Sleep Apnea in Children May Affect Brain Development

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Abstract
Childhood obstructive sleep apnea (OSA) is associated with neuropsychological deficits of memory, learning, and executive function. There is no evidence of neuronal brain injury in children with OSA. We hypothesized that childhood OSA is associated with neuropsychological performance dysfunction, and with neuronal metabolite alterations in the brain, indicative of neuronal injury in areas corresponding to neuropsychological function.

Methods and Findings: We conducted a cross-sectional study of 11 children (19 with OSA and 12 healthy controls, aged 6–16 y) group-matched by age, ethnicity, gender, and socioeconomic status. Participants underwent polysomnography and neuropsychological assessments. Proton magnetic resonance spectroscopic imaging was performed on a subset of children with OSA and on matched controls.

Conclusions: Childhood OSA is associated with deficits of IQ and executive function and also with possible neuronal injury in the hippocampus and frontal cortex. We speculate that untreated childhood OSA could permanently alter a developing child’s cognitive potential.

Keywords: Children, Sleep, Apnea.

Introduction
Individuals require a wide range of cognitive skills in order to function in society, so if the acquisition of these skills is perturbed during development, there may be a long-term effect on cognitive and psychological function. Obstructive sleep apnea (OSA) is defined as obstructed breathing efforts during sleep [1] with resultant gas exchange abnormalities and sleep fragmentation [2]. It has been linked to increased cardiovascular mortality, increased automobile accidents, and cognitive function impairments in adults.

Untreated childhood OSA enormously increases health resource utilization [1], and has been associated with growth problems, cardiovascular consequences, and neuropsychological dysfunctions such as learning and memory problems [1,5], decreased attention, and poor school performance [6]. From a cognitive standpoint, adult OSA has been linked to deficits of executive function (flexible adaptation to novel situations with an organized, goal-directed approach) [7]. In children, gains of executive function skills occur during developmental periods.
corresponding to the neuronal myelination and maturation of the prefrontal cortex \cite{8,9}. Executive function is considered critical for school-age children to develop complex problem solving \cite{10} and perform other volitional tasks in response to new situations with demands on working memory \cite{11}.

If untreated OSA causes neuropsychological or executive dysfunction in developing children, and if these skills are permanently impaired before maturation of the prefrontal cortex, it could severely alter a child’s cognitive potential, ultimately impacting both the child’s health and his or her functioning level in society. Symptomatic childhood sleep-disordered breathing (SDB), which includes simple snoring and labored breathing, and partial obstructions that might not meet the adult criteria for OSA \cite{12,11}, has long been associated with behavioral dysfunctions including aggression, impulsivity, hyperactivity, and decreased attention based on subjective data provided by parents or teachers \cite{11}. These behaviors mimic those associated with attention deficit hyperactivity disorder (ADHD), a disorder that presents with alterations in executive function.

Objective measurements of specific neuropsychological performance deficits related to sleep problems in children have been limited; however, recent studies have begun to identify significant differences in cognitive function between children with SDB and healthy controls. For example, Gottlieb and colleagues found significantly lower performance on measures of memory, executive function, and general intelligence in 5-year-old children with symptoms of SDB than in asymptomatic children.

O’Brien et al. demonstrated decreased general intelligence, language, and visual–spatial skills in 87 habitually snoring children. O’Brien’s group demonstrated even more significant neuropsychological deficits in children with more severe apnea. The mechanisms causing these neuropsychological deficits have not been fully delineated.

While sleepiness and sleep fragmentation might be readily reversible with treatment, neuronal injury resulting from long-term oxygen saturation abnormalities might represent a more pervasive health risk. There is evidence of altered brain function associated with blood gas abnormalities. Patients with sleep apnea have reduced cerebral blood flow and altered cerebrovascular responses to hypercapnia.

Hypoxia causes neuronal injury in vulnerable parts of the brain, especially the cerebellum and hippocampus, where the formation of lactate and free radicals is thought to lead to cellular injury. The hippocampus is critically involved in learning and memory. Sleep deprivation in rats alters the synaptic plasticity of the hippocampus and impairs hippocampus-mediated contextual learning \cite{11} and spatial learning \cite{12}. Intermittent hypoxia also causes spatial learning deficits and increased motor activity in juvenile rats \cite{11}. The mechanism proposed for the spatial learning deficits observed in rats involved apoptosis of subpopulations of hippocampal neurons \cite{11}.

Functioning in a complex integrated network, these brain areas are important for executive function, motor regulation of breathing \cite{15,17}, and memory function, respectively. Altered central nervous system metabolites of neuronal white and gray matter in OSA patients have been demonstrated using proton magnetic resonance spectroscopy imaging (MRSI).

The authors suggested that hypoxemia resulting from sleep apnea might have caused cerebral neuronal injury. There is recent evidence that suggests a link between hippocampal metabolite alterations and deficits of cognitive function in adults with OSA \cite{18}. These studies provide evidence that SDB is associated with observable reductions in cognitive function in both adults and children. In adults with sleep apnea, there are measurable morphological abnormalities in the brain, but adults with OSA often suffer from co-morbid health problems such as diabetes \cite{19}, hypertension, and cardiovascular disease \cite{10}, which could confound the association. There have
been no studies demonstrating such neuronal injury in children with sleep apnea. These studies are crucial, since childhood OSA impacts a rapidly developing brain, and thus the long-term consequences of neuronal injury may be far greater than those seen in adults. The purpose of this study was to examine the neuropsychological deficits associated with moderate to severe childhood sleep apnea, and to determine whether these deficits are associated with neuronal changes in vulnerable target areas of the brain. We hypothesized that SDB would be associated with neuropsychological dysfunction in the areas of executive function, learning, and memory; and that central nervous system metabolite alterations would be observed in brain regions associated with these functions, i.e., the hippocampus and frontal cortex.

Methods Design
This was a cross-sectional study of participants aged 6–16 y with moderate to severe OSA compared to non-snoring healthy children group-matched by age, ethnicity, gender, and socioeconomic status (SES). OSA patients were identified by polysomnographic sleep studies. All tests were performed while the OSA patients were awaiting surgical management. OSA participants met enrollment criteria if they had moderate to severe OSA by our definition, i.e., an apnea hypopnea index (AHI) ≥ 8 (see “Polysomnography” for definition of apnea). All participants underwent polysomnography and a battery of neuropsychological tests. Proton MRSI of the brain was performed on a subset of OSA participants and control children (those who met inclusion criteria and could tolerate imaging time without sedation).

Polysomnography
Polysomnography was performed on all participants. During the sleep study, surface electrodes and monitoring devices measured signals from central EEG, right and left electro-oculogram, surface EMG, ECG, chest and abdominal wall motion, and end-tidal PCO2. Pulse oximetry with an 8-s averaging time was used to record the time in minutes of any oxygen saturation less than 95% to detect brief oxygen saturation changes. Airflow was measured by oro-nasal thermistor in all children. The arousal index (AI) was the number of arousals and awakenings measured by a shift of EEG signal to the alpha or beta range for greater than 1 s (as previously defined by the American Sleep Disorders Association [11]) divided by the total sleep time in hours. An apnea was defined as an absence of airflow for two or more breath cycles. Hypopnea was a visible decrease in airflow by nasal pressure signal (or by thermistor when pressure signal was unavailable) and either an EEG arousal or a drop in oxygen saturation of 1% or greater. A mixed apnea was an obstructive apnea in combination with a central (absent effort) apnea. The AHI comprised the obstructive, mixed, and hypopnea events divided by total sleep time in hours; central apneas were not included in the AHI. SpO2 was the time (in minutes) with oxygen saturations less than 95% (in order to detect mild intermittent desaturations), and SaO2N was the severity of oxygen desaturation. Hypercapnia time was the time in minutes that the end-tidal CO2 monitor detected a CO2 level greater than 50 mm Hg. There is no established definition of mild, moderate, or severe sleep apnea in children. The AHI in normal non-snoring children has been determined to be less than 1.0 with little hypercapnia (time with CO2 > 50 mm Hg) [15–17]. For this protocol, mild OSA was defined as AHI 1–5, moderate OSA as AHI 5–10, and severe OSA as AHI greater than 10.

Neuropsychological Evaluation
The protocol was selected to include areas considered to be vulnerable in children with OSA executive function and memory as abnormalities of these brain systems may negatively impact
psychosocial function and have been shown to be affected in adults with sleep apnea [18]. In addition, domains hypothesized to be less affected in children with OSA (visual–spatial perception and motor speed) were also included for comparison. Global intelligence was measured using the full scale IQ scores from WISC-III [19] (n = 15) or WISC-IV [50] (n = 16). In addition to IQ, the assessment protocol included measures of executive function (i.e., response preparation, inhibition, and working memory), attention, verbal and visual memory, neuromotor function, cerebellar function (i.e., perceptual and motor timing), and visual–spatial perception.

Magnetic Resonance Spectroscopy
The children were asked to lie still and they were supported with foam pillows to reduce movement. They were able to listen to music or watch movies with specially designed headphones and mirrors inside the actual scanner. No sedation was used in any study. Two different approaches were used for proton MRSI of the brain: multi-slice MRSI for coverage of supratentorial brain regions, and single voxel methods for the hippocampus and cerebellum. Outer volume saturation pulses were used for suppression of lipid and water signals originating from the skull and scalp, and a chemical-shift selective saturation pulse was used for water suppression. The three interleaved slices were recorded with a repetition time (TR) of 1,700 ms and an echo time (TE) of 280 ms (field of view, 211.18 cm; matrix size, 121.21; signal average, 1), giving a total of 15 min for data acquisition with circular k-space sampling. The nominal voxel size was 0.8 cm1.

Spectra were evaluated from the following brain regions: putamen, thalamus (predominantly pulvinar region), dorsal parietal cortex, parietal white matter, frontal white matter, medial premotor cortex, and frontal cortex. In order to minimize partial volume effects, only voxels that appeared completely encompassed by the boundaries of the anatomic regions of interest were included. Single voxel methods utilized a PRESS sequence with a short echo time (TR/TE 1,500/15 ms) placed in the body of the left hippocampus and the mesial left cerebellum. Voxel size was 2 1.5 1.5 cm.

For both spectroscopic methods, metabolites were expressed as ratios in comparison to levels of other metabolites, specifically, the NAA/Cr, Cho/Cr, and NAA/Cho ratios. This measurement method effectively detects metabolite changes that move in opposite directions such as the decreased NAA to increased Cho seen in ischemic brain injury [11] and in the injury reported in adult OSA [12].

Figure 1 shows an example of single voxel imaging of the hippocampus in a normal male child, with blue outer volume suppression bands used to improve the accuracy of the hippocampal signal by suppressing surrounding lipid signal.

Statistical Analysis
For neuropsychological testing, the primary predictor variable was group status (control versus OSA measured by the AHI). Secondary predictor variables were other polysomnographic parameters (AI, SaO2T, SaO2N, and CO2 . 50) and body mass index (BMI).

Primary outcomes were mean standard neuropsychological test scores. Levene’s test was used to ensure homogeneity of variance between groups. The Mann–Whitney U statistic for nonparametric analysis was used for all variables in which the Levene’s test was significant. Analysis of variance was used to determine differences in the outcomes assessed as a function of group status.

T-tests were performed assuming equal variance, and the two-tailed significance is reported. Group differences were also compared by effect size, measured by eta squared (g2), a measure of contrast between groups independent of sample size [11]. According to Cohen [11], values of 0.01, 0.06, and 0.11 are used to indicate small, medium, and large associations between variables, respectively.
Brain Magnetic Resonance Spectroscopy

For brain imaging studies, sleep apnea patients were compared to group matched normal children where the outcome variable was mean cerebral metabolite ratios determined by measurement of mean cerebral metabolite ratios of target areas of the brain on MRSI. T-tests were performed assuming equal variance, and the two-tailed significance is reported.

Sample size and statistical power

Previous reports of cognitive dysfunction in severe childhood OSA demonstrated significant effects when comparing healthy controls to as few as five OSA patients and nine snoring patients without OSA [15].

Power analysis was conducted to determine the appropriate sample size needed in each group in order to detect group differences between the sleep apnea patients and normal participants on mean neuropsychological test scores. Using the criteria of a power of 0.80, a type I error rate of 0.05, a mean test–retest reliability of selected instruments of 0.80, and estimates of moderate to large effect size (i.e., $g^2 > 0.07$), based on our preliminary data, it was determined that a sample size of 11 participants in each group would be adequate to detect group differences in neuropsychological test score results between sleep apnea patients and normal participants.

Results

Thirty-four children were initially enrolled after screening for exclusionary criteria, but two did not return for testing, and one control was excluded after a finding of snoring and prolonged end-tidal CO2 levels greater than 50 mm Hg (158 min) despite a normal AHI and oxygen saturation. There were no significant group differences in SES, measured by median household income, or maternal education between groups. Additionally, the Hollingshead index, an index of SES based on parental education and job type, was not different between the groups. There were no significant differences between the two groups in age, gender ratio, handedness, or racial distribution. Of the 19 OSA patients, five had a history of hyperactivity or diagnosis of ADHD, and analyses are presented separately for OSA and OSA excluding ADHD ("OSA/not ADHD") groups.

No normal children with ADHD answered the recruitment advertisements; therefore the control group does not include any individuals with ADHD. After excluding the children with ADHD (n = 5) from the OSA group, there were still no differences between groups in age, SES, gender ratio, handedness, or racial distribution. The individuals in the OSA groups had significantly higher BMIs than did controls.
Polysomnography Results
The mean and median AHI in the OSA group fell into the severe range by our criteria, although there was a large standard deviation in time with oxygen saturation less than 95% (SaO2T; 0–271 min), SaO2N (18%– 96%), and time with CO2 levels greater than 50 mm Hg (0– 171 min).

Neuropsychological Function
Children with OSA had significantly lower scores than matched controls on full scale IQ. The OSA group also had significantly lower performance on measures of executive function, including verbal working memory (sentence span) and word fluency.

In contrast, the executive functions reported to be impaired in adult sleep apnea [5] (i.e., problem solving and planning, inhibitory control, sustained attention, and vigilance) were not affected in children with severe sleep apnea. Motor speed, perceptual timing, and motor timing (dependent on cerebellar functioning) were also not affected in our full sample of sleep apnea patients; however, when the children with ADHD were excluded from the OSA group, there was a significant deficit noted on the perceptual timing task (g2 ¼ 0.29, p , 0.05). The group differences in full scale IQ, verbal working memory, and word fluency remained significant after the children with ADHD were excluded. BMI was noted to correlate with decreased IQ (r ¼ 0.15, p ¼ 0.019); however, when BMI was controlled for the AHI (after confirming BMI overlap between the groups), this effect was no longer significant (r ¼ 0.12, p ¼ 0.106).

Conclusion
Childhood OSA has a prevalence of about 2% in the general population [11, 15], and severe sleep apnea cases represent 17% of the otherwise normal school-aged children referred to our sleep center. OSA in adults has been linked to increased cardiovascular morbidity and mortality, increased automobile accidents, and cognitive function impairments.

We found that childhood OSA is associated with deficits of IQ and executive function and also with abnormal neuronal metabolites in the hippocampus and frontal cortex, indicating possible neuronal injury.

We speculate that untreated childhood OSA could permanently alter the trajectory of a developing child’s ultimate cognitive potential, resulting in a lifetime of health and economic impacts. It remains to be determined if early identification and treatment can reverse the neuronal and performance deficits identified in this study of childhood OSA. Future studies will need to address the effect of treatment, and explore gender- and age-related differences in vulnerability to help target early diagnosis and treatment most effectively.

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