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Memory and Obstructive Sleep Apnea: A Meta-Analysis

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Study Objectives: To examine episodic memory performance in individuals with obstructive sleep apnea (OSA).

Design: Meta-analysis was used to synthesize results from individual studies examining the impact of OSA on episodic memory performance. The performance of individuals with OSA was compared to healthy controls or normative data.

Participants: Forty-two studies were included, comprising 2,294 adults with untreated OSA and 1,364 healthy controls. Studies that recorded information about participants at baseline prior to treatment interventions were included in the analysis.

Measurements: Participants were assessed with tasks that included a measure of episodic memory: immediate recall, delayed recall, learning, and/or recognition memory.

Results: The results of the meta-analyses provide evidence that individuals with OSA are significantly impaired when compared to healthy controls on verbal episodic memory (immediate recall, delayed recall, learning, and recognition) and visuo-spatial episodic memory (immediate and delayed recall), but not visual immediate recall or visuo-spatial learning. When patients were compared to norms, negative effects of OSA were found only in verbal immediate and delayed recall.

Conclusions: This meta-analysis contributes to understanding of the nature of episodic memory deficits in individuals with OSA. Impairments to episodic memory are likely to affect the daily functioning of individuals with OSA.

Keywords: Obstructive sleep apnea, memory, meta-analysis, review

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INTRODUCTION

OSA is a respiratory disorder characterized by repeated collapses of the upper airway, causing episodes of airflow cessation (apnea), or decreases in airflow (hypopnea), during sleep for periods greater than 10 seconds.[1] A diagnosis of OSA is made when an individual experiences more than five apneas or hypopneas per hour during sleep (apnea-hypopnea index > 5).[2] Untreated OSA is associated with an increased incidence of cardiovascular disease,[3] hypertension,[4] stroke,[5] type 2 diabetes,[6] and motor vehicle accidents.[7] OSA is characterized by excessive daytime sleepiness,[6] reduced quality of life,[8] and psychological difficulties such as depression.[9] Cognitive impairments are also common.[10-12] Specifically, OSA has been linked to deficits in executive function,[13] episodic memory,[14] and attention.[15]

A model by Beebe and Gozal[16] proposes that sleep fragmentation and hypoxemia due to OSA are linked to deficits in executive function and other cognitive areas.[17] Sleep fragmentation refers to the disturbance of normal sleep architecture (disrupting sleep cycles and stages) due to frequent arousals caused by apneas and hypopneas.[18] Fragmented sleep is linked to daytime sleepiness.[16] Airway obstructions also lead to hypoxemia (low blood oxygen), which results in a lack of oxygen being delivered to the brain (cerebral hypoxia).[19] Beebe and Gozal[16] propose disrupted sleep and hypoxemia disturb the restorative benefits of sleep and cause chemical and structural damage at the cellular level. This disturbance affects functions of the prefrontal cortex and the hippocampus: areas of the brain involved in memory and executive function.

In 2003, Beebe and colleagues[10] published a thorough meta-analysis investigating the neuropsychological effects of untreated OSA. Two types of studies were included. The first was "controlled" studies that compared the neuropsychological performance of adults with OSA to a healthy control group. The second was "uncontrolled studies"; for example, those that assessed adults with OSA prior to an intervention. The authors examined the overall effect of OSA on a variety of neuropsychological outcomes by comparing individuals with OSA to healthy controls (control-referenced) and comparing all included OSA samples (across both types of studies) to normative data (norm-referenced). They concluded that in both control- and norm-referenced studies, OSA did not affect general intellectual or verbal performance; however, vigilance and executive functioning were significantly impaired. Evidence of the effect of OSA on episodic memory performance was inconclusive. This may have been due to the way memory tasks were grouped.

Episodic memory is memory for daily events and experiences specific to a time and place.[20] The meta-analysis by Beebe et al.[10] divided episodic memory first into visual and verbal domains, then further into short-term and long-term memory. Short-term memory measures included recall of information presented once, recall of information presented over multiple trials, and cued recall tasks. Long-term memory measures included recall of information following a delay. Beebe and colleagues reported a number of deficits in episodic memory functioning in OSA samples; however, results were inconsistent across the norm- and control-referenced datasets. Norm-referenced samples showed that individuals with OSA performed significantly worse than age-matched norms on tasks assessing long-term verbal memory ($d = 0.52$, $P < 0.01$), but not on short-term verbal memory. In contrast, the control-referenced studies did not reveal differences in any verbal memory domain.

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OSA participants performed less well than controls on short-term and long-term visual memory tasks ($d = 0.56$, $P < 0.01$ and $d = 0.55$, $P < 0.01$, respectively), whereas no notable differences were found in the norm-referenced dataset in the visual memory domain. The division of episodic memory into visual and verbal short-term and long-term memory may have contributed to these discrepant findings. To examine the nature of the episodic memory deficits more accurately, the outcome domains may need to be more specific.

Episodic memory tasks often record immediate recall, total recall over multiple trials, recognition memory, and delayed recall. Immediate recall assesses short-term memory capacity and the ability to encode into longer term memory after a single trial. In addition to this, measures with multiple trials assess the ability to learn across trials. Delayed recall measures provide information about the ability to retrieve information following a delay. Recognition memory tasks are a heavily cued retrieval measure as the original stimulus is presented among distractor items.[21] Arguably, these aspects of memory capacity (immediate recall, learning, delayed recall, and recognition) are supported by different neurological substrates.[22] When Beebe et al.[10] collapsed immediate recall, learning, and cued recall measures into "short-term" memory, measures were combined that may be differentially impaired, which could explain the inconsistent results in their meta-analysis.

Some research has reported differential effects of OSA on immediate and delayed recall ability, and there is debate as to where the impairments manifest. There is some evidence that immediate recall of information is intact, but retrieval from long-term memory is impaired.[23] Conversely, Salorio and colleagues[13] showed immediate recall was impaired, but there was no impairment in delayed recall when the number of words recalled immediately was taken into account. The authors explained their findings by linking recall performance with the ability to organize and store information efficiently—a process that is thought to be driven by executive function.[13] As past research has shown executive functions are impaired in individuals with OSA,[10] it is likely that the information to be recalled is not stored in a manner that allows successful immediate or delayed retrieval.

Fewer studies have investigated the effect of OSA on recognition. Those that have report no impairment in OSA.[13,23,24] Beebe and colleagues[10] did not include recognition memory as an outcome, which may reflect the dearth of research in that area at the time their meta-analysis was conducted. Assessing recognition memory is useful in untangling episodic memory deficits. For example, impairments to both recall and recognition memory suggest the information was never encoded. Alternatively, intact recognition memory paired with deficient immediate and delayed recall suggests the information was encoded, but not efficiently, or that there are retrieval difficulties.[21]

Including older measures of memory with questionable reliability and validity may have contributed to previous inconsistent findings. A considerable amount of research examining the relationship between OSA and episodic memory has been published since the review by Beebe and colleagues using newer measures of memory. Both verbal[23,24] and visual episodic memory impairments[25] have been found in OSA using such measures, while other studies have found no impairments in either type of memory.[26,27]

In summary, results from studies investigating episodic memory impairment in OSA appear to be contradictory. By reviewing the performance of individuals with OSA on tasks that assess immediate recall, delayed recall, recognition, and learning, any deficits to episodic memory can be more closely examined. It is difficult to compare the impact of OSA on memory across studies because of the differences in measures and experimental design. However, combining the results of these studies systematically using meta-analysis enables analysis of overall effects of untreated OSA on individual episodic memory measures.

The relationship between OSA and memory impairment may not be direct; instead it may be moderated by a number of factors.[28] Beebe and colleagues[10] investigated the moderating effects of publication status, disease severity, study design (controlled vs. uncontrolled), and source of OSA sample (whether the sample was recruited from a clinical setting such as a sleep clinic or through advertising in the community). These variables did not significantly moderate the relationship between the presence of OSA and performance on memory tasks in their study. Nonetheless, these variables were examined in the present study, given the larger sample size and more specific memory categorization employed. In addition to these variables, the moderating effect of two further factors was explored: the screening of healthy controls for OSA (sleep study vs. no sleep study) and the effect of age. It is estimated that 93% of women and 82% of men who have OSA are undiagnosed.[29] Therefore, it is possible healthy control comparison groups may contain individuals with OSA if they are not screened with overnight polysomnography. The differences found between norm-referenced and control-referenced studies in the review of Beebe and colleagues[10] may reflect insufficiently rigorous screening of healthy controls for OSA. Therefore, this meta-analysis was also completed with only those studies that assessed both controls and patients for the presence of OSA with an overnight sleep study. Further, it has been proposed that the combination of older age and the presence of OSA overwhelms the ability of the brain to cope with cognitive challenges.[30] Consistent with this, studies have found a moderating effect of age on neuropsychological functioning such that older participants show more impairment on tasks assessing immediate word recall, attention, and reaction time.[30,31] Thus, age was also considered as a moderator.

A meta-analysis was warranted that examined studies published until 2011 that used memory theory to categorize memory tasks and considered moderating variables. This meta-analysis divided episodic memory into visual and verbal immediate recall, delayed recall, recognition memory, and learning to examine the effect of OSA on these measures individually. The relationship between memory impairments and OSA severity, age, publication status, and study design was also examined. Controlled and uncontrolled studies were included.

Key Questions

1. Which specific episodic memory outcomes (immediate recall, delayed recall, recognition memory, and learning) are affected by the presence of untreated OSA?
2. Are any episodic memory deficits specific to the visual or verbal domains?

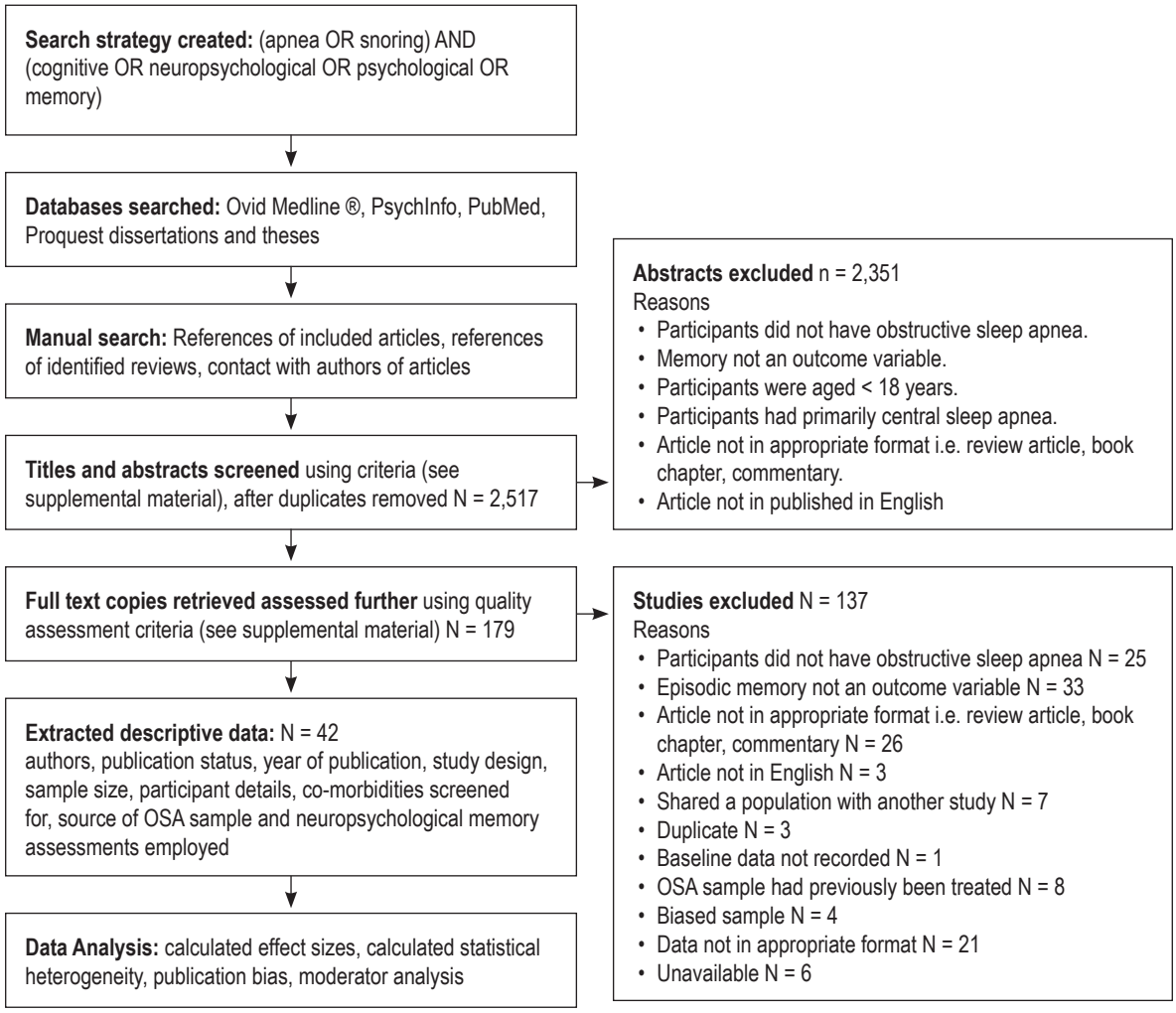

Figure 1—Flow chart of search, retrieval and inclusion process.

3. If memory impairment is present, is the effect moderated by publication status, study design, age, disease severity, or screening method for healthy controls?

METHOD

Search Strategy

Procedural details of the methodology employed in this review are outlined in Figure 1. In contrast to the meta-analysis of Beebe et al.,[10] the present review specifically explored the impact of OSA on episodic memory. The terms 'apn*ea OR snoring' were searched as MeSH terms and keywords and combined with the keywords 'cognit* OR neuropsych* OR psycho* OR memory'. Memory was also searched as a MeSH term. Preliminary searches also revealed this strategy had high sensitivity but low specificity, which maximized the yield of pertinent articles.

Three electronic databases were searched for studies: Ovid Medline ® (from 1948 to Week 2 May 2011), PsychInfo (Ovid, 1804 to 24 May 2011), and PubMed (through 24 May 2011). The search terms were adapted to locate unpublished papers relevant to the meta-analysis using the Proquest Dissertations and Theses: Full text database (from 1861 to 26 May 2011).

Relevant articles were also retrieved from the reference lists of included studies. The reference lists of two related reviews examining the impact of OSA on neuropsychological performance were scanned for relevant studies.[10,32] Finally, the authors of papers included following abstract screening were contacted asking if they had any other relevant published or unpublished studies.

Study Selection Criteria

This review included studies that assessed adults with OSA following diagnosis with an overnight sleep study. This review only considered studies with adult participants (≥ 18 years). Similarities exist between the pathophysiology of OSA in adults and children; however, because of etiological differences between adult and childhood OSA, the latter was not addressed in the present review.[6] Central sleep apnea is characterized by repeated apnea and hypopnea resulting from decreased neural output to the respiratory motoneurons rather than airway obstruction as seen in OSA.[6] As the pathophysiology, epidemiology, and clinical characteristics of central sleep apnea and obstructive sleep apnea are distinct,[6] this review considered only OSA.

Studies that examined the impact of untreated OSA on episodic memory performance by using a quantitative neuropsy-

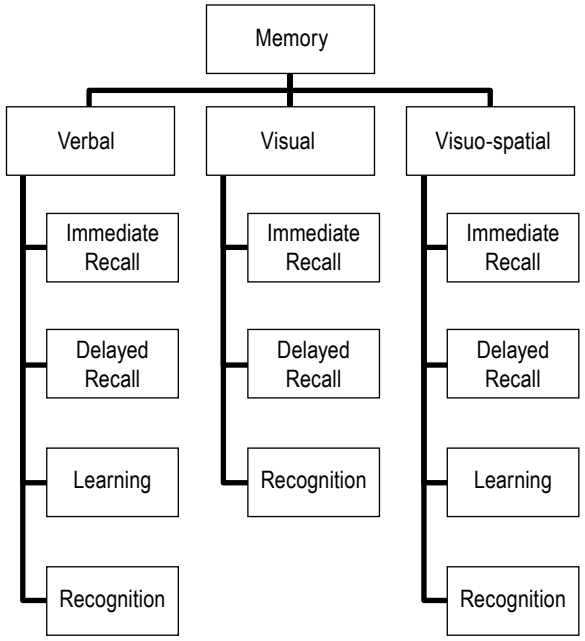

Figure 2—Memory assessments were categorized into these domains.

chological assessment were included. Additionally, studies were required to report episodic memory performance in a format that enabled the calculation of effect sizes (ideally sample size, mean, and standard deviation). If sufficient data to calculate effect sizes were not provided in the article, the corresponding author was contacted and asked to provide these data. All study designs that reported baseline neuropsychological test results on the episodic memory performance of untreated adults with OSA were considered for inclusion in this review. Finally, this review was limited to studies published in English. Research suggests including non-English studies changes the overall effects by a maximum of 2%,[33] and translating papers was beyond the scope of this review. Unpublished studies were included in the search to diminish the possible effect of publication bias.

Study Selection

The study selection procedure was a multistage process (see Figure 1). Firstly, selection criteria were applied to titles and abstracts (see supplemental material for details). Articles were excluded that clearly failed to meet the inclusion criteria. Full-text English articles that were potentially relevant were retrieved. Secondly, the criteria were applied to the retrieved full articles. Studies were included that assessed adults with untreated OSA on a neuropsychological test of episodic memory. Studies were examined for overlapping databases. Consistent with Beebe et al.,[10] if an overlap was suspected, confirmation was sought from the authors; when this was not possible, overlap was assumed and the most complete memory dataset was included in the meta-analysis. Studies were excluded for the following reasons:

1. The sample did not meet a diagnosis of OSA as defined by AHI ≥ 5 (or equivalent) as assessed with a full night in-lab or out-of-lab sleep study (see footnote 1);
2. The sample included participants younger than 18 years of age;
3. Episodic memory was not assessed;
4. Tests used were inadequate: either the test was poorly described so norms could not be found, or acceptable validity and/or reliability could not be confirmed;
5. Selection bias was present: for example, studies were excluded if they selected participants based on poor performance on a memory assessment;
6. Participants had previously received treatment for OSA prior to the collection of baseline data;
7. Patients had a diagnosis of primarily central sleep apneas;
8. Data were not reported in a way that allowed effect sizes to be calculated.

The first author independently screened the titles and abstracts of all 2,517 studies for inclusion/exclusion (full criteria in supplemental material). This resulted in 179 papers that were screened independently by both authors. The authors resolved any disagreement as to whether to include a paper (of which there were very few) through discussion.

Quality Assessment

Following study screening, the methodological quality of included studies was examined by a quality assessment tool (see supplemental material). The purpose, design, sample characteristics, methodology, outcome measures, and statistical analyses were extracted to examine the level of bias in each study.

Data Extraction and Coding

Data extracted and coded from the final articles included: authors, publication status, year of publication, journal, study design, sample size, diagnostic criteria, participant details (gender, years of formal education, body mass index, and age), exclusion criteria, source of OSA sample, and neuropsychological memory assessments employed. Table 1 lists the sample characteristics for each study included. Memory assessment details were extracted and categorized (see Figure 2). It was observed that visual memory assessments often required spatial skills (e.g., Rey Osterrieth Figure—participants are required to copy a design, which they later recall from memory). Therefore, tests were classified as visual, visuo-spatial, or verbal. Further, verbal memory—and occasionally visuo-spatial memory—was assessed using tasks with multiple "learning trials." When results of the first trial were reported, this was coded as "immediate recall." The total recall across all learning trials was also extracted and coded as "learning." Recognition memory can be measured using several different methods. The total number of times a target was correctly identified (total number of "hits") was extracted and coded as this measure was used most consistently. Effect sizes and standard deviations were extracted to examine the nature of relationships between the variables of interest. Table 2 describes the domains used and lists the studies that contributed to each domain. The data for all included studies were extracted and coded by the first author. The second author extracted and coded the data for 10 randomly selected studies. The intra-class correlation coefficient between the data extracted by the first and second author was $r = 0.99$ (95%CI: 0.98-0.99).

The results of each OSA sample were compared to normative data when norms were available. The closest normative group to the OSA sample was sourced in terms of age, then

Table 1—Sample characteristics

	Citation		Source**	Controls		OSA					% Time at SaO_2 < 90%
				N	Age	N	Age	AI	RDI	AHI	
A	Adams et al.*	2001	A			100	47			24	
B	Aloia et al. (adherent)	2010	A			95	53			39	19.6
C	Aloia et al. (non-adherent)	2010	A			55	51			49	34.7
D	Antic et al.	2011	A	113		174	50				
E	Antonelli Incalzi et al.	2004	A			49	62			39	27
F	Ayalon et al.	2006	A	12	43	12	44			35	
G	Bailey (sample 1)	1993	D			10	44	51	84		
H	Bailey (sample2)	1993	D			7	44	20	39		
I	Bedard et al. (moderate)	1991	A	10	50	10	53	21			16.7
J	Bedard et al. (severe)	1991	A	10	50	10	52	69			55.5
K	Borak et al.	1996	A			20	46			67	
L	Cammermeyer	1991	D			11	51			53	26
M	Canessa et al.	2011	A	15	42	17	44			56	
N	Cosentino et al.	2008	A	121	58	124	58			40	
O	Dahlof et al.	2002	A			53	50				
P	Daurat et al.	2008	A	29	50	28	28			21	
Q	Daurat et al.	2010	A	27	51	26	53			24	31.7
R	Engleman (Study 1)	1995	D			37	53			53	
S	Engleman (Study 2)	1995	D			64	49			35	
T	Ferini-Strambi et al.	2003	A	23	56	23	57			> 40	
U	Findley et al.	1991	A	21	59	50	61	46			
V	Froehling	1991	D			41	47	32		65	70
W	Gale et al.	2004	A			14	14		84		65
X	Gast et al. (treated)	2006	A			17	53			46	
Y	Gast et al. (untreated)	2006	A			12	52			40	
Z	Greenberg et al.	1987	A	14	44	14	44	48			
AA	Kim et al.	1997	A	642		199				≥ 5	
BB	Kloepfer et al.	2009	A	20	47	15	47			20	
CC	Klonoff et al.	1987	A			11	49	49			
DD	Lee et al.	1999	A	16	45	17	49		39		
EE	Lim et al.	2007	A			46	48			63	
FF	Lojander et al.	1999	A			49	39				
GG	Mathieu et al. (Older)	2008	A	18	63	14	62	34		43	25.1
HH	Mathieu et al. (Younger)	2008	A	12	39	14	38	38		51	42.2
II	Merrion	1991	D			25	49				
JJ	Naegele et al.	2006	A	54	50	54	50		44		11.6
KK	Naismith et al.	2004	A			100	49			26.3	
LL	Neu et al.	2010	A	16	37	15	37			> 15	
MM	Rouleau et al.	2002	A	18	47	29	47	28		53.2	
NN	Salorio et al.	2002	A	24	44	28	44				
OO	Saunamaki		UP	20		40	47			41	
PP	Sharma et al.	2010	A	25	46	50	43			54	46.5
QQ	Sloan (with hypoxia)	1989	D	19	45	22	48			94.6	
RR	Sloan (without hypoxia)	1989	D	19	45	20	43			63.2	
SS	Torelli et al.	2010	A	14	58	16	56			53	21.9
TT	Twigg et al.	2010	A	60	50	60	51			23	
UU	Valencia-Flores et al.	1996	A			37	49		47		
VV	Verstraeten et al.	1997	A			26	54			48	
WW	Walker (Tx Sample)	1990	D			9	47			40	
XX	Walker (No Tx sample)	1990	D			9	53			30	

*Redline et al.[48] was included by Beebe et al.[10], but excluded here as the study shared a sample with Adams et al.[26] which was included as it was a more complete dataset. Citations are displayed alphabetically by first author and are given a letter to aid the presentation of information in Table 2. Tx = treatment. **Source corresponds to the publication status of the study (A, peer reviewed published article; D, dissertation; UP, unpublished). % Time at SaO_2 < 90% refers to the percentage time spent with an oxygen desaturation below 90%. An individual should spend all their time with an oxygen desaturation level at 90% or higher. The sample details of age and disease severity (AHI, AI, RDI, % Time at SaO_2 < 90%) are given as group averages.

Table 2—Description of included domains, measures, normative comparisons, and number of OSA patients

Domain	Definition	Measures	Normative comparisons used	Studies included in analysis*	Number of OSA patients in analysis	
					Control-referenced	Norm-referenced
Verbal Immediate Recall	The ability to recall verbal information immediately after presentation.	Buschke SRT, CVLT, RAVLT, WMS Logical Memory, 'Verbal Recall', 'Serial Verbal Learning Task'	[49-54]	**D**, **F**, **I**, **J**, K, **U**, V, **Z**, **BB**, DD, **GG**, **HH**, II, **JJ**, **LL**, **MM**, **NN**, **PP**, **QQ**, **RR**, **TT**	530	228
Visual Immediate Recall	The ability to recall visual information immediately after presentation, e.g., pictures. Does not include cued recall tests.	WMS Figural Recall	[53]	V, FF, **QQ**, **RR**	42	83
Visuo-spatial Immediate Recall	The ability to recall information that has visual and spatial elements, e.g., drawing a diagram immediately after presentation	BVRT, ROCF, WMS Figural Memory, WMS Visual Reproduction	[52,55-58]	**I**, **J**, K, L, O, S, **U**, **Z**, **OO**, **QQ**, **RR**, UU, VV, WW, XX	166	532
Verbal Delayed Recall	The ability to recall verbal information following a delay	AVLT, Buschke SRT, CVLT, HVLT, Serial Verbal Learning Test, Test of Prose Memory, WMS-Logical Memory.	[49-52,54,59-62]	A, B, C, **D**, **F**, G, H, **I**, **J**, R **U**, V, **Z**, **BB**, EE, **GG**, **HH**, **JJ**, **LL**, **MM**, **NN**, **PP**, **QQ**, **RR**, **TT**	755	1,278
Visuo-spatial Delayed Recall	The ability to recall visual and spatial information following a delay.	ROCF, WMS-Figural memory, WMS-Visual Reproduction	[52,54,55,57,61,63,64]	A, **I**, **J**, **U**, W, **Z**, EE, II, **MM**, **OO**, **QQ**, **RR**, **SS**, **TT**, WW, XX	270	343
Verbal Learning	Total number of items recalled in verbal list learning tasks across multiple trials.	Buschke SRT, CVLT, HVLT, HVLT-R, RAVLT, Serial Verbal Learning Task	[50,60,61]	A, B, C, E, K, **M**, **N**, R, V, W, X, Y, **AA**, EE, **GG**, **HH**, **JJ**, KK, **LL**, **MM**, **SS**, UU	481	1,079
Visuo-spatial Learning	Total number of items recalled in visuo-spatial learning tasks across multiple trials.	Brief Visuo Spatial Memory Test Revised	[65]	P, TT	88	0
Verbal Recognition	The ability to recognize a verbally presented target among distractor items.	CVLT, RAVLT, WMS-Logical memory recognition. Recollection of temporal information[25]	[50,60]	**M**, **AA**, **P**, **GG**, **HH**, **TT**	414	272

*The letters this column correspond to studies listed in Table 1; bold letters refer to control-referenced studies. Buschke SRT, Buschke Selective Reminding Test; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; HVLT or HVLT-R, Hopkins Verbal Learning Test (original or revised); WMS or WMS-R, Wechsler Memory Scale (original or revised); BVRT, Benton Visual Retention Test; ROCF, Rey Osterrieth Complex Figure.

gender and education (years). Consistent with Beebe et al.,[10] when studies did not report the information required to find normative information, the following information was substituted: male gender, age 50, 12.5 years of education.

Data Synthesis

To evaluate the magnitude and direction of the effect of OSA on memory performance, effect sizes were calculated and reported for each study. As the included studies used different instruments to measure the outcome variables, the effect size statistic most appropriate to use was the standardized mean difference. The current meta-analysis computed effect sizes (*ES*) from independent groups (OSA, healthy controls, or norms). Typically, the standardized mean difference is calculated by dividing the mean difference between the patient and control group performance by the pooled standard deviation.[34] However, following Beebe and colleagues,[10] the standard deviation was not pooled across groups, as the standard deviation of the OSA group may be inflated due to individual

Table 3—Mean effect sizes for the norm-referenced data set

	d	95% CI		Z	P	Homogeneity Statistics			
Domain		**LL**	**UL**			**Q(df)**	**P**	**Tau**	**I²**
Verbal Immediate Recall	0.63	0.39	0.74	6.39	< 0.01	34.76(10)	< 0.01	0.47	71.23
Verbal Learning	0.17	-0.08	0.41	1.35	0.18	73.90(20)	< 0.01	0.46	72.94
Verbal Delayed Recall	0.44	0.20	0.60	3.55	< 0.01	96.49(21)	< 0.01	0.49	78.24
Verbal Recognition	-0.14	-0.50	0.23	-0.74	0.46	0.10(3)	0.99	0	0
Visuo-spatial Immediate Recall	-0.12	-0.35	0.10	-1.07	0.28	47.78(15)	< 0.01	0.37	68.6
Visuo-spatial Learning	NO STUDIES								
Visuo-spatial Delayed Recall	0.05	-0.16	0.27	0.48	0.63	31.83(12)	< 0.01	0.31	62.29
Visuo-spatial Recognition	NO STUDIES								
Visual Immediate Recall	-0.27	-0.50	-0.04	-2.27	0.02	2.68(3)	0.44	0	0
Visual Delayed Recall	NO STUDIES								
Visual Recognition	NO STUDIES								

LL, lower limit; UL, upper limit.

differences related to the effect of OSA (see footnote 2). Thus, the equation below was used. The word "control" in the equation can be substituted with "norm" to represent the equation to calculate effect sizes in the normative dataset.

$$ES = \frac{\overline{X}_{control} - \overline{X}_{OSA}}{s_{control}}$$

A random-effects model was used. This assumes that each study has a different underlying effect and accounts for the amount of variance caused by differences between studies in addition to differences among participants within studies.[34] The studies included were conducted by different researchers in various locations, using different measures to assess memory, and with participants with varying degrees of disease severity. Thus, a random-effects model is more appropriate than the alternative, a fixed-effects model, which assumes a single common effect underlies all the studies in the meta-analysis and that differences are a result of chance alone. Each study was weighted by the inverse of its variance. As a random-effects model was used, the variance included within-studies plus the between-studies variance, tau squared. Comprehensive Meta-Analysis 2.0 software was used.[35]

Moderator analysis was undertaken to answer key question 3. OSA samples with an average AHI between 5 and 29.9 were classified as having mild/moderate OSA. Samples were categorized as having severe OSA if they had an average AHI ≥ 30, apnea index (AI) ≥ 20, or a respiratory disturbance index (RDI) > 50.[2,36] RDI takes into account the number of inspiratory flow limitations per hour of sleep in addition to apneas and hypopneas.[2,36] Moderator analysis was also used to investigate the effect of study design (control-referenced and norm-referenced), publication status, age, and control screening on results. If the effect size for a given outcome was found to be significantly moderated by disease severity or study design, follow-up weighted random effects analyses for the different groups were conducted.

RESULTS

Description of Studies

From the 2,517 articles identified, 42 controlled and uncontrolled studies satisfied the inclusion criteria, representing 50 samples. In total, 90% of samples were recruited from a clinical setting.

The control-referenced dataset consisted of 26 samples: 1,413 participants with OSA and 1,346 healthy controls. The norm-referenced dataset included 39 samples and 1,289 participants with OSA. Individual sample size, source, age, disease severity (AHI, AI, or RDI), years of education, and the percentage of time spent with oxygen saturation < 90% are displayed in Table 1. The average age across patient samples was 48.04 ± 8.07 years. In the samples reporting a measure of disease severity (AHI, AI, or RDI), 33 were classified as severe and 11 as mild/moderate. Three samples used the oxygen desaturation index (ODI) as a measure of severity. These samples were classified as mild/moderate, as there is no consensus on the severity of OSA based on the ODI. Two samples reported AHI ≥ 5, and one sample reported the range of AHI scores included but not a mean. These three samples were also conservatively labeled as mild/moderate for the purposes of meta-analysis.

Calculation of Effect Sizes

Cohen's classification of effect sizes was used, such that effect sizes of $d \leq 0.20$ are small, $d = 0.50$ are medium, and $d \geq 0.80$ are large.[37] The average effect size estimates for each outcome variable of interest are displayed in Tables 3 and 4. Forest plots for each outcome can be found in Figures 4-18. The effect size estimates show the performance of individuals with OSA on episodic memory tasks compared to healthy controls or norms. A positive effect size indicates controls or norms performed better than individuals with OSA.

Norm-Referenced Data

There was a significant, moderate, and positive effect for verbal immediate recall, indicating individuals with OSA performed significantly worse on tasks, requiring them to encode and immediately recall information presented verbally (see Table 3). Likewise, delayed recall was also significantly poorer in OSA; however the effect size was smaller. Visual immediate recall performance in OSA was better than in controls: a surprising finding likely related to the difficulty of matching norms with OSA patients. The domains of verbal learning, verbal rec-

Table 4—Mean effect sizes for control-referenced studies

	d	95% CI		Z	P	Homogeneity Statistics			
Domain		**LL**	**UL**			**Q(df)**	**P**	**Tau**	**I^2**
Verbal Immediate Recall	0.55	0.18	0.93	2.89	< 0.01	122.41(16)	< 0.01	0.73	86.93
Verbal Learning	0.46	0.12	0.80	2.65	0.01	39.34(8)	< 0.01	0.42	79.67
Verbal Delayed Recall	0.50	0.27	0.73	4.21	< 0.01	94.92(20)	< 0.01	0.44	78.93
Verbal Recognition	1.71	0.69	2.74	3.28	< 0.01	121.20(5)	< 0.01	1.20	95.88
Visuo-spatial Immediate Recall	0.63	0.38	0.88	4.85	< 0.01	6.17(6)	0.41	0.06	2.72
Visuo-spatial Learning	1.72	-1.90	5.33	0.93	0.35	58.13(1)	< 0.01	2.48	98.28
Visuo-spatial Delayed Recall	0.67	0.30	1.03	3.55	< 0.01	33.05(9)	< 0.01	0.52	72.77
Visuo-spatial Recognition	NO STUDIES								
Visual Immediate Recall	0.05	-0.38	0.49	0.24	0.81	0.17(1)	0.68	0	0
Visual Delayed Recall	NO STUDIES								
Visual Recognition	NO STUDIES								

LL, lower limit; UL, upper limit.

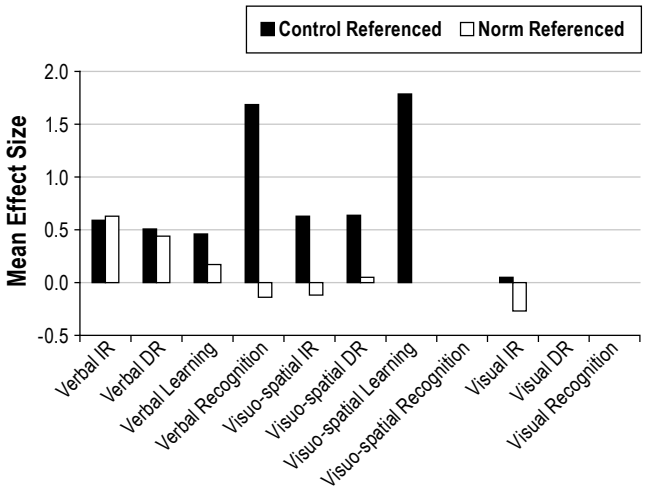

Figure 3—Summary of mean effect sizes for control-referenced and norm-referenced studies across the domains. Positive values indicate better performance by healthy controls or norms relative to individuals with OSA. Negative values indicate better performance by individuals with OSA compared to norms and controls. Effect size data are reported only for domains that included at least two studies. See Table 2 for a description of the domains; IR, immediate recall; DR, delayed recall.

ognition, visual delayed recall, and visuo-spatial memory yielded small and nonsignificant findings, suggesting no evidence of impairment in these areas in OSA.

Control-Referenced Data

Consistent with the results of the norm-referenced dataset, the control-referenced dataset yielded significant, moderate, and positive effect sizes for the immediate and delayed recall of verbal information (see Table 4 for mean effect sizes for the control-referenced dataset, and refer to Figure 3 for a comparison between control- and norm-referenced datasets). In contrast to the norm-referenced dataset, however, individuals with OSA showed deficits on verbal learning tasks and verbal recognition when compared to controls. Also in contrast to the norm-referenced dataset, studies that compared OSA performance to healthy controls showed individuals with OSA were impaired on tasks assessing visuo-spatial immediate and delayed recall. Visuo-spatial learning was not impaired, and no studies assessed visual recognition memory. Consistent with the norm-referenced dataset, the two samples that examined visual immediate recall did not show evidence that the presence of OSA negatively affected performance. Only one study examined visual memory following a delay, so it was not possible to perform a meta-analysis on this domain.

Heterogeneity

Heterogeneity was investigated visually with forest plots and using Cochrane's *Q* statistic, which, when significant, shows the observed variability in study effect sizes is greater than expected by chance. Inspection of the forest plots for norm-referenced and control-referenced studies for each domain showed effect sizes were variable, suggesting heterogeneity was present. The *Q* statistic was significant for both reference groups for verbal immediate and delayed recall and verbal learning. Significant heterogeneity was also present in visuo-spatial immediate recall in the control-referenced group and visuo-spatial delayed recall in both datasets.

However, the *Q* statistic is vulnerable to bias from sample size. To overcome this bias, the I^2 statistic is often used in combination with the *Q* statistic to quantify the degree of heterogeneity. When the *Q* statistic for a domain was significant, I^2 ranged between 62.29 and 98.28, suggesting at least 62.29% of the variance is generated from real differences between studies and may be explained by study-level covariates. Moderator analysis was conducted to explore potential moderator variables that may explain this heterogeneity.

Moderator Analysis

Moderator analysis was conducted using a random-effects model. A priori, age, publication status, study design, sample source, disease severity, and control screening criteria were identified as potential modifying variables. As 90% of samples were recruited from a clinical setting, sample source did not warrant moderator analysis. Only outcomes with at least 10 samples were examined for moderator effects.[34] Study design

Table 5—Effect sizes and significance levels for each memory domain for all control studies compared with those control studies that screened all participants with a full-night in-lab polysomnography

	All control-referenced studies			Control-referenced studies that screened controls with an overnight sleep polysomnography		
Domain	Number of samples	*D*	*Sig*	Number of samples	*D*	*Sig*
Verbal Immediate Recall	18	0.55	< 0.01	12	0.64	0.02
Verbal Learning	9	0.46	0.01	6	0.51	0.15
Verbal Delayed Recall	21	0.50	< 0.01	13	0.49	0.01
Verbal Recognition	6	1.71	< 0.01	5	0.86	0.01
Visuo-spatial Immediate Recall	7	0.63	< 0.01	4	0.74	< 0.01
Visuo-spatial Learning	2	1.72	0.35	1	ONLY ONE STUDY	
Visuo-spatial Delayed Recall	10	0.67	< 0.01	6	0.88	< 0.01
Visual Immediate Recall	2	0.05	0.81	0	NO STUDIES	

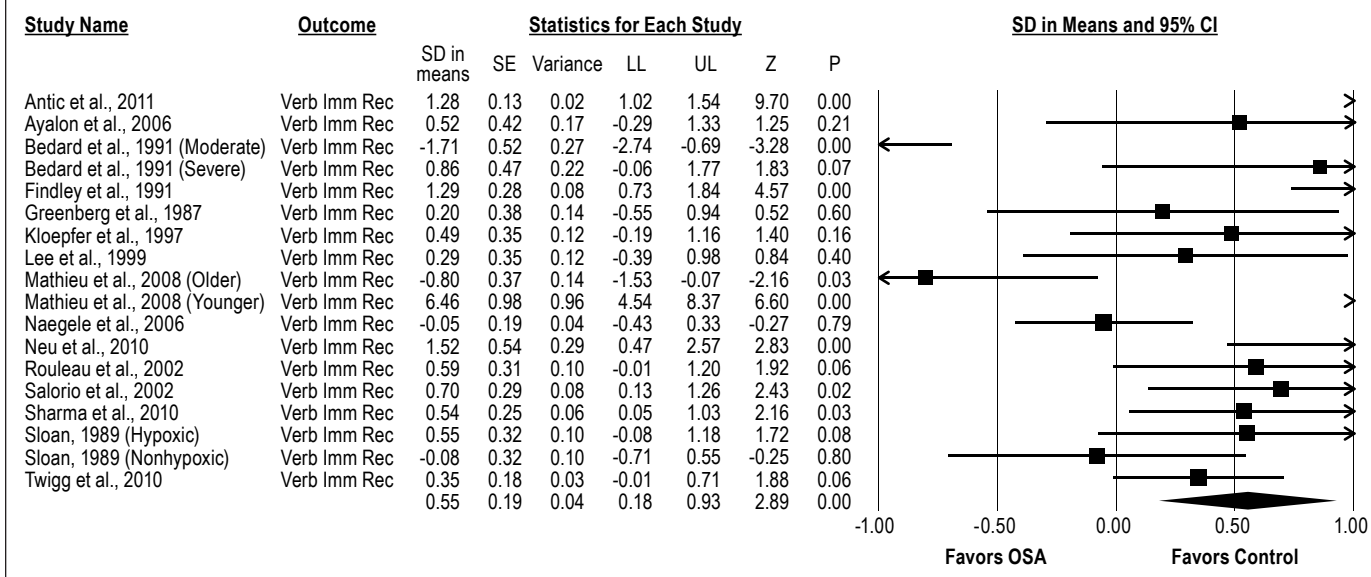

Figure 4—Forest plot comparing the performance of OSA samples on verbal immediate recall compared to healthy controls. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

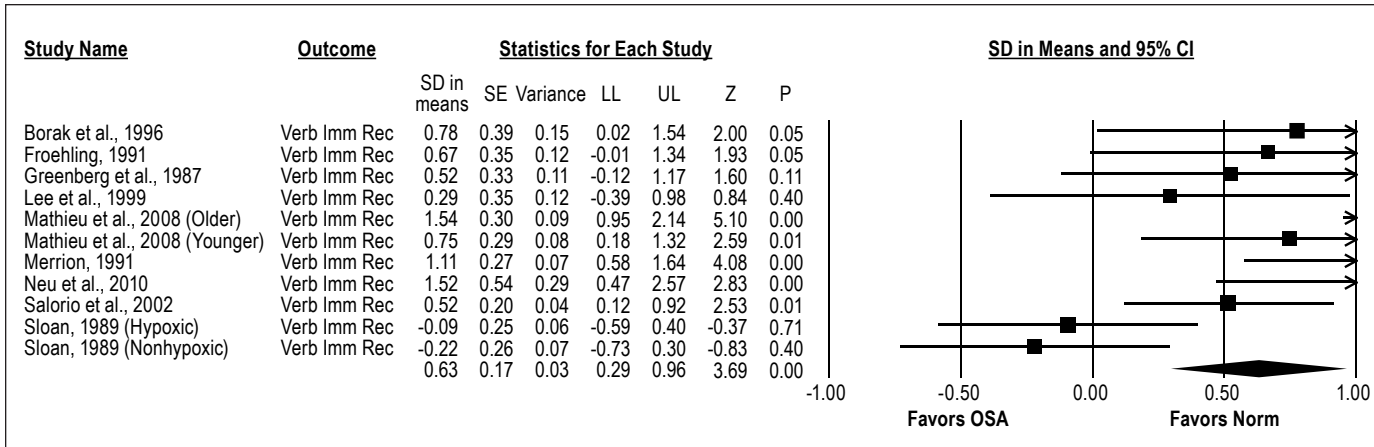

Figure 5—Forest plot comparing the performance of OSA samples on verbal immediate recall compared to norms. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Antic et al., 2011	Verb Del Rec	0.45	0.12	0.01	0.21	0.69	3.67	0.00
Ayalon et al., 2006	Verb Del Rec	0.37	0.41	0.17	-0.44	1.18	0.90	0.37
Bedard et al., 1991 (Moderate)	Verb Del Rec	-1.09	0.48	0.23	-2.03	-0.15	-2.28	0.02
Bedard et al., 1991 (Severe)	Verb Del Rec	-2.18	0.56	0.32	-3.29	-1.07	-3.86	0.00
Canessa et al., 2011	Verb Del Rec	1.23	0.39	0.15	0.47	1.99	3.18	0.00
Cosentino et al., 2008	Verb Del Rec	0.57	0.13	0.02	0.32	0.83	4.37	0.00
Ferini-Strambi et al., 2003	Verb Del Rec	0.73	0.30	0.09	0.13	1.33	2.40	0.02
Findley et al., 1991	Verb Del Rec	1.00	0.27	0.07	0.46	1.54	3.66	0.00
Greenberg et al., 1987	Verb Del Rec	0.48	0.38	0.15	-0.27	1.23	1.25	0.21
Kim et al., 1997	Verb Del Rec	0.12	0.08	0.01	-0.04	0.28	1.45	0.15
Mathieu et al., 2008 (Older)	Combined	0.37	0.38	0.15	-0.39	1.12	0.95	0.34
Mathieu et al., 2008 (Younger)	Combined	2.80	0.59	0.35	1.65	3.96	4.76	0.00
Naegele et al., 2006	Verb Del Rec	0.47	0.20	0.04	0.09	0.86	2.43	0.02
Neu et al., 2010	Verb Del Rec	1.53	0.54	0.29	0.48	2.58	2.85	0.00
Rouleau et al., 2002	Verb Del Rec	0.54	0.31	0.09	-0.06	1.14	1.76	0.08
Salorio et al., 2002	Verb Del Rec	0.45	0.28	0.08	-0.10	1.01	1.61	0.11
Sharma et al., 2010	Verb Del Rec	0.79	0.25	0.06	0.29	1.28	3.10	0.00
Sloan, 1989 (Hypoxic)	Verb Del Rec	0.60	0.32	0.10	-0.02	1.23	1.89	0.06
Sloan, 1989 (Nonhypoxic)	Verb Del Rec	-0.49	0.32	0.10	-1.12	0.13	-1.55	0.12
Torelli et al., 2010	Verb Del Rec	1.43	0.41	0.17	0.63	2.23	3.49	0.00
Twigg et al., 2010	Verb Del Rec	0.43	0.18	0.03	0.07	0.79	2.34	0.02
		0.50	0.12	0.01	0.27	0.73	4.21	0.00

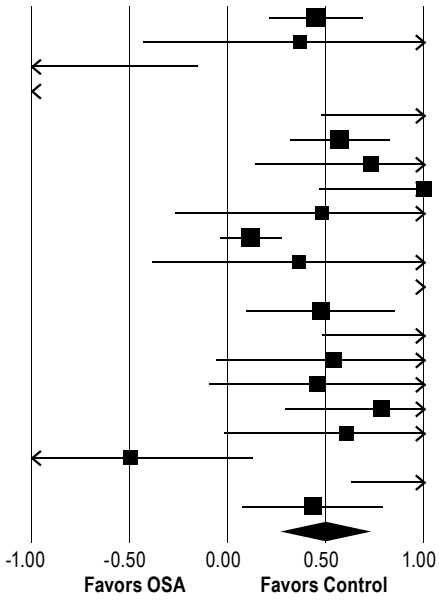

Figure 6—Forest plot comparing the performance of OSA samples on verbal delayed recall to healthy controls. The last line of data in the table gives the averaged effect size estimate. Combined outcome is the average of multiple measures within one study. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Adams et al., 2011	Verb Del Rec	-0.19	0.21	0.04	-0.60	0.21	-0.94	0.35
Aloia et al., 2010 (adherent)	Verb Del Rec	0.39	0.14	0.02	0.12	0.66	2.85	0.00
Aloia et al., 2010 (non-adherent)	Verb Del Rec	0.44	0.16	0.03	0.13	0.76	2.73	0.01
Antonelli-Incalzi et al., 2004	Verb Del Rec	0.70	0.22	0.05	0.27	1.14	3.18	0.00
Bailey, 1993 (sample 1)	Verb Del Rec	0.51	0.37	0.14	-0.21	1.23	1.39	0.17
Bailey, 1993 (sample 2)	Verb Del Rec	1.32	0.45	0.20	0.45	2.19	2.97	0.00
Canessa et al., 2011	Verb Del Rec	-0.03	0.39	0.15	-0.79	0.73	-0.09	0.93
Cosentino et al., 2008	Verb Del Rec	0.31	0.32	0.10	-0.31	0.93	0.98	0.33
Engleman, 1995 (Study 1)	Verb Del Rec	-0.08	0.34	0.12	-0.75	0.60	-0.22	0.82
Froehling, 1991	Verb Del Rec	-0.55	0.37	0.14	-1.28	0.18	-1.48	0.14
Greenberg et al., 1987	Verb Del Rec	1.61	0.37	0.13	0.89	2.33	4.39	0.00
Lim et al., 2007	Verb Del Rec	0.63	0.16	0.03	0.31	0.95	3.85	0.00
Mathieu et al., 2008 (Older)	Combined	0.74	0.37	0.13	0.02	1.45	2.02	0.04
Mathieu et al., 2008 (Younger)	Combined	2.09	0.40	0.16	1.31	2.88	5.24	0.00
Merrion, 1991	Verb Del Rec	1.17	0.27	0.07	0.64	1.71	4.29	0.00
Naismith et al., 2004	Verb Del Rec	-0.35	0.32	0.10	-0.98	0.28	-1.08	0.28
Neu et al., 2010	Verb Del Rec	1.53	0.54	0.29	0.48	2.58	2.85	0.00
Salorio et al., 2002	Verb Del Rec	0.20	0.20	0.04	-0.20	0.60	0.99	0.32
Sloan, 1989 (Hypoxic)	Verb Del Rec	-0.14	0.25	0.06	-0.64	0.35	-0.56	0.58
Sloan, 1989 (Nonhypoxic)	Verb Del Rec	-0.60	0.26	0.07	-1.11	-0.10	-2.34	0.02
Torelli et al., 2010	Verb Del Rec	0.88	0.41	0.17	0.08	1.69	2.16	0.03
Valencia-Flores et al., 1996	Verb Del Rec	0.16	0.30	0.09	-0.43	0.75	0.53	0.60
		0.44	0.12	0.02	0.20	0.68	3.55	0.00

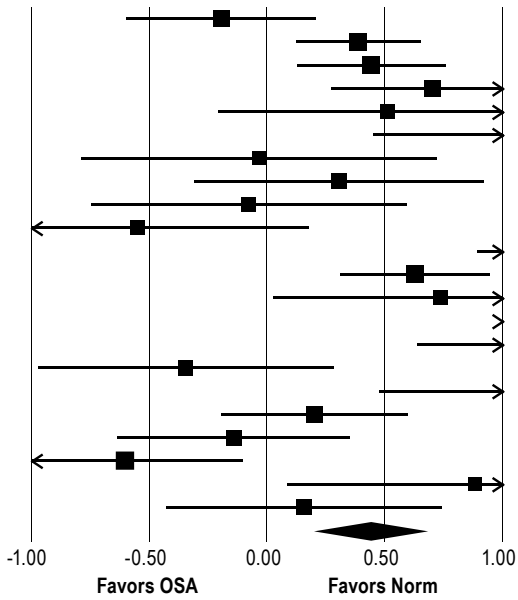

Figure 7—Forest plot comparing the performance of OSA samples on verbal delayed recall to norms. The last line of data in the table gives the averaged effect size estimate. Combined outcome is the average of multiple measures within one study. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

significantly moderated visuo-spatial immediate recall, with norm-referenced studies having significantly higher effect sizes than control-referenced studies, $Q_{model}(1) = 6.04$, $P = 0.01$. However, the $Q_{residual}$ statistic remained significant, suggesting there were other factors that also explain between-study variance. As this result was supported by the inconsistent effects found between norm- and control-referenced datasets for this variable, no further follow-up analysis was necessary. No other outcome variables were significantly moderated by any other moderators.

Post Hoc Subanalysis

As recommended by a reviewer, a meta-analysis was conducted using only those studies that screened both controls and patients with an overnight sleep study. Other screening proce-

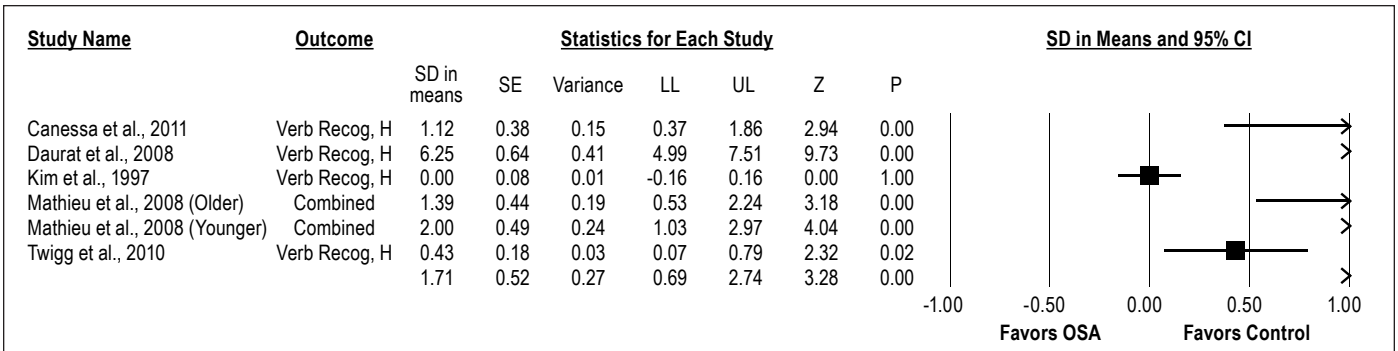

Figure 8—Forest plot comparing the performance of OSA samples on verbal recognition to healthy controls. The last line of data in the table gives the averaged effect size estimate. Combined outcome is the average of multiple measures within one study. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

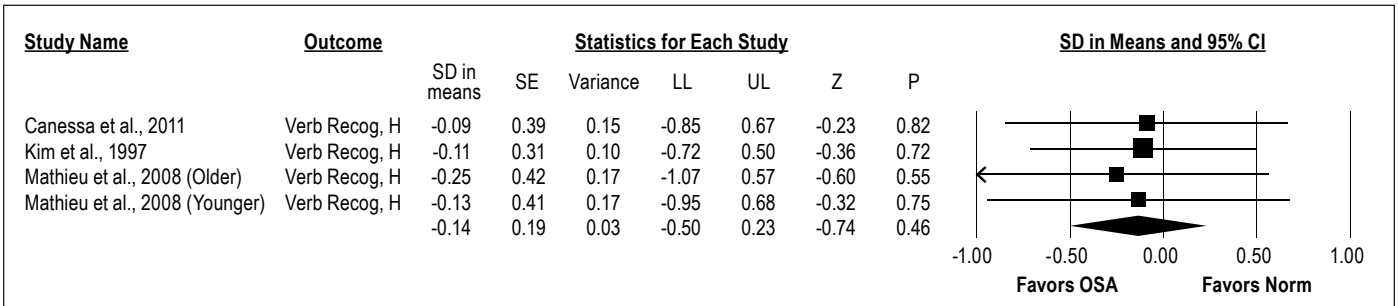

Figure 9—Forest plot comparing the performance of OSA samples on verbal recognition to norms. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

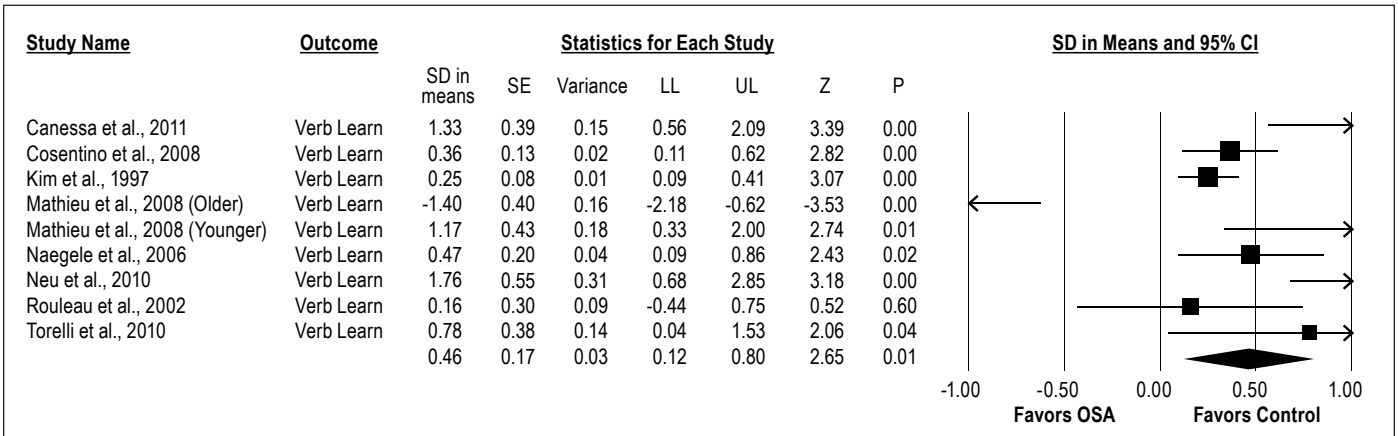

Figure 10—Forest plot comparing the performance of OSA samples on verbal learning to healthy controls. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

dures used included questionnaires (e.g., Epworth Sleepiness Scale) and interviews with the participant and their partner about sleep, and these studies were not included. For two domains (visuo-spatial learning and visual immediate recall) no studies remained for meta-analysis. For one domain, the effect size was substantively unchanged (0.46 to 0.51), but the effect was no longer significant, likely because of a drop from 9 to 6 studies. For the remaining 5 domains, all effects remained significant (see Table 5). This finding supports the moderator analysis, which found no effect of control screening on the results. This suggests the meta-analyzed memory deficits present in the OSA samples are large enough to be detected even when control samples are screened by either questionnaire/medical history or by PSG.

Risk of Publication Bias

Funnel plots were constructed for each domain to investigate the presence of publication bias. On visual inspection, the funnel plots appeared symmetrical, suggesting no bias was present. Publication bias was further investigated using statistical analysis. Egger's test for asymmetry[38] was significant only for verbal recognition (intercept 5.99; 95% CI: 1.27 to 10.71; P = 0.02). However, Rosenthal's *Fail-safe N*[39] revealed 114 studies with null results would be required to generate a nonsignificant overall effect in this domain. This indicates it is unlikely that the true difference between individuals with OSA and healthy controls on verbal recognition tasks is zero. Further, Duval and Tweedie's *Trim and Fill* procedure[40] was used to determine the best estimate of an unbiased overall effect

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Adams et al., 2011	Verb Learn	0.08	0.21	0.04	-0.32	0.49	0.41	0.68
Aloia et al., 2010 (adherent)	Verb Learn	0.49	0.14	0.02	0.22	0.76	3.56	0.00
Aloia et al., 2010 (non-adherent)	Verb Learn	0.49	0.16	0.03	0.17	0.81	3.00	0.00
Antonelli-Incalzi et al., 2004	Verb Learn	-0.04	0.35	0.12	-0.72	0.64	-0.10	0.92
Borak et al., 1996	Verb Learn	1.63	0.43	0.18	0.79	2.47	3.80	0.00
Canessa et al., 2011	Verb Learn	-0.14	0.39	0.15	-0.90	0.61	-0.37	0.71
Cosentino et al., 2008	Verb Learn	0.55	0.32	0.10	-0.07	1.17	1.75	0.08
Engleman, 1995 (Study 1)	Verb Learn	-0.02	0.34	0.12	-0.69	0.65	-0.06	0.95
Froehling, 1991	Verb Learn	0.57	0.34	0.12	-0.11	1.24	1.65	0.10
Gale et al., 2004	Verb Learn	-0.65	0.41	0.17	-1.46	0.16	-1.57	0.12
Gast et al., 2006 (no treatment group)	Verb Learn	-0.05	0.39	0.15	-0.82	0.72	-0.13	0.90
Gast et al., 2006 (treatment group)	Verb Learn	0.26	0.36	0.13	-0.45	0.97	0.73	0.47
Kim et al., 1997	Verb Learn	-0.40	0.31	0.10	-1.01	0.21	-1.29	0.20
Lim et al., 2007	Verb Learn	0.66	0.16	0.03	0.34	0.98	4.02	0.00
Mathieu et al., 2008 (Older)	Verb Learn	-1.10	0.44	0.20	-1.96	-0.23	-2.47	0.01
Mathieu et al., 2008 (Younger)	Verb Learn	0.05	0.41	0.17	-0.77	0.86	0.11	0.91
Naismith et al., 2004	Verb Learn	-0.59	0.32	0.10	-1.22	0.04	-1.82	0.07
Neu et al., 2010	Verb Learn	1.76	0.55	0.31	0.68	2.85	3.18	0.00
Rouleau et al., 2002	Verb Learn	-1.08	0.38	0.14	-1.82	-0.35	-2.88	0.00
Torelli et al., 2010	Verb Learn	0.79	0.41	0.16	-0.01	1.58	1.94	0.05
Valencia-Flores et al., 1996	Verb Learn	0.29	0.30	0.09	-0.29	0.88	0.98	0.33
		0.17	0.12	0.02	-0.08	0.41	1.35	0.18

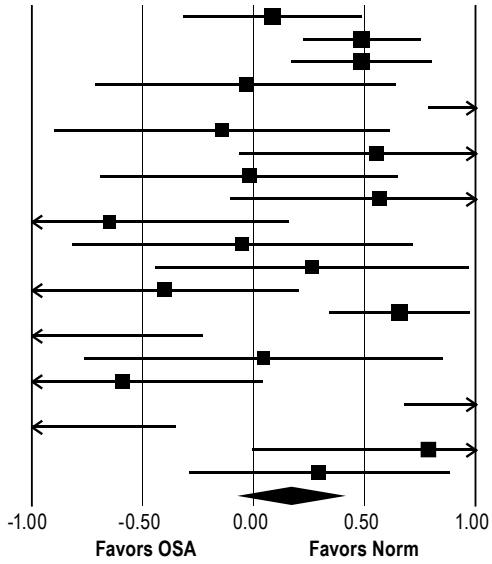

Figure 11—Forest plot comparing the performance of OSA samples on verbal learning to norms. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Bedard et al., 1991 (Moderate)	Vis Spat Imm Rec	0.92	0.47	0.22	-0.00	1.84	1.96	0.05
Bedard et al., 1991 (Severe)	Vis Spat Imm Rec	0.98	0.47	0.22	0.05	1.91	2.07	0.04
Findley et al., 1991	Vis Spat Imm Rec	0.60	0.26	0.07	0.08	1.12	2.27	0.02
Greenberg et al., 1987	Vis Spat Imm Rec	0.15	0.38	0.14	-0.59	0.90	0.41	0.68
Saunamaki, 2011	Vis Spat Imm Rec	0.39	0.28	0.08	-0.15	0.93	1.41	0.16
Sloan, 1989 (Hypoxic)	Vis Spat Imm Rec	1.20	0.34	0.12	0.53	1.86	3.52	0.00
Sloan, 1989 (Nonhypoxic)	Vis Spat Imm Rec	0.53	0.33	0.11	-0.11	1.17	1.62	0.10
		0.63	0.13	0.02	0.38	0.88	4.85	0.00

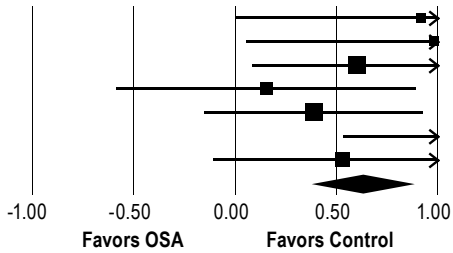

Figure 12—Forest plot comparing the performance of OSA samples on visuo-spatial immediate recall to healthy controls. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Bedard et al., 1991 (Moderate)	Vis Spat Imm Rec	0.26	0.34	0.12	-0.41	0.92	0.75	0.45
Bedard et al., 1991 (Severe)	Vis Spat Imm Rec	0.30	0.34	0.12	-0.37	0.97	0.89	0.37
Borak et al., 1996	Vis Spat Imm Rec	0.07	0.32	0.11	-0.57	0.71	0.22	0.82
Cammermeyer, 1991	Vis Spat Imm Rec	-0.10	0.31	0.10	-0.71	0.52	-0.30	0.76
Dahlof et al., 2002	Vis Spat Imm Rec	0.04	0.16	0.03	-0.28	0.36	0.25	0.80
Engleman, 1995 (Study 2)	Vis Spat Imm Rec	0.21	0.19	0.04	-0.15	0.58	1.14	0.25
Findley et al., 1991	Vis Spat Imm Rec	-1.19	0.22	0.05	-1.61	-0.76	-5.49	0.00
Greenberg et al., 1987	Vis Spat Imm Rec	-0.30	0.33	0.11	-0.93	0.34	-0.91	0.36
Merrion, 1991	Vis Spat Imm Rec	0.20	0.23	0.05	-0.25	0.65	0.86	0.39
Saunamaki, 2011	Vis Spat Imm Rec	-0.19	0.20	0.04	-0.59	0.20	-0.95	0.34
Sloan, 1989 (Hypoxic)	Vis Spat Imm Rec	-0.77	0.26	0.07	-1.28	-0.26	-2.95	0.00
Sloan, 1989 (Nonhypoxic)	Vis Spat Imm Rec	-0.47	0.26	0.07	-0.99	0.05	-1.78	0.07
Valencia-Flores et al., 1996	Vis Spat Imm Rec	0.53	0.29	0.09	-0.04	1.10	1.81	0.07
Verstraeten et al., 1997	Vis Spat Imm Rec	-0.15	0.22	0.05	-0.57	0.27	-0.70	0.49
Walker, 1990 (No treatment group)	Vis Spat Imm Rec	0.16	0.38	0.14	-0.58	0.91	0.43	0.67
Walker, 1990 (Treatment group)	Vis Spat Imm Rec	-0.28	0.26	0.07	-0.79	0.23	-1.07	0.28
		-0.12	0.11	0.01	-0.35	0.10	-1.07	0.28

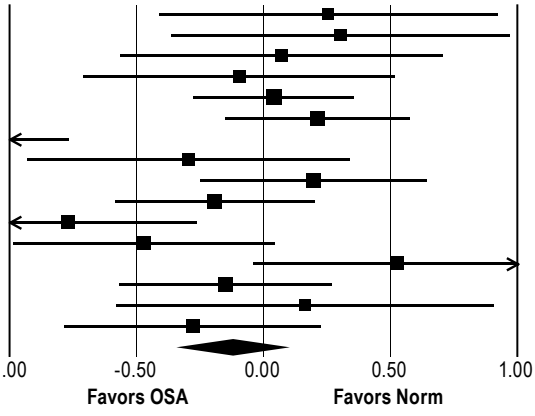

Figure 13—Forest plot comparing the performance of OSA samples on visuo-spatial immediate recall to norms. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Bedard et al., 1991 (Moderate)	Vis Spat Del Rec	0.67	0.46	0.21	-0.23	1.57	1.45	0.15
Bedard et al., 1991 (Severe)	Vis Spat Del Rec	1.17	0.48	0.23	0.22	2.11	2.41	0.02
Findley et al., 1991	Vis Spat Del Rec	1.90	0.31	0.09	1.30	2.50	6.23	0.00
Greenberg et al., 1987	Vis Spat Del Rec	0.88	0.40	0.16	0.11	1.66	2.23	0.03
Rouleau et al., 2002	Vis Spat Del Rec	0.89	0.32	0.10	0.27	1.51	2.81	0.00
Saunamaki, 2011	Vis Spat Del Rec	0.31	0.28	0.08	-0.23	0.85	1.11	0.27
Sloan, 1989 (Hypoxic)	Combined	-0.03	0.32	0.10	-0.66	0.59	-0.10	0.92
Sloan, 1989 (Nonhypoxic)	Combined	-0.04	0.32	0.10	-0.67	0.58	-0.14	0.89
Torelli et al., 2010	Vis Spat Del Rec	0.65	0.38	0.14	-0.09	1.39	1.73	0.08
Twigg et al., 2010	Vis Spat Del Rec	0.48	0.19	0.03	0.12	0.85	2.61	0.01
		0.67	0.19	0.04	0.30	1.03	3.55	0.00

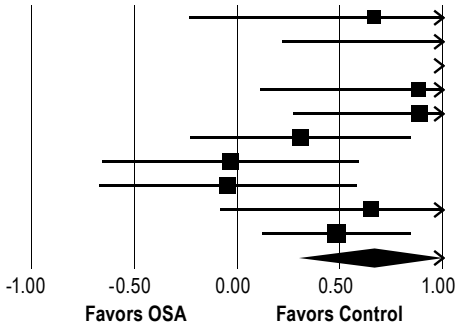

Figure 14—Forest plots comparing the performance of OSA samples on visuo-spatial delayed recall to healthy controls. The last line of data in the table gives the averaged effect size estimate. Combined outcome is the average of multiple measures within one study. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Adams et al., 2011	Vis Spat Del Rec	0.21	0.21	0.04	-0.21	0.62	0.98	0.33
Findley et al., 1991	Vis Spat Del Rec	-0.47	0.20	0.04	-0.87	-0.08	-2.34	0.02
Gale et al., 2004	Vis Spat Del Rec	0.28	0.32	0.10	-0.35	0.91	0.87	0.39
Greenberg et al., 1987	Vis Spat Del Rec	0.31	0.33	0.11	-0.33	0.95	0.95	0.34
Lim et al., 2007	Vis Spat Del Rec	-0.62	0.17	0.03	-0.95	-0.28	-3.57	0.00
Merrion, 1991	Vis Spat Del Rec	0.31	0.23	0.05	-0.14	0.76	1.37	0.17
Rouleau et al., 2002	Vis Spat Del Rec	0.16	0.23	0.05	-0.29	0.60	0.70	0.49
Saunamaki, 2011	Vis Spat Del Rec	-0.16	0.20	0.04	-0.55	0.24	-0.77	0.44
Sloan, 1989 (Hypoxic)	Vis Spat Del Rec	-0.04	0.25	0.06	-0.53	0.46	-0.15	0.88
Sloan, 1989 (Nonhypoxic)	Vis Spat Del Rec	0.04	0.26	0.07	-0.48	0.55	0.13	0.89
Torelli et al., 2010	Vis Spat Del Rec	0.73	0.29	0.08	0.16	1.29	2.54	0.01
Walker, 1990 (No treatment group)	Vis Spat Del Rec	0.49	0.38	0.15	-0.26	1.25	1.28	0.20
Walker, 1990 (Treatment group)	Vis Spat Del Rec	0.02	0.26	0.07	-0.48	0.53	0.09	0.93
		0.05	0.11	0.01	-0.16	0.27	0.48	0.63

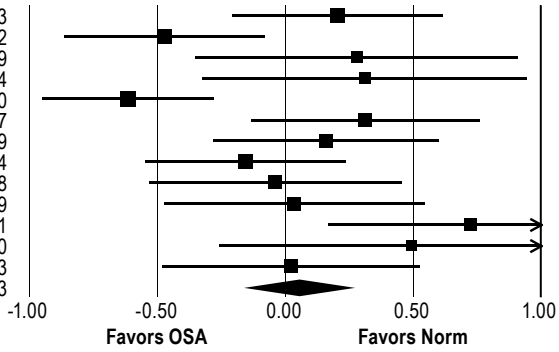

Figure 15—Forest plots comparing the performance of OSA samples on visuo-spatial delayed recall to norms. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Daurat et al., 2008	Vis Spat Learn	3.58	0.43	0.18	2.74	4.42	8.38	0.00
Twigg et al., 2010	Vis Spat Learn	-0.11	0.18	0.03	-0.47	0.25	-0.60	0.55
		1.72	1.84	3.40	-1.90	5.33	0.93	0.35

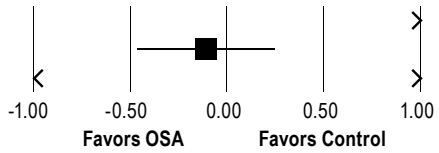

Figure 16—Forest plot comparing the performance of OSA samples on visuo-spatial learning to healthy controls. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	SD in means	SE	Variance	LL	UL	Z	P
Sloan, 1989 (Hypoxic)	Vis Imm Rec	0.14	0.31	0.10	-0.47	0.76	0.46	0.65
Sloan, 1989 (Nonhypoxic)	Vis Imm Rec	-0.04	0.32	0.10	-0.67	0.59	-0.13	0.90
		0.05	0.22	0.05	-0.39	0.49	0.24	0.81

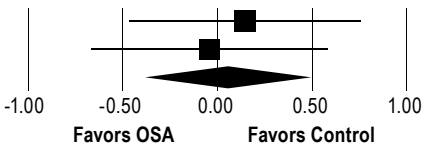

Figure 17—Forest plot comparing the performance of OSA samples on visual immediate recall to healthy controls. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

Study Name	Outcome	Statistics for Each Study						
		SD in means	SE	Variance	LL	UL	Z	P
Froehling, 1991	Vis Imm Rec	-0.49	0.21	0.04	-0.90	-0.08	-2.32	0.02
Lojander et al., 1999	Vis Imm Rec	-0.03	0.23	0.05	-0.49	0.43	-0.11	0.91
Sloan, 1989 (Hypoxic)	Vis Imm Rec	-0.38	0.25	0.06	-0.88	0.12	-1.49	0.14
Sloan, 1989 (Nonhypoxic)	Vis Imm Rec	-0.12	0.26	0.07	-0.63	0.40	-0.45	0.65
		-0.27	0.12	0.01	-0.50	-0.04	-2.27	0.02

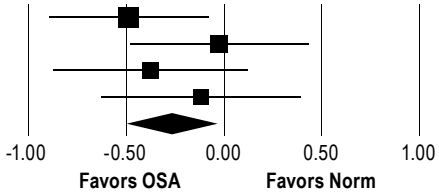

Figure 18—Forest plot comparing the performance of OSA samples on visual immediate recall to norms. The last line of data in the table gives the averaged effect size estimate. SD, standard difference; SE, standard error; LL, lower limit; UL; upper limit; Z; Z-value; P, P-value.

size. However, the overall effect size was unchanged, suggesting the original effect size was unbiased.

Inspection of the norm-referenced funnel plot suggested there was no publication bias present in the domains. Further inspection of the domains showed Egger's test was significant for visuo-spatial delayed recall (intercept 5.56; 95% CI: 2.17 to 8.95; P = 0.01). As this domain did not yield a significant effect size, the *Fail-safe N* was not applicable. The *Trim and Fill* method identified the best effect size as very similar to the original, suggesting the original effect size was unbiased.

DISCUSSION

The current paper builds on previous reviews by focusing on episodic memory within theoretically driven outcomes, analyzing immediate recall, learning, recognition, and delayed recall individually. It includes studies conducted in the last 10 years. Three questions were posed: (1) Which specific episodic memory outcomes are affected by the presence of untreated OSA? (2) Are any deficits specific to visual or verbal domains? and (3) If memory is impaired, is the effect moderated by publication status, sample source, study design, age, disease severity, or control screening?

To answer the first question, this meta-analysis revealed significant impairments in immediate and delayed recall of verbal information in OSA samples compared both to controls and norms. Furthermore, while results for the norm-referenced dataset were mixed, consistent impairments were found in individuals with OSA compared to healthy controls in verbal learning, verbal recognition, visuo-spatial immediate recall, and visuo-spatial delayed recall.

The Effect of OSA on Verbal Memory

The ability to recall verbal information immediately after it was presented was significantly impaired in individuals with OSA compared to both controls and norms. This result contrasts with the meta-analysis conducted by Beebe and colleagues,[10] who did not find a significant effect of OSA on verbal immediate recall. The effect found in the present study is likely to be due to two factors: analyzing verbal immediate recall independently of short-term working memory, verbal learning, and cued recall; and the greater number of studies included, thus adding more power to the present analysis.

In addition to difficulties recalling information immediately, individuals with OSA were significantly impaired when recalling verbal information following a delay compared to controls or norms. Impaired delayed recall can result from inefficient storage of information impeding retrieval, poor retention of information in long-term memory, or difficulties with retrieving information once stored. This meta-analysis supports recent research that reports intact retention in OSA and suggests that impaired delayed recall performance may be a consequence of poor encoding of information.[13,41] The effect sizes for verbal immediate recall and verbal delayed recall were comparable. As observed in studies investigating memory deficits in individuals with Alzheimer disease, if individuals with OSA had particular difficulties with the retrieval or storage of encoded information, the effect sizes for delayed recall would likely be larger than those for immediate recall.[42] The comparable effect sizes observed in the present study suggest individuals with OSA have an encoding deficit but can recall information once it is successfully encoded. Individuals with OSA may encode less information overall, or they may use inefficient encoding strategies that result in difficulties retrieving information. Salorio and colleagues[13] suggest individuals with OSA have an encoding deficit as a consequence of failing to use strategies—for example semantic clustering—to aid retrieval. Difficulties encoding information may occur as result of attention or executive function deficits, implicating the prefrontal cortex.[16] Further exploration of the nature of the proposed encoding deficit in OSA would be important. The delayed recall deficit found here contrasts with Beebe and colleagues,[10] who found a significant effect of OSA on verbal long-term memory in the norm-referenced dataset but not their control-referenced dataset. Again, this is likely to reflect the greater number of studies examining delayed recall since 2003.

Verbal recognition memory tasks assess the ability to recognize previously presented information among distractor items. Recognition memory tasks can be used further to clarify the nature of recall deficits.[43] Impaired free recall combined with intact recognition memory suggests information has been encoded but cannot be efficiently retrieved. Conversely, impaired recognition memory implies that information has either not been encoded or has not been retained and therefore cannot be retrieved even when cued. Given that immediate recall of information was impaired, it would be expected that recognition memory would also be impaired, which would provide additional evidence that individuals with OSA have an encoding deficit. Results from the control-referenced dataset confirmed this view, showing that individuals with OSA were impaired compared to controls on verbal recognition memory tasks.

Verbal learning reflects the individual's capacity to recall information when it is presented multiple times. Consistent with

an encoding deficit, the current meta-analysis found a verbal learning deficit in control-referenced studies. Individuals with OSA had an impaired ability to encode and immediately recall the information, even when it was presented a number of times.

For both verbal learning and verbal recognition domains, no impairments were observed in the norm-referenced dataset. This pattern of results, in which the control-referenced dataset showed individuals with OSA were impaired but the norm-referenced dataset revealed no impairments, suggests it is the comparison group that is influencing the results, not the OSA group—a point we will return to later.

The Effect of OSA on Visual Memory

Visual memory was distinguished from visuo-spatial memory in the current meta-analysis. Visual memory requires participants to recall visual material. Individuals with OSA showed intact visual immediate recall compared to norms and controls. At least two studies are required to conduct a meta-analysis, and this criterion was not reached for any other aspect of visual memory.

The Effect of OSA on Visuo-spatial Memory

Visuo-spatial memory tasks require participants to recall an image, for example, by drawing it later or recalling the specific location of the image on a grid. The control-referenced dataset provided evidence that there was significant impairment in the ability of individuals with OSA to recall visuo-spatial information immediately and following a delay. Similar to the verbal domain, the effect sizes for visuo-spatial memory were comparable for the immediate-recall and delayed-recall domains. This suggests individuals with OSA have an encoding deficit that affects recall of both visuo-spatial and verbal information.

This finding was not supported by the visuo-spatial learning result for the control-referenced dataset; however, the analysis for visuo-spatial learning was based on only two studies with contrasting results, suggesting more research is required in this domain. The same OSA samples from the control-referenced dataset showed reduced or no impairment when compared to normative data.

Taken together, the visual and visuo-spatial memory analyses reveal evidence of intact immediate visual recall but impaired immediate and delayed visuo-spatial recall in OSA compared with controls. However, more evidence relating to visual memory deficits (both immediate and delayed) in OSA is needed before the second question (is the deficit specific to visual or verbal memory?) can be adequately addressed.

Moderator Analysis

The final key question related to whether the memory deficits of OSA are influenced by age, study design, publication status, OSA severity, or screening of controls. Moderator analysis was used to explore each of these factors. In line with Beebe et al.,[10] publication status did not significantly moderate the effect in any memory domain, suggesting that the results of published studies did not differ significantly from those of unpublished studies. Similarly, age did not significantly moderate any outcome variables. In primary research studies, older adults have been found to be more impaired than younger adults on tests of memory functioning.[30,44] The lack of effect in the current meta-analytic review may reflect assessment of the effect of age using group averages, which resulted in similar age distributions across samples. Primary comparison studies exploring the interaction of age and OSA would help to clarify this relationship.

Disease severity did not significantly moderate effects, which suggests that the pattern of deficits reported is present across both mild/moderate and severe OSA. Disease severity was usually assessed using AHI. Other measures used were the AI and RDI. None of these measures consider the length of time an individual's breathing is interrupted resulting in oxygen desaturation. Studies did not consistently report an alternative measure of disease severity (e.g., the percentage of time with an oxygen desaturation level less than 90%) for further analysis to be conducted in the present review. As both hypoxemia and sleep fragmentation are proposed to contribute to cognitive impairments,[16] future case-control research should investigate the relationship between memory functioning and measures of disease severity beyond AHI, perhaps using oxygen desaturation.

Finally, participants included in studies as healthy controls were not consistently screened with an overnight sleep study. Control screening was examined as a moderating variable with studies that screened controls with a sleep study compared to those that used other measures, such as questionnaires. There was no significant moderating effect of control screening.

Future Research

Six methodological issues were identified in the present meta-analysis that should be considered for future research in this field. First, the classification of memory tasks must be meaningful. This review was unique in that it used memory theory to examine the effect of OSA, classifying visual, visuo-spatial, and verbal memory tasks into immediate recall, delayed recall, recognition memory, and learning. Impairments in immediate and delayed recall for visuo-spatial and verbal memory were observed in individuals with OSA compared to controls, as were impairments in immediate visual recall. This suggests future research should continue to assess immediate and delayed recall of information when examining cognitive deficits in individuals with OSA.

Second, to better capture the nature of recognition memory deficits in individuals with OSA, researchers need to make sure they are accurately measuring recognition ability. Recognition was measured in this meta-analysis using the total number of targets correctly identified ("hits"). This measure was chosen as it was the most consistently reported in studies assessing recognition memory. The conflicting results between datasets in the current study suggest a total "hits" score may not adequately reflect the performance of individuals with OSA on recognition tasks. An individual can appear unimpaired on a "hits" recognition measure if, when in doubt, they have a tendency to respond to every stimulus as a "hit" (positive response bias). Equally, an individual may appear impaired if they have a negative response bias and when unsure respond "no" to a target. *Discrimination* scores assess the ability to differentiate between targets and distractors. A measure of *bias* examines the tendency to say "yes" or "no" to a target when unsure whether a stimulus is a target or a distractor.[45] Future studies should employ discrimination and bias measures to provide a more accurate representation of recognition memory performance in individuals with OSA.

Third, the choice of comparison group largely influences the nature and degree of episodic memory deficits. The performance of individuals with OSA on episodic memory tests was compared to controls when the study included a control comparison and to norms when appropriate norms were available. The advantage of comparing to a normative group is that this usually provides a large sample, which results in smaller standard errors. When there was a discrepancy between datasets in the current review, it was always the case that the control-referenced dataset identified impairment in the OSA sample and the norm-referenced dataset did not. This occurred even when the same OSA samples were included in both datasets. Arguably, normative samples are screened less rigorously than the control samples used in OSA research and, therefore, may inadvertently include individuals with undiagnosed OSA and other possibly confounding conditions. As previously described, there is a high prevalence of OSA in adult populations, with estimates that 82% of middle-aged men and 93% of middle-aged women with moderate to severe OSA remain undiagnosed.[29] For this reason, more weight has been given to the results found in the control-referenced dataset, as each control subject underwent some screening for OSA, with 62% of the control studies using in-lab overnight polysomnography to screen control participants.

Fourth, within the control-referenced data set, there is still debate about whether it is necessary to conduct full PSG with controls (see footnote 3). Accordingly, the meta-analyses were recalculated with only those control studies that screened participants with overnight polysomnography. Inspection of the effect sizes reveals broad consistency of the deficits found irrespective of the control screening method used, with the exception of verbal recognition, where the effect size halved but remained significant, and verbal learning, where the effect size remained moderate (0.51) but was no longer significant. However, the effect size increased or remained significant for 5 of the 6 studies with sufficient data for this subanalysis.

Together, three sources of evidence contribute to the discussions about the best comparison group to use: comparison of effects in normative and control-referenced meta-analyses; moderation analyses by type of control study within the control-referenced group; and meta-analysis of only those control-referenced studies with controls screened using PSG. The evidence reported here suggests that, assuming there are sufficient control-referenced studies available, future meta-analyses of cognitive deficits in OSA should focus only on control-referenced studies, but that such meta-analyses may not need to select only those primary studies which screen controls with overnight polysomnography.

Five, in all of the memory domains that generated a significant result, significant heterogeneity in sample effect sizes was present. This suggests there are factors influencing results that were not identified in the current meta-analysis. Other possible factors may include aspects at the individual level (oxygen levels, as already mentioned, IQ, or education) or study level (diversity of measures included). Unfortunately, a measure of academic achievement or premorbid intelligence (IQ) was not consistently included. Therefore, studies that stratify the sample into age and IQ groups when examining the impact of OSA on memory and other cognitive areas would improve understanding of the impact of cognitive reserve in protecting individuals with OSA from demonstrating cognitive impairments as they age.[46,47]

CONCLUSION

This theoretically driven meta-analysis of memory problems in OSA has identified significant deficits in immediate and delayed verbal and visuo-spatial memory and in immediate visual recall. Clearly, aggregating cognitive functions for meta-analyses in OSA should be conducted based on relevant theory, since this affects findings. Furthermore, while deficits were revealed when compared to normative samples, comparisons with control samples produce the strongest and most consistent effects, suggesting that future meta-analyses of cognitive impairments in OSA should focus on control-referenced studies. Although age and disease severity were not moderators of the effects found, primary data exploring the impact of age and disease severity combined with premorbid ability (cognitive reserve) are now needed. Finally, a similarly stringent, theoretically based meta-analysis of memory performance before and after patients have received continuous positive airway pressure (CPAP) is needed to determine the reversibility of these deficits by CPAP.

FOOTNOTES

1. One study (Antic et al., 2011) screened OSA patients using overnight home oximetry, and then tested 50% of the sample with a full night in-lab sleep study. This study was included as all the patients who were followed up with a sleep study tested positive for OSA
2. Given that one reviewer preferred the pooled SD to the control SD, we also calculated all analyses using the pooled SD. This did not change the significance of the effects reported below.
3. A point made by one reviewer.

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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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SUPPLEMENTAL MATERIAL

Study ID _____

Study _____

First Author _____ Publication Date _____

Publication Journal _____

Mark *Yes*, *No*, or *Unclear* for Each Item

Comments _____

_____

_____

_____

INCLUSION/EXCLUSION CRITERIA:	
Does the study involve adults with untreated obstructive sleep apnea?	❑ YES ❑ UNCLEAR ❑ NO (exclude)
Is memory measured as an outcome variable using valid neuropsychological assessments? If memory is tested, but how it is measured is not clarified, include at this stage	❑ YES ❑ UNCLEAR ❑ NO (exclude)
Are the data recorded at baseline (i.e. prior to any treatment)?	❑ YES ❑ UNCLEAR ❑ NO (exclude)
Are results presented in a way which allows effect sizes to be calculated?	❑ YES ❑ UNCLEAR ❑ NO (exclude)
Include article in study?	❑ YES ❑ UNCLEAR (include subject to clarifying criteria) ❑ NO

Figure S1—Screening tool to select studies from abstract scans.

Study ID _____

Study _____

First Author _____ Publication Date _____

Publication Journal _____

STUDY PURPOSE Was the aim clearly stated? ❑ YES ❑ NO	Outline the purpose of the study. Does the study relate to the literature?
DESIGN ❑ Experimental ❑ Observational	Describe the study design. Was it appropriate?
SAMPLE N =	Sampling (who; demographics; how many; how was sampling done)?
Was the sample described in detail? ❑ YES ❑ NO	Details:
Were groups matched? (Age, IQ, gender, SES, confounding factors) ❑ YES ❑ NO ❑ N/A	Details:
Were exclusion criteria defined? ❑ YES ❑ NO ❑ N/A	Details:
Was sample size justified? (power calculation) ❑ YES ❑ NO ❑ N/A	Details:
Is the sample based on a representative sample selected from a relevant sample? ❑ YES ❑ NO ❑ N/A	Details:
Was informed consent obtained?: ❑ YES ❑ NO ❑ N/A	Describe ethics procedures.

Figure S2—Quality assessment tool adapted from Law et al.[66]

Figure S2 continues on the following page

<table>
<tr><td rowspan="2">OUTCOMES

Were the outcome measures adequately described (and thus replicable)?
❑ YES
❑ NO
❑ N/A

Were the outcome measures reliable?
❑ YES
❑ NO
❑ N/A

Were the outcome measures valid?
❑ YES
❑ NO
❑ N/A

Was polysomnography performed on all patients with suspected OSA?
❑ YES
❑ NO
❑ N/A

Was AHI reported?
❑ YES
❑ NO
❑ N/A

Were any control subjects also tested using polysomnography?
❑ YES
❑ NO
❑ N/A</td><td colspan="2">Specify the frequency of outcome measurement (i.e., pre, post, follow-up):</td></tr>
<tr><td>Outcome areas:</td><td>List measures used:</td></tr>
<tr><td>RESULTS

Results were reported in terms of statistical significance?
❑ YES
❑ NO
❑ N/A

Were the analysis method(s) appropriate (were corrections used for when multiple comparisons were made to avoid Type 1 errors)?
❑ YES
❑ NO
❑ N/A

Drop-outs were reported?
❑ YES
❑ NO</td><td colspan="2">What were the results? Were they statistically significant (i.e., P < 0.05)? If not statistically significant, was study big enough to show an important difference if it should occur?

Did any participants drop out from the study? Why? (Were reasons given and were drop-outs handled appropriately?)</td></tr>
</table>

Figure S2 (*continued*)—Quality assessment tool adapted from Law et al.[66]

Figure S2 continues on the following page

HOW DOES THE STUDY ADDRESS BIAS? Blinding of assessors? ❑ YES ❑ NO ❑ N/A Did the authors declare any interests with regards to funding? ❑ YES ❑ NO ❑ N/A	
CONCLUSIONS AND IMPLICATIONS Conclusions were appropriate given study methods and results ❑ YES ❑ NO	What did the study conclude? What are the implications of these results for practice? What were the main limitations or biases in the study?

Figure S2 (*continued*)—Quality assessment tool adapted from Law et al.[66]