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Executive Dysfunction in OSA Before and After Treatment: A Meta-Analysis

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Study Objectives: Obstructive sleep apnea (OSA) is a frequent and often underdiagnosed condition that is associated with upper airway collapse, oxygen desaturation, and sleep fragmentation leading to cognitive dysfunction. There is meta-analytic evidence that sub-domains of attention and memory are affected by OSA. However, a thorough investigation of the impact of OSA on different sub-domains of executive function is yet to be conducted. This report investigates the impact of OSA and its treatment, in adult patients, on 5 theorized sub-domains of executive function.

Design: An extensive literature search was conducted of published and unpublished materials, returning 35 studies that matched selection criteria. Meta-analysis was used to synthesize the results from studies examining the impact of OSA on executive functioning compared to controls (21 studies), and before and after treatment (19 studies); 5 studies met inclusion in both categories.

Measurements: Research papers were selected which assessed 5 sub-domains of executive function: Shifting, Updating, Inhibition, Generativity, and Fluid Reasoning.

Results: All 5 domains of executive function demonstrated medium to very large impairments in OSA independent of age and disease severity. Furthermore, all sub-domains of executive function demonstrated small to medium improvements with CPAP treatment.

Discussion: Executive function is impaired across all five domains in OSA; these difficulties improved with CPAP treatment. Age and disease severity did not moderate the effects found; however, further studies are needed to explore the extent of primary and secondary effects, and the impact of age and premorbid intellectual ability (cognitive reserve).

Keywords: Obstructive sleep apnea, executive function, cognition, neuropsychology, review

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INTRODUCTION

Obstructive sleep apnea (OSA) is a frequent and often underdiagnosed condition associated with upper airway collapse, oxygen desaturation, and sleep fragmentation leading to sleepiness, hypertension, increased risk of cardiac disease, and neurocognitive disturbance.[1-3] Untreated OSA is associated with increased healthcare utilization, occupational injuries, motor vehicle accidents,[4-6] and neurocognitive sequelae in memory, attention, and executive function.[2,7] The gold standard treatment for OSA is continuous positive airway pressure (CPAP).[8,9]

To date, most reviews of cognitive functioning in OSA have inspected cognition as a whole, collapsing research findings into "memory," "executive function," or "attention" domains.[10,11] As the evidence base grows, however, it is both possible and desirable to explore the cognitive burden of OSA within subcomponents. Based on current neurocognitive theory, there are functional and biological grounds for segregating cognitive domains or functional systems into such subcomponents.[12,13] These subcomponents work in concert to produce what we colloquially know as memory, attention, and executive function.[14,15]

Recently, Wallace and Bucks[16] divided episodic memory into theoretically driven subcomponents, revealing deficits in individuals with OSA in 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. This theoretically driven division of memory reveals that not all components of memory are dysfunctional in OSA, and provides an explanation for the mixed findings in this field. A similar approach might prove fruitful when exploring executive dysfunction in OSA. In a review, Saunamäki and Jehkonen[17] demonstrated that aspects of executive function may also be impaired or preserved in OSA. They divided executive functioning by test, demonstrating deficits in Digit Span Forwards, Corsi Block Tapping task, Double encoding task, Wisconsin Card Sorting Test, Phonemic fluency, Rey-Osterreith Complex Figure test, and Maze tasks. However, by meta-analyzing the data by test, this review did not aggregate executive functions using a theoretical framework. In addition, Saunamäki and Jehkonen included some tests that do not primarily measure executive function (i.e., Digit Span Forwards, Rey-Osterreith Complex Figure test, the Trail Making Test Part A, and the Corsi Block Tapping task), making it difficult to determine which subcomponents of EF, mapped by which tests, are impaired in OSA.

Executive function is an individually controlled and conscious effort to guide the operation of various cognitive processes and thereby regulate cognition.[13,14,18-21] Like other cognitive domains, executive function is multidimensional.[13,20-22] Miyake et al.,[20] Fisk and Sharp,[23] and Adrover-Roig et al.[12] present an empirical basis for specifying how executive functions are organized, and what roles different subcomponents play. Miyake et al.[20] divide executive functioning into (a) *Shifting* between tasks or mental sets, (b) *Updating* and monitoring of working memory representations and (c) *Inhibition* of dominant or pre-potent responses. Fisk and Sharp[23] and Adrover-Roig et al.[12] utilized this same 3-factor structure, but proposed a fourth component; efficiency of access to long term memory (called Generativity in the present report, for brevity). This four-component structure has been confirmed in multiple populations with factor analysis (exploratory and confirmatory).[12,23,24,25]

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Lezak et al.[13] and Strauss et al.[26] define a set of tasks that do not tap executive function per se, but rather an overarching system of reasoning and problem solving. These tasks involve complex, higher order abstraction, problem solving, and concept formation, and include tasks such as Porteus mazes and clock drawing tasks. The four-factor model defined above does not account for such tasks; however, they abound in OSA literature on executive function and are considered a part of executive functioning in neuropsychological theory.[13,26] Hence, in the present paper a class of executive function tasks, called Fluid Reasoning, was created to capture this concept.

The present paper builds on past reviews and meta-analyses examining executive functioning in adults with OSA within current neuropsychological theory of executive function. No previous meta-analysis in OSA has assessed EF dysfunction, or the effect of treatment, within these 5, theoretically motivated domains: Shifting, Updating, Inhibition, Generativity, and Fluid Reasoning. We addressed three questions: (1) which specific executive functions are affected by the presence of untreated OSA?; (2) if executive functions are impaired, does treatment help to remediate these deficits?; and (3) are any of these effects moderated by publication status, sample source, study design, age, disease severity, or control screening?

METHODS

Search Strategy

Data for this meta-analysis consisted of empirical articles published in peer-reviewed journals over the past 24 years (Jan 1987-Nov 2011). Details of the search methodology employed are outlined in Figure 1.

An extensive computer assisted literature search was conducted using electronic databases (Keyword and MeSH explode) for published articles (Medline R, PsychInfo, PubMed, EMBASE, CINAHL, CCTR, NHS EED), grey literature (SIGLE, NTIS), conference proceedings (Conference Proceedings Citation Index: Science), dissertations and theses (Proquest Dissertations and Theses), the Internet (Dogpile, Omni Medical search engine, Mednet), and via hand searching (Index Medicus, Exerpta Medica, references of included articles, contact with authors of unpublished studies). Unpublished studies were included in the search, to avoid publication bias.

The terms "apnea OR sleep-disordered breathing" were combined with "Cognition OR Cognitive ability OR Mental Status OR Neuropsychology OR Memory OR Attention OR Vigilance OR Executive OR Psychomotor." The terms chosen covered a wide range of cognitive functions to capture tests that had been mislabelled or utilized to measure other cognitive domains.

Additional relevant articles were retrieved from the reference lists of studies included in the original search, conference proceedings and dissertations. Furthermore, key authors who have published articles on the relationship between OSA, cognition, and CPAP treatment were contacted asking if they were aware of any other relevant published or unpublished studies.

Study Selection Criteria

This review included studies that assessed executive function in adults with OSA as defined by an apnea-hypopnea index (AHI) > 5 per hour of sleep.[27] In all instances except one, studies were excluded if OSA participants were not diagnosed using overnight polysomnography and/or if they did not include a control sample, if group matching was inappropriate (e.g., IQ statistically different between control and OSA groups), or there were no baseline data (participants were assessed after treatment only). The exception to this rule was Antic et al.,[28] where participants were administered overnight oximetry instead of PSG. This paper was included as the oximetry was validated against in-laboratory PSG in a random selection of 50% of the participants.

Additionally, papers were excluded if the PSG was conducted more than 12 months before/after neuropsychological profiling was completed. These studies were excluded as individuals may lose or gain weight, or change their lifestyle habits (e.g., drink, smoke, or exercise more or less), which may alter the severity of their sleep apnea.[29,30]

This review considered only studies with adult participants (≥ 18 years), not from special populations (e.g., people with Down syndrome, insomnia, or traumatic brain injury). Research demonstrates that there are etiological differences between adult and childhood OSA[31]; thus the latter was not addressed here.

The present review aimed to delineate the pattern of executive deficits in OSA; hence, studies that included a majority of central or mixed sleep apnea patients were excluded. Research demonstrates that the pathophysiology, epidemiology, and clinical characteristics of central sleep apnea and OSA are distinct.[32]

Papers were excluded if the tests used were inadequately described such that acceptable validity and/or reliability could not be confirmed, the paper was a review paper not a study, if it reported data already included in the present review (in this instance the most complete data set was selected) or was a crossover trial. Crossover trials were excluded as research does not provide any definitive information regarding length of washout period required.[33-35]

The present study was only able to examine CPAP treatment, as after evaluating studies with the exclusion criteria, there remained an insufficient number of other treatment studies (no oxygen therapy, positional therapy, drug trial or weight loss studies, 1 surgical study, 3 mandibular advancement splint [MAS] studies, 3 studies with mixed treatments). Nor did the present review examine medication studies as these (e.g., modafinil and armodafinil) may alter alertness, cognitive function, and judgment without treating underlying nocturnal symptoms.[36,37] Although research demonstrates that these medications can be helpful in conjunction with CPAP where there is residual sleepiness, the present study aimed to look at the effect of OSA on cognitive function, and such medications may have confounded these results.

Furthermore, studies were not considered if the data were presented in such a way that effect sizes could not be calculated even after contact with the author. We contacted 32 authors for further details on 33 research papers. Five authors or their representatives replied. Of these, 2 authors were deceased, 1 had no more detail to provide, and 2 emailed further data. Data received from N. Antic (personal correspondence, September 2012) were utilized in the present meta-review. We also received further data from M. Barnes[38]; however, these data were later excluded as they were from a crossover trial.

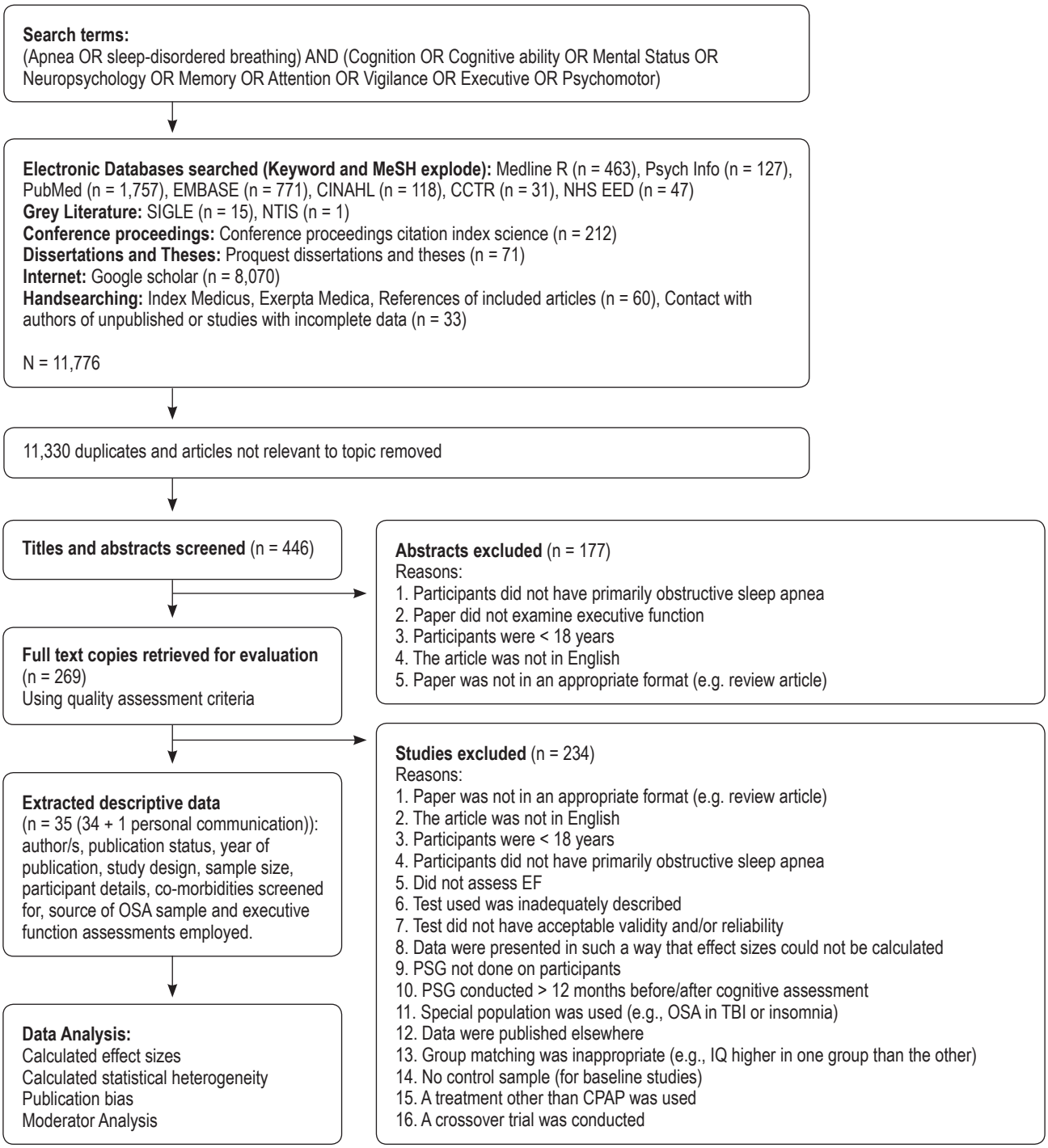

Figure 1—Flow chart of search, retrieval and inclusion process

Given that it is difficult to keep participants and experimenters blinded to group (OSA or Control, Treatment, or No treatment) in OSA studies when assessing neuropsychological function,[39] this review did not exclude unblinded studies.

Finally the present paper included studies in which controls were screened using PSG or with questionnaires. Despite the risk of undetected OSA in the control sample,[40] evidence from Wallace and Bucks[16] suggested that comparing OSA participants with controls within memory domains, with and without PSG screening of controls, did not dramatically reduce the significance of the effects found, and would have reduced the number of studies available per subcomponent. Rather, the present meta-analysis considered control screening method as a moderator instead.

Quality Assessment

The authors (MO, RSB) independently reviewed articles according to the selection criteria. Where there were disagreements about whether or not to include an article, the authors discussed and came to an agreement.

Table 1—The five sub-domains of executive function and the tests that measure these facets that were utilised in the studies included in the present meta-analysis

Category	Description	Tests that tap this cognitive skill
Shifting	Shifting back and forth between multiple tasks, operations or mental sets. Requires the disengagement of an irrelevant task set and subsequent engagement of a relevant task set when a new operation must be performed on a set of stimuli, necessary to overcome proactive interference or negative priming due to having recently performed a different operation.	• Wisconsin Card Sorting Test* (18) • Trails B (3) • Switching task (26)
Updating	Updating and monitoring of working memory representations. Requires the monitoring and coding of incoming information for relevance to the task, and then appropriately revising items held in working memory by replacing old, no longer relevant information with new more relevant information. Dynamically manipulate the contents of working memory.	• N-back tasks (24) • Digit span backwards* (9) • WAIS-R Arithmetic (13) • ANAM Mathematical processing (14) • ANAM running memory (17)
Inhibition	Inhibition of prepotent, dominant, or automatic responses when necessary. An internally generated act of control.	• Towers* (19) • Stroop task (6) • Go No-go task (4)
Generativity	Speed and efficiency of access to long-term memory. An independent ability to create, generate or produce content without any input from what or whom?	• Verbal fluency tasks* (2)
Fluid reasoning	Concept formation/abstraction & problem solving tasks. An intentional cognitive process that does not occur automatically, but rather involves the use of deliberate and controlled mental actions to solve novel problems.	• Mazes† (12) • Ravens progressive matrices† (1) • Picture completion† (22) • WAIS-R Picture arrangement† (11) • WAIS-R Block design (8) • Stockings of Cambridge (23) • WAIS-R Similarities† (7) • Object assembly (10) • Clocks (20) • Twenty questions† (21) • Category tests† (5) • ANAM Matching to sample (15) • ANAM logical relations (16) • Five point design task (25)

*Mapping of tests to category as recommended by Miyake et al.,[20] Fiske and Sharp,[23] Adrover-Roig et al.[12] †Mapping of tests to category as recommended by Lezak et al.,[13] Strauss et al.[26] Numbers in parentheses relate to which tests were used in individual articles, for more details see Appendix 1.

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 $r = 0.99$ (CI: 0.99-1.00).

Study Categorization

Included studies (N = 35; 34 studies + 1 personal communication) were divided into two non-exclusive categories: (1) comparisons of pre-treatment OSA groups to controls were used to identify the specific pattern of executive dysfunction present in untreated OSA (n = 21*)*, and (2) CPAP treatment efficacy studies were used to establish whether executive impairments were permanent in OSA (n = 19): 5 studies met criteria for inclusion in both groups.

Categorization of Executive Function

Table 1 presents the sub-domains of executive function and the tests ascribed to these sub-domains.

Data Extraction and Analysis

Data extracted and coded from the final articles included author/s, whether published or not, journal and year of publication (if applicable), study design, sample size and participant details when available (gender, years of formal education, body mass index [BMI], age, diagnostic criteria, AHI or RDI, oxygen desaturation indices [time spent below 90%: CT90] and sleep fragmentation indices [Arousal Index: ArI]), source of OSA sample (clinical vs. community) and neuropsychological assessments employed (see Appendix 1 for further details). Means, standard deviations and sample size were extracted to examine the relationships between the variables of interest.

In the instance that participants had been assessed at multiple time points after CPAP treatment we chose the most distant time point, as we wanted to examine the effect of continuous treatment on executive dysfunction. Furthermore, if participants were divided into compliant (> 4 h for 80% of nights) and noncompliant users, only the compliant user information was included. These 2 decisions were made so as best to evaluate the benefit to individuals who utilize their CPAP devices as recommended over the long term. These choices led us to lose only 1 subsample from a paper, but no whole papers.

Data Processing

The program Comprehensive Meta-Analysis version 2.2.064[41] was used to synthesize data, calculate effect sizes, and create forest plots.

Table 2—Mean effect sizes for the differences between OSA to control groups, and pre-treatment to post-treatment groups

		Effect Size Statistics					Homogeneity Statistics			
			95% CI							
Domain	N	*d*	Lower	Upper	Z	P	Q (df)	P	Tau	I^2
OSA to controls										
Shifting	15	0.53	0.38	0.92	4.78	< 0.001	41.68 (14)	< 0.001	0.42	66.41
Updating	14	0.91	0.49	1.32	4.30	< 0.001	71.12 (13)	< 0.001	0.71	81.72
Inhibition	9	1.12	0.55	1.69	3.83	< 0.001	57.17 (8)	< 0.001	0.79	86.01
Generativity	8	0.59	0.34	0.85	4.58	< 0.001	8.25 (13)	0.311	0.14	15.18
Fluid Reasoning	11	0.80	0.42	1.19	4.11	< 0.001	44.12 (10)	< 0.001	0.55	77.33
Pre to post CPAP treatment										
Shifting	14	0.66	0.31	1.00	3.75	< 0.001	47.12 (13)	< 0.001	0.58	72.41
Updating	10	0.46	0.15	0.77	2.90	0.021	15.94 (9)	0.068	0.33	43.55
Inhibition	9	0.57	0.31	0.86	4.17	< 0.001	10.75 (8)	0.216	0.21	25.57
Generativity	8	0.33	0.13	0.53	3.27	0.001	5.21 (7)	0.635	0	0
Fluid Reasoning	10	0.37	0.18	0.56	3.85	< 0.001	10.02 (9)	0.349	0.10	10.27

RESULTS

Description of Studies

From the articles identified (N = 35), 21 studies compared people with untreated OSA to a control sample, 19 compared people with OSA before and after treatment; 5 studies had both a comparison to controls participants and neurocognitive testing performance before and after treatment. These studies represent 40 samples. Only 1 study was recruited from a community setting,[42] thereby making 98% of studies from clinical settings.

In total, there were 551 healthy controls (74% male; mean age 49.46 ± 8.96 years; mean ESS 5.52 ± 2.41; mean BMI 25.42 ± 2.50) and 1,010 participants with OSA (81% male; mean age 50.40 ± 7.43 years; mean AHI/RDI 47.58 ± 15.98; mean arousal index (ArI) 36.15 ± 17.66; mean cumulative time below 90% oxygen saturation (CT90) 40.07 ± 28.55; mean education 13.73 ± 1.48 years; mean months of CPAP treatment 2.89 ± 2.22 months; mean hours CPAP use per night 5.34 ± 1.01; mean Epworth Sleepiness Scale (ESS) score 12.02 ± 2.38; mean body mass index (BMI) 33.12 ± 2.76. Individual study details for sample size, publication source, age, indices of disease severity (AHI or RDI), oxygen desaturation (CT90), and sleep fragmentation (ArI), years of education, and length of CPAP treatment are given in Appendix 1.

In the present meta-analysis, only studies with matched control and OSA participant variables were chosen, except that as expected, the control and OSA groups differed significantly in BMI, $t(1228) = -56.03$, $P < 0.001$, and ESS, $t(1118) = -51.15$, $P < 0.001$ scores.

Calculation of Effect Sizes

Random effect sizes were calculated. The random effects model assumes that each study has a different underlying "true" effect size due to differing sample demographic variables.[43] In the present meta-analysis, samples differed on such variables as disease severity, age, gender, screening measures, oxygen saturation, and sleep fragmentation (for full descriptive details of each study see Appendix 1). A random effects model accounts for these between-studies differences, as well as within-study participant differences.

An effect was calculated for each sample across each of the 5 domains. For comparisons between the OSA group and healthy controls, Cohen's d was calculated according to the following formula:

$$d = \frac{mean\ controls - mean\ OSA}{pooled\ SD}$$

where effect sizes of $d \leq 0.20$ are considered small, $d = 0.50$ medium, $d \geq 0.80$ large and $d \geq 1.00$ very large.[44] Larger, positive effects indicate poorer performance for the OSA group.

In OSA group pre-treatment compared to post-treatment, Cohen's d effect sizes were calculated with the following formula:

$$d = \frac{mean\ post\text{-}treatment - mean\ pre\text{-}treatment}{pooled\ SD}$$

Higher scores indicate greater improvement post CPAP treatment.

The random effect size estimates between OSA and control groups for each domain are displayed in Table 2. All 5 subdomains of executive function were impaired, compared to controls. A very large effect was noted for Inhibition, a large effect was present for Updating and Fluid Reasoning, and medium effect sizes were present for Shifting and Generativity. These results indicate medium to very large deficits in executive function performance across all 5 domains in individuals with OSA, when compared to control.

The random effect size estimates between OSA pre-treatment and post-treatment are displayed in Table 2. All 5 subdomains of executive function demonstrated improvement after CPAP treatment. Medium effect sizes were found in Shifting and Inhibition, and small effect sizes were noted in Updating, Fluid Reasoning, and Generativity. These results indicate small to medium size improvements across all 5 domains of executive function with CPAP treatment.

Forest plots for individual studies are available in Appendices 2 and 3.

Heterogeneity

Heterogeneity of effect sizes is a measure of difference between a study's true effect size and the observed effect size. The true effect size is the actual effect size in the underlying population, while the observed effect size is the effect measured in the sample.[45] Heterogeneity was investigated visually with forest plots (Appendices 2 and 3), and statistically using Cochrane's Q statistic, the T^2 and I^2 statistics (Table 2). When the Q statistic is significant, this suggests there is a significant difference between the observed and true effect. However the Q statistic is vulnerable to small sample size, hence T^2 and I^2 can provide an estimate of the proportion of real variance caused by extraneous study variables such as age or test used.[45] In any instance that Q was significant, I^2 was examined to quantify the degree of heterogeneity.

For the comparisons between controls and individuals with OSA, significant heterogeneity was present in all domains. However, the I^2 ranged between 77.33 and 86.01, suggesting at least 77% of the variance was generated from real, between-group differences.

For the comparisons of pre- and post-treatment, significant heterogeneity was present in the domain, Shifting. However, the I^2 was 72.41 suggesting at least 72% of the variance was generated from real, between-time differences.

Moderator analysis, using a random effects model, was conducted to explore potential, between-study differences that may explain this heterogeneity.

Moderator Analysis

Pre-treatment OSA to Controls

Moderators investigated were age (Group 1 < 0, Group 2 ≥ 50 years), stringent inclusion/exclusion criteria (Group 1 = no, Group 2 = yes), control group selection criteria (Group 1 = PSG, Group 2 = Questionnaire), and publication status (Group 1 = Published, Group 2 = Not published). Papers were considered to have stringent inclusion/exclusion criteria if they excluded participants with factors that could potentially affect cognition, such as a history of traumatic brain injury, certain medications or diseases. None of these moderators changed the effect significantly.

We were unable to examine the impact of disease severity as measured by AHI as there were insufficient studies reporting effects of moderate OSA (AHI 15-29) in each of the 5 sub-domains. A reviewer suggested dividing only those with AHI ≥ 30 into 2 groups and rerunning analyses. Accordingly, we divided the samples into severe OSA (AHI 30-50, N = 15) and very severe OSA (AHI 51+, N = 17). Where there were sufficient samples (i.e., 2 or more) for each executive domain, all effects remained significant and severity did not moderate the findings.

Pre-Treatment to Post-Treatment Differences

Between-study differences were also investigated using moderator analysis. Moderators were age, stringent inclusion/exclusion criteria, control selection criteria (PSG or questionnaire), length of CPAP use, and publication status. No variables significantly moderated the effect of CPAP treatment on the executive burden of OSA.

Likewise, disease severity, as measured by AHI, could not be examined as there were insufficient studies reporting effects of moderate OSA in each of the 5 sub-domains. As above, as recommended by a reviewer, we explored the impact of severity within individuals with AHI ≥ 30. As before, all effects remained significant, and severity did not moderate the findings.

Furthermore, we were unable to examine the impact of CPAP compliance on effect sizes as only one study divided the participants into compliant and noncompliant users; all other studies excluded noncompliant individuals or reported only the group mean compliance which was always above 4 h.

However, and as recommended by a reviewer, we explored months on CPAP by dividing samples into short (0-5 months, N = 13) and long (≥ 5.5 months, N = 5) term CPAP use. Where there were sufficient samples (i.e., ≥ 2) for each executive domain, all effects remained significant and months on CPAP did not moderate the findings.

Risk of Publication Bias

There is evidence to suggest that studies with a significant result are more likely to be published, and that published studies are more likely to be available for meta-analysis.[45] Publication bias was inspected visually using funnel plots. These were asymmetrical, indicating the presence of bias. The Egger test for asymmetry[46] was used to investigate this further.

Pre-treatment OSA to Controls

For the OSA to control samples, the Egger test was nonsignificant for Inhibition (intercept 4.79; 95% CI: 0.04 to 9.54; P = 0.05), and Updating (intercept 5.84; 95% CI: -0.63 to 12.32; P = 0.07), but was significant for Fluid Reasoning (intercept 4.49; 95% CI: 0.84 to 8.13; P = 0.02), Generativity (intercept 4.55; 95% CI: 0.65 to 8.45; P = 0.03) and Shifting (intercept 4.48; 95% CI: 1.72 to 7.25; P = 0.002). However, Rosenthal's fail-safe N, which represents the number of studies needed to create an overall nonsignificant effect,[47] was 172 nonsignificant studies for Fluid Reasoning, 49 studies for Generativity, and 232 studies for Shifting.

Duval and Tweedie's *Trim and Fill* procedure[48] was used to determine the best estimate of an unbiased, overall effect size for the OSA (cf. control samples for the domains of Fluid Reasoning, Generativity, and Shifting). For Fluid Reasoning, the overall effect size was reduced from a large effect of 0.80 to a small effect of 0.26. For Generativity, the overall effect size shifted from a medium effect of 0.59 to a small effect of 0.45. For Shifting, the overall effect size was reduced from a medium effect of 0.53 to a small effect of 0.37. This suggests publication bias may be inflating the estimates in the domains of Fluid Reasoning, Generativity, and Shifting, but that there were still significant differences between those with OSA and controls in these domains.

Pre-Treatment to Post-Treatment Differences

For the pre- to post-treatment effects, the Egger test was nonsignificant for all 5 domains; Shifting (intercept 1.62; 95% CI: -1.39 to 4.63; P = 0.26), Generativity (intercept 0.70; 95% CI: -1.16 to 2.56; P = 0.39), Fluid Reasoning (intercept 0.17; 95% CI: -1.43 to 1.76; P = 0.82), Inhibition (intercept 8.61; 95% CI: -8.29 to 25.52; P = 0.27), and Updating (intercept 0.86; 95% CI: -12.73 to 14.45; P = 0.89). This indicates no publication bias in these domains.

DISCUSSION

The current paper builds on previous reviews by focusing on executive function within five theoretically driven subcomponents. Three questions were posed: (1) which specific executive functions are affected by the presence of untreated OSA?; (2) if executive functions are impaired, does treatment help to remediate these deficits?; and (3) are any of these effects moderated by publication status, sample source, study design, age, disease severity, treatment length or control screening?

Findings of the Present Review

The results from the present analysis indicate that executive function is impaired in OSA compared to control participants across all five subcomponents. People with OSA have difficulty *Shifting* between tasks or mental sets, *Updating* and monitoring working memory representations, *Inhibiting* dominant or prepotent responses, they struggle with G*enerating* new information without external input or efficiently accessing long term memory, and they have significant problems with *Fluid Reasoning* or problem solving. Further to this, the present research demonstrated that if participants undertake CPAP treatment, executive function difficulties across these five sub-domains are reduced.

This meta-analysis was unable to assess the impact of CPAP compliance on improvement in executive function. Articles assessed in the present review excluded individuals who were not compliant with treatment, or reported only the group mean number of hours CPAP was used, except in one instance where participants were divided into compliant or noncompliant; hence, we cannot make any concluding statement on improvements in executive function in individuals who do not follow their treatment regime optimally. However, exploration of the impact of months of CPAP use revealed no additional gain with extended use (6 months or more).

A recent review[49] summarized the current understanding of cognitive function across a number of domains including executive function. The authors found that in two reviews[10,17] and two meta-analyses[11,50] meeting inclusion criteria, executive function was impaired by comparison with controls and norms. The present results provide further support that executive function is impaired in people with OSA. Furthermore this review[49] examined improvement in executive function following CPAP treatment in one meta-analysis[10] and one literature review.[17] The reviews examined came to opposing conclusions; hence, the summary was inconclusive. The present meta-analysis suggests that, overall, CPAP treatment is successful in improving executive function difficulties caused by OSA, and adds to the available evidence supporting the benefits of CPAP treatment.

Past reviews have grouped executive function into one combined domain, or collapsed them by test, making it impossible to delineate the subcomponents of executive function that are impaired. The present paper views executive dysfunction within current neuropsychological understanding of executive function. Such a framework provides a possible explanation for relationship or work difficulties seen in OSA. Individuals with OSA may experience relationship[51,52] or work productivity difficulties,[5,53] as they may not be able to *inhibit* inappropriate responses to aggravating social situations, or solve novel problems in a work place with *Fluid Reasoning*.

Effect of Moderators

The present study was not able to examine the impact of disease severity on OSA across the full range of AHI, as there were insufficient numbers of mild (AHI 5-14) and moderate samples (AHI 15-29). However, comparison of severe (AHI 30-50) and very severe (AHI 50+) OSA samples revealed no impact of severity on the deficits found, and no impact on executive consequences of CPAP treatment. The literature is divided with regard to whether there is a relationship between disease severity as measured by AHI and cognitive dysfunction.[7,10,54] In a recent meta-analysis of episodic memory function, Wallace and Bucks[16] found no relationship with disease severity. In a systematic review, Aloia et al.[10] found no relationship between disease severity and executive function; however, they did find a positive relationship between disease severity and global cognitive function and attention/vigilance. As yet, the link between OSA disease severity and cognition is unclear. This is most likely due to the complex picture of comorbidity, and as yet, no definitive way of measuring disease onset in OSA.[55]

Previous studies have demonstrated that age and OSA results in a double burden, with older individuals exhibiting poorer cognition.[56,57] The present meta-analysis did not find this same relationship, as age did not significantly moderate the results. In studies comparing older and younger participants with OSA, older adults have been found to be more impaired on tests of executive functioning.[56,57] The lack of effect in the current meta-analytic review may be due to assessing the effect of age using group averages, which resulted in similar age distributions across samples. Primary comparison studies which explore the interaction of age and OSA on these executive function subcomponents will be important for clarifying this relationship.

Furthermore, selection of controls with PSG or questionnaires did not significantly moderate the findings. This result may seem surprising, given that estimates of undiagnosed OSA are high.[1,2,58] However, this finding is consistent with that recently reported by Wallace and Bucks.[16] While it is still the case that some control participants in primary studies may have undiagnosed OSA, including studies which have used questionnaire screening procedures does not appear to confer a risk of failing to find an effect in meta-analyses in OSA.

Heterogeneity among Results

Many of the domains demonstrated a high level of heterogeneity in the test results, indicating that there may be other factors in each domain influencing the observed mean. However, further analysis demonstrated this heterogeneity did not obscure real differences in each subdomain of EF. The domain that exhibited the most heterogeneity was the domain with the largest number of different tests, Fluid Reasoning, in which there were thirteen different tests. Neurocognitive tests, especially executive function tests, even purportedly measuring the same domain or sub-domain, will also capture facets of other cognitive or motor skills. For example Trails B, a measure of Shifting, also requires attention and taps into psychomotor speed.[13] Furthermore, few tests currently used to assess executive function were originally designed for the specific purpose of measuring executive function.[18,21]

Future research exploring the executive dysfunction of OSA may benefit from selecting measures more closely targeted at

executive functions and designed to fractionate performance into theoretically driven and dissociable subcomponents. One such measure is the random number generation (RNG) task.[59] This task takes only a few minutes, is easily administered with a laptop computer, and provides measures of Shifting and Inhibition.[20,59]

One other factor that might lead to heterogeneity is premorbid IQ or intelligence. This is because greater IQ and/or education appears to provide "protection" against cognitive decline because of greater cognitive reserve.[60,61] Unfortunately, not all studies provided a measure of academic achievement or premorbid intelligence (IQ). Given that age decreases reserve and IQ increases it, primary studies that stratify the sample into age and IQ groups when examining the impact of OSA on executive function are needed.

Limitations

An issue that cannot be addressed by the current review is whether the deficits evidenced in the literature are primary or secondary; i.e., whether the deficits found in OSA in executive function are due to neurological damage (primary effect) or to impairments in attention which themselves are the result of sleep fragmentation, sleep deprivation and the associated excessive daytime sleepiness.[62,63] Given evidence of frontal activation in participants completing these tasks[64] and the presence of structural abnormalities in the frontal lobes of individuals with OSA,[65] it seems likely that these executive function deficits are a primary and direct consequence of OSA (see Beebe and Gozal[66] for a review; but see Durmer and Dinges[67] for evidence that similar frontal changes are also seen post sleep loss). Indeed, one study,[62] which controlled for attention deficits while exploring executive dysfunction differences between OSA and controls, concluded that most of the executive difficulties were secondary to attention problems. This study demonstrated that the one area with deficits remaining after controlling for attention was Shifting. More studies of this nature and the development of tasks that can tease apart the contributions of attention and executive cognitive processes to task performance are required.

CONCLUSIONS

People with OSA have difficulty with the executive facets of *Shifting*, *Updating*, *inhibiting*, *Generativity*, and with *Fluid Reasoning*. Further, the present research indicates that all these difficulties improve with CPAP treatment. Age and disease severity did not moderate the effects found, however, further studies are needed exploring the extent of primary and secondary effects, and the impact of age, and premorbid ability (cognitive reserve).

DISCLOSURE STATEMENT

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

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Appendix 1—Participant characteristics for each study for Controls, OSA, and Treatment samples

First Author	Year	Source	Type	Controls						OSA											Tests
				N	Age	%Male	Select	ESS	BMI	N	Age	%Male	AHI/ RDI	Ar I	CT90	IQ/Ed	Mnths CPAP	Hrs CPAP	ESS	BMI	
Antic [1]	2011	UP	T	–	–	–	O/PSG	–	–	113	50.1	74.9	67.9	–	–	–	3.0	4.3	13.4	34.7	12
Aloia ± [2]	2010	P	T	–	–	–	–	–	–	95	53.6	–	38.9	–	19.6	15.2	5.5	5.5	11.9	34.2	2, 3
Ayalon (older age group) [3]	2010	P	C	7	49.4	93	PSG	–	29.5	7	53.2	93	33.5	30.4	26.7	15.4	–	–	–	31.5	4
Ayalon (younger age group) [3]	2010	P	C	7	37.9	93	PSG	–	27.8	7	32	93	36.5	46.7	23.1	16.8	–	–	–	28.9	4
Bailey ± [4]	1993	D	T	–	–	–	–	–	–	10	43.8	100	31.9	–	7.46	14	2.6	7.3	–	40.6	3, 5, 6, 7, 8
Barbé ± [5]	2001	P	T	–	–	–	–	–	–	29	54	90	54.0	44	–	–	1.5	5.0	7	–	3, 8
Bardwell ± [6]	2001	P	T	–	–	–	–	–	–	20	47	81	56.8	56.8	–	–	0.2	–	–	32.8	2, 3, 6, 8, 9
Bédard [7]	1993	P	C/T	10	50	100	PSG	–	27.3	10	51	100	65.4	75.7	50.8	11.1	6.0	–	–	34.3	2, 3, 8, 10, 11, 12
Canessa [8]	2011	P	C/T	15	42.2	100	PSG	3.0	26.1	17	44	100	55.8	–	30.4	12.2	2.7	4.0 #	11.9	31.2	1, 3, 6, 9
Castronovo [9]	2009	P	C/T	14	42.2	100	PSG	3.0	26.1	14	43.9	100	50.4	–	26.2	12.6	3.0	4.0 #	11.9	30.3	6, 24
Daurat [10]	2008	P	C	29	50	76	Q	9.0	–	28	52.3	79	21.0	–	27.4	12.7	–	–	12.2	28.5	9
Dolan (40-60 age group) [11]	2009	D	T	–	–	–	–	–	–	17	46.1	47	44.2	–	–	15.0	1.0	5.6	–	34.9	14, 15, 16, 17
Dolan (Over 60 age group) [11]	2009	D	T	–	–	–	–	–	–	12	68.1	42	29.8	–	–	15.0	1.0	5.9	–	31.9	14, 15, 16, 17
Engleman ± [12]	1995	D	T	–	–	–	–	–	–	14	53	–	57.0	54	–	–	3.3	4.5	–	34.0	3, 8, 13
Ferini-Strambi [13]	2003	P	C/T	23	55.8	83	PSG	3.3	–	23	56.5	91	55.0	–	41.33	10.9	4.0	5.2	11	33.5	1, 2, 3, 6, 9
Findley [14]	1991	P	C	21	59	86	PSG	–	–	50	61	86	46.0	12	–	–	–	–	–	–	3
Froehling [15]	1991	D	T	–	–	–	–	–	–	21	46.6	100	70.2	–	–	14.3	0.6	–	–	–	2, 6
Gale [16]	2004	P	T	–	–	–	–	–	–	14	52.2	86	83.6	–	–	14	6.0	–	–	–	2, 3, 8
Gast [17]	2006	P	T	–	–	–	–	–	–	17	52.5	–	45.5	–	–	15.5	0.2	–	–	40	3, 6 , 9, 18
Greenberg ± [18]	1987	P	C	14	44.2	79	Q	–	–	14	43.8	81.3	48.0	–	–	12.7	–	–	–	–	2, 3, 8, 9
Grenèche [19]	2011	P	C	10	49.6	70	PSG	6.7	21.3	12	51.8	67	58.9	21.3	29.5	–	–	–	12.7	31.1	9
Kribbs ± [20]	1993	P	T	–	–	–	–	–	–	15	45.9	93	56.6	–	–	–	2.5	5.7	–	36.8	6, 9

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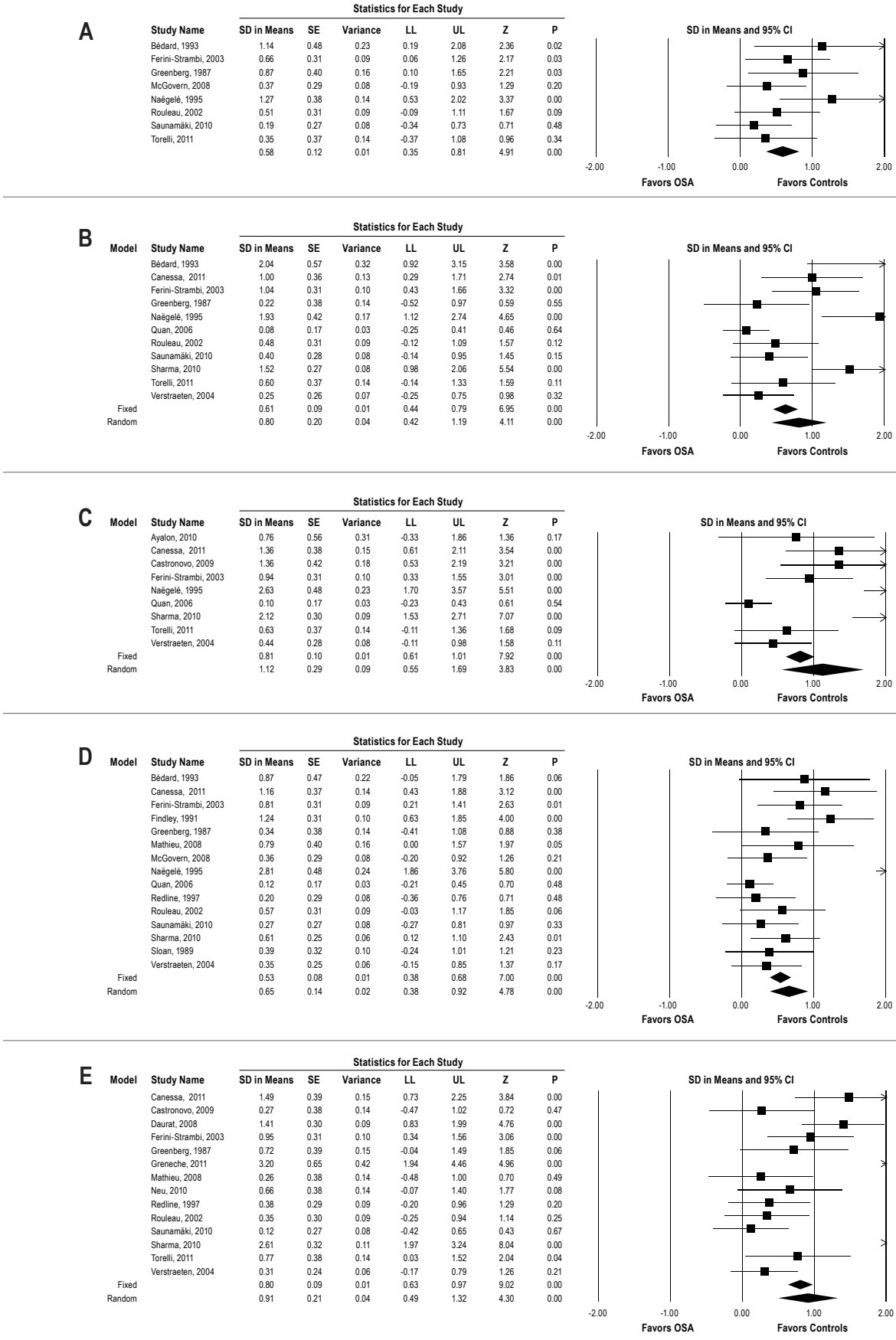
Appendix 1 continues on the following page

Appendix 1—Participant characteristics for each study for Controls, OSA, and Treatment samples

First Author	Year	Source	Type	Controls						OSA											Tests
				N	Age	%Male	Select	ESS	BMI	N	Age	%Male	AHI/ RDI	Ar I	CT90	IQ/Ed	Mnths CPAP	Hrs CPAP	ESS	BMI	
Lojander** [21]	1999	P	T	–	–	–	–	–	–	10	50	100	–	–	–	–	–	–	–	31	3, 20
Mathieu (Under 50 age group) [22]	2008	P	C	12	38.9	86	PSG	5.9	23.1	14	37.7	93	38.2	19.5	42.2	13.1	–	–	10.8	34.6	3, 9, 18
Mathieu (Over 50 age group) [22]	2008	P	C	18	62.5	86	PSG	6.1	25.1	14	62.3	93	38.2	19.5	42.2	14.1	–	–	14.4	31.6	3, 9, 18
McGovern [23]	2008	D	C	30	66.1	33	Q	–	–	21	61.7	76	44.0	–	–	15.1	–	–	–	–	2, 3
Meurice ± [24]	1996	P	T	–	–	–	–	–	–	16	54	100	43.6	–	–	–	0.7	6.4	14.8	34.2	3
Naëgelé [25]	1995	P	C	17	49	100	Q	–	–	17	49	100	41.0	–	–	–	–	–	–	32.4	2, 6, 18, 19, 21
Neu [26]	2011	P	C	16	36.9	0	PSG	3.8	20.9	15	40.4	0	40.4	–	–	–	–	–	13.2	34.2	9
Quan [27]	2006	P	C	74	57.4	53	hPSG	7.0	25.9	67	59.4	53	22.4	24.8	–	15.2	–	–	–	30.8	3, 6, 22
Redline [28]	1997	P	C	20	48.9	40	PSG	9.0	27.5	32	51.4	47	17.0	16.2	–	13.8	–	–	9.8	34.9	9, 18
Rouleau [29]	2002	P	C	18	47.2	78	PSG	–	–	28	47.4	89	–	–	130.5	12.8	–	–	–	–	2, 3, 7, 8, 12, 13, 18, 22
Saunamäki [30]	2010	P	C/T	17	44	100	PSG	3.8	24.4	20	50	100	49.5	38.2	–	12	7.2	6.2	12	31.8	2, 3, 8, 9
Sharma [31]	2010	P	C	25	45.6	84	PSG	8.6	–	50	43	84	54.2	33.2	46.4	–	–	–	17.3	–	6, 9, 12, 18
Sloan (hypoxic group) [32]	1989	D	C	19	44.8	100	Q	–	–	22	47.6	93	94.6	–	60.3	–	–	–	–	–	3
Sloan (non-hypoxic group) [32]	1989	D	C	19	44.8	100	Q	–	–	20	43.2	93	63.2	–	11.3	–	–	–	–	–	3
Torelli [33]	2011	P	C	14	57.6	64	Q	–	–	16	55.8	81	52.5	–	21.9	12.3	–	–	8.5	31.7	1, 2, 6, 9
Verstraeten [34]	2004	P	C	32	47.4	64	Q	–	–	36	49.2	89	60.5	52.3	72.1	12.7	–	–	–	–	3, 6, 9, 25, 26
Walker [35]	1990	D	T	–	–	–	–	2.6	25.5	30	47.3	–	–	–	–	13.6	6.0	–	–	–	2, 3, 6

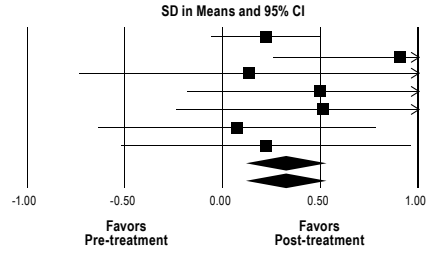
Articles are displayed alphabetically by first author. Superscript numbers following first author names correspond to reference list following the appendicies. 'Source' corresponds to the publication status of the study (P, peer reviewed published article; D, dissertation; UP, unpublished data). 'Type' indicates to whether the study was comparing people with OSA to controls or pre and post treatment (C, people with OSA to controls, T, people with OSA pre and post-treatment and C/T, controls and pre/post treatment). The variable 'Select' indicates how the study chose controls (PSG, hospital sleep study screening, hPSG, Home or portable sleep study screening, Q, Questionnaire, O, Oximetry screening). Disease severity in the OSA sample is represented by AHI or RDI, Sleep fragmentation index and Time spent below 90% SaO_2. Length CPAP indicates how long in months the individuals with OSA were given CPAP treatment for that study. '#' indicates that this CPAP value was estimated from the information given in the report. The symbol '**' indicates that the values in these studies gave median and range values which were transformed into mean and standard deviation values using formulae and recommendations of Hozo et al., 2005.[36] The symbol '–' indicates that these details were not given in or not applicable to the study. 'Test' indicates which individual tests were used in the study (1, etc).The symbol '±' indicates that the data used in this meta analysis are only from one group presented in the original paper (Aloia, only the adherent group data are examined; Bailey, only group 1, the group treated with CPAP were used; Barbé, only the true CPAP not the sham CPAP group is used; Bardwell 2001,[6] only the CPAP not the placebo group are included; Engleman 1995,[12] Ch 5, only patients who received CPAP treatment and had good compliance are included here not the patients who received conservative treatment; Greenberg 1987,[18] only patients in the apnea and healthy group were included; Kribbs 1993,[20] only data for before and after CPAP treatment is included, not for CPAP withdrawal; Meurice, 1996,[24] means were combined for the auto-CPAP and constant-CPAP groups; Walker 1990,[35] only group 1 the treated group were used, not the treatment rejecters).



Appendix 2—Forest plots of the effect size and confidence intervals for each study for pre-treatment OSA participants compared with controls studies in all 5 sub-domains of executive function **(A)** Generativity, **(B)** Fluid Reasoning, **(C)** Inhibition, **(D)** Shifting and **(E)** Updating. SD, standard difference; SE, standard error; LL, lower limit; UL, upper limit.

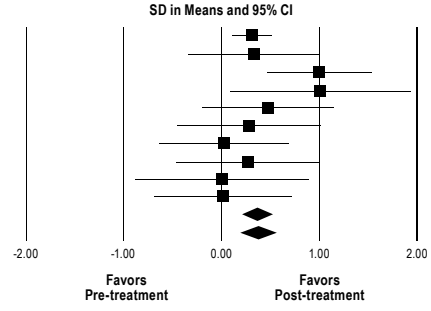
A

Model	Study Name	SD in Means	SE	Variance	LL	UL	Z	P
	Aloia, 2010	0.22	0.15	0.02	-0.06	0.51	1.53	0.13
	Bardwell, 2001	0.91	0.33	0.11	0.25	1.56	2.71	0.01
	Bédard, 1993	0.14	0.45	0.20	-0.74	1.01	0.31	0.76
	Ferini-Strambi, 2003	0.50	0.35	0.12	-0.19	1.18	1.43	0.15
	Gale, 2004	0.51	0.38	0.15	-0.24	1.27	1.34	0.18
	Saunamäki, 2009	0.07	0.37	0.13	-0.64	0.79	0.20	0.84
	Walker, 1990	0.22	0.38	0.15	-0.52	0.97	0.59	0.56
Fixed		0.32	0.11	0.01	0.11	0.53	3.05	0.00
Random		0.32	0.11	0.01	0.11	0.53	3.05	0.00



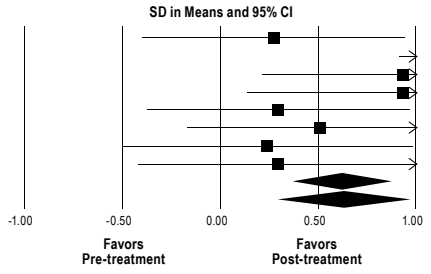
B

Model	Study Name	SD in Means	SE	Variance	LL	UL	Z	P
	Antic, 2009	0.31	0.11	0.01	0.10	0.53	2.91	0.00
	Bailey, 1993	0.33	0.35	0.12	-0.35	1.01	0.96	0.34
	Barbé, 2001	1.00	0.28	0.08	0.45	1.55	3.59	0.00
	Bédard, 1993	1.01	0.48	0.23	0.08	1.95	2.13	0.03
	Canessa, 2011	0.48	0.35	0.12	-0.21	1.16	1.37	0.17
	Engleman, 1995	0.28	0.38	0.14	-0.46	1.03	0.75	0.45
	Ferini-Strambi, 2003	0.03	0.34	0.12	-0.65	0.70	0.08	0.94
	Gale, 2004	0.27	0.38	0.14	-0.48	1.01	0.71	0.48
	Lojander, 1999	0.00	0.46	0.21	-0.90	0.90	0.00	1.00
	Saunamäki, 2010	0.01	0.37	0.13	-0.71	0.73	0.03	0.98
Fixed		0.36	0.08	0.01	0.20	0.52	4.44	0.00
Random		0.37	0.10	0.01	0.18	0.55	3.85	0.00



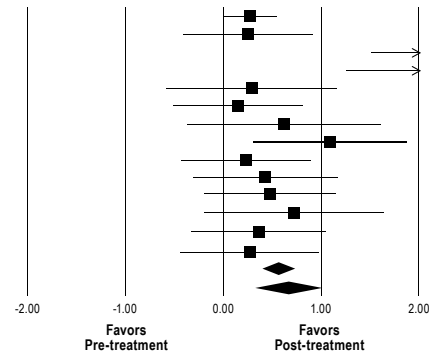
C

Model	Study Name	SD in Means	SE	Variance	LL	UL	Z	P
	Bailey, 1993	0.27	0.34	0.12	-0.40	0.95	0.79	0.43
	Bardwell, 2001	1.64	0.38	0.14	0.91	2.38	4.38	0.00
	Canessa, 2011	0.94	0.37	0.14	0.21	1.66	2.52	0.01
	Castronovo, 2009	0.93	0.41	0.17	0.13	1.74	2.28	0.02
	Ferini-Strambi, 2003	0.30	0.35	0.12	-0.38	0.97	0.86	0.39
	Gast, 2006	0.51	0.35	0.12	-0.17	1.20	1.46	0.14
	Walker, 1990	0.24	0.38	0.15	-0.51	0.99	0.63	0.53
	Kribbs, 1993	0.30	0.37	0.13	-0.42	1.02	0.81	0.42
Fixed		0.62	0.13	0.02	0.36	0.87	4.77	0.00
Random		0.63	0.17	0.03	0.29	0.97	3.62	0.00



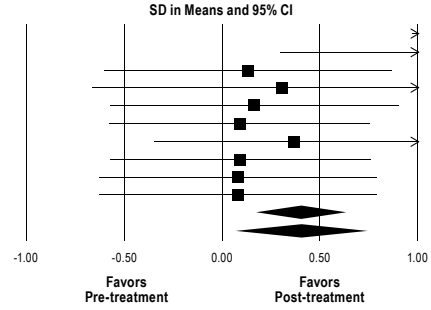
D

Model	Study Name	SD in Means	SE	Variance	LL	UL	Z	P
	Aloia, 2010	0.28	0.15	0.02	-0.01	0.56	1.90	0.06
	Bailey, 1993	0.26	0.34	0.12	-0.42	0.93	0.74	0.46
	Barbé, 2001	2.15	0.33	0.11	1.51	2.80	6.52	0.00
	Bardwell, 2001	2.03	0.40	0.16	1.25	2.81	5.10	0.00
	Bédard, 1993	0.29	0.45	0.20	-0.59	1.17	0.64	0.52
	Canessa, 2011	0.15	0.34	0.12	-0.52	0.82	0.44	0.66
	Dolan, 2009	0.62	0.51	0.26	-0.38	1.62	1.22	0.22
	Engleman, 1995	1.09	0.41	0.16	0.30	1.89	2.70	0.01
	Ferini-Strambi, 2003	0.23	0.34	0.12	-0.44	0.91	0.68	0.50
	Gale, 2004	0.43	0.38	0.15	-0.32	1.18	1.12	0.26
	Gast, 2006	0.48	0.35	0.12	-0.21	1.16	1.37	0.17
	Lojander, 1999	0.72	0.47	0.22	-0.21	1.65	1.52	0.13
	Meurice, 1996	0.36	0.36	0.13	-0.34	1.06	1.01	0.31
	Saunamäki, 2010	0.27	0.37	0.13	-0.45	0.99	0.74	0.46
Fixed		0.56	0.09	0.01	0.39	0.72	6.51	0.00
Random		0.66	0.18	0.03	0.31	1.00	3.75	0.00



E

Model	Study Name	SD in Means	SE	Variance	LL	UL	Z	P
	Bardwell, 2001	1.69	0.37	0.14	0.97	2.41	4.58	0.00
	Canessa, 2011	1.00	0.36	0.13	0.29	1.72	2.76	0.01
	Castronovo, 2009	0.13	0.38	0.14	-0.61	0.87	0.35	0.72
	Dolan, 2009	0.30	0.50	0.25	-0.67	1.28	0.61	0.54
	Engleman, 1995	0.16	0.38	0.14	-0.58	0.91	0.43	0.66
	Ferini-Strambi, 2003	0.09	0.34	0.12	-0.58	0.76	0.26	0.79
	Froehling, 1991	0.37	0.37	0.14	-0.36	1.09	1.00	0.32
	Gast, 2006	0.09	0.34	0.12	-0.58	0.77	0.27	0.79
	Saunamäki, 2009	0.08	0.37	0.13	-0.63	0.80	0.23	0.82
	Kribbs, 1993	0.08	0.37	0.13	-0.64	0.80	0.22	0.83
Fixed		0.40	0.12	0.01	0.17	0.63	3.39	0.00
Random		0.40	0.17	0.03	0.06	0.74	2.33	0.02



Appendix 3—Forest plots of the effect size and confidence intervals for pre-treatment to post-treatment studies in all 5 sub-domains of executive function **(A)** Generativity, **(B)** Fluid Reasoning, **(C)** Inhibition, **(D)** Shifting and **(E)** Updating. SD, standard difference; SE, standard error; LL, lower limit; UL, upper limit.

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