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Original Article

Working memory impairment and its associated sleep-related respiratory parameters in children with obstructive sleep apnea

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ABSTRACT

Study Objective: Working memory deficits in children with obstructive sleep apnea (OSA) have been reported in previous studies, but the results were inconclusive. This study tried to address this issue by delineating working memory functions into executive processes and storage/maintenance components based on Baddeley's working memory model.

Methods: Working memory and basic attention tasks were administered on 23 OSA children aged 8–12 years and 22 age-, education-, and general cognitive functioning-matched controls. Data on overnight polysomnographic sleep study and working memory functions were compared between the two groups. Associations between respiratory-related parameters and cognitive performance were explored in the OSA group.

Results: Compared with controls, children with OSA had poorer performance on both tasks of basic storage and central executive components in the verbal domain of working memory, above and beyond basic attention and processing speed impairments; such differences were not significant in the visuo-spatial domain. Moreover, correlational analyses and hierarchical regression analyses further suggested that obstructive apnea–hypopnea index (OAHI) and oxygen saturation (SpO_2) nadir were associated with verbal working memory performance, highlighting the potential pathophysiological mechanisms of OSA-induced cognitive deficits.

Conclusions: Verbal working memory impairments associated with OSA may compromise children's learning potentials and neurocognitive development. Early identification of OSA and assessment of the associated neurocognitive deficits are of paramount importance. Reversibility of cognitive deficits after treatment would be a critical outcome indicator.

1. Introduction

Obstructive sleep apnea (OSA) is a frequently diagnosed nocturnal breathing disorder, with a prevalence rate of around 1%–3% in the western pediatric populations [1,2]. In the Hong Kong population, the prevalence of childhood OSA has been found to affect 5% of school-aged children [3]. Childhood OSA is characterized by snoring associated with sleep fragmentation, exaggerated upper airway resistance, obstructive breathing, intermittent hypoxia, hypercapnia, and repeated arousals [4].

It was well documented that children with OSA experience difficulties on a wide cognitive spectrum, including vigilance, sustained attention, visual sequencing, and memory, as well as executive functions such as planning and organization, inhibition, mental flexibility, metacognition, and working memory [5–13]. Among the cognitive functions previously studied in OSA populations, executive functions and, in particular, working memory have been highlighted [14–16]. Working memory deficits measured by the n-back task have been demonstrated in adult OSA populations [17] and have been shown to persist even after treatment [18]. Neurocognitive outcomes, especially working memory functions in childhood OSA, are less clear. Halbower et al. [19] reported deficits in verbal executive functioning measured by sentence span and word fluency tasks. Kohler et al. [20] identified poor working memory functions in both verbal and nonverbal domains in sleep-disordered breathing children on standardized test batteries, such as the Developmental

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NEuroPSYchological Assessment (NEPSY) and the Standford–Binet Intelligence Test [20]. Biggs et al. [14] assessed working memory in children with sleep-disordered breathing using both parent-rating and neuropsychological tests. Although working memory deficits were reported by parents, no significant impairments were identified on the objective tests. The authors attributed the lack of significant objective deficits to possible sampling bias and the lack of sensitivity of the digit span test as a working memory task. Other studies also reported working memory performance in children with OSA comparable to that of controls [7,21,22]. On the other hand, some treatment studies have demonstrated that impaired neurocognitive functions could mostly be reversed after adenotonsillectomy or tonsillectomy [7,13,23]. However, changes in executive function in these studies were measured only by test batteries or combinations of stand-alone neuropsychological tests, such as digit span, verbal fluency tests, and cancellation tests, none of which sufficiently differentiate the contribution of basic cognitive processes in executive tasks. Taken together, there has been a lack of systematic and theory-driven studies on working memory functions in pediatric OSA, leading to inconsistent findings. Specifically, a closer look at the methodology of the studies reporting null findings revealed that these studies treated the executive controller and the underlying basic cognitive processes (ie, maintenance capacity/speed) of working memory as a whole, without delineating the individual components [18]. In addition, most previous childhood OSA studies measured only the verbal domain of working memory, rendering the visuo-spatial domain understudied. Therefore, a comprehensive model of working memory encompassing both the verbal and the visuo-spatial domains that could be captured by well-validated tests was called for, to shed light on the complex questions regarding working memory functioning in children with OSA.

The application of Baddeley's working memory model has been shown to be fruitful in previous studies in western [18] as well as in Chinese [17] adult OSA populations. Elucidating potential deficits in working memory in childhood OSA is critical, given its underlying role in a wide range of complex cognitive processes, including reading comprehension, mathematic ability, planning, reasoning, and problem solving, which are regarded as pivotal to children's learning and development [24]. The working memory model involves a supervisory (executive) attention system that controls the processes of two domain-specific storage components responsible for maintaining verbal (phonological loop) and visuospatial information (visuospatial sketchpad), and also an episodic buffer that provides a limited capacity multi-modal interface between systems [24,25]. By adopting the multi-component model of working memory proposed by Baddeley and Hitch [25], our experimental tasks were specifically developed to distinguish the basic and the higher-ordered functions in both verbal and visuo-spatial domains of working memory, respectively [26].

In terms of the underlying mechanisms of the OSA-related cognitive deficits, intermittent hypoxia and sleep disruption have been proposed to be the two major pathways [5]. Previous studies have suggested the role of stage 1 sleep, rapid eye movement (REM) sleep, and movement-related arousals in neurocognitive deficits in sleep-disordered children [21,27,28]. Other studies have investigated the associations between oxygen saturation, REM sleep, arousal index on cerebral oxygenation, and endothelial functions in sleep-disordered breathing [29–31]. However, other studies have shown that sleep disruptions alone were sufficient to result in neurobehavioral deficits [32]. A more recent study reported the associations of executive deficits with nocturnal hypoxemia levels in children with OSA [15]. Working memory, as one of the executive functions, might also be susceptible to respiratory disturbances during sleep. Therefore, an exploration of potential respiratory predictors of working memory functioning in children with OSA would be warranted.

To our knowledge, the present study was the first attempt to isolate the basic storage from the executive processes within each domain (verbal and visuospatial) of the working memory system in comparing children with and without OSA. It was also the first to investigate the correlations between objective sleep-related respiratory parameters with specific working memory components in this population. We hypothesized that Chinese children with OSA would perform worse than controls on working memory tests. Tasks of basic attention and vigilance would be included to control for their potential contribution to performance on working memory tasks. We also tested whether respiratory parameters would predict working memory performance in the OSA group.

2. Methods

2.1. Participants and design

This study was prepared in accordance with the Declaration of Helsinki and approved by the Chinese University of Hong Kong and Hospital Authority New Territories East Cluster Clinical Research Ethics Committee. Altogether 51 children (23 children with OSA and 28 controls) aged 8–12 years were recruited. The children with suspected OSA were from the Pediatric Respiratory Sleep Disorder and Obesity Clinic at the Prince of Wales Hospital of Hong Kong, whereas the age-matched controls were recruited from a population-based study conducted by one of our colleagues [33]. The test administrator was blinded to the background of the participants. Exclusion criteria comprised neurological co-morbidity such as history of head injury, an intercurrent upper respiratory tract infection within four weeks of recruitment, craniofacial anomalies, syndromic disorders such as Down syndrome, history of other sleep pathologies including primary snoring, prior upper airway surgery, and obesity (body mass index [BMI] > 30). Children who were diagnosed with developmental or psychiatric disorders (eg, autism, attention-deficit/hyperactivity disorder (ADHD), and specific learning disability) and/or who were on medications that could affect cognitive functions were also excluded. Written consent from parents and assent from children were obtained. Individual participants were first given the test battery consisting of experimental tasks, a general cognitive functioning screening tool (Raven's Standard Progressive Matrices), and standardized paper-and-pencil neuropsychological tests. Together with their parents, the children were then asked questions regarding their health condition. Afterward, the children underwent standard single-night polysomnography (PSG) at the hospital with the PSG montage detailed below.

2.2. Measures

2.2.1. Polysomnographic assessment

In this study, a standardized sleep study was carried out using Siesta ProFusion III PSG monitor (Compumedics Telemed, Abbotsford, Victoria, Australia). The following parameters were measured: electroencephalogram (EEG), left and right electrooculogram (EOG), electromyogram (EMG) (chin and bilateral anterior tibialis muscle), and electrocardiogram (ECG). Respiratory movements of the chest and abdomen were measured by piezo crystal effort belts. Arterial oxyhemoglobin saturation (SaO_2) was measured by a built-in oximeter with finger probe. Respiratory air-flow pressure signal was measured via nasal catheter placed at the anterior nares and connected to a pressure transducer. An oronasal thermal sensor was also used to detect any absence of airflow. Snoring was measured by a snoring microphone placed near the throat. Body position was monitored via a body position sensor. All computerized sleep data were manually scored by registered PSG technologists according to standardized criteria [34]. Obstructive apnea–hypopnea index (OAHI) was defined as the total number of obstructive and mixed apneas

and hypopneas per hour of sleep. Arousal was defined as an abrupt shift in EEG frequency during sleep, which may include θ, α, and/or frequencies >16 Hz but not spindles, with a duration of 3–15 seconds. In REM sleep, arousals were scored only when accompanied by concurrent increases in submental EMG amplitude. Arousal index (ArI) was the total number of arousals per hour of sleep. A successful PSG was defined as total sleep time ≥6 hours. The conventional and well-accepted diagnostic criterion of OAHI ≥1 was chosen as the diagnostic cut-off of OSA in the current study. For this protocol, each child was classified as either OSA (OAHI ≥ 1) or control (OAHI < 1) for data analyses. Children with OAHI < 1 and with a history of snoring ≥3 nights per week were classified as primary snorers and excluded from the current study, because of potential differences in the etiology and cognitive outcomes between individuals with OSA and those with primary snoring [35–37].

2.2.2. Neurocognitive measures

For working memory tasks, phonological loop capacity was assessed using the Forward Span of the Digit Span subtest of the Hong Kong Wechsler Intelligence Scale for Children (HK-WISC) [38] and the verbal 0-back task. Visuospatial sketchpad was measured by the Forward Span of the Spatial Span subtest of the Wechsler Memory Scale – Third Edition (WMS-III) [39] and the visuospatial 0-back task. Central executive was assessed using the Backward Span of Digit Span subtest of HK-WISC, the Backward Span of Spatial Span subtest of the WMS-III, the verbal and spatial 2-back tasks [40], and the Children's Paced Auditory Serial Addition Task (CHIPASAT). The number of correct responses and correct dyads in the two conditions (ie, 2.4-second ISI and 1.6-second ISI) were recorded in the CHIPASAT task [41]. Sequences of events in the 2-back tasks are shown in Supplementary Fig. S1a and b.

For attention tasks, because attention and working memory were two closely related constructs, we included attention tasks so that the performance could be tested as covariates in our analyses to examine the effects of OSA on working memory above and beyond its effects on basic attention processes.

Two subtests of the validated Chinese version of the Test for Everyday Attention in Children (TEA-Ch) [42,43], Sky Search and Creature Counting, were chosen to assess selective attention and attention switching, respectively. Vigilance was measured using the Digit Vigilance Test (DVT) [44].

Additional details regarding neurocognitive tasks can be found in the supplementary materials (Appendix S1).

2.3. Statistical analysis

Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL). The normality of distribution was assessed with a Q–Q plot and the Shapiro–Wilk test. Group differences in demographic data, sleep parameters, and all of the neuropsychological tests were compared. An independent *t* test was used to compare parametric data, and the Mann–Whitney *U* test was used to analyze nonparametric data. Nominal demographic data were analyzed using the χ^2 test. The effect size (Cohen's *d*) was calculated for significant difference revealed by an independent *t* test, whereas rank–biserial correlation (*r*) was used to present the effect size for the Mann–Whitney *U* test. For the n-back tasks, accuracy rates were analyzed by mixed analysis of covariance (ANCOVA) with a between-subject factor, Group (OSA vs. control), a within-subject factor, Condition (0-back vs. 2-back), and age and attention test scores as covariates. As follow-up analyses, a one-way ANCOVA with the between-subject factor Group (OSA vs. control) and age as covariate was also conducted to further test the group differences on the 0-back and 2-back tasks. To evaluate the relationships between working memory and attention with respiratory variables, correlation analyses were performed between respiratory variables (including OAHI, SpO_2 nadir) and cognitive task scores showing deficits, including time for completion (*z* scores) on TEA-Ch Sky Search and TEA-Ch Creature Counting, Forward Digit Span, reaction time of verbal 0-back reaction time, and accuracy rate of verbal 2-back accuracy rate) in the OSA group. Based on the significant correlations, hierarchical regression analyses were used to explore the contribution of respiratory variables to working memory deficits, with age in the first step and the related respiratory variables in the second step. All *p* values reported were two-tailed, with statistical significance set at 0.05. Data are presented as mean and standard error of the mean (SEM) unless otherwise stated.

3. Results

3.1. Demographic and sleep characteristics

Six of the 51 recruited participants were excluded from the current study. One control participant was excluded in the current analyses because of problems in understanding and completing the neuropsychological tests. Another five, older control participants were excluded to ensure better matching of age with the OSA group, such that any group differences would not be attributable to age. Therefore, data for 23 children with OSA and 22 controls were included in the current analyses. Demographic and polysomnographic data are summarized in Table 1. There were no significant differences between the groups with respect to age, gender, education level, and BMI. Moreover, no significant group differences in the general cognitive functioning measured on the Raven's Standard Progressive Matrices were found. As expected, significant between-group differences were found in OAHI, arousal index, and SpO_2 nadir. There were, however, no significant differences in sleep architecture parameters between the groups.

3.2. Attention

The performance of the OSA group and controls on the attention tests is summarized in Table 2. The OSA group had significantly longer reaction time (*z* score) on TEA-Ch Sky Search ($t = -2.47$, $p = 0.019$) and TEA-Ch Creature Counting ($U = 106$, $p = 0.018$) than the control group. There were no significant group differences found on the Digit Vigilance Test ($p > 0.05$).

3.3. Working memory

3.3.1. Phonological loop and visuospatial sketchpad

The OSA group had a significantly shorter Forward Digit Span ($U = 182.5$, $p = 0.039$) and longer reaction time in the verbal 0-back condition ($t_{42} = -3.34$, $p = 0.003$), whereas accuracies of the verbal 0-back condition did not differ between the groups. On the contrary, there were no significant group differences found on the Spatial Span or the visuospatial 0-back condition ($p > 0.05$) (Table 2).

3.3.2. Central executive

For verbal n-back task, the covariate, age, was significantly related to the accuracies ($F_{1,42} = 8.07$, $p = 0.007$). After controlling for the effect of age, a significant main effect of Conditions was still found ($F_{1,42} = 13.95$, $p = 0.001$), with worse performance in the 2-back than in the 0-back condition. The Group × Condition interaction was also significant ($F_{1,42} = 4.99$, $p = 0.031$), showing a larger difference between the 0-back and 2-back conditions in the OSA group than in the control group. The main effect of Group was not significant ($F_{1,42} = 1.96$, $p = 0.169$). Further analyses were conducted to test the covariate effect of completion time for TEA-CH Sky Search and Creature Counting on the interaction effect. Both TEA-Ch scores were not significant covariates ($p > 0.05$), and the Group × Condition interaction still held ($p = 0.044$). In addition, one-way ANCOVA further

Table 1
Demographic and sleep characteristics of controls and children with OSA.

	Controls ($n = 22$)		OSA ($n = 23$)		P	Effect size[a]
	Mean (SD)	Range	Mean (SD)	Range		
Demographic data						
Age (y)	8.89 (1.2)	8.06–12.3	9.91 (1.49)	8.01–12.43	0.965	
Gender (male : female)	10:12		17:6		0.071	
Body mass index	18.28 (3.36)	13.21–26.56	20.04 (3.45)	15.03–27.52	0.091	
Education	4.32 (1.17)		4.13 (1.29)		0.612	
General intelligence						
Raven's Standard Progressive Matrix	106.36 (10.58)	/	102.7 (8.86)	/	0.214	
Polysomnography indices						
OAHI (/h)	.29 (.29)	0–0.9	5.6 (7.38)	1–28.5	0.002**	1.02
ArI (/h)	9.11 (2.52)	5.5–13.8	15.45 (7.78)	6–40.9	.001**	1.1
SpO_2 nadir (%)	94.82 (2.04)	89–98	91.52 (4.55)	76–97	0.004**	0.94
TST (min)	498.04 (80)	200.5–619.5	492.48 (48.51)	411–575	0.778	
Sleep efficiency (%)	89.69 (8.89)	54.5–97.5	89.70 (6.97)	76.3–97.5	0.998	
WASO (min)	25.48 (16.5)	1–59	30.77 (6.42)	2.5–111.5	0.134	
Stage 1 (%TST)	4.08 (2.36)	.8–9.1	4.67 (3.53)	.9–11.3	0.514	
Stage 2 (%TST)	35.31 (4.69)	27.2–44.8	35.79 (4.77)	23.9–43.2	0.734	
Stage 3 (%TST)	7.51 (3.49)	2.4–16.9	7.19 (2.36)	3.9–12.1	0.721	
Stage 4 (%TST)	30.63 (6.24)	18.4–43.1	30.44 (5.42)	21.5–41	0.912	
Stage REM (%TST)	22.46 (4.24)	12.5–28.8	21.88 (2.95)	16.7–29.2	0.595	
SWS (%stage3 + 4)	36.14 (8.14)	23.7–56.8	37.63 (6.52)	26.8–51.8	0.817	

ArI, arousal index; OAHI, obstructive apnea–hypopnea index; OSA, obstructive sleep apnea; REM, rapid eye movement; SD, standard deviation; SpO_2, oxygen saturation; SWS, slow wave sleep; TST, total sleep time; WASO, wake after sleep onset.
** $p < 0.01$.
[a] Effect size is presented as Cohen's *d*.

revealed that the OSA group had a significantly worse performance than the controls on the 2-back task ($F_{1,42} = 6.091$, $p = 0.018$), whereas there was no significant group difference on the 0-back task ($p > 0.05$). For the visuospatial *n*-back task, although age was a significant covariate ($F_{1,42} = 11.71$, $p = 0.001$), the main effect of Condition ($F_{1,42} = 0.039$, $p = 0.845$) and Group ($F_{1,42} = 1.71$, $p = 0.198$) as well as the Group × Condition interaction ($F_{1,42} = 1.03$, $p = 0.315$) was non-significant. No significant difference was found on CHIPASAT ($p > 0.05$) (Table 3).

3.4. Associations between respiratory variables and cognitive functions

Forward Digit Span was correlated negatively with OAHI ($r = -0.423$, $p = 0.002$) and positively with SpO_2 nadir ($r = 0.477$, $p < 0.001$). Verbal 2-back accuracy was negatively correlated with OAHI ($r = -0.362$, $p = 0.01$). No significant correlations were found between the respiratory variables and other working memory or attention scores.

Based on the significant correlations, OAHI and SpO_2 nadir were entered in the second step of regression analysis of Forward Digit Span; and OAHI in the second step of analysis of the verbal 2-back task. SpO_2 nadir was a significant predictor of performance of Forward Digit Span, whereas OAHI negatively predicted accuracy of the verbal 2-back task (Table 3).

4. Discussion

The goals of this study were to characterize the impact of childhood OSA on working memory, and to explore the relationship between sleep-related respiratory parameters of OSA with cognitive performance. Our findings showed that children with polysomnographically defined OSA had significant impairment in both the basic storage and the central executive components of working memory in the verbal domain when compared to controls. Impairments in the central executive component of verbal working memory in the OSA children were indicated by the significantly poorer performance in accuracy rates on the verbal 2-back condition but not the 0-back. Given that the two groups were matched on the Raven's Standard Progressive Matrices score and the attention scores were controlled for, the differences in verbal working memory should be regarded as specific and not accounted for by discrepancies in general cognitive functioning or attention, routinely considered as major confounding factors in interpreting findings of higher-ordered cognitive functions.

Our current findings showed that OSA children also demonstrated significantly poorer performance on basic attention, in line with the well-documented notion of impaired basic attentional processes such as sustained attention and visual sequencing in childhood OSA [5,7,9,12,13]. Although attention and working memory are two closely related neuropsychological constructs, our ANCOVA results suggested that the verbal working memory impairment found in the OSA group could not be explained purely by basic attention deficits. It is conceivable that selective aspects of OSA may differentially impact different structures or systems of the brain responsible for the basic and executive components of verbal working memory. Such speculation can be examined by adopting Baddeley's well-defined working memory model and neuroimaging techniques in children with OSA before and after treatment.

Weak working memory was consistently shown to be a significant risk factor for poor educational progress. In particular, verbal working memory was associated with language learning [45]. Of note, verbal working memory was often implicated as a significant predictor of Chinese word reading and text comprehension in children, as the language relies heavily on semantics and requires children to memorize and form strong character–semantic routes for fluent reading [46–49]. The role of verbal working memory in bilingualism was also suggested in several studies [50,51], underlining the potential far-reaching impact of working memory deficits in language acquisition in multilingual societies such as Hong Kong. The effect of verbal working memory also extended beyond the language domain to other abilities such as mathematic skills [52]. It would be fruitful for future studies to examine learning in children with OSA and its association with working memory deficits both before and after treatment. Such findings would shed light on the neurodevelopmental significance of OSA.

Table 2
Working memory and neuropsychological test performance of controls and children with OSA.

	Control ($n = 22$)	OSA ($n = 23$)	U/t[a]	p	Effect size[a]
	Mean (SD)	Mean (SD)			
Phonological loop					
Longest forward digit span	8.86 (0.35)	8.39 (0.89)	182.5	0.039*	0.31
Verbal 0-back					
Reaction time (ms)	653.53 (88.30)	788.65 (169.23)	–3.34[a]	0.003**	0.5
Accuracies (%)	88.92 (14.78)	89.24 (10.26)	242.5	0.81	
Visuospatial sketchpad					
Longest forward spatial span	5.64 (1.36)	5.78 (1.04)	222.5	0.467	
Visuospatial 0-back					
Reaction time (ms)	741.37 (143.82)	847.3 (298.54)	209	0.318	
Accuracies (%)	84.93 (8.48)	78.56 (16.98)	214	0.375	
Central executive					
Longest backward digit span	4.27 (1.24)	5.26 (2.00)	183	0.104	
Longest backward spatial span	5.09 (1.11)	5 (1.21)	238	0.723	
Verbal 2-back					
Reaction time (ms)	871.5 (144.17)	954.85 (325.52)	232	0.633	
Accuracies (%)	76.17 (11.25)	67.11 (17.36)	2.085[a]	0.044*	.32
Visuospatial 2-back					
Reaction time (ms)	840.32 (189.79)	928.68 (336.79)	233	0.65	
Accuracies (%)	67.48 (12.92)	65.77 (16)	0.393[a]	0.696	
Central executive					
CHIPASAT 2.4-s ISI					
Total correct response	40.09 (10.3)	38.52 (12.02)	0.46[a]	0.648	
Total dyad	12.18 (16.70)	16.59 (18.45)	212	0.456	
CHIPASAT 1.6-s ISI					
Total correct response	36.76 (10.16)	32.71 (10.74)	1.255[a]	0.217	
Total dyad	23.57 (14.89)	18.67 (13.06)	1.135[a]	0.263	
Attention					
TEA-Ch Sky Search					
Accuracy (z score)	–1.06 (3.64)	–0.88 (3.03)	230	0.6	
Time for completion (z score)	–0.66 (.58)	0.06 (1.31)	–2.466[a]	0.019*	0.4
Attention score (z score)	–0.39 (.64)	0.16 (1.35)	–1.83[a]	0.76	
TEA-Ch Creature Counting					
Accuracy (z score)	0.09 (1.42)	0.03 (1.02)	239	0.75	
Time for completion (z score)	–0.99 (1.54)	0.19 (.95)	106	0.018*	0.35
Digit vigilance test					
Total reaction time (ms)	527.5 (170.09)	616.74 (284.56)	–1.27[a]	0.211	
Total error	16.14 (10.07)	17.04 (10.61)	–0.294[a]	0.211	
Total omission	16.09 (10.09)	17.04 (10.61)	–0.308[a]	0.759	
Total commission	0.0455 (.21)	0 (0)	241.5	0.307	

CHIPASAT, Children's Paced Auditory Serial Addition Task; OSA, obstructive sleep apnea; SD, standard deviation; TEA-Ch, Test for Everyday Attention in Children.
* $p < 0.05$.
** $p < 0.01$.
[a] Effect size for t test is presented as Cohen's d, whereas effect size for Mann–Whitney U test is presented as rank–biserial correlation (r).

Table 3
Respiratory variables predicting working memory performance as shown in hierarchical regression analyses.

	Longest forward Digit span		Verbal 2-back Accuracy	
	ß	p	ß	p
Step 1				
Age	0.163	0.251	0.449	0.001**
Step 2				
OAHI	–0.054	0.796	–0.324	0.015*
SpO_2 nadir	0.49	0.025*	—	—
$R^2\Delta$	0.274		0.105	
Model R^2	0.28		0.316	
Adjusted R^2	0.227		0.284	
F (df)	5.309(3.41)		9.709(2.42)	
P	0.003*		0.001***	

ß, standardized regression coefficient; OAHI, obstructive apnea–hypopnea index; SpO_2, oxygen saturation.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

We found no group differences in either the basic or executive components of visuospatial working memory. The pattern of findings seemed to suggest a greater impact of OSA on children's verbal domain than on the visuospatial domain in the realm of working memory. Our evidence of a differential impact of childhood OSA on verbal vs. visuospatial abilities also echoed the pattern identified in an adult OSA study, in which OSA was found to be associated with impairment in verbal but not visual memory [53]. Nevertheless, visuospatial abilities were measured differently in different studies, and visuospatial working memory was seldom tested previously. Hence, it would be difficult to make meaningful comparisons across studies, and we look forward to more independent replications using well-validated working memory models in OSA populations.

We identified OAHI and SpO_2 nadir as two distinct, sleep-related respiratory variables predictive of verbal storage and executive working memory functions in the OSA group. These two parameters of OSA are often treated as proxies of hypoxic damage to the brain [5]. Beebe and Gozal put forward the notion that OSA-related sleep disruption and intermittent hypoxia would alter the efficacy of restorative processes and functional biological viability within the prefrontal cortex in the brain [5]. Our findings were also somewhat consistent with the positive correlation found between

verbal IQ and SaO_2 nadir reported in a previous study [12]. One plausible explanation of the correlation between oxygen desaturation and verbal working memory could be the reduced blood flow during apneic episodes to the frontal–parietal–temporal neural network, which is closely associated with verbal working memory [54–56]. Furthermore, altered neuronal metabolites (NAA/Cho ratios) and brain abnormalities (gray matter volume), both known to be susceptible to gas abnormalities, were associated with poorer performance in verbal working memory and attention in OSA children [19,57]. Taken together, although our findings do not indicate any causal relationship between respiratory variables and interrupted brain development, our evidence of verbal working memory impairment is in line with existing knowledge on the neural substrates of the verbal working memory processes, which are known to be susceptible to hypoxic damage.

The lack of significant findings on the relationship between cognitive deficits and sleep architecture in our study was also interesting. To start with, our results showed that although OSA children exhibited significantly more respiratory disturbances than controls, no differences were observed in the sleep stages and sleep efficiency. This pattern appeared to echo the findings of sleep architecture being grossly intact in pediatric OSA in other studies also [58,59]. As the role of sleep deprivation and disruption in pediatric OSA was deemed elusive, blood-gas abnormalities were more often highlighted in explaining cognitive dysfunctions in childhood OSA [5]. To draw a definitive conclusion regarding the role of sleep architecture in cognitive functioning of children with OSA, it would be advisable for future studies to use more sophisticated sleep architectural parameters, such as EEG power spectral analysis and cyclic alternating pattern, to detect OSA-related sleep abnormalities associated with cognitive deficits.

A major limitation of our study should be noted. Our sample size did not allow us to compare the performance of children with different degrees of OSA. Having multiple severity groups of OSA would enable us to decluster the cognitive deficits found in the OSA population, and to examine the relationship between neuropsychological outcomes and levels of sleep/respiratory disturbances.

To conclude, we identified OSA-associated basic storage and central executive deficits in verbal working memory in children. Impaired basic attentional processes were also present in the OSA group, but such impairments could not account for the deficits identified in verbal working memory. Furthermore, oxygen saturation level and obstructive apnea–hypopnea index were found to be significant predictors of performance in basic and executive verbal working memory in children with OSA. We contend that OSA-associated impairment in verbal working memory may alter the trajectory of school-age children's learning potentials. This study paves the way for further outcome studies on post-treatment reversibility of deficits in working memory in children with OSA. Patients and their families should be informed of the neuropsychological correlates of the disorder, and early detection, thorough assessment, and targeted intervention should be recommended to prevent or alleviate long-term damage of the disorder to the developing brain.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.04.025.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2015.04.025.

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