THE EFFECT OF CONTINOUS POSITIVE AIRWAY PRESSURE (CPAP) ON MEMORY

by

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LIST OF ABBREVIATIONS

Abbreviation	Description
ANOVA	Analysis of Variance
CPAP	Continuous Positive Airway Pressure
EEG	Electroencephalogram
LTM	Long-Term Memory
NPSG	Diagnostic Patient
NREM	Non-Rapid Eye Movement
OSA	Obstructive Sleep Apnea
REM	Rapid Eye Movement
RNA	Ribonucleic Acid
STM	Short-Term Memory
SWS	Slow Wave Sleep
tDCS	Transcranial Direct-Current Stimulation

ABSTRACT

Obstructive sleep apnea (OSA) is a clinical sleep disorder that is characterized by frequent pauses in breathing during sleep due to obstructions of the upper airway, and can lead to a range of cardiovascular and neuropsychological deficits, including memory problems. During sleep, recent memories are actively processed and consolidated into pre-existing knowledge networks. Consolidation is also discriminatory, such that memories that are relevant for future behavior are enhanced more so than other memories. It is possible that the memory deficits associated with untreated OSA are due to deficits in memory consolidation from disrupted sleep. Continuous positive airway pressure (CPAP) is the standard treatment for OSA, and long-term use has been shown to ameliorate the physiological, psychological, and memory impairments associated with OSA. This study investigated the effect of a single night of CPAP treatment on memory consolidation. The study included treatment-naïve OSA patients (no-CPAP group) and OSA patients receiving their first night of CPAP treatment (CPAP group). All participants completed two consecutive rounds of study followed by a test for picture-location memories from two categories of objects before a sleep period. In addition, just prior to sleep, all participants were informed that they would complete the memory test again in the morning and if their memory for one specific category of objects improved from the evening test they would receive additional compensation. Before the morning test, all participants were informed that, counter to the previous instruction, they would

receive the monetary bonus upon improvement in both reward-relevant and reward – irrelevant object categories. There were no differences in memory accuracy or in memory change from the evening to the morning test between groups. Furthermore, both groups showed better retention of reward-irrelevant compared with reward-relevant items from the evening to the morning test. These results suggest that a single night of CPAP use is not sufficient to improve memory. Furthermore, while both groups became less confident in their responses from the evening to the morning test, the no-CPAP group showed a greater confidence decrease for reward-irrelevant compared with reward-relevant items. This suggests that memory consolidation processes may have actually been more efficient for the no-CPAP group compared with the CPAP group, perhaps due to the difficulty adjusting to initial CPAP use. Overall, these results suggest that future research including objective sleep measures is necessary to fully understand the relationship between OSA, CPAP, and memory consolidation.

I. INTRODUCTION

Approximately 26 percent of U.S. adults between ages 30-70 are afflicted with obstructive sleep apnea (OSA), and its prevalence has increased up to 55 percent in the past twenty years (Peppard et al., 2013). OSA is a sleep disorder that causes fragmented sleep due to brief periods of oxygen deprivation, and it is considered a serious medical condition due to the severity of consequences if left untreated. The combination of sleep and oxygen starvation are known to deteriorate the cardiovascular system (Stansbury & Strollo, 2015), and in recent years, OSA has become associated with memory deficits (Beebe, Groesz, Wells, Naëgelé et al. 2006, Nichols & McGee, 2003). Similarly, research unearthing a causal relationship between sleep and memory has been concurrently accumulating (Diekelmann & Born, 2010). During sleep, memories undergo a transformation process where they are stabilized for long-term storage; this process is called consolidation (Diekelmann & Born, 2010). Therefore, sleep disruptions concomitant with OSA may impair consolidation. This thesis will first review the literature on OSA, treatments for OSA, and memory consolidation. Given the logical relationship between these three factors, this study investigated if the memory deficits associated with OSA can be alleviated with treatment.

Memory

Memory is the ability to encode, store, and retrieve information. One way to conceptualize different types of memory is by the duration of the memory; whether or not the memory is kept temporarily or permanently. Short-term memory (STM) refers to memories that are held briefly, 15-30 seconds, and in a limited capacity (Atkinson & Shiffrin, 1968). Long-term memory (LTM) refers to memories that last indefinitely. LTM

is also believed to have no capacity limit, but the integrity of a memory can decay over time (Ebbinghaus, 1913). LTM is further divided by the nature of the memory. If the memory is consciously retrieved it is referred to as declarative. If the memory is unconsciously expressed, it is referred to as non-declarative. This paper will focus on declarative, long-term memories.

All long-term memories were once short-term memories, but not all short-term memories become long-term memories. Memory consolidation refers to the processes that ensue after a memory is initially encoded that stabilize memory traces for long-term storage. There are two types of consolidation: synaptic and systems. Synaptic consolidation takes place in minutes to hours after encoding and involves molecular changes at individual synapses. Systems consolidation involves the redistribution of memory storage sites and integration of memory traces with existing long-term memories over the course of days to years (Dudai, 2004; Diekelmann & Born, 2010). Declarative memories are initially dependent on the hippocampus. However, over time, through systems consolidation, they are thought to be entirely cortically mediated and stored independent of the hippocampus. Moreover, it is now believed that systems consolidation optimally occurs during sleep (Diekelmann & Born, 2010). This study focuses on systems consolidation.

Sleep

Like memory, sleep can be divided into subtypes. During sleep, humans pass through four distinct stages in 90-120 minute cycles throughout the night. Electroencephalography (EEG) is used to monitor and record the electrical activity of the brain through electrodes placed on the scalp. The waveforms that are generated are used

to characterize the four stages of sleep. Non-rapid eye movement (NREM) stages occur first. Stage 1 is the lightest level of sleep and is characterized by attenuating alpha rhythms (8-13 Hz), and slower theta frequencies (4-7 Hz; Payne, Ellenbogen, Walker & Stickgold, 2009). Next is Stage 2, during which EEG frequencies continue to diminish. During Stage 2, units of sharp, negative oscillations immediately followed by high amplitude slow waves called K complexes begin to emerge (Culebras, 1996) as well as sleep spindles, short (1-3 s) oscillations of 11-16 Hz that are synchronized across the cortex (Payne et al. 2009). The third NREM stage is slow wave sleep (SWS), which is characterized by EEG oscillations that are high in amplitude, but low in frequency (1-4 Hz). During this stage, the body is relaxed and muscle tone decreases. Rapid eye movement (REM) sleep typically follows SWS. During REM sleep, the EEG oscillations are similar to EEG oscillations seen when people are awake; low in amplitude and high in frequency. However, the stage is named after the random spurts of eye movements that occur even though the eyes are closed. Also, muscles are the most relaxed in this stage, meaning there is virtually a complete surrender of muscle tone.

Systems Consolidation During Sleep

Research suggests that SWS in particular is involved in the redistribution of declarative memories from hippocampal to cortical storage sites (Diekelmann & Born, 2010). The slow oscillations during SWS are synchronized across the cortex, and they are thought to facilitate cross-talk between different subcortical regions and the cortex or between different regions of the cortex (Buzáki, 1998; Marshall, Helgadóttir, Mölle & Born, 2006; Mölle, Marshall, Gais & Born, 2002; Wolansky, Clement, Peters, Palczak & Dickson, 2006). The importance of SWS for memory consolidation is supported by a

large body of literature. For example, Plihal and Born (1999) determined that declarative memory retention improves following a sleep period rich in SWS compared with a sleep period rich in REM sleep. Expanding on Plihal and Born's finding, many studies have shown that the amount of slow-wave activity that occurs during SWS is positively correlated with post-sleep performance on declarative memory tasks (Alger, Lau & Fishbein, 2010; Alger, Lau & Fishbein, 2012; Ruch et al., 2012). Takashima et al. (2006) examined neural changes concomitant with systems consolidation over the course of 90 days using functional magnetic resonance imaging (fMRI) and found that the duration of SWS following encoding predicted reductions in hippocampal activity, which was associated with the correct recognition of declarative memories over time. Further, activity in the ventral medial prefrontal cortex increased over time for the same declarative memories. This is in line with the theory that consolidation involves a simultaneous strengthening of cortical connections related to a memory trace, and a decrease in hippocampal activity. Finally, other evidence has shown that SWS has a causal role in declarative memory consolidation (Huber, Esser, Ferrarelli, Massimini, Peterson & Tononi, 2007; Huber et al., 2008; Marshall, Mölle, Hallschmid & Born, 2004; Marshall, Helgadóttir, Mölle & Born, 2006). For example, Marshall, Mölle, Hallschmid, and Born (2004), showed that anodal transcranial direct-current stimulation (tDCS), a focal, low-current electrical stimulation oscillating at the typical slow-wave frequency, applied via electrodes placed on the scalp during sleep increased the post-sleep retention rate of word pairs compared with memory following a night of sleep when tDCS was not applied. This was the first study to demonstrate that declarative memory improvement was a direct result of the induced slow-oscillations during sleep.

Systems consolidation is hypothesized to move forward through the reactivation of memory traces during SWS. In support of this view, the temporal firing patterns of neurons associated with specific memories are "replayed" during sleep in rodents (Wilson & McNaughton, 1994). Further, the "replays" occur in the same order in which the memories were learned, and the number of "replays" corresponds with later memory (Skaggs, McNaughton, Wilson & Barnes, 1996; Wilson & McNaughton, 1994). Reactivation of memories during sleep has been demonstrated in humans also. Studies have shown that when specific sounds or odors are present at encoding and are re-exposed to participants while they are in SWS, there is an increase in the retention of the memories previously associated with these odors and sounds after sleep (Cairney, Durrant, Hulleman & Lewis, 2014; Rasch, Büchel, Gais & Born, 2007; Rudoy, Voss, Westerberg & Paller, 2009). Collectively, these results suggest that reactivation of memories during SWS promotes consolidation.

However, not all recently encoded memories are reactivated during sleep. Rather, sleep-dependent memory processing appears to discriminate between memories, such that some memories are strengthened whereas others are not. Although the mechanism used to discriminate between memories is not known, research has identified several factors that can influence the extent to which memories are consolidated (Stickgold & Walker, 2013).

One factor that can influence consolidation is the future relevance of the memory (Saletin, Goldstein & Walker, 2011; van Dongen, Thielen, Takashima, Barth & Fernandez, 2012). For example, Wilhelm, Diekelmann, Molzow, Ayoub, Mölle and Born (2011) had participants encode word pairs before a sleep period. Immediately after

encoding and prior to sleep, half of the participants were informed that they would need to recall the word pairs after waking, whereas the other half were not aware of the recall test. They found that memory was better for participants who were aware of the post-sleep memory test compared with those who had not been instructed to remember or with those who had remained awake post-learning. They also found that participants who were expecting a post-sleep memory test spent more time in SWS, and had more powerful slow oscillations during SWS than the group that was not expecting the post-sleep memory test. Additionally, memory retention correlated with the amount of slow-wave activity in the expectant group, but not in the not-expectant group. In sum, these results suggest that memories that are relevant for the future are consolidated to a greater extent than memories that are not.

Emotional memories are also more likely to be consolidated. For example, studies have found that memories with emotional content show a greater benefit after sleep compared with memories without emotional content (Hu, Stylos-Allan & Walker 2006; Payne, Stickgold, Swanberg & Kensinger 2008). Further, even when participants do not know their memory will be tested, emotional information is still remembered better than neutral information (Payne et al. 2008).

Lastly, memories associated with a monetary reward appear to preferentially benefit from sleep-dependent consolidation (Bennion, Payne & Kensinger, 2016; Fischer & Born, 2009, Oudiette, Antony, Creery & Paller, 2013; van Dongen et at., 2012). For example, van Dongen et al. (2012) showed that reward-related memories are preferentially consolidated compared with other memories. In their study, participants learned two sets of picture-location associations, and after learning, they were told that

they would only be tested on one set of associations after a delay, and further were promised a monetary reward for each correctly recalled association from this set. After the delay, during which participants either slept or remained awake for 14 hours, the participants were tested on both sets of associations. Results showed a sleep-dependent benefit for the picture-location set associated with a reward, as well as a correlation between sleep duration and retention of reward-related memories. Similarly, studies have shown that this effect is modulated by the value of the reward; memories associated with a high-value reward show a greater memory benefit than those associated with a low value reward (Bennion, Payne & Kensinger, 2016; Oudiette, Antony, Creery & Paller, 2013).

The research reviewed above indicates that memories associated with future use, emotion, and monetary reward are preferentially consolidated. These findings fit with the theory that memory consolidation is the mechanism whereby recent experiences are evaluated in relation to future goals (Winson, 2004), such that memories most relevant for achieving our goals are prioritized for consolidation. Emotions are hypothesized to prepare us for future actions (Lazarus, 1991). Thus, memories with emotional content would receive preferential access to consolidation processing. For example, imagine you cut through an alley on your way home from work at night and you are mugged. This memory would be prioritized for consolidation so that the next time you are on your way home you remember this experience, and avoid the alleyway in favor of the lit sidewalk to bypass another potentially negative experience. Likewise, monetary rewards could be associated with positive emotions, and/or a future goal of maximizing financial gain.

Obstructive Sleep Apnea

Given that sleep is important for memory consolidation, it is reasonable to assume that sleep disorders may impede this process. A common sleep disorder is OSA, in which a person experiences bouts of shallow breaths and/or pauses in breathing while sleeping. According to the National Institutes of Health (2012), the temporary lapses of breathing, called apnea-hypopneas (apneas), can range in duration from seconds up to several minutes, and the frequency can exceed over thirty occurrences within one hour. A diagnosis of OSA is based on the number of apneas a sleeper experiences in an hour, known as the apnea-hypopnea index (AHI). A positive diagnosis is achieved with either 5 apneas an hour with other symptoms present, or 15 apneas within an hour and no other symptoms present (Qaseem. Dallas, Owens, Starkey, Holty, & Shekelle, 2014). Apneas are associated with hypoxemia, defined as an abnormally low blood oxygen concentration (Dewan, Nieto & Somers, 2015). Intermittent hypoxemia alerts the brain to briefly wake the individual, resulting in sleep fragmentation. Hypoxemia can result in hypoxia, wherein the low blood oxygen level leads to abnormally low oxygen concentrations in body tissues.

OSA is caused by the partial or complete blockage of the airway due to the relaxation of the neck muscles. Muscles become increasingly relaxed during SWS, leading to a total relaxation during REM. Thus, OSA typically disrupts SWS and REM more than other sleep stages. Other physical effects of long-term intermittent hypoxia on the body are severe and can lead to physical ailments like high blood pressure, heart disease, and stroke. OSA is a chronic condition that can be successfully managed with long-term treatment compliance. However, untreated patients face dire outcomes. One

study found that the 5-year survival rate for untreated patients is 80%, while the survival rate for treated patients is 97% (Marti et al., 2002). Despite the severe consequences of untreated OSA, treatment adherence is minimal; 46-83% of patients report non-adherence to treatment (Weaver & Grunstein, 2008).

Further, areas of the brain implicated in cognitive processing, including the hippocampus, fornix, mammillary bodies, multiple white matter tracts, anterior thalamus, and cortex, have shown focal size reductions and structural injury in untreated OSA patients (Castronovo et al., 2014; Kumar et al., 2008; Macey et al., 2002; Morrell, McRobbie, Quest, Cummin, Ghiassi & Corfield, 2003; Tummala, et al. 2016). Not surprisingly, OSA has been associated with significant impairments to a broad range of cognitive functions (Aloia et al., 2004; Bawden, Oliveira & Caramelli, 2011; Matthews & Aloia, 2011; Naëgelé et al., 2006; Salorio et al., 2002). Many studies have found that OSA severity as measured by hypoxemia, sleep fragmentation, and AHI is related to impairments in sustained attention, monitoring information, and reaction times (Matthews & Aloia, 2011). The fatigue and excessive daytime sleepiness caused by OSA is thought to underlie deficits in attention, vigilance, and mental flexibility (Mazza, Pèppin, Naëgelé, Plante, Deschaux & Lèvy, 2005).

Increasing evidence suggests that the bouts of hypoxemia and consequent sleep disruptions may also impair memory. The most comprehensive study to examine memory deficits in OSA patients was done by Naëgelé et al. (2006) who evaluated verbal declarative memory, procedural (non-declarative) memory and working (short-term) memory through a subset of a neuropsychiatric test battery. Compared with controls, OSA patients showed significant deficits in both declarative and non-declarative memory

(Naëgelé et al. 2006). These results corroborate earlier studies (e.g., Beebe, Groesz, Wells, Nichols & McGee, 2003). However, declarative memory for non-verbal materials has seldom been examined in patients with OSA (Twigg et al., 2010; Salorio, White, Piccirillo, Duntley & Uhles, 2002; Naëgelé et al., 1995; Kloepfer et al., 2009). Furthermore, most researchers have looked at the effects of OSA on cognition with neuropsychiatric assessments, and by testing before or after a period of sleep, not both. Accordingly, the literature regarding this topic mainly exists to categorize the cognitive deficits associated with OSA rather than to determine how these deficits are occurring. Studies have found that OSA patients show less overnight improvement of non-declarative memories compared to healthy sleepers, and that cognitive deficits related to OSA are worsened by age (Djonlagic, Guo, Matteis, Carusona, Stickgold & Malhotra, 2014). No studies have examined how declarative memory changes across one night of sleep in OSA patients. Doing so could shed light onto the mechanisms responsible for the memory deficits associated with OSA.

Studies have also shown that the cognitive deficits in OSA patients could have a genetic basis. The APOE gene codes for a protein primarily responsible for packing and carrying cholesterol in the brain and through the bloodstream, and comes in three variants, E2, E3, and E4 (Kadotani et al. 2001). Kadotani et al. (2001) found that the probability of developing moderate to severe sleep apnea and experiencing a clinically significant AHI was significantly greater in those that carry APOE E4 than those who do not. Similarly, Cosentino et al. (2008) found that the presence of the APOE E4 allele in OSA patients corresponded with verbal declarative memory impairments. Decreased APOE function has been associated with increased susceptibility to neurocognitive

dysfunction in mice (Kheirandish, Row, Li, Brittian & Gozal, 2005). Further, hippocampal and cortical cell loss due to pro-apoptotic mechanisms has been found in rodents exposed to intermittent hypoxia, resulting in impaired learning (Gozal, Daniel & Dohanich, 2001; Row, Liu, Xu, Kheirandish & Gozal, 2003). Kheirandish et al. (2005) amplified this effect in rodents by mutating their APOE gene to be less active and found that less active APOE alleles lead to increased activation of inflammatory and oxidative mechanisms that lead to increased apoptotic cell loss in the hippocampus and cortex (Kheirandish et al., 2005). It is possible that the E4 allele of APOE is an underperforming allele.

It is of interest to note that the E4 allele of APOE is also a marker of late-onset Alzheimer' disease (Poirier et al., 1993). Similar APOE associated inflammation and oxidative apoptic cascades have been discovered in Alzheimer rodent models (Anderasson et al., 2001; Nogawa, Zhang, Ross & Iadecola, 1997). For carriers of APOE E4, OSA might prematurely express or accelerate the memory impairments similar to Alzheimer's. Likewise, hypoxia also mediates posttranslational modifications of Rpb1, the binding subunit of RNA Polymerase II, in the prefrontal cortex as well as the hippocampus (Ignacak et al., 2009). These translational modifications were isolated to these two regions and were accompanied by cognitive deficits. It is possible that the translational modifications of Rpb1 could be regulating the expression of genes like APOE, or other genes known to mediate cognitive deficits.

Continuous Positive Airway Pressure

The primary treatment for OSA is continuous positive airway pressure (CPAP). CPAP counteracts airway obstructions by using air pressure to force the airway open.

CPAP effectively reduces gas-exchange perturbations, respiratory effort, blood pressure surges, sleep arousals, blood pressure, and the overall AHI value (Basner, 2007; Garpestad et al., 1992; Giles, Lasserson, Smith, White, Wright & Cates, 2006; Gleeson, Zwillich & White, 1990; Younes, 2004). Similarly, the white-matter detriment associated with OSA is reversible with CPAP treatment; white-matter improvement is visible at 3 months, and nearly restored by 12 months (Castronovo et al., 2014). Moreover, white matter restoration corresponds with improvements in executive functioning, attention, and memory (Castronovo et al., 2014). Thus, the restoration of white matter could ameliorate the cognitive deficits associated with OSA.

Many studies have examined the restorative effects of CPAP treatment on the cognitive deficits in OSA. Most of these studies quantify the effect of long-term treatment on cognitive measures with different neuropsychological test batteries and varied treatment adherence durations. That being said, due to the lack of standardized characterization of disease severity across the literature, the accumulated research on the topic is often contradictory (Aloia et al., 2004).

Some research has shown a positive effect of CPAP treatment on cognitive performance, including vigilance, declarative memory, and executive functioning (Aloia et al., 2004; Davies & Harrington, 2016). The majority of studies report that attention and vigilance show the greatest gain from CPAP treatment, and some studies show improvement in attention and vigilance after a single night of CPAP. (Pan, Deng, Xu, Liu & Liu, 2015). The literature in other cognitive domains, however, is varied. Studies have found mixed results on the effect of a single night of CPAP on nondeclarative memory consolidation (Djonlagic et al., 2014; Djonlagic et al. 2015). Declarative memory has

been shown to improve as a result of long-term CPAP treatment (Dalmases et al. 2015). However, the effect of a single night of CPAP treatment on declarative memory consolidation has never been studied. Thus, it is possible that impaired sleep-dependent consolidation is contributing to the declarative memory deficits associated with OSA.

Purpose of the Current Study

This experiment is the first to study the effect of a single night of CPAP on the consolidation of non-verbal declarative memories in patients with OSA. The mechanism responsible for declarative memory improvements with repeated CPAP use is currently unknown. One possibility is that these improvements are a result of improved sleep-dependent memory consolidation. However, it is also possible that reduced daytime sleepiness due to long-term CPAP use may improve attention and vigilance during learning and/or retrieval, rather than improving sleep-dependent consolidation. Using a declarative, non-verbal test previously shown to be sensitive to sleep-dependent consolidation processes (van Dongen et al., 2012), this study investigated the effect of CPAP on declarative memory consolidation in patients with OSA across a single night of sleep. A greater pre- to post-sleep memory improvement in OSA patients receiving CPAP treatment compared with patients with untreated OSA would suggest that CPAP treatment improves sleep-dependent memory consolidation. As a further test of this hypothesis, after study, a monetary reward was offered for post-sleep memory performance for some but not all of the studied material. In this way, a greater improvement in reward-associated memories compared with memories for information not associated with a reward is expected for OSA patients receiving CPAP treatment compared with the OSA patients not receiving treatment.

II. METHODS

This project was approved by the Institutional Review Board at Texas State University.

Participants

Participants were individuals who completed an overnight sleep study at the Texas State University Sleep Center. The final participant group consisted of 34 individuals with confirmed OSA, including 18 participants with a diagnostic appointment (no-CPAP group), and 16 participants with a confirmatory appointment (CPAP group). One participant from each group was excluded due to poor memory performance (<30%) on the initial memory test, and two additional participants from the diagnostic group were excluded due to computer error during data collection. Diagnostic appointments are conducted to confirm the presence of OSA. Confirmation of OSA in diagnostic patients was based on their AHI as calculated by the sleep technician. Participants were included if their AHI was at least 5, meaning they suffered at least 5 apnea events an hour. Confirmatory appointments are conducted after an individual has confirmed OSA, to test the influence of CPAP on sleep measures. The final sample of 30 participants (mean age = 52.63 years, *SD* = 16.30) with OSA included 15 participants who received overnight CPAP treatment for OSA (CPAP group) and 15 who did not (no-CPAP group). The CPAP group had 10 males, and the no-CPAP group had 8 males. Age was not significantly different between the CPAP (*M* = 55.66, *SD* = 14.90) and no-CPAP (*M* = 49.17 years, *SD* = 17.66) groups; $t(28) = 1.092$, $p > 0.3$. All patients had normal or corrected-to-normal vision, were not actively taking central nervous system-active medications or psychotropic medications, and were not diagnosed with dementia or any

other serious cognitive disorder. All participants received $30 for participating in the study.

Procedure

Appointments at the Texas State Sleep Center were conducted starting at 9:00 pm or 10:00 pm. Potential participants were initially taken to a bedroom by a Texas State Sleep Center sleep technician. At this time, a research assistant gave the potential participant a brief description of the study and asked if he/she would be interested in participating in the study. Potential participants were also informed that if they participated in the study they would be compensated a minimum of $20, with the potential to earn a maximum of $30. If the person agreed, the research assistant obtained informed consent. Next, the participant was prepped for his/her sleep study by a Texas State Sleep Center sleep technician. The prep work included applying electrodes to the head, face, chest, abdomen, and legs in addition to other various sensors to obtain information regarding brain activity, muscle tone, eye movements, breathing patterns, and leg movements during subsequent sleep. This process typically lasted 45-60 minutes, and ended approximately 1 hour after the participant arrived. The participant then had a one-hour break before his/her sleep session began at either 11:00 p.m. or 12:00 a.m. During this break, the researcher met the participant in his/her room to conduct part 1 of the experimental task. The next morning between 5:00 a.m. and 7:00 a.m., the sleep technician woke up the participant and removed the recording sensors. Immediately following sensor removal, the researcher met with the participant in his/her room and part 2 of the experimental task was completed.

Part 1. During part 1 of the experimental task, participants were seated in a chair in the sleep-testing bedroom and studied objects presented on a laptop resting on a cart. Immediately after, participants took a memory test for those objects. Each participant completed two identical study-test cycles during part 1. The first cycle was a learning cycle to provide adequate exposure to the stimuli, as well as to minimize participant error due to unfamiliarity with the computer interface, and the second cycle was used to determine baseline memory performance.

During the study phase, 64 color photographs of common everyday objects from 2 of 4 possible categories (kitchen items, animals, food, and furniture) were presented one at a time in 1 of 8 possible screen locations for 400 ms each, randomly intermixed (see Figure 1 for possible object locations). All images were 200x256 pixels, and all objects appeared against a white background. All locations were used equally as often with the caveat that four locations were always occupied by objects from one category, and the remaining four locations were occupied by objects from the other category. The two specific categories seen by a given individual was counterbalanced across participants. Prior to each object presentation, a fixation cross appeared in the center of the screen for 200 ms. Before the study phase began participants were instructed to study the location of each object because they would be tested on them later. Participants were also informed that three vigilance trials would be randomly intermixed with the 64 study trials, and that unlike the other study trials, they required a response to continue. The vigilance trials were added to ensure that participants were paying attention and actively engaged in the task. During the vigilance trials, the screen asked participants to press a

keyboard key (“B” or “K”) and the study phase did not continue until the patient pressed

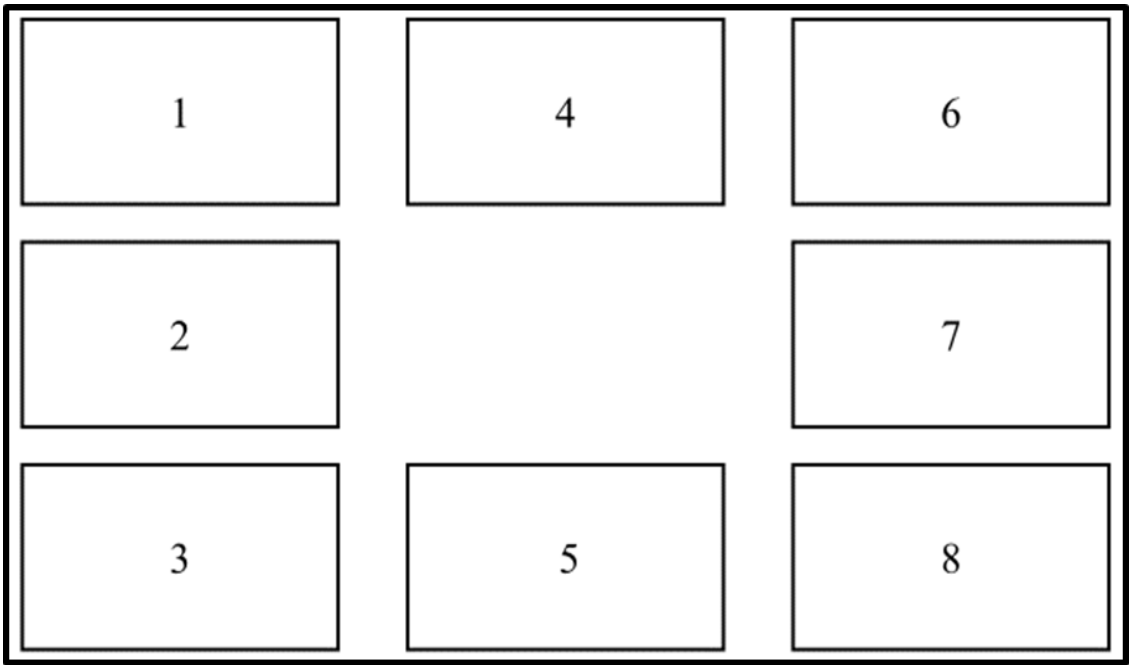

Figure 1: The eight possible locations objects could appear in during the study phase.

the specified key. The study phase took approximately five minutes to complete.

During the test phase, the locations associated with each of the 64 previously studied objects were tested in individual trials that proceeded in a random order (see Figure 2 for the sequence of events in each test trial). Each trial began with a fixation cross that was displayed in the center of the screen for 400 ms. Next, one of the previously studied objects was displayed in the center of the screen surrounded by eight 250x256 pixel white squares with a black border appeared on the screen. Each square included a number (1-8) in black font in the center, representing each of the eight possible image locations. Participants were instructed to select the correct location of each object by pressing the number key corresponding to the square they believed represented the studied location (1-8) on the keyboard at any time during the trial. If the

participant did not respond after the squares had been on the screen for 400 ms, the same eight box configuration would appear on the screen with the exception that the object in the center of the screen would be replaced with a text box with a black border and white background that read “Please make your selection now” in black 26 point Times New Roman font for a maximum of 800 ms. Once the participant made his/her selection (which could occur anytime during the 1200 ms trial), or if the participant failed to respond in the allotted 1200 ms, a screen prompting a confidence rating was displayed. This included a white background with black 26 point Times New Roman text centered in the middle of the screen that read “Please rate your confidence now”, and a 5-point Likert scale directly beneath the text instructions. The Likert scale was labeled by text that read “Unsure” and “Sure” centered below the 1 and 5, respectively. The participant was asked to select a number, 1-5, that represented his/her confidence in his/her answer with 1 being the least confident and 5 being the most confident, by pressing the corresponding key on the keyboard. Participants were instructed to choose the lowest confidence rating, 1, if they did not remember the location. A response was required to continue the test.

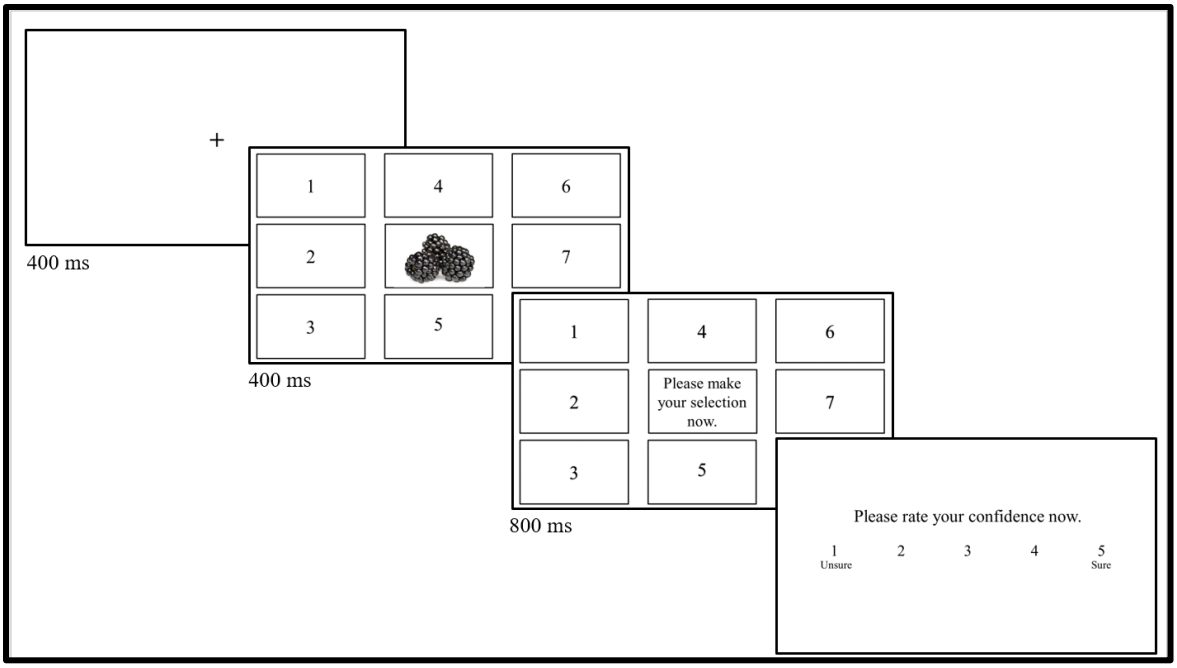

Figure 2: An example test trial.

After the second study-test cycle was complete, participants were instructed that there would be a final memory test in the morning. Furthermore, similar to van Dongen et al. (2012), they were also instructed that they would receive $10 additional compensation if their performance for one object category (specific category counterbalanced across participants) improved relative to their evening memory performance.

Part 2. After waking, the sleep recording sensors were removed, and participants took the same memory test that was administered during part 1, with the exception that the trials were presented in a new random order. Immediately prior to testing, participants were given new instructions. Specifically, participants were told that they were going to be tested on both object categories, and that the additional $10 payment was going to depend on memory accuracy in both categories rather than just one (Fischer & Born, 2009; van Dongen et al., 2012). After the test was complete, each participant was paid $30 regardless of his/her performance.

III. RESULTS

Percent correct was calculated for each of the two object categories (relevant, irrelevant; where relevant indicates the category for which participants expected to receive additional money if they showed improvement) for the second evening test (test) and for the morning test (retest) for each participant. To determine whether there were baseline memory differences across groups, percent correct for test was compared between the CPAP (M = 0.667, SD = 0.145) and no-CPAP group (M = .703, SD = 0.155) using an independent samples t-test. No significant difference was present, $t(28) = -0.655$, $p > 0.5$, see Table 1.

Table 1: Percent correct for the CPAP and No-CPAP groups for relevant and irrelevant objects at test and retest. Standard deviations in parentheses.

	CPAP		*No-CPAP*	
	Test	Retest	Test	Retest
Relevant	0.681 (0.176)	0.597 (0.190)	0.710 (0.178)	0.607 (0.156)
Irrelevant	0.652 (0.153)	0.626 (0.163)	0.696 (0.161)	0.633 (0.169)

To determine whether overnight CPAP treatment improved declarative memory consolidation, a 2x2x2 ANOVA was conducted to examine the effect of three factors on percent correct: group (between-subjects; CPAP and no-CPAP), session (within-subjects; test and retest) and category (within-subjects; relevant and irrelevant). A main effect of session showed that both groups did significantly better at test (M = 0.685, SD = 0.027) than at retest (M = 0.616, SD = 0.27), $F(1,28) = 30.336$, $p < 0.001$. Results also showed a 2-way interaction between session and category, $F(1,28) = 5.053$, $p < 0.04$. To explore

this interaction, memory change between test and retest for relevant and irrelevant objects was computed for each participant (percent correct at test minus percent correct at retest). A paired samples *t*-test between memory change for relevant objects versus memory change for irrelevant objects showed that memory for irrelevant objects ($M = 0.044$, $SD = 0.063$) declined less overnight than memory for relevant objects ($M = 0.094$, $SD = 0.112$), $t(29) = 2.281$, $p < 0.03$. No other main effects or interactions were significant (all p values >0.05).

Confidence Ratings

In line with previous research, confidence ratings for correct responses were also examined (van Dongen et al, 2012). For this analysis, two participants from the no-CPAP group were excluded due to errors in data collection. The final sample for the confidence analysis totaled 28 participants with OSA (17 males, mean age: 52.26, *SD*: 16.83) and included of 15 participants in the CPAP group and 13 in the no-CPAP group. Age was not significantly different between the CPAP ($M = 54.83$, $SD = 15.04$) and the no-CPAP groups ($M = 49.29$, $SD = 18.84$); $t(26) = 0.865$, $p > 0.05$. Memory confidence was calculated by averaging the confidence ratings (1-5) of accurate responses in each category for each participant (see Figure 3). A 2x2x2 ANOVA with session (test and retest) and category (relevant and irrelevant) as the within-subjects independent variables, and group (CPAP and no-CPAP) as the between-subjects independent variable was conducted. The results showed a significant main effect of session, $F(1,26) = 7.027$, $p < 0.02$. Memory confidence was significantly higher at test ($M = 3.903$, $SE = 0.193$), than at retest ($M = 3.703$, $SE = 0.221$). No other main effects were significant (all other p values > 0.05). The results also indicated a significant 2-way interaction between session and

category, $F(1,26) = 5.917$, $p < 0.03$. To examine the session x category interaction, we computed confidence change, i.e., the change in memory confidence between test and retest (confidence at test minus confidence at retest), for each object type for each participant. The confidence change for relevant and irrelevant objects was then compared for all participants using a paired samples *t*-test, which showed that the confidence change was decreasing less for relevant ($M = 0.122$, $SD = 0.370$) compared to irrelevant objects ($M = 0.274$, $SD = 0.509$), $t(27) = 1.923$, $p < 0.07$.

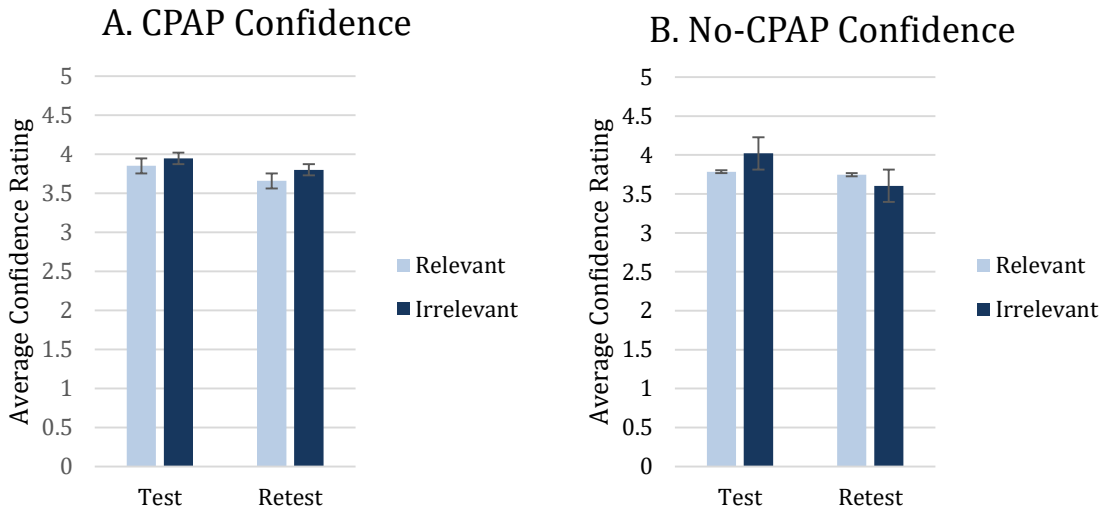

Figure 3: Confidence in accurate responses for relevant and irrelevant object locations at test and retest for the A) CPAP group, and B) no-CPAP group.

However, the session x category interaction was mediated by a significant 3-way interaction between group, session, and category, $F(1,26) = 9.865$, $p < 0.004$. To explore this interaction, a series of a paired samples *t*-tests was conducted. In the CPAP group, confidence significantly decreased between test and retest for relevant items, $t(14) = 2.223$, $p < 0.05$, and was approaching significance for irrelevant items, $t(14) = 1.961$, $p < 0.07$. However, the confidence change from test to retest for relevant items ($M = 0.193$, $SD = 0.336$) was not significantly different than the confidence change for irrelevant items ($M = 0.144$, $SD = 0.285$), $t(14) = 0.646$, $p > 0.05$. In the no-CPAP group,

confidence significantly decreased between test and retest for irrelevant items $t(12) = 2.298$, $p < 0.04$, but not for relevant items, $t(12) = 0.356$, $p > 0.7$, and a *t*-test confirmed that confidence decreased more for irrelevant items ($M = 0.424$, $SD = 0.665$) than for relevant items ($M = 0.0399$, $SD = 0.404$), $t(12) = -3.206$, $p < 0.01$.

Age

We found that our data set had a wide age range of participants in the study, 23.83 – 79.58 years. Research shows that memory declines with age, so we wanted to know if that relationship was present in our sample as well (Craik, 1994). If memory is systematically related to age, it is possible that poor performance by older adults could be clouding potential effects of the CPAP manipulation. A Pearson's correlation between age and percent correct at test was run within each group, and was not significant for the CPAP group [$r(15) = -0.291$, $p > 0.2$] or the no-CPAP group [$r(15) = -0.217$, $p > 0.4$]. Correlations between age and retest percent correct were also not significant [CPAP: $r(15) = -0.399$, $p > 0.05$; no-CPAP: $r(15) = -0.39$, $p > 0.05$].

IV. DISCUSSION

The consolidation of declarative memories moves forward through reactivation of memory traces during SWS (Cairney, Durrant, Hulleman & Lewis 2014; Rasch, Büchel, Gais & Born 2007; Rudoy, Voss, Westerberg & Paller, 2009). OSA patients experience brief arousals during sleep, including SWS, which interrupt sleep cycles and cause sleep fragmentation (Black, 2003). It is possible that the SWS disruptions caused by OSA may be concomitantly disrupting memory consolidation. Since CPAP, the primary treatment for OSA, is believed to improve sleep quality in OSA patients, it is possible that it could also improve memory consolidation (Loredo, Ancoli-Israel & Dimsdale, 1999). The present experiment tested whether a single night of CPAP treatment could improve declarative memory consolidation in treatment-naïve patients with OSA. Overall, the results of this study suggest that a single night of CPAP treatment has little effect on memory consolidation.

The CPAP and no-CPAP groups performed similarly before sleep, signifying that there were no differences between the groups with respect to memory ability before sleep. Both participant groups also remembered more before compared with after sleep, which is not uncommon (Fischer & Born, 2009; Marshall & Born, 2007; van Dongen et al., 2011). However, no group differences were found in memory accuracy after sleep either. Past research has found that CPAP treatment benefits declarative memory (Aloia et al., 2004; Dalmases et al., 2015), although these studies typically test the effect of long-term (> 1 month) CPAP use and evaluate declarative memory as an improvement on short-delay verbal measures from pre-treatment to post-treatment (Canessa et al., 2010;

Ferini-Strambi, Marelli, Galbiati & Castronovo, 2013; Tonon et al., 2006). This study was the first to examine the effect of a single night of CPAP treatment on declarative memory. The results indicate that a single night of CPAP use is not sufficient to impact memory, suggesting memory improvements require extended time with CPAP use. Since declarative memory improvements have been found to map onto grey matter increases in the hippocampus and cortical areas (Canessa, et al., 2010), one possibility is that long-term use facilitates structural gains, which in turn help memory consolidation (Klystra, Aaronson, Hofman & Schmand, 2013; Rosenzweig et al., 2016). Future research examining how sleep contributes to structural brain changes could help to shed light on this issue. However, an alternate possibility is that CPAP does not affect memory consolidation per se. Rather, improved declarative memory with long-term CPAP use could be due to gains in attention and vigilance functioning (Aloia et al., 2004; Davies & Harrington, 2016; Djonlagic, Guo, Matteis, Carusona, Stickgold & Malhotra, 2014), which may improve memory encoding and/or retrieval processes.

One interesting yet unexpected finding was that memory declined more for relevant (associated with a reward) objects than for irrelevant objects for all participants. Although several studies have shown that when items are associated with a reward, and when participants are expecting memory for certain items to be tested again, they are consolidated more strongly than items that were not associated with future reward or with future testing (Fischer & Born, 2009; Saletin, Goldstein & Walker, 2011; Wilhelm et al., 2011). However, other studies have shown that this effect can be mediated or even reversed (Abel & Bäuml, 2013; Fischer, Diekelmann & Born, 2011). For example, Abel and Bäuml (2013) found that when encoding was immediately followed by a night of

sleep, there was no difference in post-sleep memory for items instructed to be remembered compared with items instructed to be forgotten. In this study, participants learned two lists of word pairs, and they were instructed to forget the first list and to remember the second list. The 'forget' instructions were given as an error message immediately after the first list was presented, which prompted participants to forget the list they had just learned as it was from the wrong file and incorrect, and to remember the next list because it would be correct. It is speculated that the benefit to the nonprioritized items (i.e., items on the "forget" list) in this and other studies, was due to a suppression effect. Previous research has demonstrated when participants are instructed to not think about certain items, they actually think about them more so than participants who were told not to think about them (Wegner, Schneider, Carter & White, 1987). In sleep studies, items that participants are instructed to suppress are more frequently reported after sleeping than items that are not suppressed (Kröner-Borowik, Gosch, Hansen, Borowik, Schredl & Steil, 2013; Schmidt & Gendolla, 2008; Wegner, Wenzlaff & Kozak, 2004). It is possible that the increase in thought frequency drove these items to be reactivated during sleep more often than the to-be-remembered items, thus facilitating consolidation to a stronger degree. It is possible that effect was taking place in this study as well. Since the instructions informed participants that both categories would be tested again, but only one category was associated with a reward, participants may have actually thought about reward-irrelevant objects more often than relevant objects.

Another possible reason for this surprising result may have to do with the age of the participants. Although this study did not find a relationship between age and memory, research has shown that elderly adults have a diminished ability to inhibit the processing

of memories that are not relevant for future behavior (Sego, Golding & Gottlob, 2006; Zacks, Radvansky & Hasher, 1996). Hogge, Adam, and Collette (2008) found that older adults showed reduced recall performance of memories instructed to be remembered and increased recall of items instructed to be forgotten. Given that the average age of participants in this study (M = 52.6, SD = 16.3) is higher than in typical studies examining factors that affect which memories are prioritized for consolidation [van Dongen et al., (2012), M = 22.1; Fischer & Born (2009), M = 25.7], it is possible that our sample behaved more like older adults and were less successful at inhibiting memories not associated with a reward.

It is also possible that the reward instruction itself was unsuccessful. Other studies have successfully found a benefit for reward-associated memories by incentivizing memory recall on an item level via a post-encoding promise of monetary reward for each correctly recalled item (Fischer & Born, 2009; van Dongen et al., 2012). In this study, $10 was promised for improvement in one category relative than the other, which could have had a negative effect on the saliency of each memory relative to an item-level monetary reward. Although, other studies, using a similar compensation level ($20 for participation, $10 bonus), found the total compensation amount ($30) to be efficient, however, these studies used a sample with a mean age under 25 years old (van Dongen et al., 2012). According to the Bureau of Labor Statistics, in 2015 the average person under the age of 25 earned less than $26,500 a year, and the average person age 45-64-year-old earned over $72,500. Since the average age of our sample was higher than in previous studies, the $10 incentive may not have been enough to motivate consolidation.

In addition to memory accuracy, memory confidence was also examined. Similar to the accuracy analysis, both participant groups reported higher levels of confidence at test than at retest. However, the rate of change between relevant and irrelevant item location confidence differed between groups. In the no-CPAP group, confidence for irrelevant objects decreased more so than for relevant objects, whereas there was no difference in confidence change between the two categories in the CPAP group. It has been suggested that confidence ratings are a more sensitive measure of memory than accuracy (Voss, Baym & Paller, 2008; Voss, Lucas & Paller, 2012; Wixted, Mickes & Squire, 2010). If this is case, the decrease in confidence for irrelevant items relative to relevant items in the no-CPAP group could indicate more elaborate consolidation processing for relevant compared with irrelevant items. That being said, there was an inverse relationship between accuracy and confidence in the no-CPAP group, which previous studies (Dobbins, Kroll & Liu, 1998; Tulving, 1981; Voss, Baym & Paller, 2008). Although speculative, it is possible that the accuracy measure reflected a large proportion of guesses (an object from a given category could appear in 1 of 4 possible locations). As such, confidence may be a more specific measure to detect changes in memory between relevant and irrelevant items.

Note, however, that the CPAP group did not show this dissociation in confidence change between relevant and irrelevant items. The absence of any differential processing of confidence responses between the two categoires suggests that the first night of CPAP treatment may actually be more disruptive to sleep-dependent memory consolidation than untreated OSA. CPAP treatment is notorious for its low adherence rate, which is largely attributed unpleasent first-time use for reasons such as being unaccustomed to the air

pressure, pain from mask, difficulty breathing, displeasure with required sleeping positions, leaking air, and feelings of claustrophobia (Basner, 2007; Edinger & Radtke, 1993; Shapiro & Shaprio, 2010; Weaver et al., 2003). One study found that 46% of treatment-compliant patients complain of being awoken at night as a result of their CPAP use, and more than half of first-time CPAP users experienced full awakenings as well (Hoffstein, Viner, Mateika & Conway, 1992). Although long-term CPAP treatment alleviates the sleep and memory impairments caused by OSA, it is probable that initial use may actually hinder sleep and memory consolidation. It is possible the CPAP group slept less, and experienced more sleep disruptions than the no-CPAP group because of these negative side effects of CPAP (Drake et al., 2003; Loredo, Ancoli-Israel, Kim, Lim & Dimsdale, 2006; Nilius, Happel, Domanski & Ruhle, 2006).

A large limitation of this study is that it relied solely on behavioral data. If measures of sleep quantity and quality were included, potential group differences in sleep quality or quantity could help to understand the lack of differences observed in memory. The amounts of SWS and REM sleep experienced by both groups in particular could help shed light on the observed results. Research is mixed with regard to whether SWS and/or REM improve with short-term CPAP use (Aldrich, Eiser, Lee & Shipley, 1989; Brillante, Cossa, Liu & Laks, 2012; Issa & Sullivan, 1986; Loredo et al., 2006; Verma, Radtke, Langingham, King & Husian, 2001). Due to discomfort with CPAP upon initial use, the CPAP group may not have shown any increase in SWS and REM that might emerge once they become accustom to CPAP treatment.

This study's sample size was another limitation. There are many side effects of OSA, and they vary from person to person. A larger sample size would have tempered

any existing individual differences. Similarly, it would have been helpful to have an OSA comparison group that stayed awake during the delay rather than going to sleep, to determine whether the current participants experienced any sleep-dependent benefit. Additionally, studies have shown that reaction time improves with CPAP use, and with sleep (Djonlagic, et al., 2015; Gais, Koster, Sprenger, Bethke, Heude & Kimmig, 2008; Kloepfer et al., 2009). It is possible that group differences would emerge if reaction time was used as a dependent variable.

Overall, this study did not find a benefit of a single night of CPAP on memory consolidation in patients with OSA. Both participant groups performed better before a period of sleep than after, and performed better for items that were irrelevant for future behavior compared to relevant items. These results suggest that memory improvements concomitant with long-term CPAP use could rely on improved sleep-dependent memory consolidation that is mediated by structural brain changes that develop over time, or through improvements in attention and alertness that primarily affect memory encoding or retrieval. However, the no-CPAP group showed signs of sleep-dependent memory consolidation, as confidence decreased from test to retest for irrelevant items but not relevant items. Thus, an alternative possibility is that consolidation was actually more efficient for the no-CPAP group compared with the CPAP group, due to increased sleep disruptions from initial CPAP use. Future research into the relationship between OSA, CPAP treatment, and declarative sleep-dependent memory consolidation is required and would be wise to include sleep measures. Further research is also necessary to determine how confidence and memory accuracy are related in OSA patients.

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