Article published online: 2023-10-16

ORIGINAL ARTICLE

Sleep Science

Associations Between Sleep Quality, Sleep Architecture and Sleep Disordered Breathing and Memory After Continuous Positive Airway Pressure in Patients with Obstructive Sleep Apnea in the Apnea Positive Pressure Long-term Efficacy Study (APPLES)

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Received: June 12, 2018; Accepted: September 27, 2018.

DOI: 10.5935/1984-0063.20180037

ABSTRACT

Objective: The role of sleep architecture in consolidation of memory has not been extensively investigated. In this study, the association of continuous positive airway pressure (CPAP) and sleep architecture and quality, and sleep disordered breathing on changes in memory are explored during the course of a 6 month clinical trial of CPAP or sham CPAP (APPLES). **Methods:** 848 participants had polysomnographic and memory assessments (Buschke Selective Reminding Test [Buschke] and Digit Symbol Substitution Test [DSST]) at baseline, CPAP/Sham CPAP titration, and the 2 and 6 month time points. Half were assigned to the CPAP and Sham CPAP groups respectively. Changes in performance on the Buschke and the DSST were analyzed over the course of the study between CPAP and Sham CPAP as well as in relationship to changes in sleep architecture, sleep quality and sleep disordered breathing (SDB). **Results:** Sleep architecture, sleep quality and SDB improved in the CPAP group at 6 months; performance on the Buschke and DSST improved equally in both CPAP and Sham CPAP groups. There also were no significant correlations between changes in the amount or percentage of sleep stages between baseline and the 6 months, and corresponding changes in either the Buschke or the DSST. However, when stratified by the upper quartile and lower 3 quartiles, greater changes in the Buschke occurred over 6 months in the top quartile of total sleep time (5.7±7.3 vs. 4.0±6.8, $p \leq 0.01$) and amount of N3 sleep (55.9±7.7 vs. 53.6±8.9 min, $p \leq 0.01$). Those with more %N3 at 6 months scored better on the Buschke as well (55.9±7.8 vs. 53.6±8.9, $p \leq 0.01$). Borderline improvement in the DSST over 6 months was observed in the top quartiles of amount of N3 and %N3. Those in the top quartile of the amount of REM and %REM also showed greater improvement in the Buschke after 6 months. No differences were observed for the AHI, but those in the top quartile of oxygen desaturation had worse scores on the Buschke at 6 months. CPAP/Sham CPAP adherence did not impact 6 month Buschke or DSST performance. **Conclusions:** CPAP improved long-term sleep duration, quality and architecture, but did not memory. However, large changes in REM and N3 sleep as well as moderate amounts of nocturnal hypoxemia are associated with changes in assessments of memory.

Keywords: Sleep; Obstructive Sleep Apnea Syndrome; Memory; Continuous Positive Airway Pressure.

INTRODUCTION

There is general consensus that retention of memories occurs through a two-step process in which sleep plays an essential role for optimum performance. Initially, new information is encoded into temporary storage. Subsequently, some of this information is consolidated into long-term storage where it can be recalled when needed[1]. Sleep has been identified as a critical component for this latter activity to occur[2]. However, the role that various sleep stages play in this process appear to differ. Substantial evidence points to the importance of neuronal activity in the hippocampus during slow wave sleep (SWS) in strengthening declarative memory[3]. In contrast, rapid eye movement (REM) sleep may be important in enhancing procedural learning as well as for contextual and spatial memory consolidation[4].

Obstructive sleep apnea (OSA) is often characterized by neurocognitive deficits including impairment in memory[5]. Some, but not all studies have demonstrated that memory improves after OSA treatment with continuous positive airway pressure (CPAP)[6-10]. Whether improvement in memory after treatment with CPAP is correlated with changes in sleep architecture is unclear and has not been extensively studied[2].

The Apnea Positive Pressure Long-term Efficacy Study (APPLES) was a 6 month randomized sham-controlled study of the impact of CPAP on various neurocognitive domains in patients with OSA. Polysomnograms and neurocognitive assessments were performed before and after intervention with CPAP or sham CPAP[11]. Thus, the study provides a vehicle for studying whether changes in memory are associated with corresponding changes in sleep architecture. It is hypothesized that improvement in memory occurs with CPAP and that it is associated with increases in REM sleep and SWS.

METHODS

PARTICIPANTS AND STUDY DESIGN

The study design, recruitment procedures, and inclusion and exclusion criteria for APPLES have been described extensively[11]. The institutional review board (IRB) at each site approved the study protocol and the study was registered at ClinTrials.gov (NCT00051363). Briefly, APPLES was a multisite study conducted at 5 clinical centers: Stanford University, Stanford, CA; University of Arizona, Tucson, AZ; Providence St. Mary Medical Center, Walla Walla, WA; St. Luke's Hospital, Chesterfield, MO; and Brigham and Women's Hospital, Boston, MA. Participants were recruited into the study primarily from patients scheduled into a regular sleep clinic for evaluation of possible OSA, and from local advertising. Recruitment began in November 2003 and was completed in August 2008.

Initial enrollment required age ≥ 18 years and clinical symptoms of OSA, as defined by American Academy of Sleep Medicine (AASM) criteria[12]. At enrollment, participants underwent a screening diagnostic polysomnogram (PSG) and baseline neurocognitive testing including the standardized assessments described below. Only participants with an apnea hypopnea index (AHI) ≥ 10 events per hour continued to the clinical trial and were randomized subsequently to sham or active CPAP for 6 months as previously reported[13]. Those participants had a CPAP or sham CPAP titration polysomnogram and subsequently had a repeat polysomnogram on their assigned treatment 2 and 6 months later.

Excluded were individuals who had 1) prior OSA treatment with CPAP or surgery, 2) household members with current/past CPAP use, 3) a sleepiness-related automobile accident within the year prior to potential enrollment, (4) oxygen saturations < 75% for > 10% of the diagnostic polysomnogram (PSG) total sleep time; or (5) conditions or use of medications that could potentially affect neurocognitive function and/or alertness. For the present analysis, only data from randomized participants who had polysomnography and neurocognitive testing at the baseline, 2 and 6 month time points were used. Some of the material related to sleepiness and neurocognitive testing reported herein represent reanalysis of data in a different format from what has been published in a previous paper[9].

POLYSOMNOGRAPHY

Polysomnography was conducted as previously described using signals from a nasal pressure cannula, nasal/oral thermistor, thoracic and abdominal piezo bands, and a pulse oximeter to classify apnea and hypopnea events[11]. An apnea was identified by a > 90% amplitude decrease from baseline of the nasal pressure signal lasting ≥ 10 sec. Hypopneas were scored if there was a > 50%, but ≤ 90% decrease from baseline of the nasal pressure signal, or if there was a clear amplitude reduction of the nasal pressure signal that did not reach the above criterion but it was associated with either an oxygen desaturation ≥ 3% or an arousal, and the event duration was ≥ 10 seconds.

Obstructive apneas were identified by persistence of chest or abdominal respiratory effort during flow cessation. Central apneas were noted if no displacement occurred on either the thoracic or abdominal channels. The severity of OSA was expressed using the apnea hypopnea index (number of apneas + hypopneas/total sleep time, AHI). Magnitude of oxygen desaturation was indicated by the % of the total sleep time less than 85% (O2LT85%). All studies were scored at the central reading center located at Stanford University.

CPAP ADHERENCE

Adherence to CPAP or sham CPAP was measured objectively using Encore Pro SmartCards (Phillips Respironics, Inc., Murrysville, PA) that were returned by the participant twice monthly. For this report, the mean hours of daily use were analyzed for the preceding 1-month period before the 2- and 6-month study visits.

Assessment of Sleepiness

Epworth Sleepiness Scale (ESS)

The ESS is a validated self-administered questionnaire that asks an individual to rate his or her probability of falling asleep on a scale of increasing probability from 0 to 3 in 8 different situations[14]. The scores for the 8 questions are summed to obtain a single score from 0 to 24 that is indicative of self-reported sleep propensity. The ESS prior to randomization was administered at the time of the clinical evaluation and on the night of the diagnostic PSG. For a baseline, the value at the time of the diagnostic PSG was used, but if not available, then the value at the time of the clinical evaluation was substituted.

Assessments of Learning and Memory

Buschke Selective Reminding Test (Buschke)

The Buschke is an assessment of verbal learning and memory[15]. The version used in APPLES consisted of a list of 12 unrelated verbally presented words which the participant was asked to recall on successive trials. Non-recalled words on 6 successive trials were selectively re-presented or until the participant recalled the entire list on 3 consecutive trials. A delayed recall trial with forewarning was administered 30 minutes later. The sum recall (total number of word recalled over 6 trials) was used in these primary analyses.

Digit Symbol Substitution Test (DSST)

The CogScreen analogue of the DSST was used in APPLES[16]. The DSST evaluates sustained attention, visual scanning, information processing speed, immediate and delayed visual paired-associate memory and working memory. The participant is asked to match numbers (1-9) to their corresponding hieroglyphic-like symbol, and type them on a keyboard as quickly as possible within a 90-second time frame. The percent correct was used for these analyses.

STATISTICAL ANALYSES

Inasmuch as this was a subgroup analysis, outcome variables were defined *post hoc* based on our initial hypotheses pertaining to the impact of CPAP on memory and preliminary exploration of the data. Changes in outcome variables over time were analyzed using a mixed model repeated measures analysis of variance with participants stratified by their randomization group (CPAP or Sham CPAP). Groups differences were determined using analysis of variance or Student's t test as appropriate. Associations between variables were assessed by calculating Pearson correlation coefficients. Data are expressed as mean ± standard deviation (SD) or percentages. $P \leq 0.05$ was considered statistically significant. Analyses were performed using IBM SPSS Statistics Version 24 (Chicago, IL).

RESULTS

As shown in Table 1, of the 1104 participants randomized at baseline, there were 848 who had polysomnographic, Buschke and DSST data at baseline, CPAP/Sham CPAP titration, and the 2 and 6 month time points. There were 442 assigned to CPAP and 406 assigned to Sham CPAP. Approximately 66% were men, and most were non Hispanic white. Their mean age was 52±12 years with a BMI of 32.2±7.1 kg/m^2. Overall, participants had severe OSA with a mean AHI of 40.7±24.9 /hour. There were no differences in OSA severity between groups (results not shown).

Table 1. Baseline Demographic Information.

	N	%
Total Participants	848	
% Men	552	65.1
Ethnicity		
Non Hispanic White	647	76.3
Black	75	8.8
Hispanic	60	7.1
Asian	50	5.9
Native American	13	1.5
Other	3	0.4
Age	52±12 years	
Body Mass Index (kg/m^2)	32.2±7.1	
Apnea Hypopnea Index (#/hour)	40.7±24.9	
% Time Oxygen Saturations < 85%	2.2±6.2	
Group Assignment		
Sham	406	47.9
CPAP	442	52.1
Compliance with CPAP/Sham CPAP at 6 months, Hours)		
Sham	354	3.5±2.3
CPAP	403	4.5±2.3

Changes in sleep and sleep architecture are displayed in Table 2. Total sleep time, sleep efficiency and arousal index improved immediately with use of CPAP in comparison to Sham CPAP. In addition, the absolute amount and % of N1 sleep decreased with a corresponding increase in the absolute amount and % of the remaining sleep stages. These changes in sleep duration, quality and architecture were generally maintained over the entire 6 month length of the study. In addition, improvements in sleep architecture correlated with better adherence to CPAP. No associations with adherence were observed in the Sham CPAP group (results not shown).

In Table 3 is presented the changes in the Buschke, DSST, ESS, AHI and O2LT85% over the course of the study. Scores on the Buschke and the DSST improved at the 2 and 6 month time points, but did so in the CPAP and Sham CPAP groups equally. In contrast, the ESS, AHI and O2LT85% were abnormally high at baseline, and had decreased at 2 and 6 months with CPAP. No changes over 6 months were observed in the Sham CPAP group.

After combining both groups, there were no significant correlations between changes in the amount or percentage of sleep stages between baseline and the 6

Table 2. Changes in Sleep and Sleep Architecture after Sham or CPAP.

	Diagnostic	CPAP	2 Months	6 Months
Total Sleep Time (TST)				
Sham	375.9±63.2	346.2±71.5	391.6±62.7	389.8±59.5
CPAP	376.1 ± 66.7	358.7±72.3†	395.5±61.7	397.8±61.2‡
Sleep Efficiency (%TST)				
Sham	78.0±12.2	75.4±13.5	81.7±11.6	81.3±11.6
CPAP	78.4±13.3	77.6±13.5†	82.0±11.7	82.8±12.3*
Arousal Index (#/h)				
Sham	30.4±21.9	32.3±19.7	30.5±20.1	30.0±20.5
CPAP	29.1±18.9	16.2±11.8§	15.5±10.3§	16.1±11.5§
N1 Sleep (Min)				
Sham	71.5±55.2	67.3±49.3	66.7±51.7	68.0±56.3
CPAP	66.9±49.8	43.3±30.1§	49.3±33.4§	46.5±31.0§
N1 Sleep (% TST)				
Sham	19.5±14.9	20.5±16.0	17.8±14.6	18.1±15.4
CPAP	18.5±14.3	12.4±8.4§	12.8±9.1§	12.1±8.5§
N2 Sleep (Min)				
Sham	227.0±67.7	214.8±70.7	237.5±70.2	236.5±66.1
CPAP	229.0±66.1	227.0±56.4‡	250.0±57.3‡	253.3±52.6§
N2 Sleep (%TST)				
Sham	60.2±14.4	61.4±15.1	60.2±14.0	60.5±13.8
CPAP	60.9±13.5	63.6±10.6‡	63.1±10.4§	63.7±9.0§
N3 Sleep (Min)				
Sham	11.4±22.2	11.7±22.3	13.1±23.3	11.7±22.2
CPAP	11.1±20.3	16.6±26.1‡	15.2±26.7	14.8±26.1*
N3 Sleep (%TST)				
Sham	3.0±5.8	3.4±6.5	3.3±5.8	2.8±5.2
CPAP	2.9±5.2	4.6±7.1†	3.8±6.7	3.6±6.3†
REM Sleep (Min)				
Sham	65.4±29.2	51.9±27.5	73.3±30.9	73.2±31.4
CPAP	67.5±30.4	71.2±33.2§	80.5±31.2‡	82.7±33.5§
REM Sleep (%)				
Sham	17.3±7.1	14.6±6.9	18.5±7.1	18.5±7.0
CPAP	17.5±6.9	19.3±7.7†	20.2±6.8‡	20.4±7.3†

*p<0.1 vs. Sham
†p<.05 vs. Sham
‡p<.01 vs. Sham
§p<.001 vs. Sham

month time point, and corresponding changes in either the Buschke or the DSST. In addition, there was no correlation between 6 month CPAP/Sham CPAP adherence at the 6 month time point, and changes in either the Buschke or the DSST (results for both analyses not shown). To explore whether there was a threshold for the amount of change in sleep, sleep architecture, sleep related breathing, and CPAP/Sham CPAP adherence variables necessary to be associated with changes in the Buschke and DSST, the distributions of these variables were divided into their top quartile and bottom 3 quartiles.

In Table 4 is shown the comparison between these 2 groups in their 6 month Buschke and DSST scores and their change over 6 months. Although there were few significant differences, greater changes in the Buschke occurred over 6 months in those participants in the top quartile of total sleep time (5.7±7.3 *vs.* 4.0±6.8, p≤0.01). Similarly, those in the top quartile of amount of N3 sleep (55.9±7.7 *vs.* 53.6±8.9 min, p≤0.01) and %N3 (55.9±7.8 *vs.* 53.6±8.9, p≤0.01) at 6 months scored better on the Buschke. In parallel, greater improvement in the DSST over 6 months was observed in the top quartiles of amount of N3 and %N3 distribution although they were only of borderline statistical significance. Those in the top quartile of the amount of REM and %REM also showed greater improvement in the Buschke after 6 months. No differences were observed for the AHI, but

Table 3. Change in Buschke, Digit Symbol Sum Recall and Epworth Sleepiness Scale After Sham or CPAP.

				Change
	Diagnostic	2 Month	6 Month	6 Month-Diagnostic
Buschke Sum Recall				
Sham	49.8±8.9	52.2±8.8	54.3±8.7	4.6±7.1
CPAP	49.7±9.1	52.4±8.6	54.1±8.7	4.3±6.9
Digit Sum Recall				
Sham	46.6±26.5	53.7±28.4	55.5±28.1	9.2±27.8
CPAP	44.6±26.9	54.0±27.7	53.7±28.8	8.6±28.3
Epworth Sleepiness Scale*				
Sham	10.2±4.6	8.5±4.8	8.3±4.6	-1.7±3.4
CPAP	10.0±4.3	7.1±4.8†	6.8±4.6†	-2.8±4.1†
Apnea Hypopnea Index				
Sham	41.2±25.2	31.5±25.5	30.5±25.2	10.9±21.3
CPAP	40.2±24.4	6.2±7.7†	6.4±8.5†	34.0±24.2†
% Time Oxygen Saturations < 85%				
Sham	2.2±6.0	2.8±8.0	2.3±7.1	0.1±6.4
CPAP	2.3±6.4	0.2±1.0†	0.3±2.3†	-2.0±6.4†

*Adjusted for 6 month adherence
†$p<.001$ vs. Sham

those in the top quartile of O2LT85% had worse scores on the Buschke at 6 months. There was no impact of overall CPAP or sham CPAP adherence on the Buschke or the DSST at 6 months or their change over 6 months. Stratification by treatment group also found no differences (results not shown).

DISCUSSION

In this analysis, after intervention with CPAP or Sham CPAP, sleep architecture and sleep quality improved immediately with CPAP, but not Sham CPAP, and these changes were maintained over the 6 months of the trial. In contrast, memory assessed by the Buschke and DSST improved to the same degree with both CPAP and Sham CPAP. Furthermore, changes in sleep, sleep architecture or indices of sleep-related breathing disorder from baseline to 6 months did not correlate with corresponding changes in memory. However, those participants in the highest quartile of change in REM sleep and SWS had greater improvements in memory than those in the lower quartiles; those in the top quartile of O2LT85% had worse scores on the Buschke. These observations support the contention that both REM sleep and SWS are important in the retention of memories and suggest that oxygen desaturation may be detrimental.

In the CPAP group, sleep duration and sleep quality as well as indices of sleep-related breathing disorder improved after this intervention; these changes were maintained for 6 months. Although these observations were expected[17-20], not all studies have found that CPAP improves sleep quality[21], and similar results from previous investigations were of shorter duration. Improvement in sleep architecture was correlated with CPAP adherence further strengthening a causal relationship. Thus, our results extend previous findings by objectively confirming that improvements in sleep and sleep quality resulting from CPAP are maintained in the long-term.

Our finding that CPAP did not improve performance on the Buschke has been reported in previous publications documenting the results from APPLES[9,22]; we now extend this finding to the DSST. The absence of a difference between the 2 groups could be a function of the low level of compliance among the CPAP users and/or the very low level of positive pressure inherent with Sham CPAP. However, we did not find any impact of CPAP compliance on Buschke or DSST performance which argues against the former explanation. In both the CPAP and Sham CPAP groups, performance on both of these memory tasks improved to the same extent thus indicating a substantial practice/learning effect. Future studies using either of these assessments need to account for this observation.

We did not observe that changes in sleep variables from baseline to 6 months corresponded to changes in either the Buschke or DSST. However, we did find that when analyses were focused on differences between more extreme changes in sleep variables, in particular, REM sleep and SWS, there was an impact on memory. As reviewed by Diekelmann and Born, reactivation of encoded memories during SWS strengthen them in the hippocampus and facilitate their transfer into neocortical and striatal networks[23].

Thus, our findings that participants who had the largest increases in the amount and percentage of N3 sleep had better performance on the Buschke and DSST support this construct. Similarly, there is substantial evidence that REM sleep plays an important role in consolidation of procedural memory as well as declarative memories that are spatially complex or emotional[4]. Although neither the Buschke nor DSST are tasks that specifically evaluate these latter components of memory, we did observe trends for better performance in those participants who had the greatest changes in the amount and percentage of REM.

With respect to sleep disordered breathing, analyses noted that greater time spent with oxygen saturations less than

Table 4. Six Month and Change After 6 Month Scores on the Buschke Selective Reminding and Symbol Digit Coding Tasks.

	Buschke Selective Reminding Test Sum Recall				Symbol Digit Coding Delay Recall Task			
	N	Six Month Score	N	Change in Score: 6 Month - Baseline	N	Six Month Score	N	Change in Score: 6 Month - Baseline
Total Sleep Time (Min)								
Top Quartile	212	54.4±8.7	211	5.7±7.3‡	211	53.3±29.1	210	8.4±26.4
Bottom 3 Quartiles	636	54.1±8.7	636	4.0±6.8	625	54.8±28.2	624	9.0±28.6
Sleep Efficiency (%)								
Top Quartile	212	53.6±9.5	212	4.7±7.3	212	51.4±29.2*	212	9.2±28.3
Bottom 3 Quartiles	636	54.4±8.4	635	4.4±6.9	624	55.5±28.1	622	8.8±28.0
Arousal Index (#/h TST)								
Top Quartile	211	53.7±8.7	211	4.5±6.8	209	53.5±27.3	208	7.5±28.1
Bottom 3 Quartiles	638	54.3±8.7	637	4.4±7.0	628	54.7±28.8	627	9.4±28.0
N1 Sleep (Min)								
Top Quartile	211	54.0±8.9	211	4.6±7.2	210	55.4±28.0	208	10.3±25.6
Bottom 3 Quartiles	638	54.2±8.6	637	4.4±6.9	627	54.2±28.6	627	8.4±28.8
N1 Sleep (%)								
Top Quartile	213	54.3±8.6	213	4.9±7.0	212	55.8±28.0	210	9.0±29.1
Bottom 3 Quartiles	636	54.1±8.7	635	4.3±7.0	625	54.0±28.6	625	8.9±27.7
N2 Sleep (Min)								
Top Quartile	213	54.1±8.5	213	5.1±7.3*	211	54.8±29.8	210	8.8±26.8
Bottom 3 Quartiles	636	54.2±8.8	635	4.2±6.9	626	54.3±28.0	625	8.9±28.5
N2 Sleep (%)								
Top Quartile	212	53.4±9.1	212	4.3±7.0	209	52.3±29.8	209	9.2±30.0
Bottom 3 Quartiles	637	54.4±8.5	636	4.5±7.0	628	55.1±27.9	626	8.8±27.3
N3 Sleep (Min)								
Top Quartile	213	55.9±7.7‡	213	4.9±6.7	208	55.7±27.2	207	12.0±28.9*
Bottom 3 Quartiles	636	53.6±8.9	635	4.3±7.1	629	54.0±28.8	628	7.9±27.7
N3 Sleep (%)								
Top Quartile	212	55.9±7.8‡	212	5.0±6.6	208	55.3±27.2	207	11.6±28.7*
Bottom 3 Quartiles	636	53.6±8.9	635	4.3±7.1	628	54.1±28.9	627	7.9±27.8
REM Sleep (Min)								
Top Quartile	213	54.9±8.8	213	5.5±7.3*	211	55.8±29.2	211	11.0±27.7
Bottom 3 Quartiles	636	53.9±8.6	635	4.2±6.9	626	54.0±28.1	624	8.2±28.2
REM Sleep (%)								
Top Quartile	214	54.7±8.8	214	5.3±7.3‡	212	55.7±28.5	212	10.9±26.8
Bottom 3 Quartiles	635	54.0±8.6	634	4.1±6.9	625	54.0±28.4	623	8.2±28.4
Apnea Hypopnea Index (#/h)								
Top Quartile	212	54.4±8.6	211	4.4±7.1	212	52.1±28.1	210	8.9±28.5
Bottom 3 Quartiles	637	53.6±8.8	637	4.3±6.7	625	55.2±28.4	625	8.9±27.9
% Time O_2 Saturation < 85%								
Top Quartile	212	52.9±8.8†	211	4.4±7.4	212	53.3±27.5	211	9.9±27.5
Bottom 3 Quartiles	639	54.6±8.6	637	4.4±6.9	625	54.8±28.7	624	8.6±28.3
Compliance with CPAP/Sham CPAP at 6 months, Hours)								
Top Quartile	180	53.4±8.8	180	4.0±7.0	178	52.9±28.5	178	9.0±26.6
Bottom 3 Quartiles	645	54.4±8.6	644	4.6±6.9	635	54.7±28.4	633	8.7±28.3

* $p<0.10$
$p<0.05$
$p<0.01$

85% were associated with worse Buschke but not DSST scores at 6 months. For the DSST task, the current results differ somewhat from findings derived from the Sleep Heart Health Study in which performance on the composite variable "Procspeed", a combination of Digit Symbol Coding and Symbol Search, was negatively associated with oxygen desaturation[24]. Previous human studies specifically addressing the impact of hypoxemia on memory in persons with OSA are sparse and conflicting. In a study of 50 OSA patients, nocturnal hypoxemia was associated with lower scores on some memory tasks[25].

However, in another study of 40 OSA patients, those with greater hypoxemia paradoxically performed better on assessments of memory[26]. Mechanistically, studies in animals indicate that hypoxemia can result in neuronal damage to the hippocampus and neocortex, areas of the brain important for memory consolidation[27]. Thus, our results from a large dataset in humans provide some support to suggest that nocturnal hypoxemia is deleterious for memory, but additional human studies to specifically address this issue are needed.

There are some limitations to this study. First, assessments of memory were restricted to only the Buschke and the DSST. A broader spectrum of tasks to evaluate memory performance may have resulted in different findings. Second, all of the participants in the study had OSA which may have influenced the results independent of changes in sleep. Finally, our results must be considered preliminary and hypothesis generating. The analytic outcomes chosen were exploratory and derived *post hoc*; our hypothesis that memory is associated with increases in REM sleep and SWS was not an initial goal of APPLES. In addition, no statistical corrections were made for multiple analytic outcomes and hence there is the possibility of increased Type 1 error. Nevertheless, strengths of this analysis include the large number of participants, long duration of the intervention and use of home-based polysomnography, with the latter avoiding the artificial environment of a sleep laboratory.

In conclusion, CPAP produced long-standing improvements in sleep duration, quality and architecture, but did not improve performance on a limited battery of memory tasks. However, large changes in REM and N3 sleep as well as moderate amounts of nocturnal hypoxemia do impact memory.

Acknowledgments

The Apnea Positive Pressure Long-term Efficacy Study (APPLES) study was funded by contract 5UO1-HL-068060 from the National Heart, Lung and Blood Institute. The APPLES pilot studies were supported by grants from the American Academy of Sleep Medicine and the Sleep Medicine Education and Research Foundation to Stanford University and by the National Institute of Neurological Disorders and Stroke (N44-NS-002394) to SAM Technology. In addition, APPLES investigators gratefully recognize the vital input and support of Dr. Sylvan Green, who died before the results of this trial were analyzed, but was instrumental in its design and conduct.

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Sleep HealthCenters for the use of their clinical facilities to conduct this research

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