Volume 12 No. 1, March 2016

Review Article

# Neurocognitive and behavioural morbidities in children with sleep-disordered breathing

**June Sin-Hang CHAN** 陳善珩
Private Paediatrician, Hong Kong

## Abstract

Sleep-disordered breathing (SDB) is a common disorder in children. Neurocognitive and behavioural deficits are important adverse outcomes of childhood SDB. The aim of this review is to summarise the current evidence of the association between SDB and neurobehavioural morbidity, to provide some plausible mechanisms on the pathophysiology, and to discuss the clinical implication of the current knowledge on the topic. There is strong evidence that SDB is associated with behavioural and cognitive deficits in children. Robust evidence exists with the association between inattentiveness and hyperaciveness in children with SDB. Cognitive and executive dysfunctions have also been suggested. Sleep fragmentation, hypoxaemia and inflammation in SDB are possible pathways to impact on the developing brain, leading to neurocognitive and behavioural deficits. Adenotonsillectomy improves SDB, behaviour and cognitive function. Early treatment of SDB may be beneficial in preventing or ameliorating behavioural and neurocognitive morbidities.

Keywords: Behavioural functioning, Cognitive functioning, Obstructive sleep apnoea, Sleep-disordered breathing

## Introduction

Sleep-disordered breathing (SDB) is a common disorder in childhood. It represents a spectrum of disorder from primary snoring (PS), defined as snoring which is not associated with gaseous exchange abnormalities or sleep disturbances on polysomnography; to obstructive sleep apnoea syndrome (OSAS). OSAS is characterised by snoring, reduction in airflow, leading to hypoxia, hypercapnoea and sleep fragmentation.

Since the original description of childhood SDB, it has been a common observation that the disorder is associated with cognitive and behavioural deficits. The effect of sleep fragmentation, hypoxia, systemic inflammation and endothelial dysfunction associated with SDB on the developing brain of children, is of particular importance in the pathophysiology. Compelling evidence has evolved that SDB is associated with neurocognitive and behavioural problems in children. Studies in earlier years were criticised for the lack of standardised measurement of SDB, the sole reliance on parental reports for neurobehavioural functioning. These studies were mostly cross-sectional. In the past decade, there have been more rigorous longitudinal studies, with polysomnography measures of SDB, including parental report as well as office-based psychometric tests as measures of neurocognitive functions. Studies of neurobiology have also offered us more insights on the pathological model between SDB and neurocognitive dysfunction.

The purpose of this review is to summarise the current evidence of the association between SDB and neurobehavioural morbidity, to provide some plausible mechanisms on the pathophysiology, and finally to discuss the clinical implication of the current knowledge on the topic.

## Behavioural and cognitive dysfunction in childhood SDB

### Inattention and hyperactiveness

Attention is the ability to remain on task and appropriately respond to stimuli. It is an important prerequisite for more complex cognitive functions. Hyperactivity refers to behaviour with excessive actions or language. It has been a consistent finding that

Email: jshchan@gmail.com

inattentiveness and hyperactiveness is more common in children with SDB as compared to controls.[1-6] The majority of the studies have utilised validated parent-report measures such as Conners' Parent Rating Scales, the Child Behavior Checklist (CBCL), the Behavior Assessment System for Children to assess behavioural functioning. Although it is possible that parents of children with SDB may be more concerned regarding their childrens' behaviour, some may seek treatment for sleep disorder in the hope to improve child's daytime behaviour, leading to possible bias. Yet, inattention and hyperactivity stood out to be fairly consistent concerns amongst all the other behavioural parameters included in the standardised measures. In a meta-analysis, the pooled effect of sleep-disordered breathing on parent-report attention, hyperactivity/impulsivity were of moderate size.[7] That means the association between SDB and hyperactivity and inattentiveness is unlikely due to methodological bias. A few studies have also included teacher-report measures, shows less prominent, but nonetheless positive association between SDB and behavioural problems.[2,8-11]

The effect of SDB on attention have also been demonstrated by studies using office-based psychometric tests such as auditory or visual continuous performance tests or subsets of NEuroPsychologiccal assessment (NEPSY).[12,13] These tests are highly standardised and objective. However, results of these office-based tests did not necessarily agree with parental reports.[14] It is possible that children may perform better in a highly controlled office-setting, but they still exhibit difficulty in remaining focused in everyday life in their natural environment. Hence, these office-based tests should be interpreted in conjunction with parental and teachers' observation.

**Cognition and academic performance**

The effect of SDB on cognition and academic performance is less clear cut. Although some studies demonstrated differences in IQ measures in children SDB as compared with controls, the IQ measures were still within normal range. One of the major criticisms for studies measuring IQ is regarding the 'super-normal' control group. Another issue in measuring intelligence and academic functioning is that these measures are subjected to numerous confounding factors such as prematurity, socio-economic status and the age of child. Regarding language functioning, most studies which measured vocabulary or verbal fluency report no significant difference between children with SDB and controls.[2,4,9,11]

Studies have mixed result regarding the association between visual perception deficit and SDB. While some demonstrated that children with SDB have difficulties in constructing geometric designs with colored tiles or blocks, and the ability to copy line drawings;[9,12] others seemed unable to replicate such results.[2,3]

Most studies have not found memory deficits in children with SDB.[2,9,13,15] This is contrary to what was thought, that sleep disruption and intermittent hypoxaemia would preferentially affect the memory domain. It is possible that only short-term memory but not the longer-term memory that could be tested in a single-day assessment.

Poor academic performance has been reported in children with SDB.[11,16,17] Poor academic performance was closely related to hyperactivity, inattention and daytime sleepiness among snorers.[18] Office-based tests showed that academic skills were not inferior in children with SDB.[11,19] It is believed that lower grades observed in children with SDB are the result of a combination of factors, and that it may be more related to children's behaviour in the classrooms rather than academic knowledge.

***Executive functioning***

'Executive functioning' refers to the ability to plan, develop, and sustain an organised and flexible approach to problem solving. It composes of high-level, goal-directed adaptive functioning. Executive functioning determines how a child utilises basic skills in a complex, changing external environment.[20,21] It is closely related to attention, cognitive flexibility and memory. Executive functioning deficits are commonly in children and adults with SDB.[2,13,15,19] Executive function is complex, hence the inconsistency in the published result can be explained by the different domains or different methodology in the measurement of executive function.

## Severity of SDB and neurobehavioural morbidity

The degree of neurobehavioural deficit does not linearly correlate with the severity of SDB. In fact, cognitive and behavioural outcome is impaired in children with all severities of SDB. Earlier reports have demonstrated inattention and hyperactivity in children with primary snoring.[15] Since then, it has drawn interests in looking into the daytime functioning of children with PS, a once considered benign condition.[2,9,22] More recent studies found that children with all severities of SDB had significantly higher rates of behavioural problems and

executive dysfunction as compared to control. Children with PS, have similar, or even poorer neurobehavioural functioning compared to children with OSAS.[23,24]

## Treatment of SDB and effect on behaviour and neurocognition

Adenotonsillectomy is the first-line treatment for childhood obstructive sleep apnoea (OSA).[25] Studies have demonstrated improvement in children's behaviour and cognition after adenotonsillectomy. Chervin reported improvement in hyperactivity and inattention one year after surgery. Improvement was noted by using both parent-reported Conner's as well as objective continuous performance test.[26] Owen performed neurobehavioural assessment on children with polysomnography-proven SDB before and after adenotonsillectomy and found improvement in executive function, attention and parental reports of internalising and externalising behaviour.[3] Friedman has observed improvement in mental processing and word recognition to the level of controls after adenotonsillectomy.[5]

To date, the only randomised study examining the effect of adenotonsillectomy on cognitive and behavioural outcome (the CHAT study) showed that adenotonsillectomy improved behaviour and quality of life, but not office-based measures of attention or executive function.[14] The improvement in parent and teacher reported performance in daily activities should not be disregarded as these reached moderate effect size. The limitation of office-based psychometric tests as an accurate reflection of how a child performs in their natural environment has been discussed earlier in this review. It is also possible that a 7-month follow-up period in the CHAT study was insufficient to detect the full response to adenotonsillectomy.

Another follow-up study of treatment after 4 years showed that improvement in obstructive apnoea-hypopnoea index was predictive of improvements in Performance IQ, but not Verbal IQ or academic measures. Children with SDB at baseline continued to exhibits poorer behaviour than controls after 4 years, irrespective of treatment.[27]

## Proposed mechanisms

### Prefrontal cortex model

Gozal proposed a model linking OSA-related sleep disruption, hypoxia and hypercarbia to insult to the prefrontal cortex, resulting in cognitive behavioural dysfunction.[28] The prefrontal cortex is essential for executive functioning. The prefrontal cortex is active during wakefulness and has reduced activity during sleep. This part of the brain is particularly sensitive to sleep deprivation and sleep disruption, as demonstrated by functional MRI. However, changes in pre-frontal cortex have not been consistently demonstrated in children with SDB.

One study looking at children with severe OSAS with significant executive dysfunction has found decreased mean neuronal metabolite ratio of N-acetyl aspartate to choline, which is a marker of neuronal injury, in the left hippocampus and right frontal cortex.[29] Adult studies have shown decreased gray matter in the hippocampus in OSAS subjects.[308] So, there exists evidence that SDB is associated with neurochemical abnormalities in specific brain areas.

### Hypoxia

Recurrent hypoxia will cause damage to a developing brain resulting in neurocognitive deficits. However, hypoxia is unlikely to be the only cause for neurocognitive impairment in children. Children with PS, without hypoxia, experience similar degree of neurocognitive deficits as children with severe OSA. In fact, the majority of the paediatric studies could not find the correlation between oxygen saturation and neurocognitive outcomes.[2,22,24]

### Sleep fragmentation

Sleep-disordered breathing causes multiple arousals and thus sleep fragmentation. It was hypothesised that these recurrent arousals would result in daytime sleepiness and cognitive impairment. However, sleep architecture is often normal in children with SDB, and the arousal index showed no difference with controls.[31,32] It is also widely observed that excessive daytime sleepiness is not commonly seen in children with SDB.

The current conventional polysomnographic measures may not be sensitive enough to pick up subtle changes in the brain. Studies that looked at more sensitive techniques such as cyclic alternating pattern (CAP) and respiratory cycle-related EEG, have found that subtle EEG changes, not picked up by conventional scoring measures, do occur in children with SDB.[33,34] Positive correlation between CAP rate and behavioural complaints has been observed.[33]

Hence, it is possible that sleep fragmentation does play a role in the neurocognitive problems seen in children

with SDB. A more sensitive measurement of the subtle dynamic changes in the brain during SDB is required.

**Inflammation**

SDB is currently viewed as a disease of systemic inflammation. Study has shown that inflammatory markers were increased in children with SDB and cognitive dysfunction than children with SDB alone, suggesting that the magnitude of systemic inflammation caused by SDB is a major determinant of cognitive impairment.[35] Endothelial dysfunction associated with SDB has also been shown to correlate with neurocognitive impairment.[36]

**Obesity**

The association between SDB and neurobehavioural abnormalities is further confounded by obesity. Obesity itself is associated with neurobehavioural problems, and obesity is an important aetiological factor for SDB, especially in adolescents. Recent study has demonstrated obese adolescents with OSAS show impaired executive and behavioural function compared to obese and lean controls.[37]

## Temporal relationship between SDB and neurocognitive deficit

One study preschool children with SDB showed behavioural but not cognitive impairment.[24] From the same group of researchers, another study showed that cognitive and academic functions are impaired in older school-aged children.[22] These findings were consistent with earlier studies showing that children who snored at an earlier age was predictive of hyperactivity and lower school performance years later. These studies highlight that perhaps the preschool age-group is more vulnerable to the neurocognitive effect of SDB. The lack of cognitive impairment seen in the school-aged group as in the preschool group could represent a potential window of opportunity, that early treatment of SDB may prevent cognitive morbidities later in childhood.

## Conclusion

Strong evidence suggests that SDB in children is associated with behavioural and neurocognitive deficits, in particular inattentiveness and hyperactiveness. Children even with mild SDB may exhibit neurocognitive dysfunction. Treatment of SDB provides improvement in behavioural and neurocognitive function. The exact mechanism linking SDB and behavioural and cognitive impairment remains to be elucidated. A more sensitive measure of SDB to predict neurocognitive deficit should be develop. Researches are required to understand the temporal relationship and the threshold effect of SDB on neurocognitive development. Timely treatment of SDB to improve neurocognitive health in children could have substantial public health impact.

Paediatricians should be aware of the behavioural and cognitive impairment in children with SDB. Effort should be made towards early detection of SDB. Children with diagnosed SDB should be asked about symptoms relating to behavioural and learning problems, even if the SDB is mild. Behavioural and cognitive outcome should be one of the considerations in treating children with milder form of SDB.

## References


1. Rosen CL, Storfer-Isser A, Taylor HG, Kirchner HL, Emancipator JL, Redline S. Increased behavioral morbidity in school-aged children with sleep-disordered breathing. Pediatrics 2004;114(6):1640-8.
2. Beebe DW, Wells CT, Jeffries J, Chini B, Kalra M, Amin R. Neuropsychological effects of pediatric obstructive sleep apnea. J Int Neuropsychol Soc 2004;10(7):962-75.
3. Owens J, Spirito A, Marcotte A, McGuinn M, Berkelhammer L. Neuropsychological and Behavioral Correlates of Obstructive Sleep Apnea Syndrome in Children: A Preliminary Study. Sleep Breath 2000;4(2):67-78.
4. Lewin DS, Rosen RC, England SJ, Dahl RE. Preliminary evidence of behavioral and cognitive sequelae of obstructive sleep apnea in children. Sleep Med 2002;3(1):5-13.
5. Friedman BC, Hendeles-Amitai A, Kozminsky E, Leiberman A, Friger M, Tarasiuk A, et al. Adenotonsillectomy improves neurocognitive function in children with obstructive sleep apnea syndrome. Sleep 2003;26(8):999-1005.
6. Melendres MC, Lutz JM, Rubin ED, Marcus CL. Daytime sleepiness and hyperactivity in children with suspected sleep-disordered breathing. Pediatrics 2004;114(3):768-75.
7. Beebe DW. Neurobehavioral morbidity associated with disordered breathing during sleep in children: a comprehensive review. Sleep 2006;29(9):1115-34.
8. Ali NJ, Piston D, Stradling JR. Snoring, sleep disturbance and behaviour in 4-5 year olds. Arch Dis Child 1993;68(3): 360-6.
9. O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Klaus CJ, Rutherford J, et al. Neurobehavioral implications of habitual snoring in children. Pediatrics 2004;114(1):44-9.
10. Mulvaney SA, Goodwin JL, Morgan WJ, Rosen GR, Quan SF, Kaemingk KL. Behavior problems associated with sleep disordered breathing in school-aged children--the Tucson children's assessment of sleep apnea study. J Pediatr

Psychol 2006;31(3):322-30.
11. Kaemingk KL, Pasvogel AE, Goodwin JL, Mulvaney SA, Martinez F, Enright PL, et al. Learning in children and sleep disordered breathing: findings of the Tucson Children's Assessment of Sleep Apnea (tuCASA) prospective cohort study. J Int Neuropsychol Soc 2003;9(7):1016-26.
12. Blunden S, Lushington K, Kennedy D, Martin J, Dawson D. Behavior and neurocognitive performance in children aged 5-10 years who snore compared to controls. J Clin Exp Neuropsychol 2000;22(5):554-68.
13. O'Brien LM, Mervis CB, Holbrook CR, Bruner JL, Smith NH, McNally N, et al. Neurobehavioral correlates of sleep-disordered breathing in children. J Sleep Res 2004;13(2): 165-72.
14. Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. N Engl J Med 2013;368(25):2366-76.
15. Kennedy JD, Blunden S, Hirte C, Parsons DW, Martin AJ, Crowe E, et al. Reduced neurocognition in children who snore. Pediatr Pulmonol 2004;37(4):330-7.
16. Gozal D. Sleep-disordered breathing and school performance in children. Pediatrics 1998;102:616-20.
17. Urschitz MS, Wolff J, Sokollik C, Eggebrecht E, Urschitz-Duprat PM, Schlaud M, et al. Nocturnal arterial oxygen saturation and academic performance in a community sample of children. Pediatrics 2005;115:e204-9.
18. Urschitz MS, Guenther A, Eggebrecht E, Wolff J, Urschitz-Duprat PM, Schlaud M, et al. Snoring, intermittent hypoxia and academic performance in primary school children. Am J Respir Crit Care Med 2003;168(4):464-8.
19. Emancipator JL, Storfer-Isser A, Taylor HG, Rosen CL, Kirchner HL, Johnson NL, et al. Variation of cognition and achievement with sleep-disordered breathing in full-term and preterm children. Arch Pediatr Adolesc Med 2006;160 (2):203-10.
20. Carlson SM. Developmentally sensitive measures of executive function in preschool children. Dev Neuropsychol 2005;28(2):595-616.
21. Hayes SC, Gifford E V, Ruckstuhl Jr. LE. Relational frame theory and executive function: A behavioral approach. In: Attention, Memory, and Executive Function. Baltimore, MD: Paul Brookes Publishing Co, 1996:279-305.
22. Bourke R, Anderson V, Yang JS, Jackman AR, Killedar A, Nixon GM, et al. Cognitive and academic functions are impaired in children with all severities of sleep-disordered breathing. Sleep Med 2011;12(5):489-96.
23. Bourke RS, Anderson V, Yang JS, Jackman AR, Killedar A, Nixon GM, et al. Neurobehavioral function is impaired in children with all severities of sleep disordered breathing. Sleep Med 2011;12(3):222-9.
24. Jackman AR, Biggs SN, Walter LM, Embuldeniya US, Davey MJ, Nixon GM, et al. Sleep-disordered breathing in preschool children is associated with behavioral, but not cognitive, impairments. Sleep Med 2012;13(6):621-31.
25. Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012;130(3): 576-84.
26. Chervin RD, Ruzicka DL, Giordani BJ, Weatherly RA, Dillon JE, Hodges EK, et al. Sleep-disordered breathing, behavior, and cognition in children before and after adenotonsillectomy. Pediatrics 2006;117(4):e769-78.
27. Biggs SN, Vlahandonis A, Anderson V, Bourke R, Nixon GM, Davey MJ, et al. Long-term changes in neurocognition and behavior following treatment of sleep disordered breathing in school-aged children. Sleep 2014;37(1):77-84.
28. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: Towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. J Sleep Res 2002;11(1):1-16.
29. Halbower AC, Degaonkar M, Barker PB, Earley CJ, Marcus CL, Smith PL, et al. Childhood obstructive sleep apnea associates with neuropsychological deficits and neuronal brain injury. PLoS Med 2006;3(8):1391-402.
30. Macey PM, Henderson LA, Macey KE, Macey KE, Alger JR, Frysinger RC, et al. Brain morphology associated with obstructive sleep apnea. Am J Respir Crit Care Med 2002; 166(10):1382-7.
31. Chervin RD, Archbold KH. Hyperactivity and polysomnographic findings in children evaluated for sleep-disordered breathing. Sleep 2001;24(3):313-20.
32. Goh DY, Galster P, Marcus CL. Sleep architecture and respiratory disturbances in children with obstructive sleep apnea. Am J Respir Crit Care Med 2000;162(2 Pt 1): 682-6.
33. Lopes MC, Guilleminault C. Chronic snoring and sleep in children: a demonstration of sleep disruption. Pediatrics 2006; 118(3):741-6.
34. Chervin RD, Garetz SL, Ruzicka DL, Hodges EK, Giordani BJ, Dillon JE, et al. Do respiratory cycle-related EEG changes or arousals from sleep predict neurobehavioral deficits and response to adenotonsillectomy in children? J Clin Sleep Med 2014;10(8):903-11.
35. Gozal D, Crabtree VM, Capdevila OS, Witcher LA, Kheirandish-Gozal L. C-reactive protein, obstructive sleep apnea, and cognitive dysfunction in school-aged children. Am J Respir Crit Care Med 2007;176(2):188-93.
36. Gozal D, Kheirandish-Gozal L, Bhattacharjee R, Spruyt K. Neurocognitive and endothelial dysfunction in children with obstructive sleep apnea. Pediatrics 2010;126(5):e1161-7.
37. Xanthopoulos MS, Gallagher PR, Berkowitz RI, Radcliffe J, Bradford R, Marcus CL. Neurobehavioral functioning in adolescents with and without obesity and obstructive sleep apnea. Sleep 2015;38(3):401-10.