., 2011). For example, a longitudinal study that followed 298 elderly women for approximately 4.7 years revealed that the women with OSA had a higher risk of developing MCI or dementia, compared with those without OSA (Yaffe et al., 2011). In the study, more women with SDB (44.8%) developed MCI/dementia throughout the 4.7 years compared to those without SDB (31.1%). Furthermore, two measures of hypoxia (ODI ≥15 and high percentage of total sleep time in apnoea or hypopnoea) were significantly associated with a higher incidence of MCI/dementia. No significant relationships were reported for sleep fragmentation.

Findings from a more recent study that followed 1,667 individuals over a period of about 15 years were less straightforward (Lutsey et al., 2018). Using the dementia hospitalisation international classification of disease codes and at-home PSG to measure OSA, no association
between OSA severity and incidence of dementia were reported. Nonetheless, a subset of 1,083 participants underwent a comprehensive cognitive assessment which allowed the authors to examine the link between OSA severity and 15-year risk of adjudicated dementia/MCI. Notably, severe OSA was associated with greater risk of dementia. It should be noted that attenuation was observed following adjustments for behaviours and cardiovascular risk factors (e.g., smoking status, diabetes, antihypertensive medication, C-reactive protein and systolic blood pressure). Besides OSA severity, Lutsey and colleagues (2018) also reported that individuals with shorter sleep duration (less than 7 hours per night) had a higher risk of dementia. The link between sleep duration and incidence of MCI/dementia was also reported in a previous study (Chen et al., 2016).

Besides the high risk of developing MCI and dementia, a recent study (Osorio et al. 2015) utilising the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database of more than 2,000 individuals, revealed that patients with untreated SDB were significantly younger at MCI or AD onset than those without. This was maintained after adjusting for various potential confounders, including APOE e4, sex, education, BMI, depression, cardiovascular disease, hypertension, diabetes and age. This result suggests that OSA not only increases the risk of further cognitive decline, it may also accelerate cognitive decline in older individuals.

1.5.5.2 Specific aspects of cognition

Only a few studies have examined specific aspects of cognitive impairment in individuals with MCI and OSA. Aspects that have been examined include nighttime driving performance, processing speed, executive functioning, verbal memory and language function (Cross et al., 2017; Kim, Lee, Lee, Jhoo & Woo, 2011; Terpening et al., 2015).

With regards to nighttime driving performance, higher ODI and arousal index in MCI patients were significantly correlated with poorer driving performance and greater number of crashes, respectively (Cross et al., 2017). This finding provides an important insight into the relationship between sleep apnoea and cognitive impairment in patients with MCI as driving relies on multiple cognitive domains including executive functioning, attention and procedural memory (Wagner, Muri, Nef & Mosimann, 2011). Accordingly, further studies are required to tease apart
and identify specific cognitive domains that are impaired in patients with comorbid OSA and MCI.

Regarding language functioning, Kim et al. (2011) reported that several measures of objective sleep (e.g., sleep efficiency, TST Stage 1, SWS) and measures of sleep apnoea severity (AHI, lowest oxygen saturation) were significantly correlated with language functioning. More specifically, a stepwise multiple regression model revealed that SWS and OSA severity in MCI patients are independently associated with impaired language function, as measured by the Boston Naming Task. However, it should be noted that Kim et al. (2011) reported significant periodic leg movement in 30% of the MCI patients and sleep-related movement disorders, including periodic limb movement disorder, have been linked to increased risk of developing dementia (Lin et al., 2015).

Terpening and colleagues (2015) utilised TMT A and B to measure processing speed and executive function, logical memory subset from the WMS III to measure verbal memory, and verbal fluency to measure language function. Processing speed was reported to be significantly inversely correlated with measures of sleep apnoea severity (AHI), intermittent hypoxia (ODI, sleep time below 90% oxygen desaturation) and sleep fragmentation (arousal index).

1.5.6 Effects of CPAP therapy in patients with OSA and AD

In view of the findings suggesting the favourable effects of CPAP therapy on memory and cognitive functioning in cognitively-normal OSA patients, studies have begun exploring the potential application of CPAP in patients with OSA and dementia. To date, five studies have examined the use of CPAP in patients with AD and OSA (Ancoli-Israel et al., 2008; Ayalon et al., 2006; Chong et al., 2006; Cooke et al., 2009; Troussiere et al., 2014).

A study conducted by Ayalon and colleagues (2006) was one of the first to explore the possibility of using CPAP to treat OSA in patients with AD. The study was interested in investigating whether patients with AD would be able to tolerate and adhere to CPAP, and if any beneficial effects could be observed after a few weeks of using CPAP. During the study, 30 patients with mild to moderate AD and comorbid OSA were randomised into two different
treatment groups: traditional CPAP treatment or sham CPAP treatment. Patients in the traditional CPAP group were given an opportunity to use CPAP for six continuous weeks while patients in the sham CPAP group were provided with a mask containing air leaks for the first three weeks and normal treatment for the following three weeks. Notably, the findings revealed that the patients were using CPAP for an average of 4.8 hours per night. While the recommended usage of CPAP is 6 hours per night (Weaver, 2006), the adherence rate is promising for future clinical use of CPAP in this patient population.

Using the same randomised placebo-controlled trial as described above, two other studies from the same research group reported an improvement in subjective daytime sleepiness (2.3 points decrease in ESS), verbal episodic memory (0.7 point increase in the Hopkins Verbal Learning Test-Revised) and cognitive processing speed (22.5 seconds decrease in TMT B) after after three weeks of therapeutic CPAP in patients with AD and comorbid OSA (Chong et al., 2006; Ancoli-Israel et al., 2008). Besides improvement in cognitive performance and subjective daytime sleepiness, three weeks of therapeutic CPAP also resulted in improvements in objective sleep measures (i.e., less time spent awake after wake onset, less arousals during sleep, and more time spent in deeper stages of sleep; Cooke et al. 2009). Five patients who continued CPAP and five who discontinued CPAP after the randomised controlled trial conducted by Ancoli-Israel and colleagues (2008) were followed-up and retested approximately 13 months later. Despite the small sample size, there was a moderate to large effect size showing that those who continued CPAP displayed less deterioration of executive functioning (effect size=0.7) and processing speed (effect size=-1.9), and had fewer depressive symptoms (effect size=1.3; Cooke et al., 2009).

A more recent observational study reported that consistent use of CPAP over a period of three years significantly slowed global cognitive decline, as measured by the MMSE, in 23 individuals with mild-to-moderate AD and severe OSA (Troussière et al., 2014). The CPAP group had a median annual cognitive decline of -0.7 points per year while the non-CPAP group had significantly greater median annual cognitive decline of -2.2 points per year. Nevertheless, as this was an observational study, there was a lack of randomisation and placebo control.
Furthermore, patients from the non-CPAP group were not refrained from using CPAP as patients with poor compliance were categorised into the non-CPAP group.

As previously mentioned, Osorio and colleagues (2015) reported that individuals with untreated SDB had significantly earlier onset of MCI/AD when compared to those without SDB. Using the same database obtained from ADNI, Osorio and colleagues (2015) were also interested in investigating if CPAP usage is linked with delayed onset of MCI and AD. Despite the smaller sample size (N=62), the findings revealed that individuals with untreated SDB had a significantly younger age at MCI onset when compared to SDB patients using CPAP. Furthermore, the age of MCI onset in SDB patients using CPAP was similar to those without SDB. Interestingly, SDB treatment status was not significantly associated with age of AD onset, suggesting that the use of CPAP may be most beneficial to individuals who are at an earlier stage of cognitive decline. Nevertheless, limited studies have examined the potential benefit of CPAP in patients with MCI.

1.5.7 Summary of OSA and MCI literature

Longitudinal and cross-sectional studies that have examined cognitive functioning in patients with comorbid OSA and MCI have reported significant association between sleep apnoea variables and cognitive impairments. Impaired cognitive domains that have been linked to OSA in MCI/AD patients include general cognition, nighttime driving performance, processing speed and language function (Cross et al., 2017; Kim, Lee, Lee, Jhoo & Woo, 2011; Lutsey et al., 2018; Osorio et al. 2015; Terpening and colleagues. 2015; Yaffe et al., 2011). Nevertheless, the majority of the studies have focused on general cognition and only a few studies have focused on specific cognitive domains, including the different memory types (e.g. visual, verbal, autobiographical and working), attention and executive function. Accordingly, studies in the current thesis further explore various cognitive domains that have not been examined or minimally examined in this patient population.

To date, five CPAP treatment studies have been conducted in patients with comorbid OSA and AD and all have reported promising findings (Ancoli-Israel et al., 2008; Ayalon et al., 2006; Chong et al., 2006; Cooke et al., 2009; Troussiere et al., 2014). Following three weeks to three years of CPAP therapy, improvements were observed in global cognition, verbal memory,
processing speed and subjective daytime sleepiness. While these are encouraging results, the majority of the studies have a relatively small sample size and some of the trials are uncontrolled. Furthermore, studies have yet examined the effect of CPAP in MCI patients. Untreated OSA patients have been shown to have significantly earlier MCI/AD onset compared to OSA patients using CPAP (Osorio et al., 2015). Accordingly, treating patients at an earlier stage of cognitive decline may be crucial. The final study in this thesis aims to address this with a randomised controlled trial in patients with comorbid OSA and MCI.

1.6 Objective and organisation of this thesis

1.6.1 Chapter 2

Chapter 2 provides a description of methods used in the research undertaken for this thesis, including materials and procedures.

1.6.2 Chapter 3

While our previous study (Lee, Trinder & Jackson, 2016) reported impairment in specific autobiographical memory recall in patients with OSA, regardless of their severity of depressive symptoms, we reported that age may be a confounding factor. The majority of the study sample (N=46 out of 58) was below the age of 50 years and following a subset analysis with younger participants (aged 22-49 years), the difference in specific autobiographical memory recall between OSA patients without depression and healthy controls did not reach statistical significance (p=0.09). While we speculated that this impairment may be more prominent in older OSA adults than in their younger counterparts, it is unknown if specific autobiographical memory can be observed and/or is more impaired in older adults with OSA.

Specific autobiographical memory impairment has been reported in MCI patients (Donix et al., 2010). Despite the high prevalence of OSA in the MCI population and the reported impairment of specific autobiographical memory in OSA patients, studies have yet to explore the impact of OSA on this particular memory impairment in MCI patients. Furthermore, while specific autobiographical memory impairment has been reported separately in OSA and MCI cohorts, the
additional burden that may be placed on this memory system when individuals have comorbid OSA and MCI has not been examined.

Accordingly, Chapter 3 presents the first objective of this thesis, which was to expand our previous work (Lee et al., 2017) and investigate specific autobiographical memory impairment in patients with comorbid OSA and MCI in comparison to OSA patients and healthy controls.

1.6.3 Chapter 4

Following the previous chapter, this chapter continues the investigation of cognitive impairment in patients with comorbid OSA and MCI. The few studies that have examined cognitive impairment in patients with comorbid OSA and MCI/dementia have focused on general cognition (Lutsey et al., 2018; Yaffe et al., 2011). Given the known impairments of different cognitive domains in OSA patients as discussed above, minimal studies have examined the relationship between specific domains of cognition and sleep apnoea in patients with comorbid OSA and MCI. While it is important to investigate the impact of OSA on general cognitive decline in this population, identifying specific cognitive domains that are impacted by OSA in MCI patients may be beneficial as OSA is treatable and, in a clinical setting, it can allow doctors to identify specific domains that may be attributed to OSA and potentially alleviated using treatment.

Chapter 4 presents the second objective of the thesis, which was to examine the relationship between OSA severity and cognitive performance in patients with comorbid OSA and MCI. Furthermore, to examine the potential underlying mechanisms of this relationship, this portion of the thesis also explored the relationship between cognitive performance and the different aspects of sleep apnoea, including intermittent hypoxia, sleep fragmentation, sleep architecture and subjective sleep measures. The differences in cognitive performance between MCI patients with and without OSA in a subset of cognitive domains were also examined.
1.6.4 Chapter 5

CPAP therapy in AD patients has shown promising results in slowing cognitive decline and reducing depressive symptoms (Ancoli-Israel et al., 2008; Chong et al., 2006; Troussier et al., 2014). Furthermore, recent findings from Osorio and colleagues (2015) reported that individuals at an earlier stage of cognitive impairment may benefit most from CPAP use and that CPAP therapy has the potential to delay the age of onset of MCI. While several CPAP trial studies have been conducted with AD patients, there have been limited studies examining the effects of CPAP therapy on cognitive performance and mood in MCI patients. As MCI is the prodromal stage of dementia, it may be more beneficial to target individuals in this earlier stage of cognitive decline.

Accordingly, Chapter 5 presents the third objective of the thesis, which was to investigate the effect of three months of CPAP therapy on cognitive performance and mood in patients with comorbid OSA and MCI.

1.6.5 Chapter 6

Chapter 6 provides a general discussion of the findings presented, along with the overall conclusion of the thesis.
Chapter Two

Materials and methods

The studies in this thesis consist of cross-sectional (Chapter 3 and 4) and randomised controlled partial crossover (Chapter 5) research designs. Chapter 3 explores autobiographical memory impairment in OSA patients. Chapter 4 investigates the association between cognitive performance, and objective and subjective sleep measures in patients with co-morbid OSA and MCI. Chapter 5 examines the effects of three months of Auto CPAP therapy on cognitive performance and mood in patients with co-morbid OSA and MCI. The present chapter outlines and describes the methods used in these studies.

2.1 Participants

A total of 115 participants were examined in this thesis, including 38 healthy controls (mean age = 45.7 years ± 15.4, range = 23-71 years), 39 individuals with OSA (mean age = 50.1 years ± 16.1, range = 26-80 years), 20 individuals with MCI (mean age = 67.9 years ± 6.6, range = 59-85 years) and 18 individuals with co-morbid OSA and MCI (mean age = 67.7 years ± 8.2, range = 54-86 years). Healthy older controls (≥50 years) and individuals with co-morbid OSA and MCI were recruited for the COMM (CPAP for OSA-MCI) study (Chapters 3, 4 and 5), the primary project of the present thesis. Additional data was gathered from three other studies as comparison groups. In Chapter 3, older OSA patients (≥50 years) were recruited from the COSAD (CPAP for OSA and Depression) study while data from younger healthy controls (<50 years) and younger OSA patients (<50 years) were obtained from the OSA-D study, both of which the candidate contributed to data collection. In Chapter 4, data of MCI patients were obtained from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing (AIBL).
2.2 Recruitment

COMM study

Human Research Ethics Committee (HREC) approval for the COMM study was obtained from the Northern Health (reference number: HREC/15/NH/7) and the Austin Health (reference number: HREC/15/Austin/393) HRECs. The HREC approvals were registered with the Royal Melbourne Institute of Technology (RMIT) University HREC (reference number: 19269). The patient group was referred from a geriatrician, sleep physician or other medical professional. Advertisements were also placed at hospitals and community centres for the patient group. The healthy control cohort was recruited via online advertising and flyers were placed at community centres, hospitals and universities.

For the healthy control group, inclusion criteria included age 50 years and above, MMSE score ≥26 and English fluency. Exclusion criteria included: sleep disorders; history of or current severe psychiatric disorder; learning disability; neurological or neurodegenerative conditions; alcohol or drug dependence; or a history of traumatic brain injury. For the patient group, inclusion criteria included age 50 years and above, untreated OSA, clinically significant memory impairment, and English fluency. Exclusion criteria included: previously diagnosed sleep disorders besides OSA (e.g., insomnia, restless leg syndrome, etc.) memory impairment due to stroke, epilepsy or traumatic brain injury; history of or current severe psychiatric disorder; learning disability; or alcohol or drug dependence.

COSAD study

HREC approval for the COSAD study was obtained from the Austin Health HREC (reference number: H2013/05076). The participants were recruited through the Outpatient Clinics of the Department of Respiratory and Sleep Medicine, Austin Hospital and the Austin Hospital Sleep Laboratory database. Potential participants were contacted by research staff and interested participants were invited to attend an initial appointment, during which information regarding the study was provided.
To be eligible for the COSAD study, participants had to have untreated OSA and recommended CPAP therapy, be aged between 18 to 60 years, and be fluent in English. Exclusion criteria included: excessive daytime sleepiness (Epworth Sleepiness Score; ESS >16); history of or current severe psychiatric disorder; previous head injury with loss of consciousness > 15-minute duration; learning disability; alcohol or drug dependence; shift work; or any neurological disorders.

To age-match the healthy control and OSA + MCI groups in the current study (Chapter 4), only data from individuals aged 50 years and above were included.

**OSA-D study**

HREC approval for the OSA-D study was obtained from the University of Melbourne HREC (reference number: 1239101). The OSA patients were recruited from the Austin Health sleep clinic and from community advertising, while the healthy controls were recruited through online advertisements and flyers placed around the university campus. Interested participants were invited to attend an initial appointment, during which information regarding the study was provided and a general screening session was conducted.

The inclusion criteria for the control group were an ESS score of ≤5, a Pittsburgh Sleep Quality Index (PSQI) score of ≤10, a Multivariate Apnoea Prediction Scale score of ≤0.5 and a Center for Epidemiologic Studies – Depression score of ≤15. The inclusion criterion for the OSA group was a clinical diagnosis of OSA, with an AHI of more than 10. Participants were excluded if they had a history of drug or alcohol dependence, learning disability, brain injury, and had been or currently involved in shift work.

**AIBL study**

HREC approval for the AIBL study was obtained from the HRECs of Austin Health and St Vincent’s Health in Victoria, and Hollywood Private Hospital and Edith Cowan University in Western Australia. An expression of interest was submitted to the AIBL study committee for the baseline neurocognitive data and questionnaire data of 20 unidentified participants with MCI.
The use of the data of interest for this thesis was subsequently approved by the committee. The AIBL study’s baseline recruitment and study procedure has been previously outlined in detail in Ellis et al. (2009). MCI patients were primarily referred from treating specialists (e.g. geriatrician, geriatric psychiatrist, neuropsychologist or other medical professional). Individuals diagnosed from the general community were also included. Interested participants were telephone screened and excluded if they had a history of non-AD dementia, schizophrenia, bipolar disorder, significant current depression, Parkinson’s disease, cancer (other than basal cell skin carcinoma) within the last two years, symptomatic stroke, uncontrolled diabetes, or current regular alcohol use exceeding two standard drinks per day for women and four per day for men. MCI was diagnosed according to the protocol based on the criteria of Winblad et al. (2004) where all participants had reported memory difficulties (personally or through an informant) and demonstrated a score of 1.5 SD or more below the age-adjusted mean on at least one neuropsychological task applied at the time of the assessment.

2.3 Neuropsychological measures

COMM study

The neuropsychological battery was administered by the candidate who was trained on the tests. The administration of the neuropsychological battery took approximately 90 minutes. The tests covered a range of cognitive domains, including verbal, visual, autobiographical and working memory, processing speed/attention and executive function. Verbal memory was measured by the older adults version of the Wechsler Memory Scale - Fourth Edition (WMS-IV) Logical Memory – Story A and B, and the older adult version of the WMS-IV Paired Associate Task (Wechsler et al., 2009). Visual memory was measured using the Rey-Osterrieth Complex Figure Test (RCFT; Meyers & Meyers, 1995). The Autobiographical Memory Test (AMT; Williams, 2005) was used to measure autobiographical memory recall, and the Weschler Adult Intelligence Scale - Fourth Edition (WAIS-IV) Digit Span (Wechsler et al., 2008) was used to measure short-term memory and working memory. Processing speed and attention was measured by Trail Making Test A (Reitan, 1979), and the WAIS-IV subtests, Symbol Search and Coding (Wechsler et al., 2008). Executive functioning was measured using Trail Making Test B (Reitan, 1979).
Global cognitive functioning was measured by the Mini-Mental Status Examination (MMSE) while an estimate of pre-morbid intelligence was measured using the WAIS-IV Vocabulary subtest (Wechsler et al., 2008). All tests are described below.

**Wechsler Memory Scale IV – Logical Memory (LM)**

The WMS-IV Logical Memory subtest is a verbal memory task that assesses learning and ability to retain short narratives. The older adult version containing Story A (Ruth and Paul) and Story B (Anna Thompson) was used for the current study. Both proses were presented orally. Story A was presented twice while Story B was presented once. This task measures immediate free recall, delayed free recall and recognition. To measure immediate free recall, participants were required to recall details of the prose immediately after it is read aloud. After approximately 20-30 minutes, participants were required to recall details of the proses that were presented previously. To measure delayed recognition, participants were asked eight yes/no questions for Story A and fifteen yes/no questions for Story B. A total raw score with a maximum of 53 was calculated for the immediate free recall (LM I) subtest. Delayed free recall (LM II recall) score was totalled with a maximum 39 and delayed recognition (LM II recog) score was totalled with a maximum of 23.

**Wechsler Memory Scale IV – Verbal Paired Associates (VPA)**

The WMS-IV Verbal Paired Associate subtest is a verbal memory task that assesses learning and retention of word pairs. This task measures immediate recall, delayed recall and recognition. During the learning phase, a list containing 10 word pairs was read to the participants. Following that, the first word of each pair was read and the participants were asked to provide the corresponding word. This was conducted four times during the learning phase. A score out of 10 was given to each round and the immediate recall score was totalled with a maximum of 40. To measure delayed recall, the first word of each pair is read after approximately 20-30 minutes and participants are required to provide the paired word. Delayed recall score was totalled with a maximum of 10. To measure delayed recognition, 30 different word pairs were read out aloud by the researcher and participants were asked to identify yes/no as to whether the word pair was
previously read during the learning phase. Delayed recognition score was totalled with a maximum of 30.

**Rey-Osterrieth Complex Figure Test (RCFT)**

The RCFT is a pen and paper task that assesses visual memory and visuo-constructional ability (Shin, Park, Park, Seol & Kwon, 2006). This task measures immediate recall and delayed recall. During the learning phase, participants were presented with the Rey-Osterrieth Complex Figure and were required to copy the figure. The copy process was timed. Following a 3 minute delay upon completion of the learning phase, participants were asked to re-draw the figure from memory to the best of their ability. This was repeated after approximately 20-30 minutes. The copy, immediate recall and delayed recall figures were scored using the Osterrieth scoring system (Canham, Smith & Tyrrell, 2000). Points were totalled and each figure was given a score out of 36. RCFT have good inter-and intra-rater reliability (coefficients = 0.85-0.97) for total scores in memory-impaired patients (Tupler, Welsh, Asare-Aboagye & Dawson, 1995).

**Autobiographical Memory Test (AMT)**

The AMT is a verbal task that assesses an individual’s ability to recall specific episodic autobiographical memory. Participants are presented with 12 cue words and are required to recall a specific event corresponding to the cue word. The cue words for the AMT were drawn from a sample of cue words used in Williams (2005), which were grouped according to the emotionality ratings and Kucera-Francis written frequency. The cue words consist of 6 positive words (happy, relieved, proud, eager, glorious, and sunny) and 6 negative words (guilty, hopeless, failure, ugly, worse, and blame). The words are presented in the same randomised order.

The participants were given the following instructions:

“*I am interested in your memory for events that have happened in your life. I am going to read to you some words. For each word, I want you to think of an event that happened to you which the word reminds you of. The event could have happened at any point in your life from when you*
were small to last week, please do not include memories from last week. It might be an important event, or trivial event.

Just one more thing: the memory you recall should be a specific event – an event that lasted less than a day, and occurred at a particular time and place. So, if I said the word “good” – it would not be OK to say, “I always enjoy a good party”, because that does not mention a specific event. But it would be OK to say “I had a good time at Jane’s party” because that is a specific event. It is important to try to retrieve a different memory or event for each cue word. Let us try some words for practice: rain, newspaper and milk.”

All the responses are recorded on paper and each response are scored as being either specific, overgeneral or no response. One point was given to each specific autobiographical memory recalled and zero for each overgeneral or no response, with a maximum total score of 12 (six for negative and six for positive cue words). Twenty percent of the transcripts were scored by a second scorer for inter-rater reliability. The AMT have moderate internal consistency reliability (cronbach’s $\alpha = 0.54$) with moderate test-retest reliability (coefficients = 0.53-0.68; Griffith et al., 2012).

*Wechsler Adult Intelligence Scale IV – Digit Span*

The WAIS-IV Digit Span subtest is a verbal task that assesses working memory and short-term memory. This test consists of three subtests – forward, backward and sequencing. During the forward subtest, participants were read a sequence of numbers and asked to recall the numbers in the same order. During the backward subtest, participants were asked to recall the numbers in a reverse order and during the sequencing subtest, participants were asked to recall the numbers in sequence, from the smallest to the biggest number. For each subtests, there were a total of eight items with two trials each, and the sequence became increasing longer after each item. The subtest was discontinued when the participant scored zero on both trials of an item. The scores for each subtests, with a maximum of 16, were totalled respectively.
**Trail Making Test (TMT) A and B**

The TMT A and B is a pen and paper task that assesses attention, processing speed and executive function (Tombaugh, 2004). During TMT A, participants were required to draw lines sequentially connecting 25 consecutive numbers as quickly as possible without making any errors. Participants were corrected during the run if any errors were made. During TMT B, similar instructions were given except participants were required to alternate between numbers and letters (e.g., 1 – A – 2 – B – 3 – C). The time taken to complete for both tests were recorded. Scores were reported in seconds. TMT A and B have good test-retest reliability (intraclass correlation coefficients = 0.84 and 0.85) and validity ($r = 0.61$ and 0.55) in older adults.

**Wechsler Adult Intelligence Scale IV – Symbol Search**

The WAIS-IV Symbol Search subtest is a pen and paper task that assesses processing speed and visual perception (Sweet, 2011). In this task, participants were presented with two target symbols, five symbol options and a ‘NO’ option in a row. Participants were asked to draw a diagonal line across a symbol if it matches either one of the target symbols or across the ‘NO’ option when there are no matches. Participants were given two minutes to complete as many rows as possible. Three demonstration items and three sample items were completed to ensure that participants understood the test. The total number of correct items and incorrect items were tallied and the total score, with a maximum of 60, was calculated by subtracting the number of incorrect items from the number of correct items.

**Wechsler Adult Intelligence Scale IV – Coding**

The WAIS-IV Coding subtest is a pen and paper task that assesses processing speed, sustained attention and motor skills (Kreiner & Ryan, 2001; Lezak, 1995). On a piece of paper, participants were presented with a code table displaying pairs of numbers and symbols, along with multiple rows of numbers. During the task, participants were required to draw the corresponding symbol below each number. Participants were given two minutes to complete as many numbers as possible. Three demonstration items and six sample items were completed to
ensure that participants understood the test. The total number of correct items were tallied and a total score out of 135 was calculated.

**Mini-Mental State Examination (MMSE)**

The MMSE incorporates verbal and non-verbal components that assess global cognitive function in older adults (Folstein et al., 1975). It consists of 30 questions that evaluates orientation to time and place, registration of three words, attention and calculation, recall of three words, language and visual construction. A total score with a maximum of 30 was calculated for the MMSE. MMSE have good inter-rater and test-retest reliability (coefficients = 0.83 ad 0.89; Folstein et al., 1975).

**Wechsler Adult Intelligence Scale IV – Vocabulary**

The WAIS-IV Vocabulary subtest is a verbal task that assesses verbal fluency and premorbid intelligence (Lezak, 1995). During this test, participants were presented with three picture items and 27 word items that were presented visually. Participants were told to name the pictures and explain the meaning of the words to the best of their ability. Participants were questioned when clarification was required. The responses were scored according to the scoring rules in the WAIS-IV. The test was discontinued after three consecutive scores of zero. All responses were recorded on paper and a total score with a maximum of 57 was calculated.

**COSAD study**

The neuropsychological battery was administered by research staff, including the candidate, who was trained in the tests. Administration of the neuropsychological battery took approximately 2 hours. The tests covered a range of cognitive domains, including autobiographical and emotional visual memory, inhibition and sustained vigilance. Only data from the AMT were included in the analysis of this thesis.
OSA-D study

Participants in the OSA-D study completed two cognitive tests that measures specific autobiographical memory and emotional visual memory. Specific autobiographical memory was measured by the Autobiographical Memory Test (William, 2005) and emotional visual memory was measured by the Emotional Memory Test. The AMT was administered by the candidate and only data from the AMT were included in the analysis of this thesis.

2.4 Affective measures (COMM study)

The Hospital Anxiety Depression Scale was sent out in the mail prior to the overnight sleep study and neuropsychological assessment.

*Hospital Anxiety Depression Scale (HADS)*

The HADS (Zigmond & Snaith, 1983) is a validated self-rating questionnaire that measures depressive and anxious symptomology. Participants were required to rate statements on a scale of 0 to 3 (e.g., 0=not at all to 3=most of the time) based on their observations over the past week. An individual score for anxiety and depression was obtained. The score ranges from 0 to 21 and a score of 11 or greater on either anxiety or depression scores is considered clinically elevated and require further clinical evaluation. The subscales have good internal reliability (depression subscale: cronbach’s α = 0.67-0.90; anxiety subscale: cronbach’s α = 0.68-0.93) and discriminant validity (Bjelland, Dahl, Haug & Neckelmann, 2002).

2.5 Subjective sleep measures (COMM study)

Sleep-related questionnaires were mailed along with the HADS prior to the overnight sleep study and neuropsychological assessment. They included the PSQI, ESS, Multivariable Apnea Prediction Index (MAPI) and Morningness-Eveningness Questionnaire (MEQ).
**Pittsburgh Sleep Quality Index**

The PSQI (Buysse, Reynolds, Monk, Berman & Kupfer, 1989) is a 10-item self-rating questionnaire that measures a global measure of sleep quality during the past month on seven domains, which are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The score ranges between 0 and 21, with higher scores indicating increasingly poor sleep. The PSQI has moderate to good internal consistency reliability (cronbach’s $\alpha = 0.69-0.80$) and construct validity in older adults (Beaudreau et al., 2012; Spira et al., 2012).

**Epworth Sleepiness Scale**

The ESS (Johns, 1991) is a self-rating questionnaire that requires the participants to rate on a scale of 0 to 3 (0=no chance of dozing to 3=high chance of dozing) the likelihood of dozing off during 8 different situations in recent times. The score ranges from 0 to 24, with higher scores indicating more daytime somnolence. The ESS has moderate internal consistency reliability (cronbach’s $\alpha = 0.70-0.76$) and construct validity in older adults (Beaudreau et al., 2012; Spira et al., 2012).

**Multivariable Apnea Prediction Index**

The MAPI (Maislin et al. 1995) is a 16-item self-rating questionnaire used as a screening tool to assess the likelihood of having OSA. The score ranges from 0 to 1 and a MAPS score of 0.5 or more indicates a clinically significant risk of having OSA. The MAPI has good test-retest reliability (coefficient = 0.79-0.92) and moderate to good internal consistency (cronbach’s $\alpha = 0.66-0.93$; Maislin et al., 1995).

**Morningness-Eveningness Questionnaire**

The MEQ is a 19-item multiple-choice questionnaire that that assesses morning and evening chronotype groups (Horne & Östberg, 1976). The total score ranges from 16 to 86, with higher
scores indicating increasingly ‘morning type’ and lower scores indicating increasingly ‘evening type’. Scores between 42 to 58 indicate ‘intermediate type’.

2.6 Objective sleep measures

COMM study

All participants given the option of an in-lab or at-home overnight sleep study. The in-lab study was conducted at the RMIT Sleep Laboratory, Bundoora and the at-home study was conducted in the participant’s home. A total of seven participants opted of an in-lab PSG study and 33 participants completed an at-home PSG study.

In-lab polysomnography (PSG)

A standard clinical PSG assessment was performed using a Compumedics Grael system and data were collected on Compumedics ProFusion PSG 4 Version 2.0.2. The PSG recordings included standard placements, based on the international 10-20 system, for continuous monitoring of central and occipital electroencephalograms (F3/F4, C3/C4 and O1/O2) with M1 and M2 as reference. Also, horizontal electrooculograms (EOG), submental and anterior tibialis electromyograms (EMG) and electrocardiograms (ECG) were included. Nasal airflow was sensed by measurement of end tidal CO$_2$ using a thermistor (Compumedics Reusable Airflow Sensor) and/or a nasal cannula (Promed Nasal Cannula, Thermo Fisher Scientific, Victoria, Australia). The thoracic and abdominal excursions were obtained by respiratory inductance plethysmography (Compumedics Thoracic and Abdominal Band). Vibration associated with snoring was recorded via a snore sensor (Grael Tracheal Microphone) and continuous arterial oxygen saturation was recorded by a finger oximeter probe (Compumedics Adult silicone soft tip finger probe-oximeter). Leg movements were recorded using limb movement sensors.

All variables were recorded on a 17-channel polysomnograph and PSG data were analysed in 30 second epochs by the candidate according to the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (2007). The outcome measures include
Apnoea-Hypopnea Index (AHI; events per hour), arousal index, sleep efficiency, total sleep time and percentage of sleep time where oxygen saturation was below 90%.

**At-home polysomnography**

The at-home PSG assessment was performed using a portable Compumedics Somté device and data was recorded locally on a Compact Flash Card. The at-home PSG included the same electrodes and equipment as outlined in the above section. The data were downloaded and analysed using the Compumedics ProFusion PSG 4 Version 2.0.2 and the same data analysis method as described above was conducted.

**COSAD study**

Participants completed a standard clinic sleep study at the Austin Health Sleep Laboratory before participating in the study. The studies were analysed by trained sleep technicians using the Compumedics ProFusion PSG 3. The outcome measures included Apnoea-Hypopnea Index (AHI; events per hour), arousal index, sleep efficiency, total sleep time and percentage of sleep time when oxygen saturation is below 90%.

**2.7 Continuous Positive Airway Pressure (CPAP) Therapy**

Participants in the CPAP trial (Chapter 5) were provided with an Auto CPAP machine (ResMed AirSense 10 AutoSet) and a mask (Fisher & Paykel Simplus Full Face Mask or ResMed AirFit N20 Nasal Mask) for three months. Chin straps (ResMed chin strap) were provided if required. All participants used the ResMed AirSense 10 AutoSet. Auto CPAP usage was recorded locally on a SD card and data was downloaded at the end of the three-month trial.
2.8 Procedure

COMM study

The candidate carried out all of the overnight sleep studies and neuropsychological assessments either at the RMIT Sleep Laboratory or at participants’ homes. All participants provided signed informed consent prior to the study. A week prior to the sleep study and neuropsychological test battery, a set of questionnaires were mailed to participants. During the testing session, participants were wired-up for the PSG assessment either in-lab or at-home approximately 2 hours prior to bedtimes and slept according to their regular sleep schedule.

The neuropsychological test battery was conducted approximately two hours after wake time at the respective venues. The order of administration of each task was the same for all participants (see Figure 1). Following the completion of the neuropsychological test battery, participants were discharged. Both patient and control groups completed the overnight PSG and neuropsychological tests described.

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<tr>
<th>1. MMSE</th>
<th>7. Verbal Paired Associates I</th>
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<tr>
<td>2. Logical Memory I</td>
<td>8. RCFT I</td>
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<tr>
<td>3. Digit Span</td>
<td>9. Symbol Search</td>
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<td>4. Vocabulary</td>
<td>10. TMT A &amp; B</td>
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<td>5. Coding</td>
<td>11. AMT</td>
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<td>13. RCFT II</td>
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BREAK

Figure 1: Order of presentation of neuropsychological tests administered to participants in the COMM study.
The sleep studies of the patient group were scored and sent to the study’s sleep physician for review. Participants who were diagnosed with moderate-to-severe OSA (AHI of 15 or more) and considered suitable by the study’s sleep physician were informed of the study and invited to participate in the 3-month CPAP trial. Interested participants were randomised into either an immediate group or a waitlist group.

**Immediate Group**

Participants in the immediate group were given an auto CPAP machine within 2 weeks of diagnosis. Participants were given instructions and asked to use the machine regularly at home. Daily phone calls were made for the first week to troubleshoot any issues and encourage optimal usage. House visits were conducted if necessary. Following this, weekly or monthly (depending on the participant) phone calls were made and participants were encouraged to call if any issue arose. After 3 months, participants attended a second appointment to complete the same questionnaires and neuropsychological assessments administered prior to starting the trial. Participants were allowed to continue any existing medications and dietary supplements throughout the trial.

**Waitlist Group**

Participants in the waitlist group were given an appointment to begin the CPAP trial 3 months from date of diagnosis. During the 3 months, participants were asked not to change their regular diet or physical activity, or commence any other treatment for their OSA. Following the three months delay period, the same questionnaires and neuropsychological assessments were administered prior to starting CPAP therapy. The same follow-up procedures were followed as per the immediate group.

**COSAD study**

The baseline neuropsychological assessments were conducted at the Austin Hospital Sleep Laboratory by trained research staff. All participants provided signed informed consent prior to the study. Prior to starting their CPAP trial, participants completed a two-hour
neuropsychological test battery and a set of questionnaires regarding general health, sleep and mood. The neuropsychological test battery was conducted during the day between 09:00 and 17:00. Data regarding the participants’ sleep study was retrieved from the existing COSAD study database.

**OSA-D study**

The testing sessions were conducted at the University of Melbourne Sleep Laboratory. All participants signed informed consent prior to the study. The testing sessions were conducted during the day between 09:00 and 17:00. Healthy controls underwent PSG on the night of the testing session while the OSA patients provided a copy of their clinical sleep study report to the researchers.

**2.9 Statistical analyses**

All statistical analyses in this thesis were carried out using IBM SPSS Statistics 24 (SPSS, Chicago, IL, USA) and an alpha level of 0.05 was considered to be of statistical significance. Statistical analyses for each study are in detailed in their respective chapters.
Chapter 3

Autobiographical memory impairment in obstructive sleep apnoea: Impact of age and comorbid mild cognitive impairment

Preface

This chapter presents two studies that assessed specific autobiographical memory impairment in OSA patients with and without MCI. Older adults tend to recall less specific autobiographical memories compared to their younger counterparts. Accordingly, Study 1 aimed to investigate if there is an age-related effect on this impairment in OSA patients. Following Study 1, the focus of Study 2 shifted towards specific autobiographical memory recall in patients with comorbid OSA and MCI. Specific autobiographical memory impairment has been reported in OSA and MCI patients separately however, studies have yet examined this cognitive domain in OSA patients with comorbid MCI. Accordingly, Study 2 aimed to assess specific autobiographical memory performance in this patient population. A subset of data from the OSA-D and COSAD studies were included in this chapter.

Candidate’s contribution

The candidate obtained ethics approval for the COMM study. The candidate recruited participants and conducted data collection and analysis of the overnight polysomnography, neuropsychological testings and questionnaire data. The candidate also collected data for the Autobiographical Memory Task in the OSA-D and COSAD studies. The candidate conducted the analyses, and formulated and wrote the chapter.
Abstract

Episodic autobiographical memory (AM) can be defined as ‘memory for events of one’s life’. AM overgenerality is the inability to recall specific AMs and previously we have reported specific AM impairment in obstructive sleep apnoea (OSA) patients. Nevertheless, this impairment may not be as prominent in younger OSA patients. The current chapter consists of two studies. Study 1 aimed to expand our previous work (Lee, Trinder & Jackson, 2016) and investigate if there is an age-related effect on specific AM recall in OSA patients. Twenty young healthy controls (32.8 ± 6.7 years), 20 young OSA patients (36.0 ± 6.0 years), 18 older healthy controls (61.9 ± 5.5 years) and 19 older OSA patients (62.8 ± 7.7 years) completed the Autobiographical Memory Test (AMT) and an overnight polysomnography. Study 1 revealed that OSA patients had significantly poorer specific AM recall when compared to their age-matched controls however, no age-related effect on specific AM recall was observed. Furthermore, poorer subjective sleep quality was significantly linked to fewer specific negative AMs recalled in OSA patients. Specific AM impairment has also been reported in patients with mild cognitive impairment (MCI). With OSA identified as a potential risk factor for the development of MCI/dementia, it is important to further investigate the role of OSA in the cognitive impairment observed in patients with MCI. Studies have yet to examine specific AM in individuals with comorbid OSA and MCI. Study 2 aimed to compare specific AM impairment in patients with OSA and MCI relative to OSA patients without any clinically significant cognitive impairment and healthy controls. Nineteen patients with mild-severe OSA without MCI (62.7 ± 7.6 years), 18 mild-severe OSA patients with MCI (67.9 ± 8.1 years) and 19 healthy controls (63.1 ± 4.9 years) completed the AMT and an overnight polysomnography. Study 2 revealed that OSA patients, regardless of MCI status, recalled significantly fewer specific memories when compared to healthy controls while no difference was observed between the two OSA groups. In patients with OSA and MCI, recalling fewer specific AMs was significantly correlated with a lower percentage of time spent in slow wave sleep. These findings suggest that OSA may contribute to the reduction of specific AMs recalled in patients with comorbid MCI. Future studies should investigate whether treatment of OSA can improve this aspect of memory impairment.
Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by repeated apnoea or hypopnoea episodes during sleep, which results in intermittent hypoxia and sleep fragmentation. Untreated OSA has been linked to impairment in several aspects of memory, such as immediate and delayed verbal, visuo-spatial episodic, and procedural memory (Naëgelé et al., 2006; Jackson, Howard & Barnes, 2011; Stranks & Crowe, 2016; Twigg et al., 2010; Wallace and Bucks, 2013). Nevertheless, one particular aspect of memory – autobiographical memory (AM), is relatively understudied in the OSA patient population. AM has been conceptualised into two different categories: episodic and semantic memory. Episodic AM involves recollecting context-rich autobiographical events from the past with autonoetic consciousness and can be defined as ‘memory for events of one’s life (e.g., last birthday party; Conway & Pleydell-Pearce, 2000; Conway and Rubin, 1993, p. 103). On the other hand, semantic AM refers to the recollection of general knowledge of self and the world without re-experiencing past events (e.g., birthdate; Levine, Svoboda, Hay, Winocur & Moscovitch, 2002). The current study focuses on episodic autobiographical memory specifically, episodic AM overgenerality, which is the inability to recall specific AM.

AM overgenerality was first recognised by Williams and Broadbent (1986), who showed that depressed individuals with suicidal behaviours had difficulty recalling specific memories, and were more inclined to retrieve overgeneral memories than healthy controls when given emotional cue words (e.g., happy, interested, clumsy, angry). Following this, the Autobiographical Memory Test (AMT), derived from the Williams and Broadbent (1986) study has been used by various studies to elicit specific AM (see review by van Vreeswijk & de Wilde, 2004). The retrieval of a specific AM is described as a memory of a single event that occurred at a particular time and place, within a time span of less than a day. Accordingly, a memory that reflects repeated activities (categoric), or a memory that describes an event that lasted longer than a day (extended), is categorised as an overgeneral AM (Williams, 2005). Congruent findings have since been observed across several clinical populations (Andersson, Ingerholt & Jahnsson, 2003; Croll and Bryant, 2000; Dalgeish et al., 2003; Ono, Devilly & Shum, 2016; Ricarte, Ros, Latorre & Watkins, 2017).
In the depression literature, AM overgenerality has been thought to be a potential coping mechanism where individuals learn to retrieve memories in a less specific way to reduce negative affect experiences during recall (Raes, Hermans, de Decker, Eelen & Williams, 2003, van Vreeswijk & de Wilde, 2004). Furthermore, AM overgenerality has been reported to be a trait marker for vulnerability towards persistent depression (Brittlebank, Scott, Williams & Ferrier, 1993; Crane et al., 2016; Liu et al., 2016; Mackinger, Pachinger, Leibetseder & Fartacek, 2000). For example, a meta-analysis that examined 15 studies of individuals with depressive symptoms reported a significant positive correlation between overgeneral memories and depressive symptoms at follow-up (Sumner, Griffith & Mineka, 2010). Nevertheless, it is possible that specific AM impairment is linked to reduced executive/working memory capacity, with the difficulty occurring during retrieval (Ros, Latorre & Serrano, 2010; van Vreeswijk & de Wilde, 2004). Several studies have reported a significant relationship between AM overgenerality and working memory function, where fewer specific AMs recalled has been linked to poorer working memory performances (Birch & Davidson, 2007; Crane, Goddard & Pring, 2011; Piolino et al., 2010; Ros, Latorre & Serrano, 2010). Moreover, this relationship has been observed in study populations without significant depressive symptoms, suggesting that specific AM impairment may not just be a trait of depression.

To date, studies examining autobiographical memory in OSA patients are limited, with the majority of the studies focusing on the predictive power of specific AM recall as a marker for the course of depression in OSA patients (Mackinger & Svaldi, 2004, Svaldi & Mackinger, 2003). Svaldi and Mackinger (2003) reported that OSA patients who recalled more specific memories to positive cue words at baseline showed better recovery from depression after 6-9 weeks of CPAP. Specifically, the second study reported that the recall of specific AM to positive cue words predicted the remissive course of the cognitive-affect, but not the somatic, symptoms of depression (Mackinger & Svaldi, 2004). Recently, we reported impaired specific autobiographical memory recall in a large sample of OSA patients compared to healthy controls (Lee, Trinder & Jackson, 2016). The findings revealed no significant difference in the recall of specific AM between OSA patients who were symptomatic and asymptomatic for depressive symptoms, suggesting that impaired specific AM recall may be a long-standing impairment in OSA patients, and not entirely due to the presence of depression. In line, another study by our
research group similarly reported that OSA patients recalled significantly more overgeneral memories when compared to healthy controls and no difference in AM recall was observed between participants with high and low depressive symptoms (Delhikar et al., 2019).

When examining whether this was an age-related effect, difference between controls and OSA patients asymptomatic for depression in a younger subset of the OSA participants (aged 25-49 years) did not reach statistical significance ($p=0.09$; Lee, Trinder & Jackson, 2016). While it is possible that the reduced sample size (N=14 OSA patients) may have limited the statistical power to see any effects, it is also possible that there may be an age-related effect on specific AM recall, in that younger OSA patients are not as impaired as their older counterparts. In healthy individuals, older adults (mean age= 66.0 years) have been reported to recall significantly fewer specific AM when compared to younger adults (mean age= 26.6 years; Ros & Latorre & Serrano, 2009). Using a different AM task, Piolino and colleagues (2010) similarly demonstrated that older individuals produced less specific memories with fewer phenomenological and spatiotemporal details when compared to younger individuals. Nevertheless, in our previous study (Lee, Trinder & Jackson, 2016), we were unable to conclude whether specific AM recall deteriorate across age in OSA patients.

Independently, episodic autobiographical memory impairments have been observed in patients with mild cognitive impairment (MCI; Leyhe, Muller, Milian, Eschweiler & Saur, 2009). MCI has been conceptualised as an intermediate stage of cognitive decline, which sits on a continuum between normal ageing and dementia (Petersen, 2004). Based on a semi-structured free recall episodic autobiographical memory interview, MCI patients were reported to recall significantly lower levels of episodic contextual details for past events when compared to healthy controls (Berna, Schönknecht, Seidl, Toro & Schröder, 2012; Irish, Lawlor, O’Mara & Coen, 2010; Leyhe, Muller, Eschweiler & Saur, 2009; Murphy, Troyer, Levine & Moscovitch, 2008; Tomadesso et al., 2015). To our knowledge, two studies have utilised the AMT to examine AM specificity in MCI patients (Donix et al., 2010; Meléndez et al., 2019), reporting that MCI patients recalled significantly fewer specific AMs when compared to age-matched healthy controls. Notably in both studies, the MCI group recalled more specific memories when compared to individuals with Alzheimer’s disease (AD). While AM overgenerality stemmed
from the depression literature and has generally been discussed as a feature of depression, Donix and colleagues (2010) reported no significant association between AM specificity and depression scores. Independent of depressive symptoms, AM specificity was more impaired with increasing levels of cognitive impairment, as measured by the Mini Mental State Examination (MMSE), in individuals above the age of 60 years (Phillips & Williams, 1997). Similar to findings in OSA patients (Lee, Trinder & Jackson, 2016), this suggests that AM overgenerality in MCI patients may reflect a long-standing impairment rather than being solely a trait marker for depression, particularly in older individuals.

The present study has been divided into two parts. Following our previous study (Lee, Trinder & Jackson, 2016), we speculated that specific AM impairment may not be as prominent in younger OSA patients, as younger patients may have had OSA for a shorter period of time, and therefore, may not have developed cognitive changes. Alternatively, younger OSA patients may have a higher ‘cognitive reserve’ that allows them to retain specific AM function. Accordingly, the research question for the first study of this chapter asks whether there is an age-related effect on specific AM impairment in OSA patients. The first study aimed to compare specific AM performance between four groups: (i) young healthy controls (<50 years); (ii) young OSA patients (<50 years); (iii) older healthy controls (≥50 years); and (iv) older OSA patients (≥50 years). It was hypothesised that older OSA patients would recall significantly fewer specific AMs when compared to their younger counterparts. It was also hypothesised that both OSA groups would have poorer specific AM recall than their respective age-matched healthy control groups.

Secondly, specific AM impairment has been reported in OSA and MCI patients independently. Despite OSA recently being suggested as a potential risk factor for the development of MCI/dementia, and the high comorbidity between these two disorders (Gagnon et al., 2014; Yaffe et al., 2011), it is unknown if the AM impairment observed in individuals with MCI can be attributed to OSA. Accordingly, the second research question asks whether patients with OSA alone have less impairment of specific AM than patients with MCI and comorbid OSA. The second study aimed to assess specific AM impairment in patients with comorbid OSA and MCI in comparison to OSA patients with no significant cognitive impairment and to healthy controls.
Given the additional burden of MCI on cognitive function, it was hypothesised that OSA patients with MCI would perform significantly worse in specific AM recall than OSA patients without any clinically significant cognitive impairment. It was also hypothesised that both OSA groups would perform significantly worse than healthy controls. The study also aimed to explore the relationship between objective sleep measures (i.e., measures of intermittent hypoxia, sleep fragmentation and sleep architecture), and specific autobiographical memory.

Study 1

Participants

Study 1 consisted of 77 individuals: (i) 20 young OSA patients (age range: 26-44 years); (ii) 20 young healthy controls with no sleep disorder (age range: 23-45 years); (iii) 19 older OSA patients (age range: 51-80 years); and (iv) 18 older healthy controls with no sleep disorder (age range: 52-71 years). The 20 young OSA patients and 20 young healthy controls were drawn from the OSA-D (OSA-Depression) study, previously conducted by the candidate at the University of Melbourne Sleep Laboratory, and data from the larger sample has been published previously (Lee, Trinder & Jackson, 2016). Of the 58 OSA patients in the OSA-D study, data from 20 individuals under the age of 45 were selected to age match the healthy controls.

Data of the older OSA patients were drawn from the COSAD study conducted at the Austin Health Sleep Laboratory who completed the Autobiographical Memory Task prior to starting CPAP therapy. Participants were included if they were 50 years and above, and had a clinical diagnosis of OSA via polysomnography (PSG), with an AHI above five. Older healthy controls were recruited through flyers placed in community areas and online advertisements, and were included if they were 50 years and above, and underwent a night of PSG to confirm the absence of any sleep disorders. Participants were excluded if they had a history of drug and alcohol dependence, history or current diagnosis of any cognitive impairment, brain injury, learning disability, and had been recently or were currently involved in shift work.

Written informed consent was obtained from all participants, and the current study was approved
by the Austin Health Human Research Ethics Committee (HREC) and registered with the Northern Health HREC and Royal Melbourne Institute of Technology HREC. The COSAD study was approved by the Austin Health HREC and the OSA-D study was approved by the University of Melbourne HREC.

**Materials**

**Autobiographical Memory Test (AMT)**

Twelve cue words for the AMT were drawn from a sample of cue words used by Williams (2005). These were grouped according to the emotionality rating and Kucera-Francis written frequency, with the positive and negative cue words being high in positive or negative emotional valence, respectively, and high-frequency words. The 12 cue words consisted of six positive words (proud, glorious, happy, sunny, eager and relieved) and six negative words (guilty, failure, ugly, hopeless, blame, worse). The words were presented in the same randomised order for each participant. Participants were prompted once for each cue word if an overgeneral memory was initially recalled. Participants completed three practice words prior to starting the task to ensure that they understood the instructions.

All the responses were written and scored. Each response was scored as being specific, overgeneral or no response. One point was given for each specific memory recalled and zero for each overgeneral or no response, with a maximum total score of 12 (six for negative and six for positive cue words). The outcome measures from the AMT include the number of positive and negative specific memories recalled, and the total specific memories recalled. Twenty per-cent of the transcripts were scored by a second scorer, an independent researcher for inter-rater reliability.
**Questionnaires**

All participants completed a set of questionnaires, including a general health questionnaire, the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman & Kupfer, 1989) and ESS (Johns, 1991).

**Polysomnography**

The young healthy controls underwent a standard clinical PSG assessment, which was performed using a Compumedics E-Series system (Abbottsford, Victoria, Australia), and data were collected on Compumedics ProFusion PSG 3 Version 3.3. The older healthy controls also underwent a standard clinical PSG assessment, which was performed using either the Compumedics Grael or Compumedics SomtePSG system (Abbottsford, Victoria, Australia), and data was collected on Compumedics ProFusion PSG 4 Version 2.0.2.

The PSG recordings included standard placements, based on the international 10-20 system, for continuous monitoring of frontal, central and occipital electroencephalogram (F3/F4, C3/C4 and O1/O2) with M1 and M2 as reference. Also, horizontal electrooculogram, submental and anterior tibialis electromyogram and electrocardiogram were collected. Nasal airflow was measured using a nasal cannula (Promed Nasal Cannula, Thermo Fisher Scientific, Victoria, Australia) or thermistor (Compumedics Reusable Airflow Sensor), while the thoracic and abdominal excursion were obtained by respiratory inductance plethysmography (Compumedics Thoracic and Abdominal Band). Continuous arterial oxygen saturation was recorded by a finger oximeter probe (Compumedics Adult silicone soft tip finger probe-oximeter). Leg movements were recorded using a limb movement sensor.

All variables were recorded on a 17-channel PSG and PSG data were analysed according to the AASM Manual for the Scoring of Sleep and Associated Events (American Academy of Sleep Medicine, 2007). All OSA participants had completed a clinical PSG prior to data collection.
**Procedure**

All participants completed a general screening session to ensure that they met the inclusion and exclusion criteria. The healthy older controls underwent at-home or in-lab PSG depending on preference. During at-home sessions, participants were wired-up at home approximately an hour prior to bedtime. The in-lab sessions were conducted at the RMIT Sleep Laboratory. For both sessions, participants maintained their regular bedtime and wake time schedule. On the following morning, the AMT was conducted as part of a 90-minute neuropsychological test battery. Participants completed the questionnaires prior to the PSG session.

Data from the young OSA and healthy control groups were obtained from the OSA-D study. A detailed procedure of the data collection was previously reported in Lee, Trinder & Jackson (2016).

Data from the older OSA group were obtained from the COSAD study. Participants from the COSAD study completed the AMT as part of a 90-minute test battery, conducted prior to starting CPAP therapy. Participants also completed the ESS, PSQI and general health questionnaires prior to their testing session. Participants from the COSAD study had completed a clinical PSG prior to enrolment and the PSG data was extracted from the Austin Health Sleep Lab database.

**Statistical analysis**

All statistical analyses were carried out using IBM SPSS Statistics 24 (SPSS, Chicago, IL, USA). An alpha level of 0.05 was considered to be of statistical significance. Inter-scorer reliability on the AMT was evaluated by Pearson’s correlation between 20% of the data scored by the first and second scorer. The total number of specific AMs recalled was analysed using a one-way analysis of variance (ANOVA) for comparison between the groups (young OSA, young controls, older OSA, older controls). Significant group effects were analysed post hoc using Tukey’s Honestly Significant Difference (HSD) tests. Paired sample t-tests were conducted to examine difference in valence (positive and negative) recall within each group. Pearson’s correlational analyses were
conducted to examine the relationship between specific AM recalled, and objective and subjective sleep measures.

Results

Sample characteristics

Demographic and PSG data of each group (young controls, young OSA, old controls, old OSA) are presented in Table 1. A chi-squared test indicated a significant difference in gender distribution between the four groups, $\chi^2 (3) = 13.21, p=0.004$, with the older control group having notably more females compared to the other groups (young controls, $\chi^2 (1) = 5.76, p=0.016$; young OSA, $\chi^2 (1) = 9.29, p=0.002$; older OSA, $\chi^2 (1) = 8.62, p=0.003$). Both young and older OSA groups had significantly higher BMI, arousal index and AHI, and poorer subjective sleep quality when compared to both the control groups. The young OSA group had notably more daytime sleepiness than young healthy controls but did not differ significantly when compared to older controls. The older OSA group had significantly worse sleep efficiency when compared to both control groups but younger OSA patients did not differ in sleep efficiency when compared to the controls.
Table 1
Demographic and polysomnography data of all controls and all OSA patients (N=77)

<table>
<thead>
<tr>
<th></th>
<th>Young (&lt;50 years)</th>
<th>Older (≥50 years)</th>
<th>Controls</th>
<th>OSA</th>
<th>Controls</th>
<th>OSA</th>
<th>F</th>
<th>p</th>
<th>Effect size</th>
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<td>18</td>
<td>19</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>4</td>
<td>13</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)*××</td>
<td>32.80 (6.69)</td>
<td>35.95 (6.04)</td>
<td>61.89 (5.51)</td>
<td>62.79 (7.67)</td>
<td>118.20</td>
<td>&lt;0.001</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)*#†‡</td>
<td>23.72 (3.43)</td>
<td>32.41 (6.27)</td>
<td>23.48 (3.52)</td>
<td>31.93 (4.34)</td>
<td>22.63</td>
<td>&lt;0.001</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESS*†‡</td>
<td>4.15 (3.05)</td>
<td>7.11 (3.72)</td>
<td>4.22 (3.42)</td>
<td>8.05 (3.61)</td>
<td>6.39</td>
<td>0.001</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI*†‡</td>
<td>4.45 (2.06)</td>
<td>7.71 (2.71)</td>
<td>4.22 (2.90)</td>
<td>7.37 (3.10)</td>
<td>9.03</td>
<td>&lt;0.001</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (/h)*#†‡</td>
<td>0.10 (0.23)</td>
<td>23.20 (10.60)</td>
<td>4.33 (18.07)</td>
<td>39.41 (18.07)</td>
<td>55.89</td>
<td>&lt;0.001</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arousal index (/h)*#†‡</td>
<td>8.48 (3.50)</td>
<td>23.71 (8.34)</td>
<td>9.61 (4.57)</td>
<td>28.37 (12.77)</td>
<td>28.95</td>
<td>&lt;0.001</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency (%)†‡</td>
<td>87.62 (9.03)</td>
<td>80.83 (11.68)</td>
<td>83.94 (7.41)</td>
<td>73.02 (14.05)</td>
<td>6.29</td>
<td>0.001</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TST (min)*#†‡</td>
<td>429.00 (50.31)</td>
<td>389.11 (91.14)</td>
<td>459.99 (51.66)</td>
<td>341.76 (69.78)</td>
<td>10.55</td>
<td>&lt;0.001</td>
<td>0.30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AHI, apnoea-hypopnoea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; WASO, wake after sleep onset; TST, total sleep time.

Note: *p < 0.05 between young OSA and young control groups; †p < 0.05 between young OSA and older control groups; ‡p < 0.05 between old OSA and young control groups; ††p < 0.05 between old OSA and older control groups; ^p < 0.05 between young OSA and older OSA groups; ×p < 0.05 between young controls and older control groups.
**Inter-rater reliability for AMT**

There was a strong agreement of 95.23% between the first and second scorer for all measures of the AMT. The Pearson’s correlations of specific AM scores between the first and second scorer is shown in *Table 2*.

**Table 2**

Pearson’s correlation of AMT scores between first and second scorer

<table>
<thead>
<tr>
<th>Second scorer</th>
<th>Positive</th>
<th>Negative</th>
<th>Total specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0.95**</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Negative</td>
<td>-</td>
<td>0.90**</td>
<td>-</td>
</tr>
<tr>
<td>Total specific</td>
<td>-</td>
<td>-</td>
<td>0.96**</td>
</tr>
</tbody>
</table>

**p<0.01

**Age differences in specific autobiographical memory recall**

A one-way ANOVA revealed a significant main effect of group for the number of specific AMs recalled, $F(3,77) = 10.83$, $p<0.001$. The effect remained significant after controlling for gender and BMI, $p=0.024$. A *post hoc* Tukey’s HSD test showed that the young OSA group (7.55 ± 2.74) recalled significantly fewer specific AMs when compared to age-matched controls (9.80 ± 1.82, $p=0.010$) and older controls (10.00 ± 1.41, $p=0.005$). The older OSA group (6.68 ± 2.54) also recalled significantly fewer specific AMs when compared to younger controls ($p<0.001$) and age-matched controls ($p<0.001$). The older OSA group recalled fewer specific AMs by almost one point (mean difference = 0.87) when compared to the young OSA patients but no statistical significance was observed ($p=0.611$). See *Figure 1*. 
Figure 1. Mean number of total specific AMs recalled in all groups (young controls, young OSA, older controls, older OSA), with bars showing standard error of means. *p<0.05
Figure 2. Mean number of specific positive and negative AMs recalled in all groups (young controls, young OSA, older controls, older OSA), with bars showing standard error of means.

*\(p<0.05\)

Regarding valence, no significant difference in positive and negative memory recall was observed in the young healthy control, \(t(19)=1.71, p=0.104\) and young OSA, \(t(19)=1.79, p=0.090\) groups. On the other hand, the older controls, \(t(17)=3.83, p=0.001\) and older OSA patients, \(t(18)=2.56, p=0.020\) recalled significantly more specific positive memories compared to negative memories.

**Correlational analyses**

When both OSA groups were combined (\(n=39\)), a Pearson’s correlational analysis revealed a significant negative correlation between the number of negative specific AMs recalled and PSQI score \((r=-0.34, p=0.037)\). This correlation was not significant in the healthy controls \((p=0.518)\).

No significant correlations were observed between total or positive specific AMs recalled and
age, BMI, ESS, PSQI, AHI, arousal index, sleep efficiency or total sleep time in OSA patients (all \( p > 0.05 \)).

**Study 2**

**Participants**

Study 2 consisted of 56 individuals: (i) 19 OSA-only patients (OSA; age range: 51-80 years; 7 females); (ii) 18 OSA patients with comorbid MCI (OSA-MCI; age range: 54-86 years; 5 females); and (iii) 19 healthy controls (age range: 52-71 years; 7 females) with no sleep disorder and cognitive impairment. As previously mentioned in Study 1, the patients with OSA only were drawn from the COSAD study conducted at the Austin Health Sleep Laboratory and healthy controls were recruited through flyers placed in community areas and online advertisements. Patients with OSA and MCI were recruited from the Cognitive, Dementia and Memory Service (CDAMS) at Austin Health and Bundoora Specialist Health Care, a private memory service. Written informed consent was obtained from all participants, and the study was approved by the Austin Health HREC and registered with the Northern Health HREC and Royal Melbourne Institute of Technology HREC.

The age inclusion for all participants was 50 years and above, and the inclusion criterion for both of the OSA groups was a clinical diagnosis of OSA via PSG (AHI > 5). Participants in the OSA-MCI group met the Petersen (2004) criteria including objective cognitive impairment (at least 1 SD below age norms –of at least one memory subtest). Participants in the OSA-only group had no history and current diagnosis of any cognitive impairment. Healthy controls underwent a night of PSG to confirm the absence of any sleep disorders. Participants were excluded if they had a history of drug or alcohol dependence, learning disability, and had been recently or were currently involved in shift work.

**Materials and procedure**

Similar to Study 1, Study 2 utilised the AMT to assess specific autobiographical memory recall, an overnight PSG and a set of questionnaires, including the PSQI, ESS and the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). Participants who
met the inclusion criteria, based on their responses to the screening questionnaire, gave written informed consent and were scheduled for a testing session.

The same procedure and 12 cue words as Study 1 were utilised during the Autobiographical Memory Test.

The OSA-MCI group and healthy controls underwent a standard clinical PSG assessment, which was conducted either in-lab at the RMIT Sleep Laboratory with the Compumedics Grael system (Abbottsford, Victoria, Australia) or at the participant’s home with the Compumedics SomtePSG system (Abbottsford, Victoria, Australia). The same electrode placements were utilised as in Study 1. All variables were recorded on a 17-channel PSG, and PSG data were analysed according to the AASM Manual for the Scoring of Sleep and Associated Events (American Academy of Sleep Medicine, 2007). The outcome measures included AHI (events per hour), measures of intermittent hypoxia (oxygen desaturation index; ODI ≥4%) and sleep fragmentation (wake after sleep onset and arousal index), sleep efficiency, total sleep time and percentage spent in each sleep stage (N1, N2, N3 and REM).

All participants in the OSA-only group had completed a clinical PSG prior to enrolment in the COSAD study. The PSG data was extracted from the Austin Health Sleep Laboratory database.

**Statistical analysis**

All statistical analyses were carried out using IBM SPSS Statistics 24 (SPSS, Chicago, IL, USA). An alpha level of 0.05 was considered to be of statistical significance. The total number of specific AMs recalled was analysed using a one-way analysis of variance (ANOVA) for comparison between the groups (healthy controls, OSA-only, OSA-MCI). Significant group effects were analysed *post hoc* using Tukey’s Honestly Significant Difference (HSD) tests. Paired sample t-tests were conducted to examine differences in valence (positive and negative) recall within each group. Pearson’s correlational analyses were conducted to examine the relationship between specific AMs recalled, and objective and subjective sleep measures in OSA patients.
Results

Sample characteristics

Demographic and PSG data of each group (control, OSA-only and OSA-MCI) are presented in Table 3. A chi-squared test indicated a significant difference in gender distribution between the three groups, \( \chi^2 (2) = 7.97, p=0.02 \), which was due to a between-group difference between the OSA group and healthy controls, \( \chi^2 (1) = 7.50, p=0.006 \), whereby there was a higher proportion of females in the control group (Table 3). No significant age differences were observed between the three groups. Seven patients from the OSA-only group and eight patients from the OSA-MCI group reported taking antidepressants. While the OSA-only group had significantly poorer subjective sleep quality, more anxiety symptoms and higher AHI when compared to the OSA-MCI group, the two groups did not differ significantly in daytime sleepiness, depressive symptoms, arousal index, ODI \( \geq 4\% \) or sleep efficiency. All three groups did not differ in the percentage of time spent in N1, N2 and N3. OSA-MCI group had significantly lower percentage of time spent in REM compared to the OSA-only group and healthy controls.
### Table 3
Demographic and polysomnography data of the study sample (N=56)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>OSA-only</th>
<th>OSA-MCI</th>
<th>F</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.11 (4.89)</td>
<td>62.79 (7.67)</td>
<td>67.94 (8.13)</td>
<td>3.10</td>
<td>0.053</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI (kg/m^2)*‡</td>
<td>23.49 (3.42)</td>
<td>31.93 (4.34)</td>
<td>30.46 (6.49)</td>
<td>16.09</td>
<td>&lt;0.001</td>
<td>0.38</td>
</tr>
<tr>
<td>ESS*‡</td>
<td>4.26 (3.33)</td>
<td>8.05 (3.61)</td>
<td>9.39 (6.37)</td>
<td>6.22</td>
<td>0.004</td>
<td>0.19</td>
</tr>
<tr>
<td>PSQI*</td>
<td>4.37 (3.00)</td>
<td>7.37 (3.10)</td>
<td>7.17 (4.53)</td>
<td>4.11</td>
<td>0.022</td>
<td>0.13</td>
</tr>
<tr>
<td>HADS (Depression)*‡</td>
<td>1.42 (1.35)</td>
<td>6.37 (4.81)</td>
<td>5.61 (3.60)</td>
<td>10.63</td>
<td>&lt;0.001</td>
<td>0.29</td>
</tr>
<tr>
<td>HADS (Anxiety)*</td>
<td>3.00 (1.94)</td>
<td>6.00 (4.06)</td>
<td>5.28 (3.30)</td>
<td>4.48</td>
<td>0.016</td>
<td>0.15</td>
</tr>
<tr>
<td>AHI (/h)*‡</td>
<td>4.19 (3.57)</td>
<td>39.41 (18.07)</td>
<td>25.89 (15.73)</td>
<td>30.80</td>
<td>&lt;0.001</td>
<td>0.53</td>
</tr>
<tr>
<td>ODI ≥ 4%*‡</td>
<td>1.31 (1.87)</td>
<td>25.34 (17.20)</td>
<td>12.08 (11.51)</td>
<td>19.09</td>
<td>&lt;0.001</td>
<td>0.42</td>
</tr>
<tr>
<td>Arousal index (/h)*‡</td>
<td>9.46 (4.49)</td>
<td>28.37 (12.77)</td>
<td>24.03 (12.78)</td>
<td>16.21</td>
<td>&lt;0.001</td>
<td>0.38</td>
</tr>
<tr>
<td>WASO (min)†‡</td>
<td>48.34 (36.11)</td>
<td>84.23 (56.09)</td>
<td>140.64 (69.20)</td>
<td>13.09</td>
<td>&lt;0.001</td>
<td>0.33</td>
</tr>
<tr>
<td>Sleep efficiency (%)*‡</td>
<td>83.25 (7.79)</td>
<td>73.02 (14.05)</td>
<td>61.74 (13.66)</td>
<td>14.50</td>
<td>&lt;0.001</td>
<td>0.35</td>
</tr>
<tr>
<td>TST (min)†‡</td>
<td>455.60 (53.73)</td>
<td>341.76 (69.78)</td>
<td>376.28 (105.68)</td>
<td>10.40</td>
<td>&lt;0.001</td>
<td>0.28</td>
</tr>
<tr>
<td>N1 (%)</td>
<td>13.92 (7.87)</td>
<td>15.02 (9.80)</td>
<td>29.08 (34.63)</td>
<td>2.99</td>
<td>0.059</td>
<td>0.10</td>
</tr>
<tr>
<td>N2 (%)</td>
<td>44.61 (8.17)</td>
<td>47.64 (15.39)</td>
<td>50.59 (33.92)</td>
<td>0.35</td>
<td>0.706</td>
<td>0.01</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>21.97 (11.19)</td>
<td>20.44 (11.26)</td>
<td>20.47 (10.70)</td>
<td>0.12</td>
<td>0.888</td>
<td>0.01</td>
</tr>
<tr>
<td>REM (%)†</td>
<td>20.02 (4.74)</td>
<td>17.43 (6.69)</td>
<td>14.06 (7.63)</td>
<td>3.98</td>
<td>0.025</td>
<td>0.13</td>
</tr>
</tbody>
</table>

AHI, apnoea-hypopnoea index; BMI, body mass index; HADS, Hospital Anxiety Depression Scale; ESS, Epworth Sleepiness Scale; OSA-MCI, patients with obstructive sleep apnoea and comorbid mild cognitive impairment; PSQI, Pittsburgh Sleep Quality Index; WASO, wake after sleep onset; TST, total sleep time; N1, sleep stage 1; N2, sleep stage 2; N3, sleep stage 3; REM, rapid eye movement stage.

* *p < 0.05 between control and OSA-only groups.
† †p < 0.05 between OSA-only and OSA-MCI groups.
‡ ‡p < 0.05 between control and OSA-MCI groups.
Specific autobiographical memory recall between controls, OSA-only and OSA-MCI

A one-way ANOVA revealed a significant main effect of group for the number of specific AM recalled, $F(2,55) = 24.21, p < 0.001$, effect size = 0.48. The group effect remained significant after controlling for age, gender, and depressive and anxiety symptoms. A post hoc Tukey’s HSD test showed that both the OSA-only group ($6.68 \pm 2.54; p < 0.001$) and the OSA-MCI ($5.44 \pm 2.09; p < 0.001$) group recalled significantly fewer specific AMs than the controls ($10.00 \pm 1.41$), while the difference between the OSA-only and OSA-MCI groups was not significant ($p = 0.80$). See Figure 3.

![Figure 3](image)

* $p < 0.001$

Similar to the healthy control and OSA-only groups, the OSA-MCI group recalled significantly more specific positive memories than negative memories, $t(17) = 4.76, p < 0.001$. See Figure 4.

Figure 3. Mean number of total specific autobiographical memories recalled in all groups (healthy controls, OSA-only, OSA-MCI) with bars showing standard error of means.

* $p < 0.001$
Figure 4. Mean number of specific positive and negative autobiographical memories recalled in all groups (healthy controls, OSA-only, OSA-MCI), with bars showing standard error of means. *p<0.05

Correlation analyses

Within the OSA-MCI group, a Pearson correlation analysis revealed a significant positive correlation between the total number of specific AMs recalled and percentage of N3 sleep \((r=0.51, p=0.03)\). This correlation was not significant in the OSA \((p=0.59)\) and healthy control \((p=0.53)\) groups. No significant correlations were observed between specific AMs recalled and other stages of sleep (N1, N2 and REM) within all groups \((all \ p>0.05)\).

AHI, ODI ≥4%, WASO, AI, HADS anxiety and depression scores, PSQI, and ESS did not significantly correlate with the total number of specific AMs recalled within all groups \((all \ p>0.05)\).
Discussion

The findings from Study 1 revealed that young OSA patients are as impaired as older OSA patients with respect to specific AM recall. Both groups performed significantly worse when compared to healthy controls, regardless of age. Nevertheless, a valence bias was observed in older individuals where the older groups recalled notably more specific positive memories than negative memories. In OSA patients, poorer subjective sleep quality was significantly associated with fewer specific negative AMs recalled.

Study 2 further revealed that OSA patients without clinically significant cognitive impairment performed as poorly as OSA patients with comorbid MCI in their recall of specific AM. When compared to age-matched healthy controls, both OSA groups recalled significantly fewer specific AM. In OSA patients with comorbid MCI, a lower percentage of time spent in SWS was significantly associated with fewer specific AMs recalled.

Age and specific autobiographical memory recall

The current findings demonstrated no age-related effect on specific AM recall in OSA patients. These findings are contrary to our previous notion that specific AM impairment may not be as prominent in younger OSA patients (Lee, Trinder & Jackson, 2016). Our previous study reported no statistically significant difference ($p=0.09$) between OSA patients with asymptomatic depressive symptoms and age-matched healthy controls in a smaller, younger subset. That study was unable to conclude if the lack of significance was due to an age-related effect on AM or if a smaller subset contributed to a lack of statistical power. The current findings suggest that if the previous study had more statistical power, the OSA groups would have performed significantly worse than healthy controls on the AMT, regardless of age.

The present findings are also inconsistent with previous studies that have reported poorer cognitive performance in older OSA patients compared to a younger group (Alchanatis et al., 2008; Ayalon, Ancoli-Israel & Drummond, 2010). For example, middle-aged OSA patients (aged ≥ 45 years) had significantly poorer immediate word recall and slower reaction time during sustained attention than younger OSA patients (<45 years; Ayalon, Ancoli-Israel &
Drummond, 2010). While age was expected to add an additional burden to OSA patients, it is possible that this aspect of cognition (i.e., specific AM) is highly sensitive to OSA and is impaired at an early stage in the pathogenesis of OSA. In this context, the mean number of specific AMs recalled in younger OSA patients from the current study (mean = 7.55 ± 2.74) is comparable to the mean score of MCI patients (mean = 6.62 ± 1.58) reported in Donix et al. (2010), suggesting that young OSA patients are already severely impaired in this area and the lack of further deterioration as OSA patients get older may be due to a floor effect. Using a different cue-based AM task, Dijkstra and Kaup (2005) revealed that older adults tended to take a longer period of time to recall memories and recalled notably more landmark, self-relevant and emotionally intense events compared to younger adults. Given the importance of episodic AM recall in our daily lives, it is possible that older adults may compensate for the burden of age by developing and employing different search strategies during AM retrieval.

While no age-related impairment was observed, older participants (both older OSA-only and healthy control groups) revealed a valence bias where significantly more specific positive AMs were recalled compared to negative memories. On the other hand, no differences were observed in positive and negative memory recall in the younger groups. These findings are in line with previous studies that have reported positive bias in memory tasks for older adults (Dijkstra & Kaup, 2005; Kensinger, Garoff-Eaton & Schacter, 2007; Leal, Noche, Murray & Yassa, 2016 Tomaszczyk, Fernandes & MacLeod, 2008). For instance, older adults tended to recall a greater number of positive AMs while younger adults tended to recall more neutral memories (Dijkstra & Kaup, 2005). Specific AMs are part of an individual’s life narrative and play a crucial role in the construction of personal identity (Wilson & Ross, 2003). Dijkstra and Kaup (2005) proposed that as people get older and experience more events, they may re-evaluate their life goals and selectively retain distinct memories that fit the overall narrative thus, retaining more self-relevant and positive memories.

When OSA-only patients were examined, a correlational analysis revealed that those who reported poorer subjective sleep quality tended to recall significantly fewer specific negative memories. This link was not observed for positive memories. This is in line with studies that have reported an association between poor sleep quality and negative cognitive bias (Gobin, Banks, Fins & Tartar, 2015; Tempesta, Gennaro, Natale & Ferrara, 2015). While the recall of both positive and negative memories in both OSA groups were significantly poorer than in
healthy controls, the current findings suggest that subjective sleep quality may play a role in the recall of specific negative memories.

While the findings of the present study are not as hypothesised, the current study emphasises the acute detrimental effect of OSA on cognition. As young OSA patients are just as impaired as older OSA patients in this aspect of cognition, it is also important to recognise the need for early intervention following a diagnosis of OSA. Preliminary findings from the COSAD study show that long-term CPAP therapy has the potential to improve specific AM deficits in OSA patients. After 12 months of CPAP usage, OSA patients (mean age=54.8 ± 9.8 years) recalled significantly fewer overgeneral memories compared to their baseline performance (Brown, Lee, Tolson, Barnes & Jackson, 2018, conference abstract). When combined with findings from the current study, it is suggested that specific AM is an aspect of cognition affected at the early stages of OSA and that long-term CPAP intervention may be helpful in reversing this impairment.

Specific autobiographical memory recall in OSA and MCI

Findings from Study 2 demonstrated that OSA patients with no clinically significant cognitive impairment were as impaired as OSA patients with MCI in specific AM recall. This result runs counter to our expectation that OSA patients with MCI would perform worse than OSA patients without MCI, due to the additional burden of MCI on cognitive functioning. However, the mean specific AM retrieval scores for both OSA groups were comparable to the mean score of MCI patients from Donix et al. (2010) and preliminary findings from an ongoing study from our research group indicating a mean total specific AM score of 6.00 ± 2.45 (N=6; age=71.0 ± 10.9 years) in MCI patients without any sleep disorders. This indicates that individuals in the OSA-only group performed as poorly as MCI patients and that comorbid OSA and MCI does not further impair specific AM recall (for example, to the level observed in patients with AD; mean specific AM score = 3.44). A conclusion to be drawn from this comparison is that OSA may contribute to specific AM impairment in both groups. Nevertheless, as the OSA-only patients did not undergo a formal cognitive assessment and were included based on the absence of any cognitive impairment diagnosis, it is also possible that the OSA-only patients have an existing underlying memory impairment. Given the high comorbidity between OSA and MCI (Guarnieri et al., 2012), this
finding highlights the importance of early identification and diagnosis of OSA, since OSA is treatable and a modifiable risk factor.

While few studies have examined AM in OSA patients, there is other evidence of long-term episodic memory deficits in individuals with OSA (Salorio et al., 2002; Twigg et al., 2010). It is thought that this is a result of underlying neurological impairment. For example, magnetic resonance imaging studies in OSA patients have demonstrated significant grey matter loss in the hippocampus and frontoparietal regions (Canessa et al., 2011; Yaouhi, 2009), that play an important role in the consolidation and retrieval of episodic memories (Addis, Moscovitch, Crawley & McAndrews, 2004; Cabeza & St. Jacques, 2007). In line with the cognitive resource allocation theory, it is plausible that neurological impairments observed in OSA patients result from having fewer cognitive resources to efficiently retrieve specific memories (see review by Moore and Zoellner, 2007). Given the severity of specific AM impairment observed in OSA patients in the current study, screening for AM overgenerality should be implemented in sleep clinics to identify individuals that require further intervention. In patients with moderate-to-severe OSA and specific AM impairment, a multidisciplinary treatment approach may be required. Preliminary data show that CPAP can improve AM overgenerality (Brown, Lee, Tolson, Barnes & Jackson, 2018, conference abstract) and five to eight weeks of cognitive training have been shown to improve recall of specific AM (Neshat-Doost, 2013; Williams, Teasdale, Segal & Soulsby, 2000). Accordingly, concurrent CPAP therapy and cognitive training can greatly benefit these individuals.

Interestingly, despite there being no difference in the percentage of time spent in SWS between the three groups (OSA-only, OSA-MCI, healthy controls), the percentage of SWS positively correlated with specific AM recall in OSA patients with comorbid MCI. SWS has previously been linked to hippocampal-dependent memory consolidation with the reactivation and redistribution of memories thought to occur during SWS (Marshall & Born, 2007; Walker, 2009). It is unclear why this association was not observed in the OSA-only group or in healthy controls but it is possible that the relationship may be mediated by a confounding variable that was not taken into account by the current study. For instance, the association between β-amyloid burden within the medial prefrontal cortex (mPFC) and hippocampal-dependent memory consolidation in older adults was reported to be mediated by non-REM slow wave activity (Mander et al., 2015). Future research would benefit from
examining biomarkers that could potentially identify individuals who are more susceptible to sleep-related cognitive impairments. Unlike previous studies that have reported associations between intermittent hypoxia and/or sleep fragmentation, and memory performance (Daurat, Foret, Bret-Dibat, Fureix & Tiberge, 2008; Champod et al., 2013; Findley et al., 1986), the present study found no significant links between AMT performance, and measures of sleep fragmentation or intermittent hypoxia in any of the groups examined.

**Limitations**

One limitation of the present study is that we did not examine temporal distribution of AM across the lifespan, and participants in the current study were specifically asked to avoid recalling memories from the past week. Individuals tend to recall significantly more recent and accessible memories during cued-retrieval AM tasks when unrestricted temporally (Brown & Schopflocher, 1998). With older adults observed to have higher levels of vividness for recent events compared to remote events (Janssen, Rubin & St. Jacques, 2011), it is possible that there is a temporal difference in the events recalled between the groups (e.g., older adults recalling predominantly recent events with a greater vividness hence, specificity while the younger adults had a more even spread of events recalled throughout all life periods). It is notable that MCI patients lack rich contextual details when recalling AMs across all life periods, with the biggest deficits in contextual detail compared to healthy controls, occurring in the “Last Week” period (Irish, Lawlor, O’Mara & Coen, 2010). It would be interesting to know whether the OSA-only and OSA-MCI groups differ with respect to contextual detail in AMs for the last week period, and if so whether there is an age effect.

Another limitation is the different study cohorts utilised. While the groups in Study 1 and 2 were matched based on age and gender, the studies (i.e. COSAD and OSA-D) had varying recruitment procedures and methodology. For instance, information on education level was not collected in the COSAD and OSA-D study, and the Center of for Epidemiological Studies Depression Scale was used in the OSA-D study to measure depressive symptoms instead of the HADS questionnaire, thus not allowing direct comparison of the groups’ depressive symptoms in Study 1. Besides that, the study cohorts underwent varying PSG methodologies. Participants from the COSAD study completed their PSG study in a hospital setting as part of
a clinical diagnostic test while other participants completed the PSG study in a lab setting or at-home as part of a research study. While Bruynell et al. (2011) have reported better sleep efficiency during home-based PSG compared to in-hospital PSG, there was no significant difference in AHI. Another study reported no evidence of better sleep quality and recording tolerance during at-home PSG when compared to in-lab PSG (Portier et al., 2000). Nevertheless, educational and depressive assessment should be better considered in future work.

A further limitation is the lack of formal MCI assessment for the OSA-only group. Individuals in the OSA-only group were included based on the absence of a history or current diagnosis of any cognitive impairment, so it is possible that some of these individuals had undiagnosed cognitive impairments unrelated to obstructive sleep apnoea. Nevertheless, all of the OSA participants from the COSAD study were followed up for a year following the baseline testing and none reported any clinical visits to a memory clinic or general practitioner regarding subjective cognitive decline during this period.

Finally, there was a higher proportion of females in the older control group compared to the OSA-only and OSA-MCI groups. A neuroimaging study reported that females demonstrated significant differences in white matter structural integrity, higher daytime sleepiness, higher anxiety and depression levels, and reduced sleep quality compared to their male counterparts, suggesting that male and female OSA patients manifest different disease characteristics and comorbidities (Macey, Kumar, Yan-Go, Woo & Harper, 2012). In a study examining AM, females have been shown to have a more specific (i.e. greater quantity, density and breath) style of recalling past memories (Pillemer, Wink, DiDonato & Sanborn, 2003). Nevertheless, a study examining the AMT have reported no significant gender differences in the number of specific autobiographical memory recalled (Anderson, Goddard & Powell., 2010).

**Conclusions**

The present study analysed specific AM recall in OSA patients with two studies: (i) the first examined age-related effect of specific AM impairment in OSA patients; and (ii) the second compared specific AM recall in OSA patients with and without MCI. Study 1 demonstrated that young OSA patients are as impaired as older OSA patients in specific AM recall. While
the current findings indicate that specific AM impairment in OSA patients does not
deteriorate further with age, the findings suggest that it may be an aspect of cognition that is
affected shortly after the onset of OSA. Furthermore, a valence bias in specific AM recall
was observed in older adults. Study 2 revealed that OSA patients without clinically
significant cognitive impairment performed as poorly as OSA patients with MCI in specific
AM recall. Furthermore, poorer specific AM recall was significantly linked to lower
percentage of SWS in OSA patients with MCI. AM overgenerality has been demonstrated in
individuals with AD (Donix et al., 2010; Meléndez et al., 2019; Moses, Culpin, Lowe &
McWilliam, 2004). Coupled with growing evidence suggesting a link between OSA and
dementia (Yaffe et al., 2011), future studies would benefit from understanding the
neurological underpinnings of specific autobiographical memory recall in OSA patients and
its association with future cognitive decline.
Chapter 4

Associations between cognitive performance and sleep measures in patients with comorbid obstructive sleep apnoea and mild cognitive impairment

Preface

Following Chapter 3, this chapter continues the investigation of cognitive impairment in OSA patients with comorbid MCI. Limited studies have examined the relationship between the different cognitive domains and measures of sleep apnoea in this patient population. Accordingly, this study aimed to investigate the relationship between sleep apnoea indices (severity, intermittent hypoxia, sleep fragmentation, sleep architecture and subjective sleep measures) and cognitive performance (global cognition, verbal memory, visual memory, working memory, processing speed, attention and executive function) in patients with comorbid OSA and MCI. This chapter also includes a subset of data from individuals with MCI and not reported sleep disorder from the AIBL study. Using this data, the study examined the difference in cognitive performance and mood between MCI patients with and without OSA in a subset of cognitive domains.

Candidate’s contribution

The candidate obtained ethics approval for the COMM study. The candidate recruited participants, and conducted data collection and analysis of the overnight polysomnography, neuropsychological testings and questionnaire data. The candidate also organised and screened the AIBL neuropsychological tests database for a subset of age-and gender-matched participants. The candidate conducted the analyses, and formulated and wrote the chapter.
Abstract

Obstructive sleep apnoea (OSA) has previously been linked to impairments in various cognitive domains, including global cognition, attention and processing speed, memory and executive function. Recently, OSA has been identified as a potential risk factor for the development of mild cognitive impairment (MCI) and dementia. To date, only a few studies have examined the relationship between OSA and neuropsychological performance in different cognitive domains in patients with comorbid OSA and MCI. Accordingly, the current study aimed to examine the relationship between OSA severity and cognitive performance in individuals with OSA and MCI. The study also aimed to further examine the relationship between cognitive performance and the different aspects of OSA, including intermittent hypoxia, sleep fragmentation, sleep architecture and subjective sleep measures. Finally, the study compared cognitive performance between MCI patients with OSA, MCI patients without OSA and age-matched healthy controls in a subset of cognitive domains.

Eighteen individuals with OSA and MCI (67.7 ± 8.2 years) and 19 healthy controls (62.7 ± 4.8 years) completed a 90-minute neuropsychological test battery and an overnight polysomnography. Neuropsychological data of 20 individuals with MCI (67.9 ± 6.6 years) were obtained from the AIBL study database. Firstly, the current findings revealed that increased OSA severity was significantly associated with poorer global cognition and working memory performance in patients with comorbid OSA and MCI. Secondly, both global cognition and working memory were significantly positively correlated to a measure of intermittent hypoxia (ODI ≥ 3%). In addition, a lower percentage of time spent in slow wave sleep (SWS) was significantly linked to poorer verbal memory, processing speed and attention performance in individuals with OSA and MCI. Thirdly, MCI patients with OSA had significantly more anxiety symptoms and poorer processing speed and attentional performance when compared to MCI patients without OSA and age-matched healthy controls. These findings suggest that OSA is linked to cognitive functioning in patients with comorbid OSA and MCI, and may contribute to poorer attention and processing speed and greater anxiety symptoms in MCI patients.
Obstructive sleep apnoea (OSA) is a clinically recognised sleep disorder that is characterised by repeated episodes of apnoeas or hypopnoeas and arousals during sleep. This recurrent cycle of apnoeas and central nervous system arousals contribute towards two significant immediate consequences of OSA, which are intermittent hypoxia and sleep fragmentation (Shamsuzzaman, Gersh & Somers, 2003). Moreover, due to the patients’ fragmented sleeping patterns, OSA is commonly accompanied by excessive daytime sleepiness (Chen et al., 2011; Gottlieb et al., 1999; Kim et al., 2017).

OSA has been linked to impairments in various cognitive domains, including global cognition (see Aloia, Arnedt, Davis, Riggs & Byrd, 2004; Olaithe, Bucks, Hillman & Eastwood, 2018 for reviews), attention and processing speed (Ayalon et al., 2009; D’Rozario et al., 2018), memory (see Wallace & Bucks, 2013 for review), and executive functions (see Leng, McEvoy, Allen & Yaffe, 2017; Stranks & Crowe, 2016 for reviews). While the exact mechanisms underlying these impairments are unknown, these cognitive deficits have been differentially attributed to several aspects of OSA (i.e., intermittent hypoxia, sleep fragmentation and excessive daytime sleepiness; Jackson, Howard & Barnes, 2011). Impairments in global cognition and executive function have generally been linked to measures of hypoxemia while impaired attention/vigilance has been associated with sleep fragmentation indices in OSA patients (Aloia, Arnedt, Davis, Riggs & Byrd, 2004; Jackson, Howard & Barnes, 2011). Longitudinal studies of sleep apnoea in older adults, have found a significant association between cognitive decline across time and hypoxia (Blackwell et al., 2015; Saint Martin et al., 2015; Yaffe et al., 2011), but not sleep fragmentation (Cohen-Zion et al., 2004; Lutsey et al., 2016). Given the link between OSA and cognitive impairments, studies have begun to explore the role of OSA in the cognitive decline observed in patients with mild cognitive impairment (MCI) and dementia.

Individuals with MCI experience considerably greater cognitive decline than expected for their age and education level but the impairment is not severe enough to meet the clinical criteria of dementia (Gauthier et al., 2006; Tangalos & Petersen, 2018). Nonetheless, a proportion of MCI patients will eventually progress to dementia (Marcos et al., 2016; Schmidtké & Hermeneit, 2008). Sleep disturbance is commonly observed in MCI patients, with studies showing that MCI patients tend to have longer sleep onset latency, shorter total sleep time, increased numbers of nocturnal awakenings, less SWS and poorer subjective sleep quality compared to healthy aged controls (Hita-Yañez, Atienza, Gil-Neciga & Cantero,
Furthermore, increased wake after sleep onset and arousals from sleep in MCI patients have been associated with reduced/poorer attention, executive functioning, non-verbal learning and problem solving performance (Naismith et al., 2010). With MCI patients already experiencing poorer subjective and objective sleep when compared to healthy controls, an additional burden of OSA may further contribute towards the sleep-related cognitive deficits observed.

Sleep disordered breathing (SDB), a broader category which includes snoring and different variations of sleep apnoea, has been identified as a risk factor for cognitive decline and dementia in older adults (Kim et al., 2011, Leng, McEvoy, Allen & Yaffe, 2017; Yaffe et al., 2011). In a community-based study of 431 patients with dementia or MCI, SDB was reported to be the most prevalent sleep disorder, being present in 60% of the study population (Guarnieri et al., 2012). Moreover, when compared to other sleep disorders, including insomnia, rapid eye movement behaviour disorder and restless legs syndrome, individuals with SDB had the highest increase risk of developing Alzheimer’s disease (AD).

Several longitudinal studies have focused on whether OSA affects the incidence rate or age of onset of MCI/dementia (Lutsey et al., 2018; Osorio et al., 2015; Yaffe et al., 2011). For example, Yaffe et al. (2011), followed 298 elderly women for approximately 4.7 years and reported that significantly more women with SDB developed MCI or dementia over the years compared to those without SDB. Furthermore, measures of hypoxia (ODI and percentage of total sleep time in apnoea or hypopnoea) but not sleep fragmentation (arousal index, wake after sleep onset) were significantly associated with a higher incidence of MCI/dementia. Additionally, Osorio and colleagues (2015) reported that patients with untreated SDB were significantly younger at onset of MCI/AD than those without SDB.

Few studies have examined the relationship between SDB/OSA and specific cognitive domains in MCI patients (Cross et al., 2017; Kim et al., 2011; Terpening et al., 2015). One study (Kim et al., 2011) examined verbal fluency, the Boston Naming Test, word list recall and recognition, and constructional praxis recall in MCI patients. It was found that both a higher apnoea-hypopnoea index (AHI) and less SWS were significantly and independently associated with poorer language functioning. Sleep apnoea severity was not associated with any other cognitive performance in the MCI patients. However, it should be noted that not all of the MCI patients had a sleep apnoea diagnosis (70% with OSA), and the group AHI mean
was 13.41 (SD=11.61). It is possible that other cognitive impairments would be more evident in patients with moderate-severe OSA. Another study that examined driving performance in MCI patients reported that measures of sleep apnoea (i.e., AHI, ODI and AI) were significantly linked with poorer driving performance (Cross et al., 2017). This association was not observed in the group of healthy controls with comparable sleep apnoea severity. Terpening et al. (2015) reported a significant negative correlation between processing speed and measures of sleep apnoea severity. However, it should be noted that both studies screened for sleep disorders and excluded individuals with known or suspected sleep disorders, including OSA, only including participants with mild levels of SDB. Accordingly, patients with clinically diagnosed moderate-severe OSA and comorbid MCI have not been examined to determine what cognitive domains are impaired, and the extent of impairment that can be attributed to OSA.

Besides cognitive impairments, both OSA and MCI patients experience mood disturbances (Schröder & O’Hara, 2005, Shapiro, 2014; Yates, Clare & Woods, 2013). For instance, a prevalence study of 118,105 sleep apnoea patients, 21.8% reported a diagnosis of depression and 16.7% reported a diagnosis of anxiety (Sharafkhaneh, Giray, Richardson, Young & Hirshkowitz, 2005). These percentages were significantly higher than those without sleep apnoea. In MCI patients, prevalence studies have reported that up to 32% of MCI patients experience depression (Ismail et al., 2017; Lyketsos, et al., 2002) and up to 45% of MCI patients reported anxiety symptoms (Feldman, 2004). Given that sleep disturbances have been linked to anxiety and depression (Alvaro, Roberts & Harris, 2013; Cho et al., 2008), there is a need to examine whether OSA contributes to mood disturbances in MCI patients.

Previous studies that have examined the relationship between sleep apnoea and cognition in MCI patients have recruited MCI patients regardless of their OSA diagnosis and/or severity. While this might provide a representation of the range of OSA severity observed in the MCI patient population, an over-representation of mild OSA may prevent some cognitive deficits associated with OSA from reaching significance. Accordingly, the current study aimed to examine the associations between cognition and OSA severity in patients with mild-severe OSA and comorbid MCI. To further explore the mechanisms that could explain this association, the present study aimed to examine the relationship between cognitive performance and different aspects of OSA (intermittent hypoxia, sleep fragmentation, sleep architecture and subjective sleep measures). Finally, the current study compared cognitive
performance and mood between MCI patients with OSA, MCI patients without OSA and age-matched healthy controls in a subset of cognitive domains, including global cognition, memory, attention and processing speed.

Methods

Participants

A total of 18 individuals with untreated OSA and MCI (OSA-MCI; age range: 54-86 years; 6 females) and 18 aged-matched healthy controls with no sleep disorder and cognitive impairment (age range: 58-71 years; 10 females) were included in the study. Patients with OSA and MCI were recruited from the Cognitive, Dementia and Memory Service (CDAMS) at Austin Health and Bundoora Specialist Health Care, a private memory service while healthy controls were recruited through flyers placed in community areas and online advertisements. Written informed consent was obtained from all participants, and the study was approved by the Austin Health Human Research Ethics Committee (HREC) and registered with the Northern Health HREC and Royal Melbourne Institute of Technology HREC.

The inclusion criteria for the OSA-MCI group was age 50 and above, and a clinical diagnosis of OSA via polysomnography (PSG), with an AHI of more than five. The group also met the Petersen (2004) criteria for MCI including objective cognitive impairment (at least 1 SD below age norms –of at least one memory subtest). Healthy controls were included if they were 50 years and above, had an MMSE score of ≥26 and no sleep disorder. Participants were excluded if they had a history of drug and alcohol dependence, learning disability, or had been recently or were currently involved in shift work.

Data from a subset of 20 age- and gender-matched individuals with MCI (MCI-only; age range: 59-85 years; 6 females) without a diagnosis of OSA were selected from the Australian Imaging, Biomarkers and Lifestyle Flagship Study of Ageing (AIBL). The AIBL study’s baseline recruitment and study procedure has been outlined in detail previously in Ellis et al. (2009).
**Procedure**

All OSA-MCI and healthy control participants completed a general screening session to ensure that they met the inclusion and exclusion criteria. Eligible participants then underwent an at-home or in-lab overnight PSG depending on preference. During at-home sessions, participants were set-up for their sleep study at home approximately an hour prior to bedtime. The in-lab sessions were conducted at the RMIT Sleep Laboratory. For both sessions, participants maintained their regular bedtime and wake time schedule. On the following morning, the neuropsychological test battery was conducted approximately two hours after wake time. A short break was offered mid-testing. A set of sleep and mood questionnaires was completed prior to the overnight sleep study or following the test battery if participants required help with the questionnaires.

Baseline data from 297 individuals with MCI were obtained from the AIBL study group. A subset of 20 MCI participants were sampled from the larger cohort by age-matching to the OSA-MCI group of the current study. Participants with missing data were excluded. Participants from the AIBL study did not undergo a night of PSG but were screened for existing sleep disorders by self-report before enrolment to the AIBL study.

**Materials**

*Polysomnography*

A standard clinical PSG assessment was performed using either the Compumedics Grael (in-lab) or Compumedics Somte (at-home) system. Data were collected on Compumedics ProFusion PSG 4 Version 2.0.2. The recordings included standard electrode placements, based on the international 10-20 system, for continuous monitoring of frontal, central and occipital electroencephalograms (F3/F4, C3/C4 and O1/O2) with M1 and M2 as reference. Also, horizontal electrooculograms, submental and anterior tibialis electromyograms and electrocardiogram were collected. Nasal airflow was measured using a nasal cannula (Promed Nasal Cannula, Thermo Fisher Scientific, Victoria, Australia) or thermistor (Compumedics Reusable Airflow Sensor), while the thoracic and abdominal excursions were obtained by respiratory inductance plethysmography (Compumedics Thoracic and Abdominal Band). Continuous arterial oxygen saturation was recorded via a finger oximeter probe.
(Compumedics Adult silicone soft tip finger probe-oximeter). Leg movements were recorded using a limb movement sensor.

All variables were recorded on a 17-channel PSG, and PSG data were analysed according to the AASM Manual for the Scoring of Sleep and Associated Events (American Academy of Sleep Medicine, 2007). The outcome measures included AHI (events per hour), arousal index, sleep efficiency, total sleep time and oxygen desaturation index (ODI).

**Neuropsychological assessment**

All OSA-MCI and healthy control participants underwent a comprehensive 90-minute battery of neuropsychological assessment to assess global cognition, memory (verbal, visual and working), executive function, processing speed, attention and premorbid intelligence. Assessments included in the test battery are presented in Table 1.

MCI participants from the AIBL study completed a neuropsychological test battery that took approximately two hours. Measures of interest included the Mini Mental State Examination, Logical Memory (Standard battery - Story A only), Rey-Osterrieth Complex Figure Test, Digit Span (Forward and Backwards) and Digit-Symbol Coding that were conducted at baseline.
### Table 1
Neuropsychological test battery used and the cognitive domains measured

<table>
<thead>
<tr>
<th>Domain</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition</td>
<td>Mini Mental State Examination (MMSE)</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>Logical memory (LM; immediate and delayed recall; Wechsler Memory Scale for Adults; WMS-IV) Older Adult Battery – Story A and B, Verbal Paired Associates (VPA; immediate and delayed recall; WMS-IV)</td>
</tr>
<tr>
<td>Visual memory</td>
<td>Rey-Osterrieth Complex Figure Test (RCFT; copy, 3-minute immediate recall and delayed recall)</td>
</tr>
<tr>
<td>Working memory</td>
<td>Digit Span Backwards (WMS-IV), Digit Span Sequencing (WMS-IV)</td>
</tr>
<tr>
<td>Short-term memory</td>
<td>Digit Span Forward (WMS-IV)</td>
</tr>
<tr>
<td>Processing speed/attention</td>
<td>Trail Making Test Part A (TMT-A), Digit-Symbol Coding (Wechsler Intelligence Scale for Adults; WAIS-IV), Symbol Search (WAIS-IV)</td>
</tr>
<tr>
<td>Executive function</td>
<td>Trail Making Test Part B (TMT-B)</td>
</tr>
<tr>
<td>Premorbid intelligence</td>
<td>Vocabulary (WAIS-IV)</td>
</tr>
</tbody>
</table>

Subjective sleep and mood measurements

All OSA-MCI and healthy control participants completed the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman & Kupfer, 1989) and Epworth Sleepiness Scale (ESS; Johns, 1991) to assess subjective sleep quality and daytime sleepiness. The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to measure depressive and anxiety symptoms, while the Morningness-Eveningness Questionnaire (MEQ; Horne & Ostberg, 1976) was used to categorise morning and evening chronotypes. The MCI-only participants completed the Hospital Anxiety and Depression Scale.
Statistical Analysis

All statistical analyses were carried out using IBM SPSS Statistics 25 (SPSS, Chicago, IL, USA). An alpha level of 0.05 was considered to be of statistical significance. Descriptive analysis was generated for all variables. Independent samples t-tests were conducted to compare objective sleep, subjective sleep, mood and cognitive performance between OSA-MCI and healthy controls. Pearson’s correlational analyses were conducted to assess the relationship between different sleep apnoea indices (measures of severity, intermittent hypoxia, sleep fragmentation, sleep architecture, subjective sleep quality, and daytime sleepiness) and cognitive performance. Five participants in the OSA-MCI group were unable to complete the VPA test, therefore 13 participants were included in the final analysis for this measure. Partial correlations were used when a covariate was included.

A one-way analysis of variance (ANOVA) was conducted to compare a subset of tests between OSA-MCI, MCI and healthy control groups. In the AIBL database, the digit span forward and backward subset scores had been combined to obtain a total score. Accordingly, the combined scores were calculated for the OSA-MCI and healthy control groups. Besides that, the AIBL study administered only Story A (Anna Thompson story) from the standard WMS battery for the Logical Memory test. Accordingly, the Logical Memory scores (standard battery Story A/older adult battery story B only) for the OSA-MCI and healthy control groups were utilised in this analysis.

Besides the standard measures of hypoxia obtained from the PSG, the total number of apnoea/hypopnoea lasting between 10-29 seconds and ≥30 seconds were calculated to explore if different apnoea/hypopnoea lengths were associated with cognitive performance in the OSA-MCI group.
Results

Sample characteristics

Demographic and PSG data of the study sample are presented in Table 2. Individuals in the OSA-MCI group had significantly higher BMI, and poorer subjective sleep quality and daytime sleepiness when compared to healthy aged adults. The OSA-MCI group also reported more depressive symptoms and anxiety symptoms, as measured by the HADS, when compared to healthy controls. Healthy controls are skewed towards a morning chronotype (moderate morning range of 59-69) on the MEQ but the OSA-MCI group was neither morning nor evening types (intermediate range of 42-58). Eight patients from the OSA-MCI group reported taking antidepressants.

In regards to sleep architecture, healthy controls had notably more total sleep time and percentage of REM sleep than the OSA-MCI group but did not differ in percentage of N1, N2 and N3 during sleep. OSA severity in the OSA-MCI group ranged from mild to severe, with the mean representing moderate OSA severity. The OSA-MCI group experienced significantly more sleep fragmentation (i.e., arousal index and WASO) and hypoxemia (i.e., ODI ≥ 3% and time with SaO2mins <90%).
Table 2
Demographic and polysomnography data of the study sample (N=36)

<table>
<thead>
<tr>
<th></th>
<th>OSA-MCI</th>
<th>Healthy controls</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>18</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.72 (8.27)</td>
<td>63.28 (4.20)</td>
<td>2.03</td>
<td>0.050</td>
</tr>
<tr>
<td>BMI (kg/m²)**</td>
<td>30.37 (6.51)</td>
<td>23.66 (3.41)</td>
<td>3.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education (years)**</td>
<td>9.67 (3.45)</td>
<td>15.06 (3.95)</td>
<td>-4.36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESS*</td>
<td>9.83 (6.10)</td>
<td>4.39 (3.87)</td>
<td>3.19</td>
<td>0.002</td>
</tr>
<tr>
<td>PSQI*</td>
<td>7.33 (4.43)</td>
<td>4.56 (3.05)</td>
<td>2.19</td>
<td>0.036</td>
</tr>
<tr>
<td>HADS (D) **</td>
<td>5.78 (3.47)</td>
<td>1.56 (1.34)</td>
<td>4.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HADS (A) **</td>
<td>5.56 (3.20)</td>
<td>3.22 (1.87)</td>
<td>2.67</td>
<td>0.012</td>
</tr>
<tr>
<td>MEQ**</td>
<td>48.39 (11.13)</td>
<td>61.39 (7.11)</td>
<td>-4.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AHI (/h)**</td>
<td>25.61 (14.85)</td>
<td>4.27 (3.65)</td>
<td>5.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arousal index (/h)**</td>
<td>22.68 (12.07)</td>
<td>9.71 (4.49)</td>
<td>4.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WASO (min)**</td>
<td>138.52 (69.43)</td>
<td>49.33 (36.89)</td>
<td>4.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>time with SaO₂ min &lt; 90%*</td>
<td>53.38 (35.29)</td>
<td>24.76 (33.69)</td>
<td>2.49</td>
<td>0.018</td>
</tr>
<tr>
<td>Min SaO₂ (min)</td>
<td>83.50 (7.52)</td>
<td>87.66 (4.75)</td>
<td>-1.98</td>
<td>0.055</td>
</tr>
<tr>
<td>Sleep efficiency (%)*</td>
<td>61.96 (13.73)</td>
<td>83.06 (7.97)</td>
<td>-5.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total sleep time (min)*</td>
<td>375.97 (91.59)</td>
<td>456.33 (55.19)</td>
<td>-2.86</td>
<td>0.007</td>
</tr>
<tr>
<td>N1 (%)</td>
<td>22.74 (17.67)</td>
<td>14.16 (8.03)</td>
<td>1.88</td>
<td>0.069</td>
</tr>
<tr>
<td>N2 (%)</td>
<td>43.84 (12.18)</td>
<td>44.50 (8.39)</td>
<td>-0.19</td>
<td>0.851</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>19.75 (11.26)</td>
<td>22.14 (11.48)</td>
<td>-0.63</td>
<td>0.532</td>
</tr>
<tr>
<td>REM (%)*</td>
<td>13.42 (7.98)</td>
<td>19.74 (4.72)</td>
<td>-2.89</td>
<td>0.007</td>
</tr>
</tbody>
</table>

AHI, apnoea-hypopnoea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; HADS (A), Hospital Anxiety Depression Scale anxiety score; HADS (D), Hospital Anxiety Depression Scale depression score; MEQ, Morningness-Eveningness Questionnaire; N1, stage 1; N2, stage 2; N3, stage 3; REM, rapid eye movement stage; ODI, oxygen desaturation index; PSQI, Pittsburgh Sleep Quality Index; SaO₂, blood oxygen saturation; WASO, wake after sleep onset.

Note: *p < 0.05; **p < 0.001.
Table 3
Neuropsychological summary data for the OSA-MCI group (n=18)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global cognition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>25.54</td>
<td>3.76</td>
</tr>
<tr>
<td><strong>Logical memory (WMS-IV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical I</td>
<td>20.08</td>
<td>11.30</td>
</tr>
<tr>
<td>Logical II</td>
<td>11.08</td>
<td>8.72</td>
</tr>
<tr>
<td>Logical recognition</td>
<td>12.92</td>
<td>6.14</td>
</tr>
<tr>
<td><strong>Digit span (WMS-IV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>7.54</td>
<td>2.30</td>
</tr>
<tr>
<td>Backward</td>
<td>5.92</td>
<td>2.10</td>
</tr>
<tr>
<td>Sequence</td>
<td>4.69</td>
<td>2.43</td>
</tr>
<tr>
<td><strong>Rey-Osterrieth Complex Figure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>12.02</td>
<td>8.27</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>11.39</td>
<td>9.04</td>
</tr>
<tr>
<td><strong>WAIS-IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coding</td>
<td>31.15</td>
<td>19.30</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>15.00</td>
<td>8.56</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>21.69</td>
<td>11.59</td>
</tr>
<tr>
<td><strong>Trail Making Test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>98.04</td>
<td>46.03</td>
</tr>
<tr>
<td>TMT B</td>
<td>241.90</td>
<td>104.25</td>
</tr>
<tr>
<td><strong>Verbal Paired Associates (WMS-IV; n=13)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>20.38</td>
<td>10.43</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>5.69</td>
<td>3.23</td>
</tr>
<tr>
<td>Recognition</td>
<td>27.23</td>
<td>3.92</td>
</tr>
</tbody>
</table>

MMSE, Mini Mental State Examination; TMT; Trail Making Test; WAIS-IV, Weschler Adult Intelligence Scale –Fourth Edition.
Correlation analyses in OSA-MCI group

**OSA severity**

A Pearson’s correlational analysis in the OSA-MCI group between AHI and cognitive performance revealed significant associations between AHI, and (i) MMSE, \( r = -0.55, p = 0.019 \); and (ii) digit span (backwards), \( r = -0.58, p = 0.012 \). The correlations remained significant after controlling for age (MMSE, \( r = -0.65, p = 0.005 \); digit span backward; \( r = -0.54, p = 0.024 \)) and education (MMSE, \( r = -0.54, p = 0.027 \); digit span backward; \( r = -0.57, p = 0.018 \)), respectively. No significant association were observed between AHI and any other neuropsychological scores, \( p > 0.05 \).

In the OSA-MCI group, higher BMI was significantly correlated with higher AHI, \( r = -0.54, p = 0.021 \). No significant associations between AHI, and PSQI, ESS, HADS (D) and HADS (A) scores were observed (\( p > 0.05 \)).

**Hypoxia**

Pearson’s correlations between cognitive scores and indices of hypoxia, including ODI ≥ 3%, time spent SaO2 <90%, minimum SaO2, total number of apnoea/hypopnoea within 10-29 seconds and total number of apnoea/hypopnoea ≥30 seconds are presented in Table 4. Controlling for age, ODI ≥ 3% remained significantly correlated with MMSE scores, \( r = -0.59; p = 0.011 \) and digit span (backward) score, \( r = -0.57; p = 0.017 \). The relationships also remained significant after controlling for education (MMSE, \( r = -0.59; p < 0.001 \); DS backward, \( r = -0.49; p = 0.002 \)).

The majority of individuals in the OSA-MCI group had a greater percentage of apnoeas/hypopnoeas within 10-29 seconds (mean percentage of apnoea/hypopnoeas within 10-29 seconds = 80.87 ± 17.34%). Only two participants had almost equal ratio of apnoeas/hypopnoeas within 10-29 seconds and ≥30 seconds. After controlling for age, total number of apnoea/hypopnoea within 10-29 seconds remained significantly correlated with digit span (backward) scores, \( r = -0.57; p = 0.033 \). Albeit on trend, the correlation between total number of apnoea/hypopnoea within 10-29 seconds and digit span (backward) score did not remain significant after controlling for education, \( r = -0.52; p = 0.057 \).
Table 4
Correlation coefficients ($r$) between indices of hypoxia and cognitive scores for the OSA-MCI group (n=18)

<table>
<thead>
<tr>
<th></th>
<th>ODI $\geq$ 3%</th>
<th>SaO$_2$ $&lt;90%$</th>
<th>Min SaO$_2$</th>
<th>Total number of apnoea/hypopnoea based on length</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10-29 sec.</td>
</tr>
<tr>
<td>Global cognition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.50*</td>
<td>0.24</td>
<td>0.01</td>
<td>-0.46</td>
</tr>
<tr>
<td>Logical memory (WMS-IV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical I</td>
<td>-0.32</td>
<td>-0.08</td>
<td>0.03</td>
<td>-0.36</td>
</tr>
<tr>
<td>Logical II</td>
<td>-0.26</td>
<td>-0.04</td>
<td>0.22</td>
<td>-0.25</td>
</tr>
<tr>
<td>Logical recognition</td>
<td>-0.26</td>
<td>0.04</td>
<td>0.30</td>
<td>-0.12</td>
</tr>
<tr>
<td>Digit span (WMS-IV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>-0.43</td>
<td>-0.13</td>
<td>0.48</td>
<td>-0.14</td>
</tr>
<tr>
<td>Backward</td>
<td>-0.60*</td>
<td>-0.22</td>
<td>0.04</td>
<td>$-0.57^*$</td>
</tr>
<tr>
<td>Sequence</td>
<td>-0.29</td>
<td>-0.14</td>
<td>0.06</td>
<td>-0.32</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>-0.23</td>
<td>0.03</td>
<td>0.09</td>
<td>-0.32</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>-0.25</td>
<td>-0.04</td>
<td>0.23</td>
<td>-0.28</td>
</tr>
<tr>
<td>WAIS-IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coding</td>
<td>-0.31</td>
<td>-0.19</td>
<td>-0.07</td>
<td>-0.50</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>-0.23</td>
<td>-0.24</td>
<td>-0.17</td>
<td>-0.29</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>-0.17</td>
<td>0.12</td>
<td>0.21</td>
<td>-0.26</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>0.39</td>
<td>0.37</td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>TMT B</td>
<td>0.35</td>
<td>0.13</td>
<td>0.04</td>
<td>0.43</td>
</tr>
<tr>
<td>Verbal Paired Associates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(WMS-IV; n=13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>-0.27</td>
<td>-0.13</td>
<td>0.02</td>
<td>0.08</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>-0.45</td>
<td>-0.33</td>
<td>0.22</td>
<td>-0.05</td>
</tr>
<tr>
<td>Recognition</td>
<td>-0.27</td>
<td>0.01</td>
<td>-0.20</td>
<td>0.11</td>
</tr>
</tbody>
</table>

MMSE, Mini Mental State Examination; ODI, oxygen desaturation index; SaO$_2$, blood oxygen saturation; TMT, Trail Making Test; WAIS-IV, Weschler Adult Intelligence Scale – Fourth Edition.

Note: *$p$<0.05
Sleep fragmentation

Pearson’s correlations between cognitive scores and indices of sleep fragmentation, including arousal index and total wake time after sleep onset are presented in Table 5. No significant associations were observed (all \( p > 0.05 \)).

Table 5

Correlation coefficients \((r)\) between indices of sleep fragmentation and cognitive scores for the OSA-MCI group (n=18)

<table>
<thead>
<tr>
<th></th>
<th>AI</th>
<th>WASO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global cognition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.31</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Logical memory (WMS-IV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical I</td>
<td>-0.44</td>
<td>0.16</td>
</tr>
<tr>
<td>Logical II</td>
<td>-0.19</td>
<td>0.13</td>
</tr>
<tr>
<td>Logical recognition</td>
<td>-0.08</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Digit span (WMS-IV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>-0.16</td>
<td>0.27</td>
</tr>
<tr>
<td>Backward</td>
<td>-0.19</td>
<td>0.22</td>
</tr>
<tr>
<td>Sequence</td>
<td>-0.33</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Rey-Osterrieth Complex Figure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>-0.39</td>
<td>0.08</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>-0.29</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>WAIS-IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coding</td>
<td>-0.35</td>
<td>0.25</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>-0.24</td>
<td>0.15</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>-0.45</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Trail Making Test</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>0.26</td>
<td>-0.21</td>
</tr>
<tr>
<td>TMT B</td>
<td>0.41</td>
<td>-0.16</td>
</tr>
<tr>
<td><strong>Verbal Paired Associates (WMS-IV; n=13)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>-0.14</td>
<td>-0.13</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>-0.37</td>
<td>-0.11</td>
</tr>
<tr>
<td>Recognition</td>
<td>-0.20</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

AI, arousal index; MMSE, Mini Mental State Examination; TMT, Trail Making Test; WAIS-IV, Weschler Adult Intelligence Scale – Fourth Edition; WASO, wake after sleep onset.
**Sleep architecture**

Pearson’s correlations between cognitive scores and measures of sleep architecture, including sleep efficiency, sleep latency, and percentage of sleep time spent in N1, N2, N3 and REM are presented in Table 6. Controlling for age, percentage of sleep time spent in N3 remained significantly correlated with Logical I (immediate free recall; \( r=0.60; p=0.011 \)), Logical II (delayed free recall; \( r=0.68; p=0.003 \)), Logical recognition (\( r=0.51; p=0.035 \)), TMT A (\( r=-0.52; p=0.033 \)), VPA delayed recall (\( r=0.62; p=0.033 \)) and VPA recognition (\( r=0.84; p=0.001 \)). These relationships also remained significant after controlling for education (Logical I, \( r=0.64; p=0.006 \); Logical II, \( r=0.71; p=0.002 \); Logical recognition, \( r=0.56; p=0.023 \); TMT A, \( r=-0.59; p=0.012 \); VPA delayed recall, \( r=0.64; p=0.025 \); VPA recognition, \( r=0.82; p=0.001 \)).

Despite a trend, the percentage of sleep time spent in N3 was not statistically significantly correlated with MMSE (\( r=0.48; p=0.050 \)), RCFT immediate recall (\( r=0.43; p=0.087 \)) and Symbol Search (\( r=0.48; p=0.053 \)), after controlling for age.
Table 6
Correlation coefficient ($r$) between measures of sleep architecture and cognitive scores for the OSA-MCI group (n=18)

<table>
<thead>
<tr>
<th></th>
<th>Sleep efficiency</th>
<th>Sleep latency</th>
<th>N1 %</th>
<th>N2 %</th>
<th>N3 %</th>
<th>REM %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global cognition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.07</td>
<td>0.06</td>
<td>-0.37</td>
<td>0.04</td>
<td><strong>0.50</strong>*</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Logical memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>WMS-IV</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical I</td>
<td>0.08</td>
<td>-0.14</td>
<td>-0.45</td>
<td>0.17</td>
<td><strong>0.63</strong>*</td>
<td>-0.14</td>
</tr>
<tr>
<td>Logical II</td>
<td>-0.06</td>
<td>-0.25</td>
<td>-0.31</td>
<td>0.03</td>
<td><strong>0.70</strong>*</td>
<td>-0.32</td>
</tr>
<tr>
<td>Logical recognition</td>
<td>-0.06</td>
<td>-0.23</td>
<td>-0.16</td>
<td>0.002</td>
<td>= <strong>0.55</strong>*</td>
<td>-0.43</td>
</tr>
<tr>
<td><strong>Digit span (WMS-IV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>-0.01</td>
<td>0.08</td>
<td>0.08</td>
<td>-0.05</td>
<td>-0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Backward</td>
<td>0.07</td>
<td>0.10</td>
<td>-0.03</td>
<td>0.02</td>
<td>0.06</td>
<td>-0.07</td>
</tr>
<tr>
<td>Sequence</td>
<td>0.03</td>
<td>0.29</td>
<td>-0.17</td>
<td>-0.13</td>
<td>0.40</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>RCFT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>0.20</td>
<td>0.05</td>
<td>-0.42</td>
<td>0.14</td>
<td><strong>0.48</strong>*</td>
<td>0.02</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>0.13</td>
<td>0.09</td>
<td>-0.39</td>
<td>0.17</td>
<td>0.45</td>
<td>-0.03</td>
</tr>
<tr>
<td><strong>WAIS-IV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coding</td>
<td>-0.05</td>
<td>0.17</td>
<td>-0.16</td>
<td>-0.17</td>
<td>0.44</td>
<td>0.02</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>0.01</td>
<td>0.17</td>
<td>-0.09</td>
<td>-0.31</td>
<td><strong>0.52</strong>*</td>
<td>0.06</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>0.08</td>
<td>0.23</td>
<td>-0.30</td>
<td>-0.01</td>
<td>0.41</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Trail Making Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>-0.21</td>
<td>0.08</td>
<td>0.20</td>
<td>0.28</td>
<td><strong>-0.55</strong>*</td>
<td>-0.11</td>
</tr>
<tr>
<td>TMT B</td>
<td>-0.17</td>
<td>-0.15</td>
<td>0.26</td>
<td>0.14</td>
<td>-0.45</td>
<td>-0.19</td>
</tr>
<tr>
<td><strong>VPA (WMS-IV; n=13)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>0.03</td>
<td>-0.09</td>
<td>-0.004</td>
<td>-0.12</td>
<td>0.54</td>
<td>-0.11</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>0.26</td>
<td>-0.21</td>
<td>-0.08</td>
<td>-0.17</td>
<td><strong>0.60</strong>*</td>
<td>-0.04</td>
</tr>
<tr>
<td>Recognition</td>
<td>0.11</td>
<td>-0.18</td>
<td>0.07</td>
<td>-0.37</td>
<td><strong>0.78</strong>*</td>
<td>-0.16</td>
</tr>
</tbody>
</table>

MMSE, Mini Mental State Examination; N1, stage 1; N2, stage 2; N3, stage 3; REM, rapid eye movement stage; RCFT, Rey-Osterrieth Complex Figure Test; TMT, Trail Making Test; VPA, Verbal Paired Associates; WAIS-IV, Weschler Adult Intelligence Scale –Fourth Edition.

*Note: *$p<0.05$; *#*$p=0.058
Subjective sleep measures

Pearson’s correlations between cognitive scores and subjective sleep measures, including PSQI and ESS scores, are presented in Table 7. No significant associations were observed (all \( p > 0.05 \)).

Table 7
Correlation coefficients (\( r \)) between subjective sleep measures and cognitive scores for the OSA-MCI group (n=18)

<table>
<thead>
<tr>
<th></th>
<th>PSQI</th>
<th>ESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>0.08</td>
<td>-0.14</td>
</tr>
<tr>
<td>Logical memory (WMS-IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical I</td>
<td>0.32</td>
<td>0.02</td>
</tr>
<tr>
<td>Logical II</td>
<td>0.33</td>
<td>-0.15</td>
</tr>
<tr>
<td>Logical recognition</td>
<td>0.25</td>
<td>-0.08</td>
</tr>
<tr>
<td>Digit span (WMS-IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forward</td>
<td>-0.44</td>
<td>-0.29</td>
</tr>
<tr>
<td>Backward</td>
<td>-0.35</td>
<td>-0.39</td>
</tr>
<tr>
<td>Sequence</td>
<td>0.06</td>
<td>-0.11</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>0.36</td>
<td>0.09</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>0.38</td>
<td>0.06</td>
</tr>
<tr>
<td>WAIS-IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coding</td>
<td>0.08</td>
<td>-0.34</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>0.02</td>
<td>-0.38</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>0.16</td>
<td>-0.03</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>-0.18</td>
<td>0.15</td>
</tr>
<tr>
<td>TMT B</td>
<td>-0.09</td>
<td>0.11</td>
</tr>
<tr>
<td>Verbal Paired Associates (WMS-IV; n=13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>0.11</td>
<td>-0.38</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>0.18</td>
<td>-0.37</td>
</tr>
<tr>
<td>Recognition</td>
<td>0.14</td>
<td>-0.44</td>
</tr>
</tbody>
</table>

ESS, Epworth Sleepiness Scale; MMSE, Mini Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; TMT, Trail Making Test; WAIS-IV, Weschler Adult Intelligence Scale–Fourth Edition.
Between group comparison (OSA-MCI, MCI-only and healthy controls)

The demographic and neuropsychological data for each group (OSA-MCI, MCI-only and healthy controls) are presented in Table 8. There were no significant differences in age between the three groups and a chi-squared test indicated no significant difference in gender distribution between the three groups, \( \chi^2(2,56)=3.69, p=0.16 \). Individuals with OSA and MCI had significantly more anxiety symptoms than those with MCI-only and healthy controls. Both OSA-MCI and MCI groups had significantly higher depressive symptoms, and lower test scores on the MMSE, Logical Memory, Digit Span and Rey-Osterrieth Complex Figure than age-matched healthy controls. Although not statistically significant, the OSA-MCI group scored 2.36 points lower than the MCI group on the digit span task.

The OSA-MCI group performed significantly worst in Digit-Symbol Coding compared to the MCI-only group and healthy controls. While the MCI-only group performed significantly better than the OSA-MCI group, they performed significantly more poorly than healthy controls.
Table 8
Demographic and neuropsychological summary data of OSA-MCI, MCI-only and healthy control groups (N=56)

<table>
<thead>
<tr>
<th></th>
<th>OSA-MCI</th>
<th>MCI-only</th>
<th>Healthy controls</th>
<th>F</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18</td>
<td>20</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>67.72 (4.83)</td>
<td>67.90 (6.55)</td>
<td>63.28 (4.20)</td>
<td>2.93</td>
<td>0.062</td>
<td>0.10</td>
</tr>
<tr>
<td>Education</td>
<td>9.67 (3.45)</td>
<td>11.90 (3.22)</td>
<td>15.26 (3.94)</td>
<td>11.72</td>
<td>&lt;0.001</td>
<td>0.30</td>
</tr>
<tr>
<td>HADS (D)</td>
<td>5.78 (3.47)</td>
<td>5.00 (2.64)</td>
<td>1.56 (1.34)</td>
<td>14.15</td>
<td>&lt;0.001</td>
<td>0.34</td>
</tr>
<tr>
<td>HADS (A)</td>
<td>5.56 (3.20)</td>
<td>3.05 (2.11)</td>
<td>3.22 (1.87)</td>
<td>6.35</td>
<td>0.003</td>
<td>0.19</td>
</tr>
<tr>
<td>MMSE</td>
<td>25.17 (3.47)</td>
<td>25.55 (1.93)</td>
<td>29.83 (0.38)</td>
<td>23.35</td>
<td>&lt;0.001</td>
<td>0.47</td>
</tr>
<tr>
<td>LM I</td>
<td>6.22 (4.43)</td>
<td>8.05 (4.86)</td>
<td>14.11 (3.23)</td>
<td>17.77</td>
<td>&lt;0.001</td>
<td>0.40</td>
</tr>
<tr>
<td>LM II</td>
<td>5.11 (4.51)</td>
<td>5.55 (5.14)</td>
<td>13.26 (3.23)</td>
<td>20.79</td>
<td>&lt;0.001</td>
<td>0.44</td>
</tr>
<tr>
<td>DS forward + backward</td>
<td>13.94 (3.47)</td>
<td>16.30 (2.96)</td>
<td>20.50 (4.18)</td>
<td>15.79</td>
<td>&lt;0.001</td>
<td>0.37</td>
</tr>
<tr>
<td>Coding</td>
<td>29.06 (17.27)</td>
<td>51.15 (16.79)</td>
<td>72.33 (11.29)</td>
<td>35.47</td>
<td>&lt;0.001</td>
<td>0.57</td>
</tr>
<tr>
<td>RCFT copy</td>
<td>25.25 (10.82)</td>
<td>26.15 (6.70)</td>
<td>34.28 (3.03)</td>
<td>7.97</td>
<td>0.001</td>
<td>0.23</td>
</tr>
<tr>
<td>RCFT copy time (sec)</td>
<td>189.70 (102.25)</td>
<td>167.27 (85.72)</td>
<td>135.07 (68.17)</td>
<td>1.82</td>
<td>0.173</td>
<td>0.06</td>
</tr>
<tr>
<td>RCFT (immediate)</td>
<td>10.99 (7.79)</td>
<td>9.95 (5.83)</td>
<td>22.79 (7.02)</td>
<td>18.46</td>
<td>&lt;0.001</td>
<td>0.41</td>
</tr>
<tr>
<td>RCFT (delayed)</td>
<td>10.19 (8.69)</td>
<td>10.33 (6.45)</td>
<td>21.64 (7.29)</td>
<td>14.05</td>
<td>&lt;0.001</td>
<td>0.35</td>
</tr>
</tbody>
</table>

DS, Digit Span; HADS (D), Hospital Anxiety Depression Scale depression score; HADS (A), Hospital Anxiety Depression Scale anxiety score; MMSE, Mini Mental State Examination; RCFT, Rey-Osterrieth Complex Figure Test.

Note: *p<0.05 between OSA-MCI and MCI-only groups; † p<0.05 between OSA-MCI and healthy control groups; ‡ p<0.05 between MCI-only and healthy control group. All significant main effect remained significant after controlling for age and education, except RCFT copy.
Discussion

The current study examined the relationships between different OSA indices and cognitive performance in patients with comorbid OSA and MCI. Furthermore, the study also investigated the difference in cognitive performance and mood between MCI patients with and without OSA in a subset of cognitive domains. There were three main findings.

First, the present study demonstrated that increased OSA severity, as measured by AHI, was significantly associated with poorer global cognition and working memory performance in patients with comorbid OSA and MCI. Second, the current study found impairments in global cognition and working memory were significantly and positively correlated with a measure of intermittent hypoxia (i.e., ODI ≥ 3%), but not with sleep fragmentation (i.e., AI and WASO) or subjective sleep measures (i.e., PSQI and ESS). In addition, lower percentage time spent in SWS was significantly linked to poorer verbal memory, and impaired processing speed and attention, after controlling for age. Third, MCI patients with OSA had significantly more anxiety symptoms and poorer processing speed and attentional performance when compared to MCI patients without OSA, or with age-matched healthy controls.

OSA severity and cognitive performance in OSA-MCI patients

After controlling for age, the current findings demonstrated a link between increased OSA severity, as measured by AHI, and poorer global cognitive functioning in individuals with OSA and MCI. This finding is consistent with previous studies that have reported links between OSA severity and global cognitive decline in older population (Cohen-Zion et al., 2004; Yaffe et al., 2011). Findings from the current study adds to the literature by extending this relationship to older adults with MCI and comorbid OSA.

The present study found that increased AHI was significantly associated with poorer working memory performance, as assessed by the digit span (backward) test, after controlling for age and education. Working memory is a cognitive system that provides short-term storage and simultaneous processing/manipulation of information over a brief period of time (Baddeley, 1992). The current findings are consistent with reports that OSA patients perform notably poorer and slower in working memory tasks when compared to age-matched healthy controls.
(D’Rozario et al., 2018; Dalmases et al., 2015; Lis, et al., 2008; Thomas, Rosen, Stern, Weiss & Kwong, 2005). Independently, working memory has been previously shown to be impaired in patients with MCI and dementia (Belleville, Chertkow & Gauthier, 2007; Gagnon & Belleville, 2011). Since a high proportion of MCI and dementia patients have comorbid OSA (Emamian et al., 2016; Guarnieri et al., 2012), the findings from the current study suggest that OSA severity may contribute to the working memory deficits observed in some MCI patients.

Besides global cognition and working memory, the current study found no significant links between OSA severity and other aspects of cognition, including verbal memory, visual memory, attention and processing speed. This finding is inconsistent with studies that have found links between OSA severity, and verbal memory, attention and processing speed (Gagnon et al., 2014; Twigg et al., 2010). While it is possible that OSA does not play a role in the impairment of these cognitive domains in the context of MCI, it may also reflect the study’s small and heterogeneous sample. Further larger studies may benefit from categorising MCI patients into their respective subtypes. However, it should be noted that AHI may not provide a reliable reflection of the underlying pathophysiology of patients. For example, different patients may have differing apnoea lengths or oxygen desaturations but have the same AHI, and not all apnoeas are accompanied by arousals. Consistent with this, correlational analyses from the current study revealed that working memory performance in patients with comorbid OSA and MCI was significantly associated with the total number of apnoeas/hypopnoeas within 10-29 seconds but not the total number of apnoeas/hypopnoeas greater or equal to 30 seconds. Besides this, the current study did not take in account the apolipoprotein E (APOE) e4 allele which has been shown to be a major genetic risk factor for AD (Liu, Kanekiyo, Xu & Bu, 2013). Higher severity of OSA has been linked with poorer memory and executive functioning in carriers of the APOE e4 allele but this was not observed in non-carriers (Nikodemova, Fin, Mignot, Salzieder & Peppard, 2013; O’Hara et al., 2005).

**Different aspects of OSA and cognitive performance in OSA-MCI patients**

The current study was also interested in exploring the basis of OSA’s (i.e., hypoxia, sleep fragmentation and subjective sleep measures) contribution to cognitive deficits in MCI. Consistent with Yaffe and colleagues (2011) who suggested hypoxia to be a likely
mechanism for the relationship between SDB and risk of MCI/dementia, correlational analyses from the current study revealed that a measure of intermittent hypoxia, ODI ≥ 3% was significantly associated with poorer global cognition and impaired working memory performance. These findings are also in line with Blackwell et al. (2015) who reported that increased ODI was significantly associated with greater global cognitive decline in older adults. Animal studies have detected notable neurological impairment after prolonged exposure to intermittent hypoxia (Gozal, Daniel & Dohanich, 2001; Snyder, Shell, Cunningham & Cunningham, 2017; Xu et al., 2004) while imaging studies of OSA patients have observed functional changes in the brain, and injury of the grey and white matter (Macey et al., 2002; Thomas, Rosen, Stern, Weiss & Kwong, 2005; Yeung, 2019). The current findings suggest that global cognition and working memory deficits in patients with comorbid OSA and MCI may be attributed to intermittent hypoxia, rather than sleep fragmentation or subjective sleep measures (i.e., daytime sleepiness and sleep quality).

Further correlational analyses revealed that poorer performance on tests measuring verbal memory, and attention and processing speed were significantly linked with lower percentage of sleep time spent in SWS in the OSA-MCI group. This is consistent with studies that have demonstrated a significant association between decreased SWS, and poorer verbal memory (Backhaus et al., 2007) and processing speed performance (Della Monica, Johnsen, Atzori, Groeger & Dijk, 2018). SWS is characterised by slow wave activity, which includes activities within the 0.75-4.5 Hz frequency range, and has been shown to be vital to memory consolidation and learning (Born, 2010; Varga et al., 2016; Walker, 2009). While previous studies that examined the role of OSA in cognitive impairment have mainly focused on intermittent hypoxia and sleep fragmentation (Champod et al., 2013; Blackwell et al., 2015; Yaffe et al., 2011), the current findings highlight the importance of including sleep architecture, in particular SWS, as a potential mechanistic pathway. Nonetheless, inconsistent with previous studies (Ferrarelli et al., 2019; Wilckens, Hall, Nebes, Monk & Buysse, 2016), the current study did not observe an association between working memory and percentage of time spent in SWS. As the association was previously observed in healthy adults and older adults with insomnia, it is possible that the additional consequences of OSA, such as intermittent hypoxia which the current findings showed to be strongly correlated with working memory performance, may influence the nature of the relationship between working memory and SWS.
Difference in cognition and mood between MCI patients with and without OSA

The current study also demonstrated a difference in processing speed and attentional deficits across the three groups, where MCI patients with OSA performed the worst, followed by OSA patients without MCI and then age-matched healthy controls. This is consistent with previous studies that have reported significant impairments in processing speed and attention in OSA patients compared to healthy controls (Saunamäki, Jehkonen, Huupponen, Polo & Himanen, 2009; Sharma et al., 2010; Verstraeten, Cluydts, Pevernage & Hoffmann, 2004). Similarly, processing speed has been shown to be impaired in patients with MCI (Gualtieri & Johnson, 2005). The current finding highlights the additional burden that OSA places on the processing speed and attention of MCI patients.

Besides a decline in cognitive processing speed, this may have implications on other aspects of cognition such as working memory. Processing speed has been reported to be a significant predictor of working memory performance in older adults, and it has been suggested that speed of encoding or rate of rehearsal may be possible reasons for the working memory deficits observed (Brown, Brockmole, Gow & Deary, 2012; Caplan & Waters, 2005). This suggestion is consistent with a post hoc correlational analysis in the current study which revealed a significant association between performance on the digit-symbol coding and digit span (backward) tasks in individuals with MCI and OSA ($r=0.54; p=0.020$). While this should have been reflected in the digit span task, no statistically significant difference was observed in the combined digit span scores between the OSA-MCI and MCI groups. It should however be noted that the digit span forward and backward scores obtained from the AIBL study were combined to obtain a total digit span score; thus the current results may not be a sensitive measure of working memory as the digit span backward task places greater demands on working memory than the forward subtest (Wilde & Strauss, 2002). While there is a large overlap in the functional neural system during the forward and backward tasks, the backward subtest produced significantly greater activation in areas associated with working memory, and additionally recruited areas that further subserve working memory including the bilateral dorsolateral prefrontal cortex, left inferior parietal lobule and Broca’s area (Gerton et al., 2004).

Regarding mood, individuals with comorbid OSA and MCI had significantly more anxiety symptoms than MCI patients without OSA and healthy controls, while no difference in
anxiety symptoms were observed between MCI patients without OSA and healthy controls. This finding is in line with studies that have reported a higher incidence of anxiety in OSA patients than in healthy controls (Sharafkhaneh, Giray, Richardson, Young & Hirshkowitz, 2005), but is inconsistent with studies that have reported higher rates of anxiety in MCI patients than age-matched controls (Forsell, Palmer & Fratiglioni, 2003; Van der Mussele et al., 2013). This difference may be due to the fact that the current study differentiated between MCI patients with and without comorbid OSA, whereas previous studies of anxiety in MCI have not. Given the high rate of comorbid OSA in patients with MCI (Guarnieri et al., 2012), it seems likely from the present results that the elevated anxiety levels reported in MCI may be associated with the presence of OSA. However, it should be noted that the current study sample had relatively low anxiety and depressive symptoms, and all groups sit below the cut-off point for clinically significant anxiety (Bjelland, Dahl, Haug & Neckelmann, 2002).

**Limitations**

There are some limitations that must be considered when interpreting findings from the current study. For instance, it is not known how long our patients have had OSA, and this is important because if OSA has a cumulative effect on cognitive function, the duration of OSA will be a significant variable. While it is possible that individuals with earlier onset may learn to adapt to the chronic sleep fragmentation, this may not be the case for hypoxia (Bonnet, 1989; Canessa & Ferini-Strambi, 2011). The cumulative effect of intermittent hypoxia during sleep has been shown to increase oxidative stress and inflammation in the brain (Row, 2007), and it is possible for individuals with an earlier onset of severe untreated OSA to have the greatest risk of future cognitive decline.

A second consideration is that due to the cross-sectional nature of the experimental design, the current study cannot make any causal inferences. While the current findings provide an indication of which variables are correlated with each other, longitudinal studies and interventional studies are needed to determine the mechanistic basis of the associations found in the present study.

Another limitation of the current study is the assessment criteria of MCI utilised. The current study employed a more liberal cut-off of 1 SD below the age-matched norm than the 1.5 SD cut-off score suggested by Petersen (2004). While this may result in the recruitment of
patients with MCI not necessarily due to AD, this was similarly done in several other studies (Crowell, Luis, Vanderploeg, Schinka & Mullan, 2002; Donix et al., 2010; Zhang, Han, Verhaeghen & Nilsson, 2007) to include patients in the early stages of cognitive impairment and to capture a wider group of individuals along the continuum. The current study also did not exclude participants with a MMSE score of less than 24. Five participants had a MMSE score below 24. Data was reanalysed excluding these participants and similar findings were reported for the correlational and between-group analyses except MMSE was not significantly associated with AHI and ODI ≤3%, and percentage of time spent in SWS was not significantly correlated to RCFT immediate recall and TMT A. While a MMSE score of less than 24 may be an indicator of dementia, participants in the current study were excluded if they had a dementia diagnosis. A further limitation is the lack of clinical sleep studies for the MCI patients obtained from the AIBL study. All individuals were screened for existing or current sleep disorders prior to enrolment into the AIBL study, however the individuals may have had sleep disturbances or undiagnosed sleep disorders. Given the widely reported links between sleep and cognition, future studies examining cognition in healthy adults or clinical populations should consider including sleep questionnaires, such as the PSQI or STOP-Bang questionnaire to gauge the subjective sleep quality or risk of OSA of the study sample.

Besides that, it should be noted that the MCI patients obtained from the AIBL study underwent different recruitment procedure and methodology from participants recruited for the current study. For instance, AIBL participants underwent a more extensive screening and assessment, including blood tests and brain imaging. The AIBL study excluded participants with significant current depression while participants recruited for the current study were not excluded based on depressive symptoms. Nevertheless, participants from the AIBL study have comparable levels of depressive and anxiety symptoms, age, education level and gender to the OSA-MCI group from the current study. Finally, antidepressant intake in participants was not controlled for. Eight participants from the OSA-MCI group were on antidepressant medication. Furthermore, the OSA-MCI group had significantly elevated depression scores on the HADS when compared to healthy controls. Depression in patients with MCI has been reported to increase the risk of developing AD, specifically those with poor response to antidepressants (Gabryelewicz et al., 2007; Gracia-Gracia et al., 2015; Modrego & Ferrandez, 2004). While HADS depression scores did not appear to correlate with any of the cognitive performance in the OSA-MCI group, future studies may benefit from examining the role of both depression and sleep apnoea on cognitive decline.
Conclusions

The present study demonstrated a significant association between OSA severity, and global cognition and working memory in patients with comorbid OSA and MCI. Furthermore, intermittent hypoxia but not sleep fragmentation appears to be linked with deficits in both cognitive functions. In addition, lower percentage of time spent in SWS was significantly associated with poorer verbal memory, and processing speed and attention in individuals with OSA and MCI. Finally, MCI patients with OSA had significantly more anxiety symptoms and poorer processing speed and attention performance than MCI patients without OSA and age-matched healthy controls. As treatment studies in OSA patients have observed partial reversibility in cognitive deficits, a randomised-control trial of CPAP in this patient population may help identify aspects of cognition that can benefit from targeting sleep apnoea in treatment.
Chapter 5

Efficacy of three months of continuous positive airway pressure therapy on cognition and mood in patients with comorbid obstructive sleep apnoea and mild cognitive impairment

Preface

Chapter 4 reported significant associations between OSA and several cognitive domains (e.g., global cognition and working memory) in patients with comorbid OSA and MCI. Furthermore, MCI patients with comorbid OSA had significantly more anxiety symptoms, and poorer processing speed and attention performance when compared to MCI patients without OSA, or with age-matched healthy controls. Following this, the current chapter investigates if treatment of OSA in individuals with comorbid MCI can improve these cognitive domains. The study reported in this chapter investigated the efficacy of three months of CPAP therapy on cognitive performance and mood (i.e. depressive and anxiety symptoms) in patients with comorbid OSA and MCI.

Candidate’s contribution

The candidate obtained ethics approval for the COMM study. The candidate collected and analysed all data for this study. The candidate also formulated and wrote the chapter.
Abstract

Recent findings suggest that individuals at an earlier stage of cognitive impairment might benefit from CPAP use, and that CPAP therapy has the potential to slow age of onset in mild cognitive impairment (MCI) patients. While several CPAP trial studies have been conducted with Alzheimer’s disease patients, limited studies have examined the effects of CPAP therapy on cognitive performance and mood in MCI patients. Accordingly, the current study aimed to investigate the efficacy of three months of continuous positive airway pressure (CPAP) therapy on cognitive performance and mood in patients with comorbid obstructive sleep apnoea (OSA) and mild MCI. Eight OSA patients with MCI (63.8 ± 10.7 years, two females) completed a randomised, controlled partial crossover trial of three months of CPAP therapy. Four participants were randomly assigned to start CPAP immediately while the other four participants were put on a three-month waitlist, and then completed three months of CPAP therapy. Prior to starting the trial and again after three months of CPAP or waitlist, all participants completed a 90-minute neuropsychological test-battery, and a set of mood and sleep questionnaires. The waitlist group completed another set of test-battery and questionnaires following the completion of CPAP therapy. The immediate CPAP group showed a trend of improvement in global cognition, subjective daytime sleepiness, subjective sleep quality and depressive symptoms while the waitlist group showed a trend of deterioration. When the results from all study participants were examined, they indicated that three months of CPAP therapy significantly improved global cognition, logical memory free recall, specific autobiographical memory recall and subjective daytime sleepiness. Further correlational analyses revealed that greater improvements in depressive and anxiety symptoms were linked with better CPAP adherence. Although these findings need to be validated in a larger study, these preliminary findings suggest that CPAP therapy has the potential to be used as a treatment option to improve cognitive functioning, by elevating the impact of OSA on cognition, in a subset of MCI patients that have OSA.
Obstructive sleep apnoea (OSA) is frequently reported in patients with MCI and dementia, with sleep-disordered breathing present in up to 59% of MCI patients and 54% of patients with AD (Guarnieri et al., 2012). Recently, OSA has been identified as a risk factor for the development of MCI and dementia (Chang et al., 2013; Lutsey et al., 2018; Yaffe et al. 2011). A longitudinal study following 298 elderly women for approximately 4.7 years revealed that women with OSA had a higher risk of developing MCI or dementia (44.8%), compared to those without OSA (31.3%) (Yaffe et al., 2011). Chang and colleagues (2013) reported that sleep apnoea patients have 1.7 times the risk of developing dementia within five years of OSA diagnosis compared to those without sleep apnoea.

The effects of untreated OSA on cognition and mood has been widely reported in the literature. Untreated OSA has been associated with impaired verbal memory (Naegele et al., 2011; Stranks & Crowe, 2016; Twigg et al., 2010), visual memory (Bédard et al., 1991; Berry et al., 1990; Olaithé, Bucks, Hillman & Eastwood, 2018), autobiographical memory (Lee et al., 2016), executive function (see Olaithé & Bucks, 2013 and Saunamäki & Jehkonen, 2007 for review), attention/vigilance (D’Rozario et al., 2018; Luz et al., 2016; Mazza et al., 2005) and mood disturbances (Aloia et al., 2005; Lehto et al., 2012). Nevertheless, only a few studies have examined the effect of untreated OSA on cognition and mood in MCI patients. Besides general cognitive decline, OSA has been linked to poorer nighttime driving performance, slower processing speed and impaired language functioning in MCI patients (Cross et al., 2017; Kim et al., 2011; Terpening et al., 2015). Adding to the literature, findings from the previous chapter (see Chapter 4) demonstrated significant associations between sleep apnoea severity, and (i) global cognition as measured by the Mini Mental State Examination (MMSE); and (ii) working memory as measured by the Digit Span (backwards) in patients with comorbid OSA and MCI.

Continuous positive airway pressure (CPAP) therapy is the most effective treatment of OSA (American Academy of Sleep Medicine, 2009; Ballester et al., 1999). Besides improvement to objective sleep measures (Cochrane Review, 2008), CPAP therapy can improve daytime sleepiness, quality of life, cognition and mood in OSA patients (Giles et al. 2008, Ferini-Strambi, Marelli, Galbiati & Castronovo, 2013; Sánchez, Martínez, Miró, Bardwell & Beula-Casal, 2009; Serrano Merino et al., 2018). In older adults, consistent CPAP usage successfully maintained memory performance over 10 years while deterioration was observed in untreated OSA patients (Crawford-Archour, 2015). As the pathogenesis of
cognitive impairment in OSA patients is still debated, with some studies attributing impairments to sleep fragmentation (Ayalon et al., 2009; Daurat, Foret, Bret-Dibat, Fureix & Tiberge, 2008; Djonlagic, Saboisky, Carusona, Stickgold & Malhotra, 2012) and some highlighting the contribution of nocturnal intermittent hypoxia (Champod et al., 2013; Ferini-Strambi et al., 2003; Yaffe et al., 2011), the mechanism of CPAP’s contribution to the reversibility of these impairments is unclear.

Neuroimaging studies in OSA patients have revealed significant impairment in several brain regions including the hippocampus, parietal cortex and prefrontal cortex (Canessa et al., 2011; Macey et al., 2008; O’Donoghue et al., 2012; Shi et al., 2017; Torelli et al., 2011; Yaouhi et al., 2009). In line with this, animal studies have reported similar hypoxia-related brain injury following exposure to chronic episodic hypoxia (Gozal, Row, Schurr & Gozal, 2001; Snyder, Shell, Cunningham & Cunningham, 2017; Xu et al., 2004). Continual CPAP usage over a 3-month period has been shown to improve neurocognitive functioning that paralleled grey matter increase in hippocampal and frontal regions, increased connectivity within the default mode network and decreased cortical thinning (Canessa et al., 2011; Dalmases et al., 2015), suggesting that CPAP therapy, through the reduction of hypoxia, has the potential to partially reverse structural and functional brain impairment related to OSA. Nevertheless, studies have also reported a lack of change in brain structure and function after six months of CPAP therapy (O’Donoghue et al., 2005; O’Donoghue et al., 2012).

Another possible explanation for the positive benefits of CPAP on cognition and mood may be attributed to the decrease of excessive daytime sleepiness and the disruption of sleep through reduction of sleep fragmentation. Sleep fragmentation has been linked to the excessive daytime sleepiness experienced in OSA patients (Zhou, Camacho, Tang & Kushida, 2016), and correspondingly, increased daytime sleepiness in OSA patients have been linked to poorer cognitive performance such as executive functioning (Naimsmith, Winter, Gotsopoulos, Hickie & Cistulli, 2004), sustained attention (Ferini-Strambi et al., 2003) and driving performance (Dinges, 1998; Howard et al., 2004). Outside of the OSA literature, excessive daytime sleepiness has been identified as a significant predictor for further cognitive decline in the elderly population (Foley et al., 2001; Gabelle et al., 2017; Jaussent et al., 2012; Merlino et al., 2010). For example, a community-based longitudinal study (Foley et al., 2001) following 2,346 Japanese-American men aged 71 to 93 years reported that individuals who reported excessive daytime sleepiness at baseline had twice the
risk of being diagnosed with dementia and were 40% more likely to have significant cognitive decline over three years. CPAP therapy has been shown to be effective at reducing daytime sleepiness, specifically subjective daytime sleepiness (Bhat et al., 2018; Sánchez, Martínez, Miró, Bardwell & Buela-Casal, 2009).

Given that findings on the effects of CPAP therapy on cognitive functioning and mood in OSA patients are promising and that OSA has been associated with an increased risk of further cognitive decline (Leng, McEvoy, Allen & Yaffe, 2017; Yaffe et al., 2011), recent studies have begun exploring the potential applications of CPAP therapy in OSA patients with Alzheimer’s disease (AD). Late-onset AD is the most common subtype of dementia with one in 10 people aged 65 years or older in the United States living with AD and up to 24.3 million individuals worldwide reported to be living with AD (Alzheimer’s Association, 2018; Ferri et al., 2005). While drug interventions such as cholinesterase inhibitors have been shown to be beneficial to cognitive symptoms of AD (Hampel et al., 2018; Schelterns & Feldman 2003), there is no known cure. Accordingly, any treatment that can potentially reduce even a portion of the burden of dementia should be further researched.

To date, five studies have examined the treatment benefits of CPAP in patients with comorbid OSA and AD (see Table 1; Ancoli-Israel et al., 2008; Ayalon et al., 2006; Chong et al., 2006; Cooke et al., 2009; Troussiere et al., 2014). Four of the five studies were conducted by the same research group. Three studies utilised a randomised controlled 3-week CPAP trial (therapeutic CPAP or sham CPAP) and reported an improvement in subjective daytime sleepiness, objective sleep measures and cognitive performance (Ancoli-Israel et al., 2008; Chong et al., 2006; Cooke et al., 2009). Ten patients from the Ancoli-Israel et al. (2008) study were followed-up to investigate the effect of long-term CPAP use on cognition and mood (Cooke et al., 2009). OSA and AD patients who continued using CPAP for up to 13 months displayed less deterioration of executive functioning, processing speed and depressive symptoms. The most recent study (Troussière et al., 2014) from a different research group revealed that individuals who used CPAP for approximately three years had a significantly slower global cognitive decline compared to those who did not use CPAP.

With an emphasis placed on early diagnosis and intervention in dementia, the use of CPAP therapy as secondary treatment during the prodromal stage of AD may potentially be more beneficial in delaying cognitive decline. A high proportion of MCI patients do progress to
AD with an annual conversion rate of 8% to 28% (Fischer et al., 2007; Petersen, 2016; Schmidtke & Hermeneit, 2008) and non-pharmacological intervention in this group of individuals have been reported to be promising (see Teixeira et al., 2012 for review). Given the reported benefits of CPAP therapy in patients with AD, targeting MCI patients can be greatly beneficial in slowing down the progression of cognitive decline. Accordingly, the current study aimed to investigate the efficacy of three months of CPAP therapy on cognitive performance and mood (i.e., depressive and anxiety symptoms) in patients with comorbid OSA and MCI.
<table>
<thead>
<tr>
<th>Author</th>
<th>Sample Description</th>
<th>Age (years)/gender</th>
<th>CPAP length</th>
<th>CPAP adherence (hrs/night)</th>
<th>Method</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancoli-Israel et al. (2008)</td>
<td>52 with mild to moderate AD and OSA</td>
<td>tCPAP (n=27)</td>
<td>3-6 weeks</td>
<td>tCPAP 5.8 ±2.1</td>
<td>Participants were randomized into 6 weeks of tCPAP or 3 weeks of placebo pCPAP followed by 3 weeks of tCPAP. Neuropsychological tests were conducted at baseline, and after 3 and 6 weeks of CPAP use.</td>
<td>A composite neuropsychological score was calculated from the test-battery. No difference in change in composite score between tCPAP and pCPAP groups however, significant improvements were reported after 3 weeks of tCPAP for both groups. Individually, significant improvements were observed in HVLT-R and TMT B after 3 weeks of tCPAP for both groups.</td>
</tr>
<tr>
<td>Ayalon et al. (2006)</td>
<td>33 with mild to moderate AD and OSA</td>
<td>78.4 ±6.8 (10 female)</td>
<td>3-6 weeks</td>
<td>4.8 ±2.0</td>
<td>Participants were randomized into 6 weeks of tCPAP or 3 weeks of placebo pCPAP followed by 3 weeks of tCPAP. A set of questionnaires were completed by participants at baseline, and after 3 and 6 weeks of CPAP use. Following a mean of 4.8 months after initial CPAP trial, telephone follow-up sessions were conducted.</td>
<td>Individuals with fewer depressive symptoms, as measured by the CSD, had better CPAP adherence. However, no difference in depressive symptoms was reported between both groups after 3 weeks. Participants that continued CPAP following the trial have significantly fewer depressive symptoms and higher CPAP adherence during the initial 3-week treatment than those that did not continue.</td>
</tr>
<tr>
<td>Chong et al. (2006)</td>
<td>39 with mild to moderate AD and OSA</td>
<td>78.0 ±7.04 (10 female)</td>
<td>3-6 weeks</td>
<td>Not reported</td>
<td>Participants were randomized into 6 weeks of tCPAP or 3 weeks of placebo pCPAP followed by 3 weeks of tCPAP. Subjective sleepiness was measured using the ESS at baseline, and after 3 and 6 weeks of CPAP use.</td>
<td>tCPAP group reported significantly decreased daytime sleepiness after 3 weeks of CPAP and further decrease after 6 weeks of CPAP. No improvements were observed in the pCPAP group following 3 weeks of sham CPAP.</td>
</tr>
<tr>
<td>Cooke et al. (2009)</td>
<td>10 with mild to moderate AD and OSA</td>
<td>75.7 ±5.9</td>
<td>13.3 months</td>
<td>Not reported</td>
<td>Following a mean of 13.3 months from the RCT conducted by Ancoli-Israel et al. (2008), five participants who continued CPAP and five who discontinued CPAP completed a follow-up session. During the follow-up session, participants completed the same set of questionnaires and neuropsychological test-battery. Caregivers also completed a set of questionnaires.</td>
<td>The CPAP+ group showed less deterioration in depressive symptoms and daytime sleepiness, and improvements in subjective sleep quality when compared to the CPAP- group. From the test battery, the CPAP+ group showed less deterioration in global cognition, and improvements in executive functioning and psychomotor speed compared to the CPAP- group. Caregivers of the CPAP+ group reported stabilisation of patients’ psychopathology symptoms and improvement of their own rating of sleep quality, depressive symptoms and quality of life.</td>
</tr>
<tr>
<td>Troussiere et al. (2014)</td>
<td>23 with mild to moderate AD and severe OSA</td>
<td>CPAP+ (n=14) 73.4 (4 female)</td>
<td>Median duration of 3.3 years</td>
<td>Median duration of 24.5 months</td>
<td>All participants completed the MMSE at baseline and subsequently every 6 months for approximate 3.3 years.</td>
<td>The CPAP+ group (-0.7 points per year) has a significantly slower annual cognitive decline, as measured by the MMSE, when compared to the CPAP- group (-2.2 points per year).</td>
</tr>
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</table>

AD, Alzheimer’s disease; CPAP, continuous positive airway pressure; CSD, Cornell Scale for Depression; MMSE, HVLT-R, Hopkins Verbal Learning Test-Revised; Mini Mental State Examination; OSA, obstructive sleep apnoea; pCPAP, placebo continuous positive airway pressure; tCPAP, therapeutic continuous positive airway pressure; TMT, Trail Making Test.
Methods

Participants

From the 18 OSA-MCI participants described in Study 2, 12 participants with moderate-to-severe OSA were identified and recommended CPAP therapy by the study’s sleep physician. Of the 12, four participants declined CPAP therapy. A total of eight participants (two females) completed the study. Participants had an age range of 54 to 86 years with a mean age of 63.8 ± 10.7 years. Five participants were reported to have hypertension and three reported to have diabetes; all were controlled with medication. Four participants had a history of or currently have depression, and three of them were on antidepressants.

Participants were recruited from the Cognitive, Dementia and Memory Service at Austin Health and Bundoora Specialist Health Care, a private memory service. Exclusion and inclusion criteria were previously described in Study 1 (Chapter 3). Written informed consent was obtained, and the study was approved by the Austin Health Human Research Committee (HREC) and registered with the Northern Health HREC and Royal Melbourne Institute of Technology HREC. The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12616000733471).

Materials

Auto CPAP machine

All participants were provided with a ResMed AirSense 10 AutoSet and a mask for three months. Six participants used a full-face mask (Fisher & Paykel Simplus Full Face Mask) and two participants utilised a nasal mask (ResMed AirFit N20 Nasal Mask). Prior to starting CPAP therapy, all participants received instructions and orientation to the CPAP machines in the presence of their caregivers, partners or family. During this session, all participants were fitted with a mask and given a trial run with two different pressures (4 cm H$_2$O and 10 cm H$_2$O). Participants were informed that the machine was auto-titrating and the pressure would vary throughout the night. Participants were also informed that CPAP usage data were being recorded by the device.
Neuropsychological testing

All participants underwent a 90-minute battery of neuropsychological assessment prior to starting and after completing CPAP therapy. The neuropsychological assessment included the Mini Mental State Examination (MMSE), Logical Memory (Logical I, II and Recognition for Story A and B), Trail Making Test (TMT) A and B, Digit Span (forward, backwards and sequencing), Coding, Symbol Search, Rey-Osterrieth Complex Figure Test (RCFT) and Autobiographical Memory Test (AMT), all described in detail in Chapter 2. Alternate versions of tests were utilised at follow-up for Logical Memory, RCFT and AMT.

Questionnaires

Participants completed a set of questionnaires prior to and after completing CPAP therapy, including the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman & Kupfer, 1989), Epworth Sleepiness Scale (ESS; Johns, 1991), and The Hospital Anxiety and Depression Scale (HADS; Snaith & Zigmon, 1983).

Procedure

A randomised, controlled partial cross-over study design was employed. Participants were informed that the study aimed to examine the efficacy of CPAP therapy on memory and mood. Following the overnight PSG study and neuropsychological testing, participants underwent in the previous study (Chapter 4), participants were screened for inclusion into the current study. Individuals with an apnoea-hypopnoea index (AHI) of ≥15 and considered suitable for CPAP therapy by the study’s sleep physician were invited to participate in the 3-month trial. Interested participants were randomly assigned into either the immediate CPAP group or the waitlist group. Block randomisation in blocks of four patients was utilised and carried out using a computer random number generator. Due to the nature of the study design, researchers and participants were not blinded to the group allocations.

Participants in the immediate CPAP group received CPAP therapy following their OSA diagnosis. Treatment commenced within a two weeks following OSA diagnosis. Participants were followed up daily during the first week of CPAP use to troubleshoot any issues. Following this, weekly and/or monthly phone calls were made to encourage optimal usage.
Participants could continue any existing medications and dietary supplements throughout the trial. After three months of CPAP therapy, participants attended a follow-up appointment to complete the neuropsychological tests and questionnaires. Participants completed the follow-up appointment within two weeks of their trial end date.

Participants in the waitlist group were given an appointment in three months’ time to begin CPAP therapy. During the wait period, participants were asked not to change their regular diet or physical activity or commence any other treatment for OSA. At the end of the waiting period and prior to starting CPAP therapy, participants completed the neuropsychological tests and questionnaires. The same follow-up procedures utilised in the immediate CPAP group were followed and participants completed another set of test-battery and questionnaires at the end of the 3-month trial.

**Statistical Analysis**

All statistical analyses were carried out using IBM SPSS Statistics 25 (SPSS, Chicago, IL, USA). An alpha level of 0.05 was considered to be of statistical significance. Descriptive analysis was generated for all variables.

Based on previous evaluations of CPAP intervention for OSA in elderly patients, the current study was designed to have >80% power to detect a small to medium effect size of 0.2 between the CPAP treatment and waitlist groups with 15 participants in each group. Due to unexpected difficulties with obtaining CPAP equipment and recruitment in this patient population, the targeted sample size was not achieved. Due to the small sample size, effect sizes were used to quantify the differences in cognitive functioning and mood between the CPAP treatment and waitlist groups. Similar to Cooke et al. (2009), the effect size for each measure was computed as standardised mean difference in change score between baseline and follow-up, \( \frac{\text{change scores in immediate group} - \text{change scores in waitlist group}}{\text{pooled standard deviation of the change score}} \). A Mann-Whitney U test was also conducted for the mean change scores between 3-month follow-up and baseline.

A paired sample t-test was conducted as secondary analysis to examine the changes in cognitive performance and mood after three months of CPAP therapy for all the participants in both groups (i.e. baseline to three months of CPAP in the immediate CPAP group, and post
waitlist to three months of CPAP in the waitlist group). A Spearman’s correlational analysis was conducted between baseline sleep and mood questionnaires for all participants, and their CPAP usage data to identify potential variables that were associated with CPAP compliance. Spearman’s correlational analysis was also conducted between CPAP usage, and changes in neuropsychological test and questionnaire scores to examine if CPAP compliance was linked to changes in cognitive performance, subjective sleep variables and mood after three months of CPAP therapy.

**Results**

**Sample characteristics**

**All participants**

Demographic data of all participants are presented in Table 2. The study sample consisted of mostly males (2 females) with high BMI (obese range >30), poor subjective sleep quality (PSQI normal range 0-5; Buysse, Reynolds III, Monk, Berman & Kupfer, 1989) and increased daytime sleepiness (ESS normal range 0-10; Johns & Hocking, 1997).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
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<tr>
<td>Age</td>
<td>63.75</td>
<td>9.91</td>
<td>54 - 86</td>
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<tr>
<td>BMI</td>
<td>33.43</td>
<td>7.43</td>
<td>26.3 - 50.0</td>
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<tr>
<td>Education</td>
<td>10.38</td>
<td>3.29</td>
<td>6 - 16</td>
</tr>
<tr>
<td>PSQI</td>
<td>8.13</td>
<td>5.33</td>
<td>2 - 16</td>
</tr>
<tr>
<td>ESS</td>
<td>11.25</td>
<td>6.09</td>
<td>5 - 22</td>
</tr>
<tr>
<td>HADS (A)</td>
<td>5.00</td>
<td>3.16</td>
<td>1 - 11</td>
</tr>
<tr>
<td>HADS (D)</td>
<td>6.38</td>
<td>3.70</td>
<td>1 - 11</td>
</tr>
<tr>
<td>AHI (/hour)</td>
<td>31.74</td>
<td>11.03</td>
<td>19.0 – 56.0</td>
</tr>
</tbody>
</table>

AHI, apnoea-hypopnoea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; HADS (A), Hospital Anxiety Depression Scale anxiety score; HADS (D), Hospital Anxiety Depression Scale depression score; PSQI, Pittsburgh Sleep Quality Index.
**Immediate CPAP and waitlist groups**

Demographic data of each group (immediate CPAP and waitlist groups) are presented in Table 3. A Mann-Whitney U test revealed no notable differences in demographic measures between the groups.

**Table 3**
Demographic data of the immediate CPAP and waitlist groups

<table>
<thead>
<tr>
<th></th>
<th>Immediate CPAP</th>
<th>Waitlist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (females/males)</td>
<td>0/4</td>
<td>2/2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.25 (4.79)</td>
<td>69.25 (11.21)</td>
</tr>
<tr>
<td>BMI</td>
<td>36.13 (9.81)</td>
<td>30.73 (3.62)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.25 (2.87)</td>
<td>10.50 (4.12)</td>
</tr>
<tr>
<td>AHI (/hour)</td>
<td>37.67 (12.55)</td>
<td>25.80 (5.69)</td>
</tr>
<tr>
<td>AHI during CPAP use (/hour)</td>
<td>2.25 (0.70)</td>
<td>-</td>
</tr>
</tbody>
</table>

AHI, apnoea-hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure therapy.

**Between-group analysis**

Baseline and 3-month follow-up data for both immediate CPAP and waitlist groups are provided in Table 4.

At baseline, the immediate CPAP group had poorer subjective sleep quality, higher daytime sleepiness, and higher anxiety and depressive symptoms compared to the waitlist group. However, a Mann-Whitney U analysis revealed no significant difference between groups in PSQI, ESS, HADS (A; \( p=0.057 \)) and HADS (D) scores. There were no notable differences between both groups on any neuropsychological test at baseline.

**Within-group analysis**

Results from the paired samples t-test to examine questionnaire and test-battery scores pre- and post-CPAP for all participants are reported in Table 5.
Table 4
Baseline and 3-month follow up questionnaire and neuropsychological data for immediate CPAP and waitlist groups

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Immediate CPAP (n=4)</th>
<th>Waitlist (n=4)</th>
<th>Effect size</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>PSQI</td>
<td>11.25 (5.62)</td>
<td>10.00 (5.35)</td>
<td>5.00 (2.94)</td>
<td>8.75 (2.36)</td>
</tr>
<tr>
<td>ESS</td>
<td>13.25 (7.97)</td>
<td>11.25 (6.70)</td>
<td>9.25 (3.50)</td>
<td>14.25 (4.03)</td>
</tr>
<tr>
<td>HADS (A)</td>
<td>7.00 (3.16)</td>
<td>8.25 (6.70)</td>
<td>3.00 (1.63)</td>
<td>6.00 (5.48)</td>
</tr>
<tr>
<td>HADS (D)</td>
<td>8.00 (3.16)</td>
<td>7.25 (4.27)</td>
<td>4.75 (3.86)</td>
<td>6.25 (6.40)</td>
</tr>
<tr>
<td>Test-battery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE*</td>
<td>26.50 (4.04)</td>
<td>27.33 (3.77)</td>
<td>26.50 (3.00)</td>
<td>25.50 (2.52)</td>
</tr>
<tr>
<td>Logical I</td>
<td>24.25 (8.26)</td>
<td>29.75 (10.91)</td>
<td>21.25 (12.12)</td>
<td>17.25 (6.75)</td>
</tr>
<tr>
<td>Logical II</td>
<td>12.50 (7.77)</td>
<td>15.50 (9.85)</td>
<td>12.00 (6.22)</td>
<td>8.25 (2.87)</td>
</tr>
<tr>
<td>Logical Recognition</td>
<td>15.25 (6.29)</td>
<td>16.67 (4.78)</td>
<td>14.75 (4.65)</td>
<td>14.00 (2.58)</td>
</tr>
<tr>
<td>DS (Forward)</td>
<td>7.75 (2.50)</td>
<td>8.00 (3.27)</td>
<td>6.75 (0.97)</td>
<td>6.50 (1.92)</td>
</tr>
<tr>
<td>DS (Backward)</td>
<td>5.00 (2.16)</td>
<td>7.25 (3.59)</td>
<td>6.75 (2.16)</td>
<td>6.75 (2.87)</td>
</tr>
<tr>
<td>DS (Sequencing)</td>
<td>5.50 (2.08)</td>
<td>5.67 (2.87)</td>
<td>4.75 (2.22)</td>
<td>5.50 (1.73)</td>
</tr>
<tr>
<td>RCFT immediate</td>
<td>18.00 (5.55)</td>
<td>16.67 (3.21)</td>
<td>12.38 (5.68)</td>
<td>12.25 (10.27)</td>
</tr>
<tr>
<td>RCFT delayed</td>
<td>16.75 (6.90)</td>
<td>15.00 (5.00)</td>
<td>12.50 (7.68)</td>
<td>13.00 (10.00)</td>
</tr>
<tr>
<td>Coding</td>
<td>41.50 (24.39)</td>
<td>46.50 (30.43)</td>
<td>30.00 (15.38)</td>
<td>30.75 (15.33)</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>18.25 (10.81)</td>
<td>18.25 (12.53)</td>
<td>16.25 (7.85)</td>
<td>14.25 (6.55)</td>
</tr>
<tr>
<td>TMT A (sec)</td>
<td>77.27 (44.00)</td>
<td>68.07 (28.06)</td>
<td>87.43 (49.32)</td>
<td>72.58 (44.61)</td>
</tr>
<tr>
<td>TMT B (sec)</td>
<td>189.48 (84.03)</td>
<td>167.17 (70.87)</td>
<td>201.37 (113.24)</td>
<td>179.96 (123.55)</td>
</tr>
<tr>
<td>AMT (specific)</td>
<td>5.25 (2.06)</td>
<td>7.50 (3.51)</td>
<td>5.25 (2.50)</td>
<td>6.00 (3.92)</td>
</tr>
</tbody>
</table>

AMT, Autobiographical Memory Test; ESS, Epworth Sleepiness Scale; DS, digit span; HADS (A), Hospital Anxiety Depression Scale anxiety score; HADS (D), Hospital Anxiety Depression Scale depression score; MMSE, Mini Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; RCFT, Rey-Osterreith Complex Figure Test; TMT, Trail Making Test. *p<0.05 Mann-Whitney test for mean change scores (between follow-up and baseline).
Table 5
Pre- and post-CPAP questionnaires and neuropsychological testing for all participants (n=8)

<table>
<thead>
<tr>
<th></th>
<th>Pre-CPAP</th>
<th>Post-CPAP</th>
<th>t</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Questionnaires</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSQI</td>
<td>10.00 (4.21)</td>
<td>8.38 (4.57)</td>
<td>1.18</td>
<td>0.28</td>
<td>0.37</td>
</tr>
<tr>
<td>ESS</td>
<td>13.75 (5.87)</td>
<td>10.50 (6.89)</td>
<td>2.66</td>
<td>0.03</td>
<td>0.51</td>
</tr>
<tr>
<td>HADS (A)</td>
<td>6.50 (4.18)</td>
<td>5.25 (5.50)</td>
<td>0.51</td>
<td>0.63</td>
<td>0.26</td>
</tr>
<tr>
<td>HADS (D)</td>
<td>7.13 (4.76)</td>
<td>6.25 (3.88)</td>
<td>0.64</td>
<td>0.54</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Test-battery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>26.00 (3.16)</td>
<td>27.63 (2.67)</td>
<td>-2.60</td>
<td>0.04</td>
<td>-0.56</td>
</tr>
<tr>
<td>Logical I</td>
<td>20.75 (7.92)</td>
<td>28.50 (11.12)</td>
<td>-2.81</td>
<td>0.03</td>
<td>-0.80</td>
</tr>
<tr>
<td>Logical II</td>
<td>10.38 (5.88)</td>
<td>16.00 (7.43)</td>
<td>-2.92</td>
<td>0.02</td>
<td>-0.84</td>
</tr>
<tr>
<td>Logical Recog</td>
<td>14.63 (4.50)</td>
<td>16.75 (4.17)</td>
<td>-2.43</td>
<td>0.05</td>
<td>-0.49</td>
</tr>
<tr>
<td>DS (Forward)</td>
<td>7.13 (2.17)</td>
<td>7.50 (2.56)</td>
<td>-0.75</td>
<td>0.48</td>
<td>-0.16</td>
</tr>
<tr>
<td>DS (Backward)</td>
<td>5.88 (2.53)</td>
<td>7.38 (2.87)</td>
<td>-1.98</td>
<td>0.09</td>
<td>-0.55</td>
</tr>
<tr>
<td>DS (Sequencing)</td>
<td>5.50 (1.77)</td>
<td>6.25 (2.77)</td>
<td>-1.11</td>
<td>0.30</td>
<td>-0.32</td>
</tr>
<tr>
<td>RCFT immediate</td>
<td>17.35 (9.34)</td>
<td>15.71 (7.74)</td>
<td>0.75</td>
<td>0.48</td>
<td>0.19</td>
</tr>
<tr>
<td>RCFT delayed</td>
<td>16.00 (6.63)</td>
<td>14.85 (6.39)</td>
<td>0.40</td>
<td>0.70</td>
<td>0.18</td>
</tr>
<tr>
<td>Coding</td>
<td>36.13 (19.72)</td>
<td>40.75 (23.74)</td>
<td>-2.08</td>
<td>0.08</td>
<td>-0.21</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>16.25 (8.55)</td>
<td>17.38 (9.05)</td>
<td>-0.94</td>
<td>0.38</td>
<td>-0.13</td>
</tr>
<tr>
<td>TMT A</td>
<td>74.93 (41.10)</td>
<td>67.38 (97.95)</td>
<td>0.97</td>
<td>0.36</td>
<td>0.10</td>
</tr>
<tr>
<td>TMT B</td>
<td>184.72 (97.95)</td>
<td>154.52 (62.69)</td>
<td>1.47</td>
<td>0.18</td>
<td>0.37</td>
</tr>
<tr>
<td>AMT (specific)</td>
<td>5.63 (2.93)</td>
<td>7.50 (3.67)</td>
<td>-2.71</td>
<td>0.03</td>
<td>-0.56</td>
</tr>
</tbody>
</table>

AMT, Autobiographical Memory Test; ESS, Epworth Sleepiness Scale; DS, digit span; HADS (A), Hospital Anxiety Depression Scale anxiety score; HADS (D), Hospital Anxiety Depression Scale depression score; MMSE, Mini Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; RCFT, Rey-Osterreith Complex Figure Test; TMT, Trail Making Test.
**CPAP adherence**

The average CPAP adherence for the study sample was on average 3.9 hours (SD=2.58) per night, which is slightly below the clinically recommended adherence of at least 4 hours per night (Weaver & Grunstein, 2008). Four participants had good adherence to CPAP (≥4 hours; mean CPAP usage=5.99 hours per night, SD=1.47) while four participants had poor adherence to CPAP (<4 hours; mean CPAP usage=1.77 hours per night, SD=1.20).

A Spearman’s correlational analysis between CPAP adherence and baseline AHI, PSQI, ESS, HADS (A) and HADS (D) showed no significant associations, \(p>0.05\). No significant association between CPAP usage and any neuropsychological change scores (between pre- and post-CPAP), PSQI change scores and ESS change scores were observed, \(p>0.05\). CPAP usage was, however, significantly correlated with change in HADS (A) scores, \(\rho=-0.74\), \(p=0.035\) and there was a trend towards significance for change in HADS (D) scores, \(\rho=-0.71\), \(p=0.050\). Negative change score indicates a decrease in HADS score from pre- to post-CPAP, suggesting that higher usage was associated with a decrease in anxiety and depressive symptoms.

Figure 1 displays the HADS (A) scores pre and post-CPAP for both adherence groups (<4h and ≥4h). While the anxiety scores for both groups were below the clinically significant cut-off of 11 (Crawford, Henry, Crombie & Taylor, 2001), the ≥4h group showed a decrease in anxiety symptoms (5.75-point reduction) while the <4h group showed an increase in anxiety symptoms (3.25-point increase; effect size=1.6).
Figure 1. HADS anxiety scores pre and post-CPAP for <4h and ≥4h adherence groups.

Figure 2 depicts that HADS (D) scores pre and post-CPAP for both adherence groups (<4h and ≥4h). The ≥4h group showed a 3-point reduction on the HADS (D) while the <4h group showed a 1.25-point increase following three months of CPAP therapy (effect size=0.83). Similar to the anxiety scores, the depression scores for both groups were below the clinically significant cut-off of 11.

Figure 2. HADS depression scores pre and post-CPAP for <4h and ≥4h adherence groups.
Discussion

The current study investigated the efficacy of three months of CPAP therapy on cognitive performance and mood in patients with comorbid OSA and MCI. The results suggested that three months of CPAP therapy in this patient population have the potential to improve daytime sleepiness, global cognition, logical memory and specific autobiographical memory. Furthermore, secondary analyses indicated associations between CPAP compliance and change in depressive and anxiety symptoms following three months of CPAP therapy.

Efficacy of CPAP therapy on cognitive performance

The immediate CPAP group showed a significant improvement in global cognition, as measured by the MMSE after three months of CPAP while in contrast, the waitlist group showed a deterioration in global cognition. When the sample was examined as a whole, the group had a significant improvement in global cognition (increase of 1.63 points in MMSE score) after three months of CPAP usage. Besides global cognition, there were significant improvements in logical memory free recall (immediate and delayed) and the number of specific autobiographical memory recalled. Trend-level improvements with small to moderate effect size were observed for logical memory recognition, digit span (backwards) and coding.

Regarding global cognition, findings are consistent with previous CPAP studies in patients with comorbid AD and OSA (Ancoli-Israel et al., 2008; Troussière et al., 2014). MMSE score improvement observed in the current study was comparable to a six-month cognitive intervention program in MCI patients which resulted in a 1.74 points improvement in MMSE score (Rojas et al., 2013). Following the completion and write up of the current study, a one-year CPAP study in 54 older adults with MCI and OSA (20 CPAP adherent, 25 CPAP non adherent; Richards et al., 2019) was published. Similarly, Richards et al. (2019) reported promising improvements and maintenance of cognition in individuals who continually used CPAP throughout the trial. Patients who did not use CPAP showed a significant decline in global cognition, attention and reported everyday function after a year while patients who used CPAP maintained their function in these cognitive domains. Both studies (the current study included) have demonstrated promising findings however, it is unclear if these improvements can be sustained or if these patients continue to decline but possibly at a
slower rate. While this warrants further investigation, results from the current study extends previous positive findings in patients with AD in the MCI patient population and confirms the findings reported in Richard et al., (2019).

Studies have reported both logical memory and specific autobiographical memory impairment in OSA patients (Lee et al., 2016; Sales et al., 2013; Twigg et al., 2010) and MCI patients (Donix et al., 2010; Meléndez et al., 2019; Nordlund et al., 2005; Wang & Zhou, 2002). Consistent with findings from this study, logical memory in OSA patients have been shown to improve after one to six months of CPAP therapy (Bédard, Montplaisir, Malo, Richer & Rouleau, 1993; Rosenzweig et al., 2016). Although a different test was utilised, improvements in episodic verbal memory were also reported in patients with OSA and AD after three weeks of CPAP therapy (Ancoli-Israel et al., 2008). Similarly, recent work from our research group showed that autobiographical memory overgenerality in OSA patients significantly reduced after 12 months of CPAP therapy (Brown, Lee, Tolson, Barnes & Jackson, 2018, conference abstract). While research in the MCI literature reported that MCI patients have the potential to improve logical memory (Sherman, Mauser, Nuno & Sherzai, 2017; Wagner et al., 2009; Wenisch et al., 2007) and specific autobiographical memory (Emsaki, NeshatDoost, Tavakoli & Barekatain, 2017) following cognitive intervention programs, the current findings indicate that the subset of MCI patients with OSA have the benefit of additional treatment options in managing cognitive decline.

**Efficacy of CPAP therapy on daytime sleepiness, subjective sleep quality and mood**

There was a trend towards improvement in daytime sleepiness, subjective sleep quality and depressive symptoms in the immediate CPAP group, while individuals in the waitlist group reported higher daytime sleepiness, poorer subjective sleep quality, and higher anxiety and depressive symptoms after three months. When the sample was examined as a whole, the group had significantly lower daytime sleepiness following three months of CPAP (decrease of 3.25 points in ESS scores). Although not statistically significant, the sample reported better subjective sleep quality, and lower depressive and anxiety symptoms. Nevertheless, it should be noted that the mean PSQI score post-CPAP remains above the normal range of 0-5 (Buysse, Reynolds III, Monk, Berman & Kupfer, 1989), indicating that while there is a trend of improvement post-CPAP, subjective sleep quality in the study sample remained poor.
Findings regarding improvements in subjective daytime sleepiness are consistent with CPAP studies in OSA patients (Antic et al., 2011; Bhat et al., 2018; Sánchez, Martínez, Miró, Bardwell & Buela-Casal, 2009). Furthermore, the ESS results are also in line with studies that have reported a significant improvement in subjective daytime sleepiness following therapeutic CPAP therapy in MCI and AD cohorts (Chong et al., 2006; Richards et al., 2019). After one year of CPAP therapy, MCI patients experienced a decrease of 2.12 points in ESS scores (Richards et al. 2019) and AD patients demonstrated a decrease in 3.36 points in ESS scores after six weeks of CPAP therapy (Chong et al., 2006), which are comparable to the improvements reported in the current study. However, it should be noted the mean ESS score post-CPAP for the current study sample remains slightly outside the normal range of 0-10 (Johns & Hocking, 1997). This along with the poor subjective sleep quality following CPAP therapy may reflect the low adherence (less than 4 hours) of the group. Nevertheless, OSA patients with an ESS score of 11 or more before starting CPAP treatment have an increased risk of experiencing residual excessive sleepiness while using CPAP (Pépin et al., 2009). Given that the study sample had a mean ESS score of 13.75 prior to starting CPAP, it is possible that participants from the current study were at risk of remaining sleepy despite CPAP treatment. While increased age and the presence of MCI have not been linked to increased daytime sleepiness (Hita-Yañez, Atienza & Cantero, 2013; Ohayon & Vecchierini, 2002), other confounding variables including BMI, diabetes and depression have been identified as a major risk factor of excessive daytime sleepiness (Bixler et al., 2005). It is also possible that subjective daytime sleepiness may continue to decrease with prolonged CPAP therapy. For instance, Richard et al. (2019) reported that daytime sleepiness in patients with comorbid OSA and MCI continued to improve after six months and one year of CPAP use.

With regards to mood, while there is a trend of improvement in anxiety and depressive symptoms following three months of CPAP therapy, the improvements were not statistically significant. Findings on the effect of CPAP therapy on mood in OSA patients have been mixed (Jackson, McEvoy, Bank & Barnes, 2018; Sánchez, Martínez, Miró, Bardwell & Buela-Casal, 2009; Saunamäki & Jehkonen, 2007). Results from this study are consistent with CPAP studies in patients with comorbid AD and OSA which reported no significant change in depressive symptoms following three weeks or one year of CPAP use (Ayalon et al., 2006; Cooke et al., 2009). However, Cooke and colleagues (2009) reported a deterioration in depressive symptoms in AD and OSA patients who did not use CPAP suggesting that CPAP therapy may benefit mood by stabilising depressive symptoms in this
patient population. Nevertheless, the depressive and anxiety symptoms of the study sample are within the normal range of 0-11 (Crawford, Henry, Crombie & Taylor, 2001) which may explain the lack to notable changes in mood symptoms following CPAP therapy. This is consistent with a 6-month CPAP study which reported that depressive symptoms were significantly reduced in OSA patients with severe depressive symptoms but not those with less severe symptoms (Millman, Fogel, McNamara & Carlisle, 1989).

Despite depressive and anxiety scores not significantly changing after 3 months of CPAP therapy, there was an association between CPAP adherence and change in depressive and anxiety scores (between post-CPAP and pre-CPAP). Specifically, increased CPAP usage was correlated with decrease in depressive (on trend towards significance) and anxiety score. When the study sample was divided into good adherence (≥4 hours) and poor adherence (<4 hours), there was trend of improvement for both depressive and anxiety symptoms in those with good CPAP adherence, while those with poor adherence showed a trend of deterioration (i.e., increasing depressive and anxiety symptoms). This is in line with four-to six-week CPAP studies that linked better CPAP adherence with greater improvement in depressive symptoms; however, no links were reported for anxiety symptoms (Engleman, Martin, Deary & Douglas, 1997; Mysliwiec et al., 2015). On the other hand, individuals with poor adherence may have experienced poorer symptom improvement which can increase the likelihood of negative experiences with CPAP therapy (Ward, Hoare & Gott, 2014).

**CPAP adherence**

While mean CPAP adherence in the current study was reasonable, half of the study sample had an average CPAP usage per night of less than 4 hours. Previously, higher OSA severity (Yetkin, Kunter & Gunen, 2008; Meurice et al., 1994) and depression (Law et al., 2014) have been associated with better CPAP adherence. Fewer depressive symptoms were also associated with better adherence in patients with OSA and AD (Ayalon et al., 2006). Nevertheless, the current study revealed no links between CPAP adherence and baseline variables, including OSA severity, subjective sleep quality, daytime sleepiness, and depressive and anxiety symptoms. This is in line with studies that have reported no associations between CPAP adherence, and baseline general sleep and mood measures. Instead, CPAP adherence was linked to more specific psychological variables including usage of effective coping strategies, recent major life event and self-efficacy (Baron et al.,
While the current study shows that MCI patients with comorbid OSA can tolerate CPAP with good adherence rate, CPAP adherence remains a significant issue in OSA patients and may limit the overall effectiveness of CPAP therapy (Sawyer et al., 2011). Accordingly, future implementation studies should further focus on CPAP adherence. For instance, a longitudinal observational study on patients that have continuously used CPAP for a longer period of time can help identify the optimal adherence required for observable cognitive changes and if these changes are sustainable. Information on optimal adherence and expected changes based on treatment length will further inform clinicians on the efficacy of CPAP treatment in their patients.

**Limitations and future directions**

While findings from this study are novel and promising, there are several limitations that should be addressed. Firstly, due to the small sample size, findings should be interpreted with caution. Despite some promising trends, the study remained underpowered and potential confounders were not taken into account in the analyses. Accordingly, further investigation with a larger sample size should be conducted to confirm current findings. The current study included several measures to encourage participation, including at-home visits and the option to keep the CPAP mask at the end of the trial. Nevertheless, given the difficulty in recruiting patients with comorbid OSA and MCI/AD, as reported in past (Ancoli-Israel et al., 2008) and current studies, further steps may be required. For instance, educational brochures on the impact of sleep apnoea for both patients and caregivers may be useful.

Secondly, given the short period of time between testing, practice effect may be observed. In several tests (DS sequencing, coding, TMT A, TMT B and AMT), trends of improvements were observed in the waitlist group after three months. While precautions were taken to
prevent practice effect (e.g., alternate stories or words for memory tests), participants may have developed familiarity with or strategies for the tasks.

Finally, while three months of CPAP therapy is often adequate to observe changes in cognitive functioning and mood (Sánchez, Martínez, Miró, Bardwell & Buela-Casal, 2009), findings from the current study is unable to shed light on whether these cognitive improvements are sustainable for a longer period of time and if these improvements are significant enough to slow down long-term cognitive decline or delay the onset of dementia. For instance, improvements in episodic verbal memory were observed in patients with OSA and AD after three weeks of CPAP therapy (Ancoli-Israel, 2008) but a longitudinal follow-up study showed evidence of deterioration in this area despite continual use of CPAP for one year (Cooke et al., 2009). Accordingly, long-term prospective studies in OSA and MCI patients using CPAP therapy should be considered. There may also be particular phenotypes of patients who respond or adhere better to CPAP (Gagnadoux et al., 2016; Saaresranta et al., 2016) thus, predicting those who will benefit from CPAP is another important step for future research.

**Conclusions**

Findings from this study demonstrate that CPAP therapy can improve global cognition, logical memory, specific autobiographical memory and subjective daytime sleepiness in individuals with comorbid OSA and MCI. While no significant improvements in depressive and anxiety symptoms were observed after three months of CPAP therapy, improvements in depressive and anxiety symptoms were seen in those patients who had better CPAP adherence. Although these findings need to be confirmed in a larger study, these results suggest that CPAP therapy has the potential to be used as a treatment option to improve cognitive functioning, by elevating the impact of OSA on cognition, in a subset of MCI patients that have OSA. Given the potential implications, clinicians should consider conducting early risk assessments for OSA and initiate prompt interventions when necessary.
Chapter 6

General discussion

6.1 Brief overview of findings

Study 1 (Chapter 3) investigated two aims - first, whether specific autobiographical memory impairment in OSA patients deteriorated with age and second, whether there were any differences in specific autobiographical memory recall between OSA patients with and without MCI. A total of 95 participants (23-86 years) completed the Autobiographical Memory Test and an overnight PSG. Findings indicated that (i) young OSA patients (<50 years) were as impaired as older OSA patients (≥50 years) in specific autobiographical memory recall; and (ii) OSA patients without MCI performed as poorly in the autobiographical memory test as OSA patients with MCI. Valence bias was also observed in the older adults where the older groups recalled significantly more positive memories than negative memories.

Study 2 (Chapter 4) continued the investigation of the relationship between sleep apnoea and cognitive impairment in 18 patients with comorbid OSA and MCI (54-86 years). The study further explored the relationship between cognitive performance and the different aspects of sleep apnoea, including intermittent hypoxia, sleep fragmentation, sleep architecture and subjective sleep measures. Finally, the study compared cognitive performance and mood between MCI patients with and without OSA in a subset of cognitive domains. Overall, results revealed that greater sleep apnoea severity in OSA patients with MCI was significantly associated with poorer global cognition and working memory. When different aspects of sleep apnoea were examined, (i) impairment in global cognition and working memory were significantly associated with measures of intermittent hypoxia; and (ii) verbal memory and processing speed deficits were significantly associated with SWS. Furthermore, MCI patients with OSA had significantly more anxiety symptoms and poorer processing speed and attention performance when compared to MCI patients without OSA, or age-matched healthy controls.
Study 3 (Chapter 5) investigated the efficacy of three months of CPAP therapy on cognitive performance and mood in OSA patients with comorbid MCI. Eight OSA patients with MCI (54-86 years) underwent three months of CPAP therapy. A neuropsychological test-battery was conducted prior to and after CPAP therapy. Overall, the results indicated that three months of CPAP therapy significantly improved global cognition, logical memory, specific autobiographical memory and subjective daytime sleepiness in patients with comorbid OSA and MCI. Furthermore, better CPAP adherence was linked with greater improvements in depressive and anxiety symptoms after three months of CPAP therapy.

6.2 Discussion of findings

6.2.1 Age and specific autobiographical memory in OSA patients

Limited studies to date have examined autobiographical memory function in OSA patients. Given that the autobiographical memory overgenerality stemmed from the depression literature and was first reported as a trait in individuals with suicidal behaviours, previous studies that have utilised the Autobiographical Memory Test in OSA patients primarily examined autobiographical memory overgenerality as a trait marker for the course of depression (Mackinger & Svaldi, 2004; Svaldi and Mackinger, 2003). More recent studies from our research group have reported specific autobiographical memory impairment in OSA patients (Delhikar et al., 2019), regardless of depressive symptoms (Lee, Trinder & Jackson, 2016). Nevertheless, there was a significant age difference between the controls and OSA patients in our previous study (Lee, Trinder & Jackson, 2016). In a smaller subset of younger participants, the difference in specific autobiographical memory recall between controls and OSA patients without depressive symptoms did not reach statistical significance, albeit there was a trend towards significance ($p=0.09$), suggesting a possible age-related effect on the impairment. Accordingly, the first part of Chapter 3 addressed this.

In contrast to what we predicted in our previous study, the findings revealed no significant difference in specific autobiographical memory recall between young and older OSA patients. This is also inconsistent with studies reporting poorer cognitive performance in older OSA patients compared younger OSA patients (Alchanatis et al., 2008; Ayalon, Ancoli-Israel & Drummond, 2010). One possible explanation is that older OSA patients may have
adapted alternative strategies to recalling specific autobiographical memory.

Autobiographical memory is an important aspect of daily life that contributes towards the formation of self-identity, social interactions and problem-solving (Addis & Tippett, 2004; Fivush, Habermas, Waters & Zaman, 2011; Pillemer, 2003). Given the importance of recalling autobiographical memories on a daily basis, it is possible that older OSA patients, who likely have had OSA for a longer period of time, have learned to draw cognitive resources from different areas to compensate for the current impairment. For example, a functional MRI study reported no significant difference in autobiographical memory retrieval between young and older healthy adults; however, bilateral hippocampal activation was evident in older adults during retrieval while only left hippocampal activation was observed in young adults (Maguire & Frith, 2003). Furthermore, the older adults had notably greater right hippocampal activation compared to young adults, suggesting that there may be a change in cognitive processes with age in autobiographical memory retrieval.

A change in strategies for autobiographical memory retrieval can also explain the valence bias observed in older adults but not their younger counterparts. The valence bias observed in older adults is consistent with studies that have reported significant positive memory bias in older adults (Dijkstra & Kaup, 2005; Kensinger, Garoff-Eaton & Schacter, 2007; Tomaszczyk, Fernandes & MacLeod, 2008). Unlike other verbal memory tests, information recalled during the Autobiographical Memory Test has personal relevance to the individual and the test administrator is unable to check the accuracy of the memory recalled. Accordingly, the memories recalled may be subjective to bias. For instance, older participants recalled the past more positively than originally reported 14 years earlier, while younger participants recalled the past more negatively than originally reported (Kennedy, Mather & Carstensen, 2004).

As young OSA patients are as impaired as older OSA patients in specific autobiographical memory recall, this also suggests that autobiographical memory may be an aspect of cognition that is acutely affect by OSA. The current findings add to the list of cognitive impairments previously reported in OSA patients (Bucks, Olaïthe & Eastwood, 2012; Jackson, Howard & Barnes, 2011; Stranks & Crowe, 2016). Furthermore, the finding also suggests that young OSA patients are equally vulnerable to the detrimental effect of OSA on cognition as their older counterparts and highlights the importance of early intervention.
6.2.2 Specific autobiographical memory in OSA and MCI patients

Independently, specific autobiographical memory impairment has also been reported in MCI patients (Donix et al., 2010; Meléndez et al., 2019). Given the high prevalence of sleep apnoea in MCI patients (Guarnieri et al., 2012) and that the deficits in specific autobiographical memory recall have been observed in sleep apnoea patients, the possibility of sleep apnoea contributing towards this impairment in individuals with MCI had not been investigated. Accordingly, the second part of Chapter 3 addressed this by comparing specific autobiographical memory recall performance between OSA patients with MCI, OSA patients without MCI and age-matched healthy controls.

In line with previous findings (Delhikar et al., 2019; Lee, Trinder & Jackson, 2016), both OSA groups recalled significantly fewer specific autobiographical memory compared to age-matched healthy controls. Specific autobiographical memory was previously reported to be impaired in MCI patients when compared to healthy controls (Donix et al., 2010; Meléndez et al., 2019). Due to the dual burden of OSA and MCI on cognitive functioning, it was expected that OSA patients with comorbid MCI would perform worse than OSA patients without MCI. However, the results revealed that both groups performed similarly with no significant difference in recall. As findings from the current study demonstrated, OSA patients without MCI performed as poorly as OSA patients with MCI. While it is possible that the task was not sensitive enough to detect small differences between these groups, the lack of difference suggests that sleep apnoea plays a significant role in contributing towards specific autobiographical memory impairment in MCI patients. This is consistent with studies that have reported long-term episodic memory deficits in patients with sleep apnoea (Kerner et al., 2017; Salorio, 2002; Twigg et al., 2010).

Interestingly, percentage of time spent in SWS, but not measures of intermittent hypoxia and sleep fragmentation, was associated with specific autobiographical memory performance in OSA patients with comorbid MCI. This contrasts with previous studies that have linked intermittent hypoxia and/or sleep fragmentation to memory impairments observed in OSA patients (Daurat, Foret, Bret-Dibat, Fureix & Tiberge, 2008; Findley et al., 1986). Nevertheless, SWS has been linked to hippocampal-dependent memory consolidation (Marshall & Born, 2007; Walker, 2009) and a study that examined the relationship between...
autobiographical memory and sleep in patients with mild AD have reported an association between higher percentage of SWS and better autobiographical memory retrieval (Rauchs et al., 2013). In MCI patients, amount of SWS along with the AHI were reported to be significant independent variables associated with verbal memory performance (Kim et al., 2011). As this relationship was only observed in OSA patients with comorbid MCI in the current study, it is possible that these individuals are more susceptible to the effect of poor sleep architecture, which can contribute to deficits in memory performance.

Overall, the findings from Chapter 3 highlight the degree of autobiographical memory impairment observed in OSA patients and the importance of addressing cognitive impairments observed in this patient population, regardless of age. Furthermore, the results suggest that sleep architecture, particularly SWS may be an important aspect of sleep to examine further. Whether treatment of OSA can improve this aspect of memory in patients with comorbid OSA and MCI will be further discussed below.

6.2.3 Relationship between OSA and cognitive performance in patients with comorbid OSA and MCI

Indices of sleep apnoea in MCI patients have been linked to poorer global cognition, language functioning and driving performance (Cross et al., 2017; Kim et al., 2011; Yaffé et al., 2011). While sleep apnoea has been associated with deficits in various cognitive domains, including attention and processing speed (Ayalon et al., 2009; Mazza et al., 2005), memory (Wallace & Bucks, 2013), and executive function (Saunamaki & Jehkonen, 2007), limited studies have examined these impairments in patients with comorbid OSA and MCI. Accordingly, Chapter 4 addressed this by examining the associations between cognition and sleep apnoea severity in patients with comorbid OSA and MCI. The chapter further explored the underlying mechanism of these relationships by examining the associations between cognitive performances and different aspects of sleep apnoea (intermittent hypoxia, sleep fragmentation, sleep architecture and subjective sleep measures).

Adding to the literature, the current findings demonstrated a significant association between greater OSA severity, and poorer global cognition and working memory in patients with OSA and MCI. This is consistent with studies that have linked sleep apnoea severity and global
cognitive decline in older populations (Cohen-Zion et al., 2004; Yaffe et al., 2011), and studies that have observed poorer working memory functioning in OSA patients compared to healthy controls (Lis, et al., 2008; Thomas, Rosen, Stern, Weiss & Kwong, 2005). Furthermore, the findings further revealed that both poor global cognition and working memory performance were significantly linked with measures of intermittent hypoxia but not sleep fragmentation and subjective sleep measures. This is consistent with previous studies that have linked intermittent hypoxia with both global cognition and working memory (Champod et al., 2013; Yaffe et al., 2011). For instance, Yaffe et al., (2011) reported a significant association between measures of hypoxia but not sleep fragmentation or sleep duration with risk of further cognitive decline in older women. Using an experimental design to induce intermittent hypoxia, Champod et al. (2013) demonstrated a link between acute intermittent hypoxia exposure and poorer spatial working memory performance. While the current findings are unable make inferences on the causal relationship between sleep apnoea and cognitive deficits in MCI patients, the findings suggest that intermittent hypoxia plays a significant role in global cognition and working memory in individuals with comorbid OSA and MCI.

Furthermore, a lower percentage of time spent in SWS was significantly associated with poorer performance on tests measuring verbal memory, attention and processing speed. This was similarly observed in Chapter 3 which revealed a significant link between percentage of time spent in SWS and specific autobiographical memory performance highlighting the role of sleep architecture in cognitive deficits in patients with comorbid OSA and MCI. Theories about the mechanisms by which SWS contributes towards cognition include the synaptic homeostasis hypothesis, which involves synaptic downscaling and plasticity during SWS (Tononi & Cirelli, 2006), and the active system consolidation model, which involves long-term memory consolidation through the repeated reactivation of memory traces and the transfer of information from the hippocampus to the neocortex (Dudai, Karni & Born, 2015; Wilckens, Ferrarelli, Walker & Buysse, 2018). More relevant to changes observed in patients with MCI and dementia, a biochemical-physiological hypothesis may better explain sleep apnoea’s contribution towards cognitive impairment through altered SWS. Studies have previously reported a link between the reduction and disruption of slow wave activity (SWA) and increase beta-amyloid (Aβ) levels in sleep apnoea patients and healthy adults (Ju et al., 2017; Ju, Zangrilli, Finn, Fagan & Holtzman, 2019; Mander et al., 2015). Sleep, in particular
SWS, has been argued to have a restorative function by facilitating the clearing of neurotoxic waste products including Aβ (Boespflug & Iliff, 2018; Xie et al., 2013). For example, an animal study reported significantly faster clearing of Aβ in sleeping mice compared to awake mice (Xie et al., 2013). Accordingly, the disruption of SWS, possibly caused by sleep fragmentation, may impair cognitive performance through decreased clearance of Aβ, thus increasing the risk of amyloid aggregation. In line, Mander and colleagues (2015) reported the relationship between medial prefrontal cortex Aβ pathology and diminished hippocampus-dependent memory consolidation was significantly mediated by decreasing SWA. In turn, increased Aβ accumulation have been shown to disrupt the sleep-wake cycle and SWA in both human and animal models (Mander et al., 2015; Roh et al., 2012). As a result, OSA patients may be trapped in a chronic cycle unless relief is provided through improving the quality of sleep.

Recently, a reduction in SWA, along with spindle maximal amplitude, theta and sigma activities, have been associated with an increased risk of isolated subjective cognitive complaint or MCI (Taillard et al., 2019). Accordingly, besides intermittent hypoxia, disrupted sleep architecture may be a major contributing factor towards further cognitive decline observed in OSA patients and should be taken into consideration in future studies to further understand the role of sleep apnoea on cognitive impairment.

**6.2.4 Difference in cognition and mood between MCI patients with and without OSA.**

While there is an overlap in cognitive deficits and mood disturbances observed in OSA and MCI patients respectively, it is not known whether sleep apnoea places any additional burden on cognition and mood of MCI patients. Accordingly, Chapter 4 also examined if there were any differences in mood and performance in a subset of cognitive domains between MCI patients with and without OSA, and age-matched healthy controls.

The current findings showed that processing speed and attention of MCI patients with OSA were significantly worse than MCI patients without OSA, followed by age-matched healthy controls. Processing speed and attention has previously been observed to be impaired in both OSA (D’Rozario et al., 2018; Luz et al., 2016; Saunamäki, Jehkonen, Huupponen, Polo & Himanen, 2009) and MCI individuals (Wadley, Okonkwo, Crowe & Ross-Meadows, 2008).
MCI patients also had significantly worse processing speed and attention compared to healthy controls. However, the current findings further reveal that OSA places an additional burden on the already impaired processing speed of individuals with MCI. While no other differences in cognitive performances were observed, this impairment may have further implications for future cognitive decline. Processing speed has been argued to be play a central role in cognitive ageing (Salthouse, 1996). The processing speed theory suggests that reduced processing speed may result in reduced cognitive processing that can be completed within a given amount of time and early information may be lost due to the length of processing. For example, processing speed has been shown to be a strong predictor for ageing changes in multiple cognitive domains, including memory, fluid intelligence and spatial ability (Finkel, Reynolds, McArdle & Pedersen, 2007; Sliwinski & Buschke, 1999; Zimprich & Martin, 2002). While evidence for this theory has mainly been reported in healthy ageing, this may be also applicable to the current patient population.

Besides processing speed and attention, the current findings also revealed that MCI patients with OSA have significantly more anxiety symptoms than MCI patients without OSA, or healthy controls. This is consistent with studies that reported high prevalence of anxiety in individuals with OSA (Rezaetalab, Moharrari, Saberi, Asadpour & Rezaetalab, 2014; Saunamäki & Jehnoken, 2007; Sharafkhaneh, Giray, Richardson, Young & Hirshkowitz, 2005). However, the elevated anxiety symptoms may have stemmed from the prospect of a recent additional sleep disorder diagnosis. In addition, it should also be noted that both MCI groups had significantly more depressive symptoms than age-matched healthy controls. This is consistent with OSA (Schröder & O’Hara, 2005) and MCI (Apostolova & Cummings, 2007) epidemiological studies. As the level of depressive symptoms in the current study sample is within the normal range and not of clinical significance (Zigmond & Snaith, 1994), the role of depression on cognitive performance was not further examined. Depression has been reported to be a risk factor for further memory decline and dementia (Dotson, Beydoun & Zongerman, 2010; Geerlings et al., 2000; Mondrego & Ferrández, 2004). Furthermore, increased depressive symptoms can impact adherence to treatment, as depressed individuals are three times more likely to be noncompliant to medical treatment recommendations compared to individuals without depression (DiMatteo, Lepper & Croghan, 2000; Law, Naughton, Ho, Roebuck & Dabscheck, 2014). Accordingly, future studies should examine the role of depression in the relationship between sleep apnoea and cognitive decline.
Overall, the findings from Chapter 4 establish the links between OSA and cognition in MCI patients with comorbid OSA. Moreover, cognitive performance was associated with measures of intermittent hypoxia and SWS. As not all OSA patients progress to clinically significant cognitive impairment, this suggests that some patients are more susceptible to the detrimental effects of OSA. Future studies identifying biomarkers to identify individuals who are more susceptible to cognitive decline are required.

6.2.5 Efficacy of CPAP therapy in patients with comorbid OSA and MCI

The use of CPAP therapy in patients with OSA and AD has shown promising results by slowing down cognitive decline (Ancoli-Israel et al., 2008; Ayalon et al., 2006; Chong et al., 2006; Cooke et al., 2009; Troussiere et al., 2014). As MCI is the prodromal stage of dementia and a high proportion of MCI patients do progress to AD (Fischer et al., 2007), targeting individuals at an earlier stage of cognitive decline and providing early intervention may be highly beneficial. Accordingly, Chapter 5 examined the efficacy of CPAP therapy in the MCI patient population.

Similar to previous studies that have examined the effect of CPAP therapy on cognition in patients with AD (Ancoli-Israel et al., 2008; Chong et al., 2006; Cooke et al., 2009; Troussiere et al., 2014) and the recently published CPAP study in MCI patients (Richards et al., 2019), the findings from the current study are promising. Chapter 4 revealed that poorer global cognition was significantly linked with sleep apnoea severity in MCI patients. Coupled with findings from Chapter 5, which demonstrated that global cognition improved following three months of CPAP therapy, findings from the current thesis suggest that sleep apnoea contributes towards global cognitive function observed in MCI patients. Cognitive decline is part of normal ageing (Royall, Palmer, Chiodo & Polk, 2005) however, the rate of decline can significantly differ between individuals (e.g. healthy older individuals compared with patients with AD). In the case of MCI patients with OSA, it is possible that sleep apnoea contributes towards the acceleration of cognitive decline in these individuals, thereby putting them at a greater risk of further deterioration. This is consistent with findings of Osorio et al. (2015) who reported that patients with sleep disordered breathing were significantly younger at MCI onset compared to those without any sleep disordered breathing.
Besides global cognition, three months of CPAP therapy improved logical memory and specific autobiographical memory recall in MCI patients. This is in line with studies that have reported improvement in episodic verbal memory in patients with OSA and AD after three weeks of CPAP (Ancoli-Israel et al., 2008), and autobiographical memory overgenerality in OSA patients after 12 months of CPAP therapy (Brown, Lee, Tolson, Barnes & Jackson, 2018, conference abstract). However, it should be noted that CPAP therapy did not completely reverse specific autobiographical memory impairment in patients with OSA and MCI (i.e., aged matched healthy controls mean=10.00; post-CPAP mean=7.50). This may translate into a long-term maintenance of specific autobiographical memory performance with CPAP therapy rather than a continual improvement. As findings from Chapter 3 demonstrates, young OSA patients are susceptible to this impairment. Given that the OSA and MCI patients are significantly older, and it is unknown when sleep apnoea first developed in these individuals, it is possible that these patients have experienced deficits in specific autobiographical memory for a prolonged period of time.

Interestingly, working memory performance in patients with OSA and MCI was significantly linked to sleep apnoea severity (as reported in Chapter 4) however, no significant improvement was observed in working memory performance after three months of CPAP therapy. This is consistent with previous CPAP studies in cognitively-normal OSA patients that have reported no significant improvement in working memory following CPAP therapy of up to four months (Ferini-Strambi et al., 2003; see Kylstra, Aaronson, Hofman & Schmand, 2013 for meta-analysis; Naegle et al., 1998). This is further supported by a functional imaging study that reported the maintenance of working memory deficit and the absence of dorsolateral prefrontal activation during the task, despite the improvements in daytime sleepiness and subjective sleep quality, after eight weeks of CPAP therapy (Thomas, Rosen, Stern, Weiss & Kwong, 2005). Given the extent of neurological changes reported in OSA patients, longer treatment time may be required to observe improvements. On the other hand, working memory may be a long-lasting impairment that is irreversible regardless of CPAP treatment length and adherence. While sleep apnoea is linked to working memory in patients with OSA and MCI, the impairment may be mediated by other confounding variables including the presence of the APOE e4 allele. In healthy middle-aged adults, while APOE e4 carriers and non-APOE e4 carriers performed similarly during working memory tasks, those with APOE e4 showed fewer increases in brain activation during moderate- and
high-load tasks while non-APOE e4 carriers continued to show increasing activation during the tasks (Chen et al., 2013). Accordingly, OSA patients with an APOE e4 allele may already have a reduced working memory capacity preceding their sleep apnoea, and thus this aspect of cognitive function may not benefit from CPAP therapy.

Overall, the findings in Chapter 5 demonstrate the usefulness of short-term CPAP therapy on cognition in MCI patients. However, the findings do not shed light on the long-term efficacy of CPAP therapy in slowing down cognitive decline across time or reducing dementia conversion rates, and further longitudinal studies are required to address this question. Nonetheless, the current study has provided a basis for future studies by demonstrating that CPAP therapy can benefit MCI patients.

6.3 Limitations

There are several limitations in this thesis that should be addressed. Firstly, MCI patients were not separated into different subgroups due to limited sample size, resulting in a heterogeneous study sample. Conceptually, MCI can be divided into two major subgroups – amnestic and nonamnestic MCI, which can be further divided into subdivisions of single- and multiple-domain (Petersen, 2004). As the different subgroups display different neuropsychological characteristics, it is possible that the effects observed in this thesis may be limited to a certain subgroup of MCI patients. Furthermore, it is also possible that several effects may be muted due to the heterogeneity of the sample population. Nevertheless, it should be noted that multiple studies that have examined the relationship between sleep and MCI have not categorised MCI patients into their subgroups, citing the importance of examining MCI patients as a heterogeneous group given the diversity in pathology and neuropsychological profiles of this patient population (Norlund, et al., 2005). OSA can also be argued to be a heterogeneous disorder with multiple contributing pathophysiological causes and furthermore, not all patients experience the same symptoms, such as excessive daytime sleepiness and poor sleep quality (Eckert & Malhotra, 2008; Young, Peppard & Gottlieb, 2002). While it can be beneficial to examine specific subgroups within a patient population, a heterogeneous sample can still provide meaningful findings with significant clinical implications.
A further limitation is the assessment of MCI utilised in the current thesis. Similar to studies including Crowell, Luis, Vanderploeg, Schinka & Mullan (2002), Donix et al. (2010) and Zhang, Han, Verhaeghen & Nilsson (2007), the current thesis employed a more liberal cut-off score of 1 SD below the norm than the 1.5 SD cut-off score suggested by Petersen (2004). The more liberal cut-off point allows the current studies to include patients who are in early stages of cognitive impairment thus, allowing the thesis to capture a broader set of individuals along the continuum. Nevertheless, this has implications to the conclusions drawn from the studies as the underlying aetiology of MCI is likely to be heterogenous and not necessarily due to AD. Given a stricter cut-off score, the OSA-MCI group may perform significantly worse than the current study sample and the relationships between cognitive impairments and sleep apnoea may differ. Recent research guidelines for AD (Jack et al., 2018) suggested the inclusion of biomarker evidence for AD classifications. With a biomarker profile, researchers are able to better describe if the MCI is attributable to AD and if there other potential non-Alzheimer’s pathological changes that may be contributing to the impairment. The current thesis is unable to shed light on the aetiology of MCI (e.g. neurodegenerative, vascular-related, depression-related) and future work in MCI and AD patients should consider the inclusion of biomarker evidence.

Another limitation of this thesis, particularly Chapters 4 and 5, was the small sample size. Due to the specific requirement of participants to have two concurrent medical disorders (i.e., OSA and MCI), recruitment was slow and difficult. Difficulties in recruiting this patient population have been previously reported (Ancoli-Israel et al., 2008). Although the current study offered the option of an at-home PSG with a portable device, multiple potential participants were still hesitant about undergoing a night of PSG. Given the length of the CPAP trial and the requirement to commit to throughout the three months, this was similarly observed in the treatment study. Although more than half of the participants who completed the overnight PSG were eligible for the CPAP trial, only 67% of the participants agreed to move on to the next phase of the study. Accordingly, while the treatment study provides novel insight to the efficacy of CPAP on patients with comorbid OSA and MCI, results should be interpreted with caution and further investigations with a larger sample size are warranted. Furthermore, this also highlights that CPAP uptake may be worse in this patient population, thus other treatments for OSA in cognitively-impaired individuals should be further explored.
While this thesis has significant novel findings regarding assessing the efficacy of CPAP therapy on cognition in patients with OSA and MCI, a common issue in studies of this nature is the placebo effect. Unlike previous CPAP trials in patients with AD that employed a placebo treatment group (Ancoli-Israel et al., 2008; Ayalon et al., 2006; Chong et al., 2006), the current thesis utilised a waiting list. Accordingly, participants knew when they were undergoing active treatment. Participants and their family members were briefed about the aims of the study and understood that the CPAP trial was investigating the effects of CPAP therapy on their cognition and mood. Patients on CPAP may therefore report improvements subjectively and actively tried to improve from their previous performance during the follow-up testing session. Nevertheless, due to the length of the CPAP trial, a placebo arm would have increased the difficulty of recruitment.

Furthermore, while patients were told to not start any new treatment or medication that may affect their cognition or mood during the CPAP trial, patients may have engaged in some casual cognitive training that could potentially result in a better performance during the second testing session. For instance, one participant mentioned after the CPAP trial that he/she had been actively practicing recalling past memories (e.g., Autobiographical Memory Test) and numbers (e.g., Digit Span). While a new set of words or stories were utilised for memory tasks, participants may have learned and adopted new strategies for the follow-up sessions. Nevertheless, explicitly telling participants to not undertake any cognitive exercises may be counterproductive as it may prompt practice and more importantly, it is arguably unethical to prevent individuals with cognitive impairment from any potential methods of improving cognitive function.

6.4 Theoretical and clinical implications

Firstly, OSA was significantly linked with certain aspects of cognitive impairment in MCI patients. While MCI or dementia patients can also experience sleep disturbances unrelated to sleep apnoea (Guarnieri et al., 2012), older adults attending memory clinics with sleep complaints warrant further clinical investigation. To help identify patients who are ‘at risk’ of sleep apnoea, screening questionnaires for sleep apnoea should be integrated into clinical practice for newly referred patients. The STOP-bang questionnaire (Chung et al., 2016) was successfully integrated and administered in a Cognitive Function Clinic over three months,
suggesting its applicability in this setting (Ziso & Larner, 2015). Given that the STOP-bang questionnaire has eight yes/no questions, it is relatively easier to administer compared to other sleep apnoea screening questionnaires, such as the Berlin Questionnaire and the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ). Furthermore, the STOP-bang has been validated in patients with AD to have a relatively good sensitivity (moderate OSA: 77% and severe OSA: 85%) and low specificity (moderate and severe OSA: 35%) to detect moderate-to-severe OSA (Jorge et al., 2019). Nevertheless, while the STOP-bang questionnaire has been validated in patients with AD, a further validation study in the MCI patient population should be considered.

Secondly, young OSA patients were as impaired as older OSA patients in specific autobiographical memory recall. Preliminary findings from our group (Brown, Lee, Tolson, Barnes & Jackson, 2018, conference abstract) on the efficacy of CPAP therapy on autobiographical memory are promising, with OSA patients recalling significantly fewer overgeneral memory following 12 months of CPAP usage. Given the importance of autobiographical memory in the construction of personal identity and life narratives (Wilson & Ross, 2003), the current finding highlights the importance of addressing OSA, regardless of age.

Thirdly, the cognitive performance of individuals with comorbid OSA and MCI was significantly associated with measures of intermittent hypoxia and SWS but not sleep fragmentation, subjective daytime sleepiness and subjective sleep quality. This further supports the notion that intermittent hypoxia contributes towards the pathogenesis of cognitive impairment observed in OSA patients. The role of intermittent hypoxia on cognitive function in OSA patients is widely researched and discussed in both animal and human studies (Row, 2007; Sforza & Roche, 2016). While the current findings support the significance of intermittent hypoxia in the relationship between sleep apnoea and cognitive impairment, they also highlight the importance of taking sleep architecture, specifically SWS, into account as a possible mechanistic pathway. Furthermore, on a micro-level, studies have previously identified the importance of slow oscillations and sleep spindles during sleep on memory consolidation (Marshall, Helgadóttir, Mölle & Born, 2006; Schabus et al., 2004). Accordingly, future studies should explore microarchitecture in this patient population and its potential role in cognitive impairment.
Finally, CPAP therapy has the potential to improve cognitive performance in patients with OSA and MCI. This is an important finding as it suggests that impairments in cognition due to OSA may be transient and partially reversibly by treatment. Previous studies that have examined the efficacy of CPAP therapy in MCI/AD patients have reported significant slowing down in cognitive decline (Cooke et al., 2009; Richards et al., 2019; Troussiere et al., 2014). Adding on to this, the current findings suggest that patients who may be in the prodromal stage of dementia are also able to benefit from CPAP therapy. This further highlights the need to screen and identify patients in memory clinics who are at risk of sleep apnoea. Early identification and treatment of sleep apnoea in elderly individuals, specifically individuals with MCI, is vital as CPAP can delay the onset of MCI (Osorio et al., 2015) and improve multiple domains of cognitive function (Richards et al., 2019). Accordingly, it is important that clinicians further investigate complaints about sleep disturbances in older adults and provide recommendations for appropriate management of sleep disorders and its associated chronic comorbidities. Further steps, including CPAP education for both patient and caregiver/partner, and consistent follow-up appointments, should be implemented to encourage adherence to treatment. As cognitive interventions (e.g. multicomponent cognitive training and interventions targeting multiple cognitive domains) in MCI patients have demonstrated promising findings (see Sherman, Mauser, Nuno & Sherzai, 2017 for review), using CPAP therapy in conjunction with cognitive intervention should be considered in patients with comorbid OSA and MCI.

6.5 Overarching conclusions

In summary, this thesis examined the relationship between cognition and OSA in older adults with and without MCI, and whether the treatment of sleep apnoea can improve cognitive functioning and mood in patients with comorbid OSA and MCI. Results indicated that multiple aspects of OSA, including severity, intermittent hypoxia and SWS were significantly linked to the impairment in several cognitive domains (i.e., global cognition, working memory, verbal declarative memory, attention and processing speed). The trial of CPAP therapy in patients with OSA and MCI showed promising results. Three months of CPAP therapy in this patient population can improve global cognition, logical memory, specific autobiographical memory and daytime sleepiness. Given the small sample size, these findings need to be confirmed in a larger study. However, these findings provide evidence that CPAP
therapy has the potential to improve cognitive functioning in a subset of MCI patients that have OSA. This is important information for clinicians as sleep apnoea is treatable and clinicians can potentially eliminate a significant risk factor of cognitive decline through proper management of sleep apnoea. The prevalence and incidence rates of dementia is projected to increase over the next 40 years (Brown, Hansnata & La, 2017). As there is no known cure, interventions to delay onset or reduce risk of conversion have mainly focused on treating modifiable factors. The current thesis provides preliminary evidence of OSA as a potential modifiable factor. Further longitudinal research is required to better understand the role of sleep apnoea on cognitive functioning and mood in MCI patients, and if early intervention of CPAP therapy is able to reduce the risk of future conversion to dementia.
Reference list


Law, M., Naughton, M., Ho, S., Roebuck, T., & Dabscheck, E. (2014). Depression may reduce adherence during CPAP titration trial. *Journal of Clinical Sleep Medicine, 10*(02), 163-169.


Mathieu, A., Mazza, S., Decary, A., Massicotte-Marquez, J., Petit, D., Gosselin, N., ... & Montplaisir, J. (2008). Effects of obstructive sleep apnea on cognitive function: a comparison between younger and older OSAS patients. *Sleep Medicine, 9*(2), 112-120.


Rauchs, G., Piolino, P., Bertran, F., de La Sayette, V., Viader, F., Eustache, F., & Desgranges, B. (2013). Retrieval of recent autobiographical memories is associated with slow-wave sleep in early AD. *Frontiers in Behavioral Neuroscience, 7*, 114


Schwartz, D. J. & Kartinos, G. (2007). For individuals with obstructive sleep apnea, institution of CPAP therapy is associated with an amelioration of symptoms of depression which is sustained long term. Journal of Clinical Sleep Medicine, 3(6), 631-635.


Sforza, E., de Saint Hilaire, Z., Pelissolo, A., Rochat, T., & Ibanez, V. (2002). Personality, anxiety and mood traits in patients with sleep-related breathing disorders: effect of reduced daytime alertness. Sleep Medicine, 3(2), 139-145.


Appendices

Appendix A: Austin HREC approval letter

AUSTIN HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL FOR NEW STUDY

Dr Melinda Jackson
Melbourne School of Psychological Sciences
The University of Melbourne

03 December 2015

Dear Dr Jackson

AU RED HREC Reference Number: HREC/15/Austin/393

Austin Health Project Number: ND 15/393

Project Title: Does treatment of Obstructive Sleep Apnoea in patients with memory impairment improve memory and mood?

I am pleased to advise that the above project amendment has received ethical approval from the Austin Health Human Research Ethics Committee (HREC). This HREC is organised and operates in accordance with the National Health and Medical Research Council’s (NHRMC) National Statement on Ethical Conduct in Research Involving Humans (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

HREC Approval Date: 03/12/2015

Participating Sites:
Ethical approval for this project applies at the following sites:

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<thead>
<tr>
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<td>Austin Health</td>
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Approved Documents:
The following documents have been reviewed and approved:

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Site Specific Assessment:

SSA Authorisation is required at all sites participating in the study. SSA must be authorised at a site before the research project can commence.

The completed Site-Specific Assessment Form and a copy of this ethics approval must be submitted to the Research Governance Office in order to obtain authorisation to commence your project. It is recommended that you check details of governance application submission requirements with each participating site.

Conditions of Ethics Approval:

- You are required to submit to the HREC:
  - An Annual Progress Report (that covers all sites listed on approval) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report, due within one month of the approval anniversary. Failure to comply with this requirement may result in suspension of the project by the HREC.
  - A comprehensive Final Report upon completion of the project.
- Submit to the reviewing HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure.
- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC Position Statement: Monitoring and reporting of safety for clinical trials involving therapeutic products May 2009.
- Notify the reviewing HREC of your inability to continue as Coordinating Principal Investigator.
- Notify the reviewing HREC of the failure to commence the study within 12 months of the HREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
- Notify the reviewing HREC of any matters which may impact the conduct of the project.
- If your project involves radiation, you are legally obliged to conduct your research in accordance with the Australian Radiation Protection and Nuclear Safety Agency Code of Practice ‘Exposure of Humans to Ionizing Radiation for Research Purposes’ Radiation Protection series Publication No.8 (May 2005) [ARPANSA Code].

The HREC may conduct an audit of the project at any time.

Yours sincerely

[Signature]

Austin Health Ethics Approval Letter Version 1, dated 03 Sept 2015 based on REx Ethics Approval letter template Version 1, dated 6 Aug 2015
Appendix B: RMIT HREC registration letter

Notice of RMIT Registration
Of an Approved External Human Research Ethics Application

Date: 16 September 2015

Approval number (principal HREC): HREC/15/NH/7

Approving HREC: Northern Health

RMIT Reference number (RM): 19269

Project title: Does treatment of obstructive sleep apnoea in patients with memory impairment improve memory and mood?

Risk classification: More than low risk

Chief investigator and institution: Dr Melinda Jackson, RMIT University

RMIT Personnel: Professor Stephen Robinson (Co-investigator)
Ms V’Vien Lee (Student researcher)

Registration: From: 1 July 2015
To: 1 December 2017

Terms of Registration:

1. Responsibilities of RMIT personnel
   It is the responsibility of the chief investigator to ensure that all other investigators and staff on a project are aware of the terms of approval and to ensure that the project is conducted as approved by external HREC and according to the terms of registration at RMIT. Registration is only valid whilst RMIT personnel hold a position at RMIT University.

2. Amendments
   Amendments to an approved application are sought according to the processes used by the external HREC. After approval for an amendment is received relevant documentation (copy of amendment and approval notice, etc) must be provided to the RMIT HREC.

3. Adverse events
   You should notify the RMIT HREC immediately of any adverse events that are reported to the external HREC.

4. Reports
   Copies of progress, annual or final reports submitted to the external HREC must be provided to RMIT HREC.

5. Complaints
   Any complaints that are received regarding this project must be reported to the external HREC and also notified to the RMIT HREC.

6. Special conditions of approval
   Nil.

In any future correspondence please quote the RMIT reference number and project title above.

A/Prof Barbara Polius
Chairperson
RMIT HREC

cc: Dr Peter Burke (HREC secretary),
Appendix C: Northern HREC approval letter

18th June 2015

RMIT
University School of Health Sciences
PO Box 71
Bundoora VIC 3083

Att: Dr Melinda Jackson
VC Senior Research Fellow

Dear Dr Jackson,

Re: Ethical Approval Letter

HREC Reference Number: HREC/15/NH/7
SSA Number: SSA/15/NH/17
Protocol Number: Version 1 dated 25/05/2015

Study Title: Does treatment of obstructive sleep apnoea in patients with memory impairment improve memory and mood?

I am pleased to advise that the above project has received ethics approval by the Northern Health HREC on 18th June 2015 and may now be conducted at Northern Health sites.

Status: Final

Approval is granted for 5 years and conditional upon receipt of an annual report or if a decision has been made to close the project prematurely for safety or other reasons. A final report is still required to be sent.

Documents approved:

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Stop Bang Questionnaire
CV - V Vien Lee, Dr Andrew Kyoong

In order to comply with the National Statement on Ethical Conduct in Human Research 2007 including all updates, Australian Code for the Responsible Conduct of Research, Guidelines for Good Clinical Research Practice (CPMP/ICH/15/95) and local research policies and guidelines, you are required to adhere to the following conditions and report to the HREC Secretariat as required:

- The principal investigator is to ensure that all associate researchers are aware of the terms of approval and to ensure the project is conducted as specified in the application and in accordance with the National Statement on Ethical Conduct in Human Research (2007), including all updates.
- Your inability to continue as principal investigator and any other change in research personnel involved in the project at Northern Health.
- Any proposed extension to the duration of the project past the HREC approval date stated above.
- Immediate notification to the Research Governance Office of any serious adverse events involving Northern Health participants.
- Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project.
- Notification and reasons for ceasing the project prior to its expected date of completion.
- Submission of amendments to the study.
- Submission of an annual report, due on the anniversary date of approval, for the duration of the study.
- Submission of a final report and papers published on completion of the project.
- Projects may be subject to an audit or any other form of monitoring by the Research Governance Office at any time.

Additional conditions:
The study must not commence until Memorandum of Understanding is signed and approved.

Please refer to the Northern Health Ethics website for access to forms, policies and procedures relating to research at Northern Health.

Yours sincerely,

Mr Kollen Sussman
Director Education & Research

On behalf of: Mr David Ruschena, Chair, Northern Health Human Research Ethics Committee

Copy: Miss V Vien Lee