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Neurocognitive and Endothelial Dysfunction in Children With Obstructive Sleep Apnea

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KEY WORDS

sleep apnea, endothelial progenitor cells, endothelial function, serum lipids, atherosclerosis

ABBREVIATIONS

OSAS—obstructive sleep apnea syndrome
PSG—overnight polysomnography
OAHI—obstructive apnea hypopnea index
DAS—Differential Ability Scales
NEPSY—NeuroPsychological Assessment Battery
T_{max}—time to maximal postocclusive reperfusion
ED^+—presence of endothelial dysfunction
ED^-— without endothelial dysfunction
NC^+—presence of ≥2 deficits in cognitive battery subtests
NC^-—no presence of neurocognitive deficits

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WHAT'S KNOWN ON THIS SUBJECT: Obstructive sleep apnea syndrome (OSAS) is associated with neuropsychological deficits and cardiovascular morbidity. However, not all children are affected, and it is unknown whether those children with 1 of these morbidities are at risk for the other.

WHAT THIS STUDY ADDS: Results show that endothelial dysfunction and neurocognitive deficits are frequent in children and are also highly likely to coincide, suggesting that these morbidities of OSAS may share similar pathophysiological mechanisms. Furthermore, a simpler test such as measurement of endothelial function may serve as a surrogate marker for cognitive dysfunction in children with OSAS.

abstract

OBJECTIVE: Pediatric obstructive sleep apnea syndrome (OSAS) is associated with neurocognitive and endothelial dysfunction. However, it is unclear whether these 2 frequent morbidities of OSAS in children represent similar or different underlying pathophysiological processes, because they have never been concurrently assessed in children.

METHODS: Consecutive children (ages 5–8 years) with polysomnographically based OSAS underwent cognitive battery evaluation (Differential Ability Scales and the NeuroPsychological Assessment Battery) and cuff-occlusion hyperemic tests for assessment of endothelial function. The presence of neurocognitive deficits (NC^+) was defined on the basis of the presence of ≥2 abnormal cognitive test results. Endothelial dysfunction (ED^+) was defined as a time to maximal postocclusive hyperemic response of ≥45 seconds (T_{max}).

RESULTS: Twenty-one control children and 87 children with OSAS completed both cognitive and endothelial tests. Of these children, 48 were NC^+ and 50 had a T_{max} of ≥45 seconds, and at least 80% of these children were in both groups. Conversely, among children in whom there was no presence of neurocognitive deficits (NC^-), only 25.6% were ED^+, whereas among those without endothelial dysfunction (ED^-) only 21.6% were NC^+. Furthermore, approximately one-third of the children with OSAS was NC^- and ED^-. Thus, findings on hyperemic vascular responses were highly predictive of neurocognitive status.

CONCLUSIONS: Endothelial dysfunction and neurocognitive deficits are more likely to coexist than otherwise predicted from the frequency of each of these morbidities alone in pediatric OSAS. Thus, both of these morbid consequences may share similar pathogenetic mechanisms. Furthermore, a simple test such as the postocclusive hyperemic vascular response may help detect at-risk patients for neuropsychological deficits. *Pediatrics* 2010;126:e1161–e1167

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Obstructive sleep apnea syndrome (OSAS) in children is a prevalent condition in which intermittent collapse of the upper airway during sleep leads to recurrent hypoxic events, intermittently elevated carbon dioxide levels, sleep fragmentation, and reduced sleep efficiency.[1] Results of substantial work from multiple laboratories have clearly shown that OSAS independently elevates the risk for neurocognitive deficits and reduced school academic performance,[2–4] alters lipid homeostasis,[5] and promotes the occurrence of cardiovascular morbidities such as systemic hypertension and endothelial dysfunction.[6–8] However, it is noteworthy that not all children with OSAS will develop evidence of either cognitive dysfunction[9] or endothelial dysfunction,[10] thereby leading to the concept that that multiple factors could be playing a role in the morbidity-associated phenotype in the context of pediatric OSAS.[11–16] Among such factors, the severity of OSAS, the magnitude of the inflammatory and oxidant stress responses, individual and genetic susceptibility factors,[11,17–21] as well as environmental modifiers[22] are all likely to either exacerbate or mitigate the degree of end-organ injury elicited by the presence of OSAS in children. In the context of cognitive deficits in pediatric OSAS, changes in brain metabolic function and systemic inflammatory responses have been identified as determinants of such adverse outcomes.[9,23] However, the magnitude of middle cerebral artery velocity, which provides an indicator of cerebral autoregulatory vasomotor activity, has also recently emerged as an important correlate of cognitive outcome in pediatric OSAS, which suggests that abnormal vascular function could underlie cognitive outcomes.[24] Taken together, it is tempting to speculate that the presence of cognitive deficits and endothelial dysfunction may not represent 2 distinct and nonoverlapping features of OSAS-induced morbidity but, rather, could reflect a shared array of pathogenetic mechanisms leading to this phenotype. In other words, abnormal postocclusive hyperemic responses of the microcirculation and neurocognitive deficits would be highly likely to coexist in children with OSAS when any 1 of such morbidities is present. Conversely, the absence of any 1 of these 2 morbidities would markedly reduce the probability of detecting the presence of the other in the same child with OSAS. This assumption is all the more probable when considering the fact that both neurocognitive deficits and endothelial dysfunction share the presence of increased inflammatory activity as a determinant for their occurrence.[8,9,25] Thus, we hypothesized that endothelial dysfunction and neurocognitive deficits would be more likely to be concomitantly present than otherwise randomly predicted in children with OSAS.

METHODS

Consecutive, otherwise-healthy, habitually snoring prepubertal children (ages 5–8 years) who were participating in a study on neurocognitive function and sleep in children at the University of Louisville Pediatric Sleep Medicine Center were also recruited to participate in assessment of endothelial function in the context of OSAS. All methods outlined in this study were approved by the University of Louisville Human Research Committee. Subjects were recruited from September 2007 until October 2008. All participants underwent baseline overnight polysomnography (PSG) and a fasting blood draw in the morning for glycemic assessments. In addition, 21 age- and gender-matched nonsnoring control subjects were recruited from the community. The rationale for assessing control children was twofold: (1) to establish a normative range of time to maximal postocclusive reperfusion (T_{max}) for age- and gender-matched children originating from the same community and using the same measuring device; and (2) to ascertain that the absence or presence of neurocognitive deficits in OSAS children was indeed present and not just the result of an artificial categorical allocation of the test findings based on established norms for these batteries in other populations.

Anthropometry

Children were weighed by using a calibrated scale, and their weight was recorded to the nearest 0.1 kg. Height (to 0.1 cm) was measured by using a stadiometer (Holtain, Crymych, United Kingdom). BMI was calculated and BMI *z* score was computed by using Centers for Disease Control and Prevention 2000 growth charts (www.cdc.gov/growthcharts) and online software (www.cdc.gov/epiinfo). A BMI *z* score of ≥1.65 (≥95th percentile) was considered to fulfill obesity criteria.

Sphygmomanometry

Arterial blood pressure was measured noninvasively in all children by using an automated mercury sphygmomanometer (Welch Allyn, Skaneateles Falls, NY) at the brachial artery using a guidelines-defined appropriate cuff size on the nondominant arm.[26] Blood pressure measurements were made in the evening before commencement of the PSG and in the morning immediately after awakening. Children with a mean systolic or diastolic blood pressure at ≥95th percentile for age, height, and gender (www.nhlbi.nih.gov/guidelines/hypertension/child_tbl.htm) were considered to be hypertensive and were excluded.

Overnight Polysomnography

PSG was conducted and scored as previously reported.[27–31] The diagnosis of children with OSAS was defined by the

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presence of an obstructive apnea index of ≥1 per hour of total sleep time and an obstructive apnea–hypopnea index (OAHI) of ≥5 per hour of total sleep time, respectively, and a nadir oxyhemoglobin saturation of <92%.[29] Control children had an OAHI of <1 per hour of total sleep time and no oxygen-desaturation events during sleep.

Neurocognitive Assessments

The cognitive tests administered the morning after polysomnographic assessment consisted of the Differential Ability Scales (DAS)[32] and the Neuro-Psychological Assessment Battery (NEPSY).[33] The DAS[32] is a battery of cognitive tests designed to measure reasoning and conceptual ability in children aged 2 to 17 years. This measure was designed to provide specific information about an individual's strengths and weaknesses across a wide range of intellectual activities. Children were administered either the preschool (aged 5 years) or the school-age (aged ≥6 years) form of the DAS. The preschool form is divided into a verbal cluster (including 2 subtests) and a nonverbal cluster (including 2 spatial subtests and 1 nonverbal reasoning subtest) and yields a global composite score that is commensurate with an IQ. The school-age form yields a spatial cluster score in addition to the verbal, nonverbal, and global composite scores. The test was designed so that the global composite scores could be examined across forms and throughout the age range. Individual DAS subtests are designed to measure separate and distinct areas of cognitive functioning and, thus, have high specificity. The ability score for a subtest is expressed as a *T* score with a mean of 50 and an SD of 10. The sum of the core subtest *T* scores is converted to a total standard score, the general conceptual ability score, with a mean of 100 and an SD of 15.

The NEPSY[33] is a relatively new neurobehavioral test battery designed to assess neurobiological development in 5 functional domains. These domains include attention/executive functions, language, sensorimotor functions, visuospatial processing, and memory and learning, with a mean score of 100 and an SD of 15. All these subtests have good to excellent reliability ($r = 0.77–0.91$). Subjects were considered to be being affected if they scored 1 SD below the mean for at least 2 composite clusters or domains on either the DAS or NEPSY batteries.

Endothelial Function

Endothelial function was assessed by using a modified hyperemic test after cuff-induced occlusion of the radial and ulnar arteries by placing the cuff over the wrist as previously reported.[8,10,34] All tests were performed at awakening to ensure that children were in a fasted state. A laser Doppler sensor (Periflux 5000 system integrated with the PF 5050 Pressure Unit [Perimed, Järfälla, Sweden]) was applied over the volar aspect of the hand at the first finger distal metacarpal surface, and the hand was gently immobilized. This site was chosen as an area to minimize the effects of motion artifact and was also found to have a density of skin capillary blood flow that was of appropriate magnitude for detection. Again, children lay supine with the head of the bed elevated 45°. Once cutaneous blood flow over the area became stable, the pressure within an inflatable cuff placed at the forearm and connected to a computer-controlled manometer was raised to 200 mm Hg for 60 seconds, during which blood flow was reduced to undetectable levels. An occlusion time of 60 seconds was chosen to minimize discomfort for the child. Using a computer-controlled pressure release to allow for consistent deflation times, the cuff was rapidly deflated and the hyperemic responses were measured by the laser Doppler device. The maneuver was performed twice within 10 minutes, and at least 2 minutes separated both trials to ensure a return to baseline perfusion. The average of both maneuvers was then computed for subsequent analyses. Laser Doppler determines the magnitude of perfusion at rest, at occlusion, and after occlusion. Although detection of microvascular perfusion varies by child according to factors such as density of capillary blood vessels and thickness of skin, all measurements were extrapolated to baseline perfusion before cuff occlusion, and analysis of reperfusion kinetics was based on time measurements. Commercially available software (Perimed) allowed for unbiased estimates of the time to peak regional blood flow response after the occlusion release, which is considered representative of the postocclusion hyperemic response, an index of endothelial function.[35]

Exclusion Criteria

All children who were hypertensive or using antihypertensive therapies were excluded ($n = 7$). Furthermore, children with diabetes (fasting serum glucose level of ≥120 mg/dL; $n = 4$); children with a craniofacial, neuromuscular, or defined genetic syndrome, children on chronic anti-inflammatory therapy ($n = 3$), and children with any known acute or chronic illness were excluded. In addition, children placed on sympathomimetic agents such as psychostimulants were not tested ($n = 9$).

Data Analysis

Results are presented as means ± SD, unless stated otherwise. All numerical data were subjected to statistical analysis using χ^2 tests, independent Student's *t* tests, or analysis of variance, followed by posthoc tests as appropriate using Statistica 8.0 (StatSoft, Inc, Tulsa, OK [available at www.statsoft.

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com). As an additional measure of concordance, the Cohen's κ coefficient was calculated by using MedCalc (Mariakerke, Belgium) software. No variance-stabilizing transformations were undertaken. A 2-tailed P value of $<.05$ was considered to define statistical significance.

RESULTS

In total, 167 children who fit the initial inclusion criteria were recruited onto the study. Of these children, 91 fulfilled criteria for OSAS. In addition, 21 children who were age-, gender-, and ethnicity-matched nonsnoring control subjects were also included to better define the validity of the cutoff values for endothelial function and to ascertain that normative cognitive performance was indeed present in the current population compared with published standards. Although children with mild sleep-disordered breathing exhibit a higher risk of neurocognitive dysfunction compared with control children,[36] we aimed to identify the degree of concordance between vascular and neurocognitive function; therefore, the remaining 76 children with primary snoring but without OSAS were not included. In addition, 4 of 91 children with OSAS did not complete all the phases of the protocol and were also excluded.

The demographic characteristics of 87 children with OSAS and 21 controls are listed in Table 1. As expected from the selection process, the mean obstructive OAHI and respiratory arousal index were significantly higher, and the nadir arterial oxygen saturation was significantly lower in the OSAS group (Tables 2 and 3). Among 21 control children, there were no abnormalities in cognitive function (no single child exhibited a score that was 1 SD below the mean), and the T_{max} was 29.7 ± 3.5 seconds; no child exhibited a T_{max} of ≥45 seconds (>3 SDs beyond the mean).

Of 87 children with OSAS, 48 exhibited evidence of cognitive deficits (NC^+) (55.1%). Of these children, 14 had abnormal performances in 5 cognitive DAS and NEPSY clusters or domains, 19 had reduced performances in 4 clusters/domains, 12 children were adversely affected in 3 clusters/domains,

TABLE 1 Demographic and Blood Pressure Characteristics in 87 Children With Polysomnographic Evidence of OSAS and 21 Matched Control Subjects

	OSAS ($N = 87$)	Control Subjects ($N = 21$)	P
Age, mean ± SD, y	7.24 ± 0.96	7.21 ± 1.1	NS
Gender (male), *n*	51	11	NS
Race, *n*			
Non-Hispanic white	52	13	NS
Black	29	6	
Hispanic	3	1	
Biracial	2	1	
Other	1	0	
Family history of premature cardiovascular disease, *n*	19	5	NS
BMI *z* score, mean ± SD	0.82 ± 0.27	0.66 ± 0.29	<.044
Mean systolic blood pressure, mean ± SD, mm Hg	117.1 ± 7.3	98.1 ± 6.7	<.01
Mean diastolic blood pressure, mean ± SD, mm Hg	68.1 ± 5.2	62.1 ± 5.5	NS

NS indicates not significant.

TABLE 2 Polysomnographic Findings in 87 Children With OSAS and 21 Matched Control Subjects

	OSAS ($N = 87$)	Control Subjects ($N = 21$)	P
TST, min	474.8 ± 43.9	469.8 ± 44.9	NS
Sleep efficiency, %	85.3 ± 11.2	90.2 ± 10.4	NS
Sleep-onset latency, min	26.8 ± 22.7	30.1 ± 27.2	NS
REM-onset latency, min	141.6 ± 61.0	152.1 ± 64.6	NS
Awakenings, *n*	16.1 ± 6.5	12.6 ± 5.6	<.04
WASO, % TST	4.1 ± 5.4	4.6 ± 4.4	NS
Stage 1, % TST	6.0 ± 3.3	4.8 ± 3.9	NS
Stage 2, % TST	48.2 ± 7.5	40.5 ± 7.3	<.05
Stage 3, % TST	7.4 ± 7.1	11.7 ± 7.7	<.05
Stage 4, % TST	17.9 ± 7.5	23.2 ± 8.8	<.05
Stage REM, % TST	15.1 ± 5.7	17.7 ± 7.7	NS
SAI, per h TST	7.9 ± 6.5	13.2 ± 7.8	<.05
RAI, per h TST	5.9 ± 2.7	0.1 ± 0.4	<.01
PLMI, per h TST	6.2 ± 9.1	4.9 ± 4.4	NS
PLMAI, per h TST	0.2 ± 0.9	0.1 ± 0.7	NS
OAHI, per h TST	14.8 ± 6.8	0.3 ± 0.2	<.0001
Oxygen saturation nadir, %	85.7 ± 6.1	94.1 ± 1.9	<.0001
Mean $ETCO_2$, mm Hg	45.7 ± 5.2	41.3 ± 6.9	NS
Peak $ETCO_2$, mm Hg	56.3 ± 6.8	47.8 ± 4.5	<.01

TST indicates total sleep time; NS, not significant; REM, rapid eye movement; WASO, wake after sleep onset; SAI, spontaneous arousal index; RAI, respiratory arousal index; PLMI, periodic leg movement index; PLMAI, periodic leg movement arousal index; $ETCO_2$, end-tidal carbon dioxide. Data are means ± SD.

TABLE 3 Polysomnographic Findings in 87 Children with OSAS and 21 Matched Control Subjects According to Presence or Absence of Neurocognitive Deficits and Endothelial Dysfunction

	OSAS ($N = 87$)				Control Subjects ($N = 21$)	P
	NC^+, ED^- ($n = 8$)	NC^+, ED^+ ($n = 40$)	NC^-, ED^- ($n = 29$)	NC^-, ED^+ ($n = 10$)		
RAI, per h TST	6.2 ± 4.1	5.9 ± 3.1	6.1 ± 3.2	5.7 ± 3.5	0.1 ± 0.4	<.01
OAHI, per h TST	13.9 ± 7.8	15.7 ± 6.9	15.1 ± 7.6	14.3 ± 8.3	0.3 ± 0.2	<.0001
Oxygen saturation nadir, %	83.4 ± 8.1	86.1 ± 6.0	84.8 ± 8.1	85.4 ± 8.1	94.1 ± 1.9	<.0001

RAI indicates respiratory arousal index.

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and 3 children had reduced scores in only 2 clusters/domains. The most frequently affected functional categories in younger children were verbal, working memory, and object recall, and a similar pattern emerged among the older children with verbal and working memory also being most frequently affected.

Fifty of 87 children with OSAS had T_{max} values of ≥45 seconds (ED^+) (57.5%). Among 48 NC^+ children, 40 were also ED^+ (83.3%). Conversely, among 50 children who were defined as being ED^+, 40 were NC^+ (80.0%), thereby indicating a high degree of overlap between ED^+ and NC^+. Of 39 children who were NC^-, only 10 (25.6%) were ED^+, whereas among 37 children who were ED^-, only 8 were NC^+ (21.6%). Thus, there was a subset of 29 children who, despite having OSAS of similar severity, showed no evidence of end-organ morbidity (ie, NC^- and ED^-), thereby accounting for approximately one-third of the cohort. The various permutations on endothelial and cognitive functional status are shown in Table 4. In total, the degree of concordance between endothelial function and the presence of cognitive deficits was 79.3% and was significantly higher than would be predicted from random agreement between the 2 phenotypes (χ^2: 29.3; $P < .00001$). In other words, if endothelial measurements were conducted in children with OSAS, the findings on this test would have a sensitivity of 83.3%, a specificity of 74.4%, a positive predictive value of 80%, and a negative predictive value of 78.4% in correctly detecting the corresponding neurocognitive functional status.

TABLE 4 Distribution of Cognitive and Endothelial Functional Status Among 87 Children With OSAS

		NC		
		+	−	
ED	+	40	10	50
	−	8	29	37
	Total	48	39	87

Cohen κ coefficient: 0.58 (SE 0.088 [95% CI: 0.407–0.752]).

DISCUSSION

Our results show that in otherwise healthy children, polysomnographic evidence of OSAS was associated with the presence of endothelial dysfunction and neurocognitive deficits in a significant proportion of these children. However, despite disease of similar severity, not all children are affected, and in fact only slightly more than half of them exhibited 1 of these 2 dysfunctional phenotypes. It should be noted that the significantly higher degree of coexistence between the 2 morbidities, as might be predicted from random association alone, would suggest that endothelial and cognitive dysfunction may share similar pathophysiological mechanisms or, alternatively, that the presence of endothelial dysfunction may lead to neurocognitive deficits. Independent from such considerations, our findings suggest that implementation of an endothelial testing protocol that requires 30 minutes at most may provide a reasonable prediction on the presence or absence of underlying OSAS-induced neurocognitive deficits, which at the moment can only be detected through extensive neuropsychological testing that is both labor intensive and time consuming (~3 hours) and, as such, cannot be routinely implemented in the clinical evaluation process of children at risk for sleep-disordered breathing.

Our results corroborate previous findings from our laboratory showing that OSAS is indeed associated with alterations in the microvasculature and that substantial variability is present regarding the status of the microvascular phenotype.[8,10] The variance in vascular function among children with OSAS seems to be, at least in part, related to systemic inflammatory processes elicited by the disease, and, as such, a strong association between T_{max} and high-sensitivity C-reactive protein (hsCRP) plasma levels was detected.[10] These results are reminiscent of the strong association between hsCRP and neurocognitive dysfunction,[9] whereby the presence of deficits was associated with markedly higher hsCRP levels in children with OSAS than in children with OSAS of similar severity who did not exhibit altered cognitive function. Taken together, it would seem that on the basis of the high degree of concordance identified herein between vascular and cognitive phenotypes, it would be possible that these 3 components, namely inflammation, microvascular damage, and neurocognitive deficits, could all be accounted for in a single unifying model (Fig 1). In this hypothetical framework, end products and mediators resulting form activation of increased inflammatory responses, and of both systemic and oxidative stress pathways induced by OSAS,[37–39] would then either directly or via their adverse effects on endothelium integrity, promote its deleterious effects on cognition. In this context, the modulatory influences of intrinsic susceptibility (ie, genomic variance within genes that play mechanistic roles in end-organ injury in OSAS) and extrinsic susceptibility dictated by lifestyle differences and other factors (eg, obesity, literacy, dietary habits, physical activity, pollution, etc) would add further layers of complexity to the

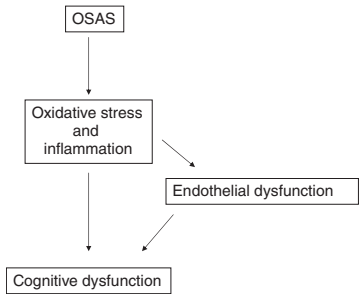

FIGURE 1
Putative pathways that lead to neuropsychological and endothelial dysfunction in children with OSAS.

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strength of these relationships when attempting to predict a specific morbidity-associated phenotype.[34,40,41]

We should also be aware of the possibility that task-evoked changes in brain activity may differ in children with OSAS even before measurable deficits become detectable.[42,43] Indeed, expanded regions of brain activation emerge in children with even mild sleep-disordered breathing during attention or memory tasks, which reflects the need to recruit larger neural resources such as to maintain performance.[42,43] These observations are remarkably similar those from to studies of adult patients with OSAS who showed 1 of 2 main brain activity patterns, namely hyperactivation and wider recruitment of brain tissue during task performance to achieve similar performances to normal subjects, or reduced brain activity while on task along with reduced task performance.[44–46] Because functional MRI strategies rely on microvascular responses to neural activation, it becomes apparent that the presence of alterations in brain microvascular responses could reflect the underlying cognitive pathology or, alternatively, lead to recruitment of larger brain regions as a compensatory mechanism aiming to maintain neural performance. Future studies aiming to assess correlates of regional brain dysfunction by using vascular recruitment patterns and bioenergetics in children will be critical for improved understanding of the nature of the relationships between endothelial and neural morbidities in pediatric OSAS. In further support of this potential association, results of work by Hogan et al[24,47] have shown that raised cerebral blood flow velocities on transcranial Doppler, which are compatible with vascular narrowing, were associated with neuropsychological deficits in children with OSAS and that treatment of OSAS was accompanied by reduced flow velocities in these children, concomitant with improvements in cognitive function.

CONCLUSIONS

We have shown that children with OSAS are not only at high risk for developing both neuropsychological deficits and endothelial microvascular dysfunction but that when any of these 2 morbidities is detectable, it is highly likely that the other morbidity will also be present. As such, it is possible that the simpler measurement of microvascular postischemic reperfusion responses may not only serve as an accurate correlate to the presence of neurocognitive deficits but may also provide valuable insights into the vascular pathophysiological mechanisms that are potentially involved in the memory and learning problems and reduced academic performances frequently observed in children with OSAS.

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