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**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 the 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; such differences were not significant in the visuo-spatial domain. The OSA group also performed worse on neuropsychological tests of attention and processing speed. Moreover, correlational analyses and hierarchical regression analyses further suggested that obstructive apnea hypopnea index (OAHI) and oxygen saturation (SpO₂) nadir were associated with verbal working memory performance.

Conclusions: Our findings support the notion that there are significant neuropsychological deficits associated with childhood OSA, specifically in the storage and executive components of the verbal working memory, above and beyond basic attention and processing speed impairments. The associations between these working memory deficits and OSA-related respiratory variables (OAHI & SpO₂)

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further highlighted the potential pathophysiological mechanisms of OSA-induced cognitive deficits. 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.

Keywords: (6 items) Working memory, OSA, neurocognitive, pediatric, hypoxemia, sleep

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1. Introduction

Obstructive sleep apnea (OSA) is a frequently diagnosed nocturnal breathing disorder, with a prevalence rate of around one to three percent in the western pediatric populations (McNicholas & Phillipson, 2002; Nixon & Brouillette, 2005). In the Hong Kong population, the prevalence for childhood OSA has been found to be affecting 5% of school-aged children (Li et al., 2010). Childhood OSA is characterized by snoring associated with sleep fragmentation, exaggerated upper airway resistance, obstructive breathing, intermittent hypoxia, hypercapnia and repeated arousals (Gozal, 2001).

It was well documented that children with OSA experienced difficulties in a wide cognitive spectrum, spanning from vigilance, sustained attention, visual sequencing, memory, to executive functions such as planning and organization, inhibition, mental flexibility, metacognition, and working memory (Beebe & Gozal, 2002; Bourke et al., 2011; Friedman et al., 2003; Giordani et al., 2008; D Gozal et al., 2001; Gozal & Kheirandish-Gozal, 2007; Landau et al., 2012; Lewin, Rosen, England, & Dahl, 2002; Owens, Spirito, Marcotte, McGuinn, & Berkelhammer, 2000). Among the cognitive functions studied previously in OSA populations, executive functions, and particularly working memory have been highlighted (Biggs et al., 2011; Esposito et al., 2013; Tan, Gozal, & Kheirandish-Gozal, 2013). Working memory deficits measured by the n-back task have been demonstrated in adult OSA populations (e.g., Lau et al., 2013) and were shown to persist even after treatment (e.g., Lau et al., 2010). The picture of neurocognitive outcomes, and especially working memory functions in childhood OSA was less clear. Halbower and colleagues (2006) reported deficits in verbal executive functioning measured by sentence span and word fluency tasks. Kohler and colleagues (2009) identified poor

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working memory functions in both verbal and non-verbal domains in sleep-disordered breathing children on standardized batteries, such as NEPSY and Stanford-Binet Intelligence Test (Kohler et al., 2009). Biggs (2011) assessed working memory in sleep-disordered breathing children using both parent-rating and neuropsychological tests. While 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 controls (Archbold, 2004; Beebe et al., 2004; Friedman et al., 2003). On the other hand, some treatment studies demonstrated that impaired neurocognitive functions could mostly be reversed following adenotonsillectomy or tonsillectomy (Friedman et al., 2003; Montgomery-Downs, Crabtree, & Gozal, 2005; Owens et al., 2000). However, changes in executive functions in these studies were only measured by test batteries or combinations of standalone 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 was 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 (i.e., maintenance capacity/speed) of working memory as a whole, without delineating the individual components (Lau et al., 2010). In addition, most previous childhood OSA studies only measured the verbal domain of working memory, rendering the visuo-spatial domain understudied. Therefore, a comprehensive model of working memory,

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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 (Lau et al., 2010), as well as in Chinese adult OSA populations (Lau et al., 2013). 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, mathematical ability, planning, reasoning and problem solving, which are regarded as pivotal to children's learning and development (Baddeley, 2003). 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 (Baddeley, 2003; Baddeley & Hitch, 1974). By adopting the multi-component model of working memory proposed by Baddeley and Hitch (1974), 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 (Andrade, 2001).

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 (Beebe & Gozal, 2002). 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 (Archbold et al., 2004; Chervin et al., 2006; Kaemingk et al., 2003). Other studies have investigated the associations

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between oxygen saturation, REM sleep, arousal index on cerebral oxygenation and endothelial functions in sleep-disordered breathing (Gozal, Kheirandish-Gozal, Bhattacharjee, & Spruyt, 2010; Khadra et al., 2008; Bass et al., 2004). However, yet other studies showed that sleep disruptions alone were sufficient to result in neurobehavioral deficits (e.g., Blunden and Beebe, 2006). A more recent study reported the associations of executive deficits with nocturnal hypoxemia levels in children with OSA (Esposito et al., 2013). 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 Helsinki Declaration and approved by the Chinese University of Hong Kong and Hospital Authority New Territories East Cluster Clinical Research Ethics Committee. Altogether 51 children

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(23 children with OSA and 28 controls) aged 8 to 12 were recruited: the suspected OSA children were from the Pediatric Respiratory Sleep Disorder and Obesity Clinic at the Prince of Wales Hospital of Hong Kong, while the age-matched controls were recruited from a population-based study conducted by one of our co-authors (See Kong et al., 2011). The test administrator was blinded to the background of the participants. Exclusion criteria included neurological co-morbidity such as history of head injury, an intercurrent upper respiratory tract infection within four weeks of recruitment, craniofacial anomalies, syndromic disorder such as Down Syndrome, history of other sleep pathologies including primary snoring, prior upper airway surgery, and obesity (BMI>30). Children who were diagnosed of developmental or psychiatric disorder (e.g. 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. Afterwards, 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, 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

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electrooculogram (EOG), electromyogram (EMG) (chin and bilateral anterior tibialis muscle) and electrocardiography (ECG). Respiratory movements of the chest and abdomen were measured by piezo crystal effort belts. Arterial oxyhaemoglobin saturation (SaO₂) was measured by a built-in oximeter with finger probe. Respiratory airflow 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 (Iber et al., 2007). Obstructive apnea hypopnea index (OAHl) 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 theta, alpha and/or frequencies greater than 16 Hz but not spindles, with 3 to 15 seconds in duration. 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 OAHl ≥ 1 was chosen as the diagnostic cut-off of OSA in the current study. For this protocol, each child was classified into either OSA (OAHl ≥ 1) or control (OAHl < 1) for data analyses. Children with OAHl < 1 and with a history of snoring ≥ 3 nights per week were classified as primary snorers and excluded from the current study, due to potential differences in the etiology and cognitive outcomes between individuals with OSA and those with primary snoring (Biggs, Nixon & Horne, 2014; Yeung et al., 2013; Zancanella et al., 2012;).

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2.2.3. Neurocognitive measures (*More details of neurocognitive tasks can be found in the supplementary materials*)

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; Psychological Corporation, 1981) 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; Wechsler, 1997b) 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 (Smith, Jonides, & Koeppel, 1996), and the Children’s Paced Auditory Serial Addition Task (CHIPASAT). The number of correct responses and correct dyads in the two conditions (i.e., 2.4-s ISI and 1.6-s ISI) were recorded in the CHIPASAT task (Dyche & Johnson, 1991). (*Sequences of events in the 2-back tasks are shown in supplementary figures 1a and 1b*).

Attention tasks. Since 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) (Chan, Wang, Ye, Leung, & Mok, 2008; Manly et al., 2001), Sky Search and Creature Counting were chosen to assess selective attention and attention switching, respectively. Vigilance was measured using the

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Digit Vigilance Test (DVT) (Lewis & Rennick, 1979).

2.3 Statistical Analysis

Data were analyzed using IBM Statistical Package for the Social Sciences (SPSS Statistics) (version 16.0). 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 the neuropsychological tests were compared. Independent t-test was used to compare parametric data, and Mann-Whitney U test was used to analyze non-parametric data. Nominal demographic data were analyzed using the chi-square test. Effect size (Cohen's d) was calculated for significant difference revealed by independent t-test whereas rank-biserial correlation (r) was used to present effect size for Mann-Whitney U test. For the n-back tasks, accuracy rates were analyzed by mixed ANCOVA with a between-subject factor, Group (OSA vs. control), a within-subject factor, Condition (0-back vs. 2-back), and with age and attention test scores as covariates. As follow-up analyses, one-way ANCOVA with 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 OAH1, SpO2 nadir) and cognitive tasks' 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, gender and BMI in the first step and the related

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respiratory variables in the second step. All p -values reported were two-tailed with statistical significance set at .05. Data are presented as mean (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 in the current study. One control participant was excluded in the current analyses due to problems in understanding and completing the neuropsychological tests. Another five older control participants were excluded in order to ensure better matching of age with the OSA group such that the any group differences would not be attributable to age. Therefore, data of 23 children with OSA and 22 controls were included in the current analyses. Demographic and polysomnographic data were 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 was found. As expected, significant between-group differences were found in OAH1, arousal index, and SpO₂ nadir. There were, however, no significant differences in sleep architecture parameters between the groups.

3.2 Attention

The performance of the OSA group and the controls on the attention tests was summarized in Table 2. The OSA group had significantly longer reaction time (z -score) on TEA-Ch Sky Search ($t=-2.47, p=.019$) and TEA-Ch Creature Counting ($U=106, p=.018$) than the control group. There were no significant group differences found on the Digit Vigilance Test, $p>.05$.

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3.3. Working Memory

Phonological loop and visuospatial sketchpad. The OSA group had significantly shorter Forward Digit Span ($U=182.5, p=.039$) and longer reaction time in the verbal 0-back condition ($t(42)=-3.34, p=.003$), 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, $p>.05$ (Table 2).

Central executive. For verbal n-back task, the covariate, age was significantly related to the accuracies ($F(1,42)=8.07, p=.007$). After controlling for the effect of age, significant main effect of Conditions was still found ($F(1,42)=13.95, p=.001$), with worse performance in the 2-back than in the 0-back condition. The Group*Condition interaction was also significant ($F(1,42)=4.99, p=.031$), 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 ($F(1,42)=1.96, p=.169$). 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 ($p>.05$) and the Group*Condition interaction still held, $p=.044$. In addition, one way ANCOVA further revealed that the OSA group had significantly worse performance than the controls on the 2-back task ($F(1,42)=6.091, p=.018$), whereas there was no significant group difference on the 0-back task, $p>.05$. For the visuospatial n-back task, while age was a significant covariate ($F(1,42)=11.71, p=.001$), the main effect of Condition ($F(1,42)=.039, p=.845$) and Group ($F(1,42)=1.71, p=.198$) as well as the Group*Condition interaction ($F(1,42)=1.03, p=.315$) were non-significant. No significant difference was found on CHIPASAT, $p>.05$ (Table 3).

3.4 Associations between Respiratory Variables and Cognitive

Functions

Forward Digit Span was correlated negatively with OAH1 ($r=-.423, p=.002$) and positively with SpO₂ nadir ($r=.477, p<.001$). Verbal 2-back accuracy was negatively correlated with OAH1 ($r=-.362, p=.01$). No significant correlations were found between the respiratory variables and other working memory or attention scores.

Based on the significant correlations, OAH1 and SpO₂ nadir were entered in the second step of regression analysis of Forward Digit Span; and OAH1 in the second step of analysis of verbal 2-back task. SpO₂ nadir was a significant predictor of performance of Forward Digit Span, whereas OAH1 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

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discrepancies in general cognitive functioning or attention, which is 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 (Beebe & Gozal, 2002; Friedman et al., 2003; Gozal et al., 2001; Lewin et al., 2002; Owens et al., 2000). 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 (Gathercole & Alloway, 2008). 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 route for fluent reading (Shu, McBride-Chang, Wu & Liu, 2006; Chung & McBride-Chang, 2011, Ho et al., 2004; Leong, Tse, Loh & Hau, 2008). The role of verbal working memory in bilingualism was also suggested in several studies (Ardila, 2003; Xue, Dong, Jin, Chen, 2004), underlining the potential far-reaching impact of working memory

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deficits in language acquisition in multilingual societies like Hong Kong. The effect of verbal working memory also extended beyond the language domain to other abilities such as mathematic skills (Swanson & Jerman, 2006). It would be fruitful for future studies to examine learning in children with OSA and its association with working memory deficits pre- and post-treatment. Such findings would shed light on the neurodevelopmental significance of OSA.

Interestingly, we found no group differences in both the basic and executive components of visuospatial working memory. The pattern of findings seemed to suggest a greater impact of OSA on children's verbal domain than visuospatial domain in the realm of working memory. Our evidence of a differential impact of childhood OSA on verbal versus 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 (Twigg et al., 2010). 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 OAH1 and SpO₂ 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. Beebe and co-authors (2002) 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. Our findings were also somewhat consistent with the positive correlation found between verbal IQ and SaO₂ nadir reported in a previous study (Lewin et al.,

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2002). 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 (Kiratli, Demir, Volkan-Salanci, Demir, & Sahin, 2010; Maiti, Singh, Mallick, Muthuraju, Illavazhagan, 2008; Shukkit-Hale, Kadar, Marlowe et al., 1996.). Furthermore, altered neuronal metabolites (NAA/Cho ratios) and brain abnormalities (grey matter volume), both known to be susceptible to gas abnormalities, were associated with poorer performance in verbal working memory and attention in OSA children (Halbower et al., 2006; Chan et al., 2014). Taken together, while our findings cannot 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 paediatric OSA in other studies too (Marcus et al., 2000; Goh, Galster & Marcus, 2000). As the role of sleep deprivation and disruption in paediatric OSA was deemed elusive, blood-gas abnormalities were more often highlighted in explaining cognitive dysfunctions in childhood OSA (Beebe & Gozal, 2002). To make definitive conclusion on the role of sleep architecture in cognitive functioning of children with OSA, it would be advisable for future studies to use more

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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-aged children's learning potentials. This study paved 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 brains.

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Author Contributions

EYYL, ESKL, EWMC, WHY, AML conceived and designed the study.

ESKL, EWMC, KNTL, CTA performed the experiment.

EYYL, ESKL, KNTL, CTA analyzed the data.

EYYL, EWMC, KNTL, ESKL wrote the manuscript.

EYYL, EWMC, KNTL, WHY, AML edited the manuscript.

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Tables

Table 1

Demographic and sleep characteristics of controls and OSA children.

	Controls (n=22)		OSA (n=23)		<i>p</i>	<i>Effect Size</i>
	Mean (SD)	Range	Mean (SD)	Range		
Demographic data						
Age (years)	8.89 (1.2)	8.06– 12.3	9.91 (1.49)	8.01– 12.43	.965	
Gender	10M:12F		17M:6F		.071	
Body mass index	18.28 (3.36)	13.21- 26.56	20.04 (3.45)	15.03- 27.52	.091	
Education	4.32 (1.17)		4.13 (1.29)		.612	
General Intelligence						
Raven's Standard Progressive Matrix	106.36 (10.58)	/	102.7 (8.86)	/	.214	
Polysomnography indices						
OAHI (/hr)	.29 (.29)	0-0.9	5.6 (7.38)	1-28.5	.002**	1.02
ArI (/hr)	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	.004**	.94
TST (min)	498.04	200.5-	492.48	411-575	.778	

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	(80)	619.5	(48.51)		
Sleep efficiency (%)	89.69 (8.89)	54.5- 97.5	89.70 (6.97)	76.3- 97.5	.998
WASO (min)	25.48 (16.5)	1-59	30.77 (6.42)	2.5- 111.5	.134
Stage 1 (% TST)	4.08 (2.36)	.8-9.1	4.67 (3.53)	.9-11.3	.514
Stage 2 (% TST)	35.31 (4.69)	27.2- 44.8	35.79 (4.77)	23.9- 43.2	.734
Stage 3 (% TST)	7.51 (3.49)	2.4-16.9	7.19 (2.36)	3.9-12.1	.721
Stage 4 (% TST)	30.63 (6.24)	18.4- 43.1	30.44 (5.42)	21.5-41	.912
Stage REM (% TST)	22.46 (4.24)	12.5- 28.8	21.88 (2.95)	16.7- 29.2	.595
SWS (%stage3+4)	36.14 (8.14)	23.7- 56.8	37.63 (6.52)	26.8- 51.8	.817

Abbreviations: SD, standard deviation; hr, hour; min, minute, OAH, obstructive apnea hypopnea index; ArI, arousal index; SpO₂, oxygen saturation; WASO, wake after sleep onset; TST, total sleep time; REM, rapid eye movement; SWS, slow wave sleep. * $p < .05$. ** $p < .01$. Effect size was presented as Cohen's d .

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Table 2

Working memory and neuropsychological tests performance of controls and OSA children.

	Control (n=22)	OSA (n=23)			
	Mean (SD)	Mean (SD)	<i>U/t</i> [#]	<i>p</i>	<i>Effect size</i> ⁺
Phonological Loop					
Longest Forward Digit	8.86 (.35)	8.39 (.89)	182.5	.039*	.31
Span					
Verbal 0-back					
Reaction Time (ms)	653.53 (88.30)	788.65 (169.23)	-3.34 [#]	.003**	.5
Accuracies (%)	88.92 (14.78)	89.24 (10.26)	242.5	.81	
Visuospatial Sketchpad					
Longest Forward Spatial	5.64 (1.36)	5.78 (1.04)	222.5	.467	
Span					
Visuospatial 0-back					
Reaction Time (ms)	741.37 (143.82)	847.3 (298.54)	209	.318	
Accuracies (%)	84.93 (8.48)	78.56	214	.375	

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(16.98)

Central executive

Longest Backward Digit 4.27 (1.24) 5.26 (2.00) 183 .104

Span

Longest Backward 5.09 (1.11) 5 (1.21) 238 .723

Spatial Span

Verbal 2-back

Reaction Time (ms) 871.5 954.85 232 .633
(144.17) (325.52)

Accuracies (%) 76.17 67.11 2.085[#] .044* .32
(11.25) (17.36)

Visuospatial 2-back

Reaction Time (ms) 840.32 928.68 233 .65
(189.79) (336.79)

Accuracies (%) 67.48 65.77 (16) .393[#] .696
(12.92)

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Table 2. (Continued)

Working memory and neuropsychological tests performance of controls and OSA children.

	Control (n=22)	OSA (n=23)			
	Mean (SD)	Mean (SD)	<i>U/t</i> [#]	<i>p</i>	<i>Effect size</i> ⁺
Central executive					
CHIPASAT 2.4-s ISI					
Total correct response	40.09 (10.3)	38.52 (12.02)	.46 [#]	.648	
Total dyad	12.18 (16.70)	16.59 (18.45)	212	.456	
CHIPASAT 1.6-s ISI					
Total correct response	36.76 (10.16)	32.71 (10.74)	1.255 [#]	.217	
Total dyad	23.57 (14.89)	18.67 (13.06)	1.135 [#]	.263	
Attention					
TEA-Ch Sky Search					
Accuracy (z-score)	-1.06 (3.64)	-.88 (3.03)	230	.6	
Time for completion (z-score)	-.66 (.58)	.06 (1.31)	-	.019*	0.4
			2.466 [#]		
Attention Score (z-score)	-.39 (.64)	.16 (1.35)	-1.83 [#]	.76	
TEA-Ch Creature					
Counting					
Accuracy (z-score)	.09 (1.42)	.03 (1.02)	239	.75	

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Time for completion -.99 (1.54) .19 (.95) 106 .018* .35

(z-score)

Digit Vigilance Test

Total Reaction Time	527.5	616.74	-1.27 [#]	.211
(ms)	(170.09)	(284.56)		
Total Error	16.14 (10.07)	17.04 (10.61)	-.294 [#]	.211
Total Omission	16.09 (10.09)	17.04 (10.61)	-.308 [#]	.759
Total Commission	.0455 (.21)	0 (0)	241.5	.307

Abbreviations: SD, standard deviation; ms, millisecond; CHIPASAT, Children's Paced Auditory Serial Addition Task; TEA-Ch, Test for Everyday Attention in Children; * $p < .05$. ** $p < .01$.

[†]Effect size for t-test was presented as Cohen's d whereas effect size for Mann-Whitney U test was presented as rank-biserial correlation, r.

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Table 3

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

	Longest Forward		Verbal 2-back	
	Digit Span		Accuracy	
	β	p	β	p
Step 1				
Age	.163	.251	.449	.001**
Step 2				
OAH1	-.054	.796	-.324	.015*
SpO ₂ nadir	.49	.025*	/	/
$R^2\Delta$.274		.105	
Model R^2	.28		.316	
Adjusted R^2	.227		.284	
F (df)	5.309 (3,41)		9.709 (2,42)	
P	.003*		.001***	

Abbreviations: OAH1, obstructive apnea hypopnea index; SpO₂, oxygen saturation; β ,

Standardized regression coefficient. * $p < .05$. ** $p < .01$. *** $p < .001$.

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ONLINE SUPPLEMENT

Methods

Neuropsychological tasks

Attention and mental flexibility

Test for Everyday Attention in Children (TEA-Ch)^{1,2}

The TEA-Ch is an assessment tool for attention which comprises of nine subtests based on the adult Test of Everyday Attention, and is applicable to children aged 6-16 to testing different aspects of attention. This test battery is built upon a three-factor model consisting of sustained attention, selective attention and higher-level “executive” control. The present study adopted two subtasks: “Sky search” and “Creature counting” to test subjects’ selective attention and attentional control.

In the Sky Search subtest, the children were given a laminated A3 sheet depicting rows of paired spacecraft and instructed to try and find all the identical aircraft pairs as quickly as possible. Twenty targets were distributed among 108 distractors. Subjects could self-determine their termination of task by marking the box. In order to control for differences stemmed from motor speed rather than visual selection, subjects are then administered a motor control version of the task. Outcome measures are the accuracy and time for completion. For the latter outcome, “motor control” time-per target-score was subtracted from the Sky Search time-per-target score to yield the attention score. Test-retest reliability reported by original author is at .90. In the three-factor model of TEA-Ch performance in Chinese children, Sky-search task is correlated to selective attention ($r=0.71$) and sustained attention ($r=0.43$).

In the Creature Counting subtest, subjects are required to switch from one set of mental task to another set of mental tasks. They were presented with a stimulus book and instructed to count aloud the number of creatures present in the burrow but they were to pay attention to the arrows which will serve as cues for them to change their direction in counting. The task begins with two practice trials followed by seven experimental trials. The outcome measure is accuracy response and time for completion. Another outcome measure is the timing score (i.e. time taken per switch), but it is only calculated if the subject gets three or more correct responses. Test-retest reliability reported by original author is 0.69 (accuracy) and 0.73 (timing). In the

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 three-factor model of TEA-Ch performance in Chinese children, Creature Counting task is correlated to attentional control/switching ($r=0.61$).

Attention and information processing

The Children's Paced Auditory Serial Addition Task (CHIPASAT)^{3,4}

CHIPASAT is developed for children based on Gronwall (1977)'s Paced Auditory Serial Addition Task for adults. Split-half reliability is approximately .90 at different ages, indicating high internal consistency. Test-retest reliability for the overall mean score after four-week interval is ranged .78-.83). The test taps on the subjects' attention, concentration, and speed of information processing. It consists of a prerecorded soundtrack with five trials of 61 random single-digit numbers. The test requires the participant to listen to the series of numbers and add successive numbers in pairs and immediately to give the answer aloud before the next number is presented. All answers do not exceed 10.

Participants were first provided with a practice trial, then required to complete 5 experimental trials at the rate of 2.8, 2.4, 2.0, 1.6 and 1.2 sec intervals between each digit. The outcome measures of CHIPASAT are the number of correct responses, errors committed, answers omitted, number of dyads (i.e. consecutive correct responses) and correct response rate (i.e. number of correct answers divided by time taken to complete each trial).

The test has been used as a measure of information processing speed and is adopted in our study as it is sensitive to the neurocognitive effects of several clinical conditions.

Vigilance

Digit Vigilance Test^{5,6,7}

The DVT is a rapid visual tracking task that taps on subjects' vigilance and sustained attention and psychomotor speed. Test-retest reliability with one-week delay was 0.88 for youthful control subjects. The test consists of two pages, with 35 single digits appearing in each and every 59 rows. Subjects are instructed to cross out all the number '6's that appears randomly on the page. The outcome measures include the time for completion, number of commission error (i.e. crossed out non-'6' digits) and number of omission error (i.e. did not cross out '6' digits). DVT is shown

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to be sensitive in detecting neuropsychological deficits in patients with even mild forms of sleep apnea.

General intelligence

Raven's Standard Progressive Matrices (RSPM)^{8,9,10}

The RSPM is designed to measure a person's fluid ability to form relations and perceptual analogies regardless of language and educational background. It is developed as a measurement of the two main components of the Spearman's g (i.e. general intelligence), which included the ability to think and make sense of complexity, and the ability to store and reproduce information. It is a 60-item test arranged in 5 sets (A, B, C, D&E). Each set contains matrix-like figures with a missing piece and the subject is required to choose the correct missing piece based on the 'theme' set in each set of figures. The outcome measure is the raw score, which will then be converted to percentile with published age-based local norm.⁶

Working memory

N-back experimental task^{11, 12}

The n-back task is a continuous memory task adapted by Smith and authors (1996), from the one developed by Gevins and Cutillo (1993) to test the participant's ability to maintain and conduct online processing of information. Letters (letter identity) and symbols (symbol location) are used as stimuli in the verbal and spatial tasks, respectively. Each task includes both the 2-back and the 0-back conditions. Participants had to complete three 0-back blocks and three 2-back blocks for each task. Each block has 26 trials, comprising of 10 controls, 8 foils and 8 matches. Practice block is available in the beginning of each trial. The 2-back condition requires the subject to decide whether or not the presented stimulus matches the one encountered two stimuli before. The 0-back condition is a baseline measure for factors like alertness, and perceptual and motor responses that can affect performance in the 2-back trials.

Verbal tasks Letters used in the verbal condition appear at the exact same location (i.e. left of fixation cross) across all trials for all subjects. In the verbal 2-back task, participants had to decide whether or not (yes/no response) each

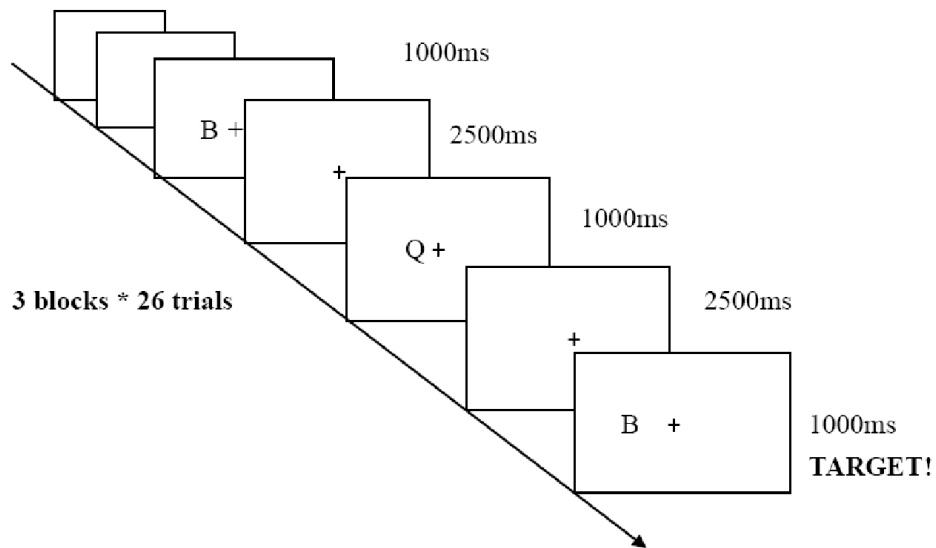
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letter matched in identity of the one presented two back (i.e. not the previous letter, but the one before that), holding location constant (Supplementary Figure 1a). In the verbal 0-back task, participants had to make a simple decision on whether the presented letter matches the identify of the first stimulus presented at the start of the trial.

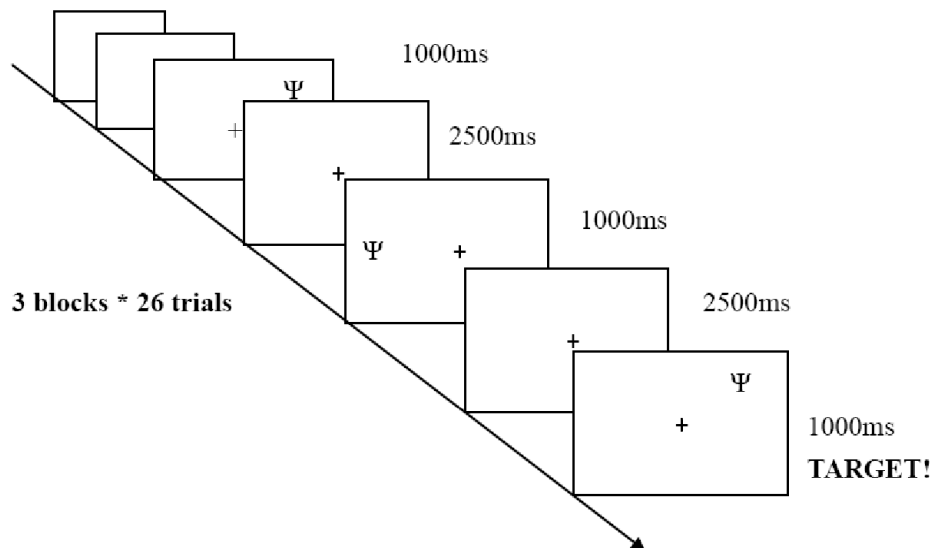
Spatial tasks Symbols used in the spatial condition were identical and appeared at a randomly chosen location amongst 12 possible positions, each of which was randomly generated within a donut-shaped area within 1.5 to 4.5 degree of radius from the screen's centre. In the spatial 2-back task, participants had to decide whether or not the position of the symbol matched the position of the symbol presented two symbols back. (Supplementary Figure 1b). In the spatial 0-back task, participants had to make a simple decision on whether the presented letter matched the location of the stimulus presented at the start of the trial.

The Python freeware was used for stimulus presentation and response data collection via button press. In each block, single stimuli was presented in a continuous stream, each for 1000ms, with a 2500ms interval between successive stimuli. Participants had to press one of two buttons with one fingers of their dominant hand to indicate positive or negative responses. Performance was measured by accuracies and reaction times. The whole task took about 20 minutes in total.

Supplementary Figure 1a. Sequence of Events in the Verbal 2-back task



Supplementary Figure 1b. Sequence of Events in the Spatial 2-back task



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