Review Article

Obstructive Sleep-Disordered Breathing in Children: Impact on the Developing Brain

Lisa M Walter, Rosemary SC Horne

The Ritchie Centre, Department of Paediatrics, Monash University and Hudson Institute of Medical Research, Melbourne, Victoria, Australia

Abstract

Obstructive sleep-disordered breathing (SDB) affects up to 11% of children and forms a continuum of severity ranging from primary snoring to obstructive sleep apnea. Children with SDB exhibit significant neurocognitive and cardiovascular dysfunction, which is associated with repetitive hypoxia and sleep fragmentation that characterize the condition. We reviewed the recent literature pertaining to the effect of SDB on the brain in children. These include studies that utilized near-infrared spectroscopy to determine cerebral oxygenation and structural and functional magnetic resonance imaging (MRI) of the brain. Studies have identified that the effect of SDB on cerebral oxygenation in children is minimal and not clinically significant. There are conflicting reports on the association between the measures of cerebral oxygenation and peripheral arterial oxygen saturation (SpO_2), and further research needs to be conducted to elucidate the relationship between peripheral SpO_2, cerebral oxygenation, and SDB in children. MRI studies have reported significant structural and functional changes to the brains of children with SDB, in brain regions associated with neurocognition, behavior, and autonomic function. These include reduced white and gray matter and structural changes to a multitude of brain areas including, but not limited to, the hippocampus, cortex, amygdala, insula, thalamus, cerebellum, and basal ganglia. These studies utilize a variety of MRI techniques to address different research questions, but contribute to the gradually developing picture of the adverse effects of SDB on the brain in children.

Keywords: Cerebral oxygenation, MRI, obstructive sleep apnea, pediatric

Introduction

Sleep-disordered breathing (SDB) is an umbrella term encompassing a number of respiratory disorders including primary snoring (PS), upper airway resistance syndrome, obstructive sleep apnea (OSA), and central sleep apnea. This review will focus on obstructive SDB, which affects up to 11% of children born at term;[1] however, population cohort studies show that SDB is three–six times more common in children born preterm.[1,2] SDB involves either partial or complete cessation of breathing during sleep and has adverse cardiovascular and neurocognitive sequelae. The brain is believed to be the conduit between the respiratory pathophysiology of SDB and the cardiovascular and neurocognitive outcomes. To understand the mechanisms that underpin this association, noninvasive tools have been utilized, with the most common being magnetic resonance imaging (MRI) and near-infrared spectroscopy (NIRS). MRI provides information on the structure, function, neuronal circuitry, connectivity, blood flow, and metabolic composition of the brain, and NIRS provides the measures of cerebral oxygenation and cerebral tissue extraction. This review will focus on the findings of studies which have examined NIRS and MRI in children with SDB.

Sleep-Disordered Breathing

SDB is characterized by habitual snoring. At the mild end of the SDB spectrum, PS is not associated with gas exchange abnormalities or sleep fragmentation. OSA is characterized by repeated hypoxia, hypercarbia, and sleep fragmentation. The most common cause of OSA is upper airway obstruction caused by abnormal anatomy (e.g., adenotonsillar hypertrophy in children) and/or inadequate control of the muscles that maintain patency of the upper airway. In OSA, respiratory effort is maintained, but airflow is either partially or completely obstructed.

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Address for correspondence: Prof. Rosemary SC Horne, The Ritchie Centre, Department of Paediatrics, Level 5, Monash Children's Hospital, 246 Clayton Road, Victoria 3168, Australia.
E-mail: rosemary.horne@monash.edu

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Adverse outcomes of sleep-disordered breathing

In both adults and children, the adverse cardiovascular outcomes of SDB are mediated by increased sympathetic activity and impaired cardiac autonomic control.[3] The cardiovascular effects of the repetitive hypoxia, reoxygenation, hypercarbia, apnea, and arousals in children with obstructive SDB include elevated blood pressure[4-6] and blood pressure variability,[7,8] together with reduced baroreflex sensitivity[7-9] and heart rate variability.[10,11] Physiological changes as a result of this autonomic dysfunction are apparent not only in the cardiovascular system, but also in the brain.[3] SDB has significant adverse neurocognitive and behavioral sequelae in children,[12-18] which are also believed to be due to the intermittent nocturnal hypoxia and sleep fragmentation that occur during SDB.

Near-Infrared Spectroscopy

Biological tissues are transparent to the near-infrared range (700–1300 nm), making it possible to measure cerebral tissue oxygen saturation.[19] Both tissue oxygen saturation and tissue hemoglobin content can be evaluated by measuring the difference in intensity between the transmitted and the received light wavelength. Hemoglobin and cytochrome are the main chromophores (light-absorbing molecules) within biological tissues. NIRS measures tissue-derived chromophores from a number of different compartments including the arteries, veins, and capillaries, with the cerebral cortex made up of approximately 70% venous blood and 30% arterial blood.[19] NIRS devices are manufactured to be specifically sensitive to wavelengths between 700 and 850 nm as these wavelengths encompass the absorption spectra of deoxyhemoglobin (DOxHb), which peaks at 650–1000 nm; oxyhemoglobin (OxHb), which peaks from 700 to 1150 nm; and cytochrome oxidase which has a peak at 820–840 nm, while also having minimal overlap with water, which peaks between 950 and 1050 nm and above 1300 nm.

Determining cerebral oxygenation noninvasively using NIRS is advantageous over measuring peripheral hypoxia as NIRS has a faster response time[20,21] and superior detection of desaturation[22] compared with oximetry. Studies using NIRS have found reduced cerebral oxygenation in adults with SDB (or OSA) compared with nonsnoring controls[23,24] and in adults with severe OSA compared with those of mild and moderate OSA.[25] A slightly different technology which is based on the similar principles (near-infrared diffuse correlation spectroscopy) reported larger variations in cerebral oxygenation during periods of apnea compared with periods without apnea, which were significantly correlated with OSA severity.[26]

The three studies that have investigated the effect of SDB on cerebral oxygenation in children have reported conflicting results.[27-29] Khadra *et al*. studied 14 nonsnoring controls, 32 with PS, and 46 with OSA (7–12 years of age), during overnight polysomnography (PSG) with continuous monitoring of cerebral oxygenation and blood pressure. An index of cerebral oxygenation was obtained during sleep by referencing the sleep values to the wake values for each child.[28] Increasing cerebral oxygenation was predicted by increasing mean arterial blood pressure, age, and rapid eye movement (REM) sleep. Decreasing cerebral oxygenation was predicted by SDB, male sex, arousal index, and non-REM (NREM) sleep. This study identified that there was a complex relationship between SDB and cerebral oxygenation, as SDB had effects that both augment and diminish cerebral oxygenation. The authors identified increased cerebral oxygenation in children with PS compared to controls; however, the differences were very small averaging 2%. A small study of five children (1.5–15.8 years) with severe OSA used NIRS to assess the change from baseline in the tissue oxygenation index (TOI), OxHb, and DOxHb that occurred in association with arterial oxygen desaturations (SpO_2) measured by peripheral oximetry.[29] A fall in SpO_2 was correlated with the change in TOI, O_2Hb, and HHb, indicating a strong relationship between arterial and cerebral oxygenation in the children with severe OSA. In the most recent study, Tamanyan *et al*. categorized children with SDB and nonsnoring controls into groups of 3–6 years (n = 87) and 7–12 years (n = 72) of age and then further divided them into control, PS, mild OSA, and moderate/severe OSA.[27] All of the children underwent overnight PSG with continuous NIRS recording of cerebral oxygenation. Cognitive performance was also assessed within 2 weeks of the PSG study in a subset of the cohort (n = 102). This study also assessed TOI, which is a measure of the mixed oxygen saturation in all cerebral vascular compartments, and the fractional tissue oxygen extraction (FTOE), which accounts for arterial SpO_2, and therefore provides a ratio of cerebral oxygen consumption to delivery.[30] The authors reported that there were no differences between the SDB severity groups for either cerebral oxygenation (TOI) or oxygen extraction (FTOE) in the 3 to 6-year-old children. In the 7 to 12-year-old children, the control children had significantly lower cerebral oxygenation during wake, N1, and REM sleep and higher oxygen extraction during N1 sleep compared with the children with PS. There were no differences between the children with PS and those with OSA for either measurement. Furthermore, cerebral oxygenation was not associated with cognitive performance at either age. These data suggest that children can compensate for falls in peripheral oxygen saturation, thereby protecting cerebral oxygenation.

Magnetic Resonance Imaging

MRI scanning utilizes strong magnetic fields, magnetic field gradients, and radio waves to generate images of internal body structures, including brain structure and function. MRI provides superior images of parts of the body that are not easily seen with X-ray, computed tomography scans, or ultrasound. Furthermore, MRI does not involve the use of ionizing radiation. To its detriment are the high costs of MRI imaging, they typically take longer time, and are louder than the other imaging modalities; subjects are required to be inside a narrow

tube that can induce feelings of claustrophobia and subjects with certain medical implants or other nonremovable metal inside the body may be unable to undergo an MRI scan. There have been a substantial number of studies in adults with OSA using MRI scanning to detect anatomical and physiological alterations in the brain; however, much less research has been conducted in children using MRI.

Using structural MRI procedures that identified tissue loss or water content and diffusion changes indicative of injury, OSA in adults has been associated with injury to areas of the brain that have multiple functions and involve both gray and white matter.[31] Areas impacted include the insular, cingulate, ventral medial prefrontal cortices, cerebella deep nuclei and cortex, anterior hypothalamus, raphé, ventrolateral medulla, and basal ganglia. Furthermore, all SDB conditions are associated with significant axonal injury, notably in limbic structures related to affective processes; pontine projections to the cerebellum, which are essential motor and blood pressure regulatory fibers; and the cingulum bundle within the anterior cingulate cortex, which is important for respiratory patterning.[31] Injury to these areas has serious consequences on affective, autonomic, and cognitive functions and on mood regulation.[31]

Utilizing task or resting-state functional MRI (fMRI) and voxel-based morphometry, studies have reported that structural atrophy and functional disturbances in the right basolateral amygdala/hippocampus and the right central insula are associated with OSA.[32] Functional characterization of these regions is indicative of associations with dysfunctional emotional, sensory, and limbic processes. Resting-state fMRI studies have shown that dysfunctional connectivity of the posterior default-mode network underlies OSA's cognitive and depressive symptoms.[33]

A recent meta-analysis found that severe OSA is associated with more severe white-matter changes that are a risk factor for oxidative ischemic injury in adults.[34] Further cerebral changes in adults with OSA identified using MRI procedures included reduced cortical thickness (associated with autonomic dysfunction and impaired upper airway sensorimotor function);[35] gray-matter hypertrophy (hypoxemia, respiratory disturbances, and sleep fragmentation);[36] changes in brain metabolites (hypoxia, anxiety, and depression);[37,38] cerebral small-vessel disease (increased risk of cerebral infarction and hemorrhage);[39] reduced cerebral blood flow (increased OSA severity);[40,41] increased cerebrovascular reactivity[42] and decreased cerebrovascular reactivity[43] (increased stroke risk); and altered midbrain chemical concentrations (neuronal loss and inflammation).[44]

Although fewer than the studies in adults, pediatric research has ventured into using MRI processes to investigate whether the structural and functional changes found in adults with OSA are replicated in children. Nineteen children with moderate/severe OSA (Apnea–Hypopnea Index [AHI] >5 events/h) and 12 healthy controls, 6–16 years of age, underwent magnetic spectroscopic imaging, overnight PSG, and neuropsychological assessment to determine whether childhood OSA is associated with neuronal metabolite alterations in areas of the brain associated with neuropsychological function.[45] There was a decrease in the mean neuronal metabolite ratio of N-acetyl aspartate/choline in the left hippocampus and right frontal cortex in the children with OSA compared with the controls, indicating possible neuronal injury. This was in conjunction with significant deficits in intelligent quotient (IQ) and executive function. Neural support for executive functions involves a distributed neural network with cortical and subcortical components that include the frontal cortex,[46] and the authors speculated that untreated OSA during childhood could permanently alter cognitive potential in developing children.[45]

Executive functioning and empathy in ten children (7–11 years) with OSA and seven aged-matched controls were assessed in specific brain regions using fMRI.[47] The children underwent an overnight PSG, and OSA was defined as an AHI ≥2 events/h. During the fMRI, the children were given a color-word Stroop task, which consisted of three words, namely red, green, and blue, with matching color font. During the course of the test, the colors of the letters were changed randomly 96 times (e.g., the word red may have been presented with the letters in blue color), and the children were required to indicate the color of the letters. The children also performed an empathy task where they were shown sixty dynamic visual scenarios, which either depicted interpersonal harm or neutral actions (no harm) between two individuals. The regions of interest investigated by the fMRI during the Stroop test were the anterior cingulate cortex, inferior frontal junction, and the inferior parietal lobule. During the empathy test, the left and right regions of the amygdala, insula, anterior midcingulate cortex, ventromedial prefrontal cortex, and inferior frontal gyrus were scanned. Findings from this study suggested that, in order to perform at the same level as children without OSA, children with OSA needed greater neural recruitment of regions associated with cognitive control, conflict monitoring, and attentional allocation. Furthermore, OSA severity predicted less sensitivity to harm in the left amygdala. The authors concluded that OSA influences neural recruitment across a range of brain activities in children.

Children with moderate/severe OSA (n = 23; 8–13 years; obstructive AHI [OAHI] >5 events/h) and age-matched nonsnoring controls (n = 15) underwent overnight PSG, neurocognitive assessment, and MRI scanning with voxel-based morphometry, which is a technique for characterizing regional cerebral volume and tissue concentration differences.[48] Compared to controls, the children with OSA had gray-matter volume deficits in prefrontal and temporal regions, which was explained as being the result of the repeated apneas and hypoxic damage that characterize OSA. In addition, the ratio of gray-matter volume to total brain volume significantly correlated with visual fine motor coordination. The prefrontal cortex is involved in attention and executive functions,[49] which were reduced in the children in this study. Furthermore, the

lateral occipital gyrus is closely related to the visual cortex, and this could explain the correlation between reduced gray-matter and visual fine motor coordination.[48] The clinical relevance of this study relates to the need to identify and treat children with OSA early and mitigate the adverse effect that OSA has on the developing brain's neurocognitive potential in these children.

Similar findings were reported recently in a study of 16 children with OSA (8.1 ± 2.2 years [mean ± standard deviation (SD)], OAHI >2 events/h, plus a SpO_2 nadir <92%, and/or a Respiratory Arousal Index >2/h) and 9 control children who also underwent overnight PSG, neurocognitive assessment, and MRI with voxel-based morphometry.[50] In addition to the control children, MRI data were also compared against 191 scans from the NIH-Pediatric MRI database. Reductions in gray-matter volume were identified throughout the areas of the superior frontal and prefrontal and superior and lateral parietal cortices. This study also identified other affected sites such as the brain stem, ventral medial prefrontal cortex, and left superior temporal lobe. In contrast to Chan *et al*.,[48] there were no significant associations between regional gray-matter volumes and either OSA severity or cognition measured using the Differential Ability Scales. The authors acknowledged this difference between the two studies and attributed it to the lack of sensitivity of psychological tests and the high degree of variability in the cognitive outcomes associated with pediatric OSA.[50] The authors also acknowledged that, while inclusion of the scans from the NIH database greatly improved the estimation of true population levels of regional gray-matter volumes, sleep status was not assessed and a proportion of these children may have had OSA. Nonetheless, these findings add additional weight to the need for early identification and treatment of children with OSA.

T1-weighted brain MRI, whereby T1 refers to the use of a short repetition time (the amount of time between successive pulse sequences applied to the same slice) and a short time to echo (the time between the delivery of the radio frequency pulse and the receipt of the echo), identified significant atrophy in the ventral posterior nucleus and the medial dorsal nucleus of the left thalamus in 25 children with OSA (mean age 10.3 ± 1.5 SD years) compared with 30 controls (10.1 ± 1.8 SD years).[51] The children with OSA also exhibited significant regional dilation in both the internal and external segments of the left pallidum. These findings are consistent with the structural deficits found in the basal ganglia of adults with OSA.[52,53] The basal ganglia contribute to the regulation of autonomic motor, somatomotor, and neuropsychological functions, and alterations to these areas of the brain may be associated with deficits in these functions in patients with OSA.

In a study on 11 children with OSA (14 ± 1.5 years, Obstructive Apnea Index >1 event/h and/or the AHI >5 events/h) and 12 controls (mean age 15.1 ± 1.4 SD years), all children underwent overnight PSG, MRI scanning, and neuropsychological evaluation, with a battery of tests for IQ and cognitive assessment including both verbal and visual learning and memory.[54] In contrast to the above studies, this study found that, across the whole brain, there was no impact of OSA on white-matter integrity using tract-based spatial statistics, or gray-matter volumes using voxel-based morphometry.[54] Focusing on the dentate gyrus of the hippocampus, diffusion tensor imaging (DTI) was used to investigate the microstructure. DTI is a MRI imaging technique that enables estimation of the location, orientation, and anistrophy of the brain's white-matter tracts by measuring the restricted diffusion of water in the tissue. Decreased mean diffusivity of the dentate gyrus correlated with a higher AHI, a higher arousal index, and a lower verbal learning score. The authors concluded that the disrupted microstructure of the dentate gyrus may, in part, explain some of the neurocognitive deficits in children with OSA.

A recent study by our group collected T1- and T2-weighted images to examine for any visible brain pathology, and DTI imaging was conducted to determine mean diffusivity in children with SDB (n = 18; mean age 12.3 ± 0.7 SD years; OAHI >1 event/h) and controls (n = 20; 12.2 ± 0.6 years; OAHI ≤1 event/h; and no history of snoring), following overnight PSG and behavioral and neurocognitive testing.[55] Reduced mean diffusivity was identified in the hippocampus, insula, thalamus, and temporal, occipital, and cerebellar sites in children with SDB compared with controls. Reduced mean diffusivity indicates acute (recently incurred) alterations in these areas and may be more amenable to intervention. These areas of the brain are involved with the control of autonomic function, respiration, cognition, mood, and memory processes.[56-60] OAHI was negatively correlated with injury in widespread brain regions, including bilateral lingual gyrus, right anterior and left posterior cingulate, right cerebellar tonsil, inferior and middle occipital gyrus, left middle temporal gyrus, and right parahippocampal gyrus. The correlation with injury, being so widespread, indicates that the OAHI has a significant potential to exert functional deficits, including worsening of SDB. Increased mean diffusivity, indicative of chronic damage, was found in the frontal and prefrontal cortices. Positive correlations were found between OAHI and mean diffusivity in the left amygdala, left middle temporal gyrus, right putamen, right anterior insula, left hippocampus, and right superior temporal gyrus. The brain sites that had positive correlations with OAHI were limited, which was suggestive of the chronic brain damage that resulted from higher OAHI values with longer durations of SDB. The damage to the brain areas identified in this study was less severe than that seen in adults,[61,62] which was attributed to the young age of the children in the study and the shorter exposure to repetitive hypoxia. The conclusion to this study was that there are both short-term and long-lasting processes at play, which most likely result from a combination of the ischemic and hypoxic mechanisms that accompany SDB in children.

The most recent study to be conducted using MRI-assessed regional brain cortical thickness using T1-weighted images was conducted in 16 children with OSA (8.4 ± 1.2 years [mean ± SD];

OAHI >2 events/h, a SpO_2 nadir <92%, and/or a respiratory arousal index >2 events/h), 9 controls (8.3 ± 1.1 years), and 138 further controls from the NIH -Pediatric MRI database.[63] The children with OSA and the nine local controls underwent overnight PSG, neurocognitive assessment, and MRI scanning using T1-weighted images. Examining the whole brain, children with OSA exhibited cortical thinning in the superior and medial frontal, prefrontal, and parietal cortices and the occipital cortex compared with the whole control group (9 local controls plus 138 controls from NIH-Pediatric MRI database). Cortical thickness increased in children with OSA in the bilateral precentral gyrus, left central gyrus, regions in bilateral posterior mid and right anterior insular cortices, posterior cingulate, sub-genu of the anterior cingulate cortices extending into medial prefrontal areas, and temporal cortex and poles. No significant relationship was determined between cortical thickness and cognition measured using the Differential Ability Scales. The cortical thinning identified in this study is consistent with reduced gray matter reported in previous studies.[48,50,51,54] Thinning was suggestive of damage to the cortex in areas related to motor function, problem solving, memory, language, impulse control, social behavior, executive function, attention, and personality development.[64] The authors posited that the cortical thinning seen in children with OSA could be attributed to the effect of repeated hypoxia and sleep fragmentation, resulting in direct neuronal injury, in addition to the disruption of the normal neural developmental processes. Cortical thickening was found in areas involved in emotional control, self-awareness, cognitive function, motor control, reward, decision-making, autonomic regulation, human awareness, pain, episodic memory retrieval, and long-term memory.[65-70] The authors suggested that cortical thickening could be due to hypoxia-induced neuroinflammation and glial activation via an immune response. The small sample size in this study was a possible reason for not detecting an association between the structural findings in the cortex and cognitive performance. This was not considered particularly surprising given the large heterogeneity in the prevalence of a cognitive deficit phenotype. Subregions of some cortical structures have distinct functions; therefore, the neuropsychological consequences of OSA may differ between the subregions. Furthermore, there is a question of how long the children have had the condition; whether cortical thickening represents a late-stage effect due to atrophy. The authors concluded that further research is required to elucidate if the presence of injury to the brain is a consequence of cell loss, disruption to maturational processes, and/or hypoxia-induced inflammation.

A limitation common to most of the pediatric studies that involve MRIs is the small sample size, which can mostly be attributed to the high cost, the time commitment required by the parents and children, and the unwillingness of the children to participate in the procedure, or their parent to consent to it. Although not as comprehensively investigated in children as in adults, the studies that have assessed changes to the brain associated with SDB in children using MRI technologies have identified a plethora of brain areas affected. There is both commonality and disparity in the brain areas identified between studies, and this may reflect the different methodologies used with regard to classification of disease severity and to the MRI procedures. Furthermore, some studies performed whole-brain analyses, others focused on particular brain areas of interest, some studies used structural MRIs, and others used fMRIs.

Conclusions

The limited studies in children which have assessed cerebral oxygenation in children with SDB have identified that, in contrast to studies in adults, children appear to be able to maintain cerebral oxygenation. Nonetheless, it is clear that pediatric SDB has significant adverse effects on the brain in areas related to autonomic control, respiration, behavior, and neurocognition, all adverse sequelae identified in children with SDB. Of concern is that these changes to brain morphology and function are occurring during childhood when the brain is still undergoing significant development. It remains unknown whether they are permanent or can be reversed with treatment of the underlying SDB. Furthermore, it is unknown if this repair is dependent on the age of the child and for how long the child has had the disorder. Evidence would suggest that some areas of the brain are better at restoring their functional abilities following resolution of SDB in children than that in others, depending on the function that they are associated with. The resolution of obstructive SDB in preschool- or elementary school-aged children is not accompanied by significant improvements in neurocognition.[16,71-73] However, the effect of the resolution of SDB on cardiovascular function and control is less clear, as some studies report improvements concomitant with an improvement in SDB severity,[74-76] whereas others report no change.[77] Further longitudinal studies utilizing both cerebral oxygenation and imaging are needed to elucidate whether the brain recovers from injury following the resolution or improvement of SDB.

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Conflicts of interest

There are no conflicts of interest.

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