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CLINICAL REVIEW

The conundrum of primary snoring in children: What are we missing in regards to cognitive and behavioural morbidity?

Sarah N. Biggs [a, b, *], Gillian M. Nixon [a, b, c], Rosemary S.C. Horne [a, b]

[a] The Ritchie Centre, Monash Institute of Medical Research – Prince Henry's Institute, Monash University, Melbourne, Australia
[b] Department of Paediatrics, Monash University, Melbourne, Australia
[c] Melbourne Children's Sleep Centre, Monash Children's Hospital, Monash Medical Centre, Melbourne, Australia

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SUMMARY

Sleep disordered breathing (SDB) is common in children and describes a continuum of nocturnal respiratory disturbance from primary snoring (PS) to obstructive sleep apnoea (OSA). Historically, PS has been considered benign, however there is growing evidence that children with PS exhibit cognitive and behavioural deficits equivalent to children with OSA. There are two popular mechanistic theories linking SDB with daytime morbidity: hypoxic insult to the developing brain; and sleep disruption due to repeated arousals. These theories apply well to OSA, but children with PS experience neither hypoxia nor increased arousals when compared to non snoring controls. So what are we missing? This review summarises the literature examining daytime morbidity in children with PS and discusses the current debates surrounding this relationship. Specifically, questions exist as to the sensitivity of our standard assessment techniques to measure subtle hypoxia and arousal. There is also a suggestion that the association between PS and daytime morbidity may not be mediated by nocturnal respiratory disturbance at all, but by a number of other comorbid, but perhaps unrelated factors. As approximately 70% of children with SDB are diagnosed with PS, but are rarely treated, a paradigm shift in the investigation of PS may be required.

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Introduction

Obstructive sleep disordered breathing (SDB) in children describes a continuum of nocturnal respiratory disturbance characterised by increasing upper airway obstruction and degrees of gas exchange abnormalities [1,2]. The cardinal symptom of SDB is habitual snoring. At the most severe end of the spectrum is obstructive sleep apnoea (OSA), which is characterised by repetitive episodes of full or partial obstruction of the airway resulting in oxygen desaturation and/or an arousal from sleep, if not a full awakening. At the mild end of the SDB spectrum is primary snoring (PS). PS is also characterised by habitual snoring, but with few respiratory events (<1 event/h), oxygen desaturation or formally defined respiratory arousals [1]. A continuous scale of respiratory effort, desaturation and arousal from sleep lie in between these two extremes, with the quantifying cut-off between one severity group and the next being relatively arbitrary. Classification of SDB severity has usually been defined by the frequency of obstructive events during sleep – variously termed the apnoea hypopnea index (AHI), or respiratory disturbance index (RDI). Throughout this review, the term SDB will be used as an encompassing term, referring to the full continuum of the disease, whereas PS and OSA will refer to those specific categories within the continuum.

In adults, the phenotype of OSA is most often described as overweight males with sedentary lifestyles, although genetic predisposition, craniofacial anatomy and abnormal regulation of upper airway musculature are also risk factors [3]. In children, who are otherwise healthy, the traditional phenotype of OSA is not related to adipose tissue, but to adenotonsillar hypertrophy that occludes a relatively small pharyngeal space [4]. Prevalence of OSA in children is reported to be 1–5% of the population [2]. The prevalence of habitual snoring reported in the literature varies widely, with population studies reporting ranges from less than 3% [5] to approximately 35% [6], with the discrepancy arising predominantly from the authors' definition of habitual snoring. Most commonly, habitual snoring is defined as snoring often or more than three times per week, for which prevalence rates are reported to be

* Corresponding author. The Ritchie Centre, MIMR-PHI Institute, Monash University, Level 5, Monash Medical Centre, 27-31 Wright St, Clayton, Victoria 3168, Australia. Tel.: +61 3 9594 4759; fax: +61 9594 6811.
E-mail address: sarah.biggs@monash.edu (S.N. Biggs).

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Abbreviations

ABAS	adaptive behavior assessment system
ACPT	auditory continuous performance test
ADHD	attention deficit hyperactivity disorder
AHI	apnoea/hypopnoea index
ArI	arousal index
BASC	behavioral assessment scale for children
BRIEF	behavior rating inventory of executive function
CAP	cyclic alternating pattern
CBCL	child behavior checklist
CMS	children's memory scale
COWAT	controlled oral word association test
CVLT-C	California verbal learning test for children
DAS	differential abilities scale
EEG	electroencephalogram
EVT	expressive vocabulary test
GDS	Gordon diagnostic system
IQ	intelligence quotient
MSOSA	moderate–severe OSA
NEPSY	neuropsychological assessment
NREM	non-rapid eye movement
OAI	obstructive apnoea index
OAHI	obstructive apnoea/hypopnoea index
OSA	obstructive sleep apnoea
pCO_2	partial pressure of blood carbon dioxide
PPVT	Peabody picture vocabulary test
PSG	polysomnography
PS	primary snoring
RAVLT	Rey auditory verbal learning test
RBMT	Rivermead behavioural memory test for children
RCFT	Rey complex figure test
RDI	respiratory disturbance index
REM	rapid eye movement
SDB	sleep disordered breathing
SE	sleep efficiency
SOL	sleep onset latency
SpO^2	blood oxygen saturation
SWA	slow wave activity
TST	total sleep time
UARS	upper airway resistance syndrome
WASI	Wechsler abbreviated scale of intelligence
WCST	Wisconsin card sorting test
WISC	Wechsler intelligence scale
WPPSI-R	Wechsler pre-school and primary scale of intelligence (revised)
WRAML	wide range assessment of memory and learning
WRAT	wide range achievement test

between 10% and 15% [7]. While adenotonsillar hypertrophy is the most common aetiology of SDB in children, with rising obesity rates in children, there is an increasing incidence of the more classical adult profile of OSA, where body weight plays a major role. Indeed, there has been some suggestion that in children there are now two distinct disease profiles of OSA with different sequelae [8]. Syndromes and conditions involving craniofacial malformation and neuromuscular factors that affect the patency of the airway can also result in OSA [9–11]. However, these conditions are beyond the scope of the current review. For the purposes of this review, we will only be discussing SDB and the associated neurocognitive and behavioural consequences in children without craniofacial or neuromuscular comorbid conditions.

Reports of cognitive and behavioural deficits in children with OSA date back to the late 1880's [12], however formal investigation of the daytime consequences of SDB has only been conducted in the last four decades. Since the first seminal studies by Guilleminault and colleagues [13,14], the literature regarding the effects of SDB on cognition, behaviour and school performance in children has increased exponentially, with more than 80 studies published in this area in the last 12 years. Although causality is difficult to establish, due to the complexities of known confounders (e.g., environment, socio-economic factors, race) and the limitations of study designs (e.g., majority are cross-sectional), it is now widely accepted that OSA is associated with cognitive and behavioural dysfunction.

There are two popular, interconnected, theories describing the mechanisms linking OSA to daytime deficits. The first proposes that the repetitive hypoxic insults to the brain interrupt normal synaptic functioning which results in neuronal injury and cognitive impairments. The second proposes that the increased sleep disruption from repetitive arousals at respiratory event termination leads to sleep deprivation and excessive daytime sleepiness, which in turn affects cognitive and behavioural functioning [15–17]. Historically, it was assumed that the level of daytime deficits would be linearly related to the severity of SDB, and until relatively recently, PS was considered benign [18]. Unexpected evidence of cognitive and behavioural deficits in children with PS, confirmed by polysomnography (PSG), was first presented by Blunden and colleagues [19]. The aim of that study was to examine cognitive and behavioural deficits in children with OSA, however few of their cohort met the criteria for OSA, instead receiving a diagnosis of PS (AHI < 1 event/h). Despite this, the results showed a significant difference in cognitive functioning between the snoring children and the control group. That study sparked much intrigue surrounding the morbidity of PS. Subsequently, a number of studies have specifically examined children with PS and compared sleep and respiratory indices, neurocognitive and behavioural outcomes to children with OSA, as well as healthy, non snoring controls with surprising results [20–31]. Specifically, behavioural, most often measured via parent-report questionnaire, and to some extent, cognitive deficits in children with PS are similar to children with OSA, when compared to non snoring controls. As by definition, children with PS do not experience gas exchange abnormalities or increased arousals compared to normative values, this begs the question: what are we missing in the relationship between PS and daytime sequelae? Furthermore, as the majority of children with PS do not get treated for their condition, are we placing them at risk of life-long deleterious consequences?

This review will summarise the current literature regarding cognitive and behavioural performance in children with PS, discuss the relevance of current mechanistic theories as applied to this group, and propose some alternate explanations for the association between PS and daytime deficits in children. There are a number of comprehensive reviews outlining the neurocognitive and behavioural consequences of parent-reported habitual snoring and SDB in more general terms, without discretely separating PS from OSA [15–17,32–38]. As such, we have chosen to present and discuss only those studies which employed PSG to confirm the severity of SDB, categorised PS as a separate group, and assessed cognition and/or behaviour as a study outcome against children with more severe SDB and/or non snoring healthy controls. Articles were

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sourced from databases such as PubMed, Scopus, MEDLINE and PsycINFO, using a combination of the following search terms: snoring, sleep disordered breathing, obstructive sleep apnoea, polysomnography, cognition, behavio(u)r and children. We identified 13 studies that fit our criteria, which are discussed in detail below.

Categorisation of PS

It is not possible to distinguish PS from OSA based on clinical history [39]. Currently, the only definitive approach for the differentiation of OSA from PS is an overnight PSG [2]. Diagnosis is based on a combination of clinical history, the number of respiratory events per hour of sleep on PSG, and the physiological consequences of these events, in terms of gas exchange abnormalities and arousals. According to international guidelines, respiratory events are separated into two categories: obstructive and central. Over the years, the definitions for scoring respiratory events have changed, particularly the rules concerning the identification of obstructive hypopnoeas, which involve partial occlusion of the airway (Table 1). In 1996, the American Thoracic Society [18] first defined an obstructive hypopnoea as a respiratory event with at least a 50% decrease in airflow compared to the preceding unobstructed breaths, accompanied by paradoxical movement of the chest and abdomen and a fall in oxygen saturation of greater than 4%. Since that time, the minimum drop in airflow required to score an hypopnea has oscillated between 50% [18,40] and 30% [41]. The minimum oxygen desaturation sequelae has also moved back and forth between 4% [18] and 3% [40,41]. While most of the changes in definition appear minimal, they can have a substantial impact on the categorisation of SDB severity, particularly at the milder end of the continuum, when there are fewer events and these events are more likely to be hypopnoeas. Depending on which scoring rules are utilised, hypopnoeas may not reach the threshold for scoring, resulting in under-diagnosis [42]. Changes in technology, especially in sensitivity of oximetry to detect rapid changes in SpO2, may also affect the detection and scoring of events [43].

Furthermore, the metric used to categorise the severity of SDB or diagnose OSA also varies. In 1999, a consensus paper [44], later referred to as the *International classification of sleep disorders: diagnostic and coding manual* [45], and most recently the Sleep Apnea Definition Task Force [41] recommended the diagnosis of OSA be derived from the sum of all apnoeas, hypopnoeas and respiratory event related arousals per hour of sleep. However, there is no clear preferred definition for this metric, and as such, a number of classifications have been used. These include the AHI and RDI, which include central events and the obstructive AHI (OAHI) and obstructive apnoea index (OAI), which only include obstructive events, either with or without hypopnoeas. Table 2 illustrates the variation in the metrics used across the 13 studies examining cognitive and behavioural morbidity in children with PS.

The most widely used cut-off values differentiating PS from OSA are based on a handful of studies examining normative values in non snoring children [46–50]. The most commonly used threshold for PS is an index of less than one respiratory event per hour, together with a clinical history of parent-reported habitual snoring. This threshold however was derived from a large cohort of healthy children [46], where the actual cut-off of 1 event/h referred to obstructive apnoeas only, and did not include hypopnoeas. Thus, other authors have used a cut off of 1.5 events/h [51] or 2 events/h [52]. Mild OSA is usually defined as between 1 and <5 events/h, moderate OSA when there are between 5 and <10 events/h, and severe OSA when there are >10 events/h [53]. These definitions also vary between studies with some authors choosing a composite respiratory disturbance score to define severity, based on a number of different factors including extent of SpO_2 desaturation and respiratory arousals [26,29].

These large variations in definition of events, terminology and classification of OSA make direct comparisons between studies difficult and the reader is advised to be cognisant of this throughout the review. Nonetheless, the consistent findings between studies, irrespective of these methodological differences, warrant analysis of the outcomes of PS.

Table 1
Differences in respiratory event scoring definitions over time.

Event type	Definition
American Thoracic Society 1996 [18]	
Obstructive apnoea	Cessation of airflow with paradoxical movement of chest and abdomen
Obstructive hypopnoea	≥50% decrease in airflow with paradoxical movement of chest and abdomen and accompanied by a >4% SpO_2 desaturation or arousal
Central apnoea	Complete absence of airflow and respiratory effort for longer than 20 s or in association with a >4% SpO_2 desaturation or >25% change in heart rate
American Academy of Sleep Medicine 2007 [40]	
Obstructive apnoea	>90% drop in airflow compared to pre-event baseline for >90% of the duration of the event, lasting at least two missed breaths, with continued effort in chest and abdomen
Obstructive hypopnoea	≥50% drop in airflow for at least 90% of the duration of the event, lasting at least two missed breaths and associated with an arousal or a >3% SpO_2 desaturation
Central apnoea	Absence of airflow, with cessation of respiratory effort, lasting more than 20 s or lasting at least two missed breaths and associated with an arousal or a >3% SpO_2 desaturation
Mixed apnoea	Apnoea that begins as a central event (absence of respiratory effort) and ends as an obstructive event (reduced airflow with respiratory effort).
Respiratory effort related arousal (RERA)	Discernible drop in airflow that is <50% of pre-event baseline, lasting at least two breaths and accompanied by snoring, increased work of breathing, and elevation in PCO_2.
Sleep Apnea Definitions Task Force 2012 [41]	
Obstructive apnoea	≥90% drop in airflow for at least 2 breaths with continuing respiratory effort
Obstructive hypopnoea	≥30% drop in airflow for at least 2 breaths and associated with a ≥3% SpO_2 desaturation or arousal
Central apnoea	Absence of airflow and respiratory effort for longer than 20 s or at least two breaths and accompanied by a ≥3% SpO_2 desaturation or arousal
Mixed apnoea	An event of at least two breaths in which one portion consists of an absence of respiratory effort and has the presence of respiratory effort with decreased airflow in the other. The order of these events is not important
Respiratory effort related arousal (RERA)	Discernible flattening of the airflow signal accompanied by increased respiratory effort, snoring or an increase in PCO_2 which leads to an arousal

Respiratory and sleep differences between PS and OSA

Clinical diagnosis of SDB severity relies on the scoring of a number of factors, including the number of events/h, the level of gas exchange abnormality and the number of arousals/h. Thus, by design, there is a linear relationship between the respiratory parameters and increasing SDB severity, as summarised in Table 2. This table highlights that there are no differences in respiratory parameters between children with PS and non snoring control children, irrespective of the classification metric or cut-off value chosen. Despite the distinct differences in respiratory parameters within each study however, there is very little difference between

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Table 2
Differences in respiratory parameters across SDB severity groups.

1st author	Group (*n*)	SDB classification (RDI/AHI/OAHI/OAI: events/h)	Age (y)	RDI/AHI/OAHI/OAI (events/h)	SpO_2 nadir (%)	Respiratory ArI (events/h)	Total ArI (events/h)
Blunden	Control (13)		5–10	0.0(0.0)	95.6(0.4)	NR	NR
2000 [19]	PS (13)	RDI < 1		0.4(0.1)	90.7(1.8)		
Beebe	PS (17)	AHI < 1	6–12	0.1(0.3)	90.2(3.7)	0.1(0.1)	NR
2004 [21]	Mild OSA (9)	AHI >1 and ≤5		2.4(1.2)	87.4(8.5)	0.7(0.8)	
	MS OSA (6)	AHI > 5		13.4(11.2)***[o]	73.2(13.0)**[o]	3.4(2.1)***[o]	
O'Brien	Control (31)		5–7	0.5(0.3)	94.5(1.6)	0.3(0.4)	0.4(0.3)
2004 [29]	PS (87)	Composite score OAI < 1, AHI < 5, SpO_2 nadir >90%, PCO_2 < 50 mmHg, and arousal index <20 events/h		0.5(0.3)	94.1(1.8)	0.7(1.3)[a]*	0.4(0.3)
Honaker	Control (76)		Grade 1–3	0.9(1.1)	92.7(3.9)	0.5(0.8)	NR
2009 [26] [p]	PS (76)	Composite score of RDI, RAI and SpO_2 desaturations ≤3 with parental history of habitual snoring (>3 times/week)	*M* = 6.7	1.1(1.3)	92.2(3.0)	1.7(3.5)	
	OSA (76)	Composite score of RDI, RAI and SpO_2 desaturations ≥4		9.9(10.0)[b]***	82.6(8.4)[b]***	7.3(5.0)[b]***	
Beebe	Control (37)		10–17	0.4(0.3)	94.0(3.6)	NR	6.5(2.0)
2010 [20]	PS (26)	OAHI < 1 but mean score >0.33 on breathing items of the Pediatric Sleep Questionnaire [53]		0.5(0.3)	91.9(4.3)		8.0(2.5)
	Mild OSA (58)	OAHI ≥1 and <5		2.7(1.1)	91.9(3.3)		9.5(4.5)
	MS OSA (42)	OAHI ≥5		11.6(9.8)[c]***	90.0(5.2)[d]**		12.0(5.5)[e,f]***
Ting 2011 [30]	Non-SDB (10)	AHI ≤ 1	6–12	NR	92.1(3.0)	0.4(0.3)	11.0(2.5)
	Mild SDB (21)	AHI >1 and ≤5			90.1(3.0)	1.0(0.5)	13.5(4.6)
	Moderate SDB (80)	AHI >5 and ≤15			91.8(2.8)	2.7(1.8)	14.5(5.2)
	Severe SDB (27)	AHI > 15			88.5(3.0)[g]**	5.7(4.2)[h]***	17.6(8.6)[g]*
Miano	PS (13)	AHI < 1, parental history of snoring and snoring observed on PSG	*M* = 9.1 ± 2.4	0.5(0.3)	95.4(2.8)	NR	9.8(3.7)
2011 [28]							
	OSA (31)	AHI > 1		8.2(9.9)[i]***	90.9(4.5)[j]**		14.9(7.9)[i]*
Bourke	Control (35)		7–12	0.1(0.0)	93.8(0.6)	NR	11.7(0.5)
2011 [22,23]	PS (59)	OAHI ≤ 1 with parental history of habitual snoring		0.3(0.0)	93.3(0.4)		11.5(0.5)
	Mild OSA (24)	OAHI >1 and ≤5		2.4(0.2)	92.7(0.6)		14.3(0.9)
	MS OSA (18)	OAHI >5		15.8(3.1)[c]*	88.6(1.1)[e]*		24.6(2.8)[c]*
Brockmann	Control (410)			NR	NR	NR	NR
2012 [24]	PS (69)	Composite score of AHI < 1, RDI < 1, and SpO_2 desaturation <4%					
	UARS/OSA (23)	AHI < 1 and RDI ≥ 1/AHI ≥ 1					
Jackman	Control (37)		3–5	0.1(0.0)	92.4(0.6)	0.6(0.1)	12.2(0.7)
2012 [27]	PS (60)	OAHI ≤ 1 with parental history of habitual snoring		0.5(0.1)	92.2(0.5)	1.2(0.1)	12.5(0.6)
	Mild OSA (32)	OAHI >1 and ≤5		2.8(0.2)	90.8(0.9)	3.9(0.4)	14.6(0.8)
	MS OSA (24)	OAHI >5		13.2(1.7)[k]**	87.6(1.2)[e]**	13.5(1.7)[k]***	25.3(18.8)[e]**
Tripuraneni	PS	AHI < 1 with clinical history suggestive of OSA	2–18	0.3(0.3)	94.3(2.3)	NR	8.0(3.5)
2013 [31]							
	Non-obese OSA	AHI ≥ 1		9.0(10.8)	87.1(5.9)		15.4(10.2)
	Obese OSA	AHI ≥ 1		20.0(18.0)[l]*	80.8(20.0)[m]**		18.1(14.7)[n]***

AHI = apnoea/hypopnoea index; ArI = arousal index; MS OSA = moderate–severe OSA; NR = not reported; OAI = obstructive apnoea index; OAHI = obstructive apnoea/hypopnoea index; OSA = obstructive sleep apnoea; pCO^2 = blood carbon dioxide; PS = primary snoring; RDI = respiratory disturbance index; SpO^2 = blood oxygen saturation; UARS = upper airway resistance syndrome. All data expressed as mean ± SD, except Blunden [20], Bourke [23,24] and Jackman [28] which are mean ± SEM.
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
[a] Control < PS.
[b] Control = PS < OSA.
[c] Control = PS < Mild OSA < MS OSA.
[d] Control > MS OSA.
[e] Control = PS < MS OSA.
[f] Control < Mild OSA.
[g] PS > Severe SDB.
[h] PS < Moderate SDB & Severe SDB (no comparison made between moderate and severe SDB).
[i] PS < OSA.
[j] PS > OSA.
[k] Control < PS < Mild OSA < MS OSA.
[l] Non-obese OSA < Obese OSA.
[m] PS > non-obese OSA > obese OSA.
[n] PS < non-obese OSA = obese OSA.
[o] Significance based on model difference. No between group differences reported.
[p] Values rounded to one decimal place.

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children with PS and those with OSA in the most commonly reported sleep parameters, such as time spent in each sleep state (Table 3). Based on these data from conventional measures, it appears there are no differences in the levels of sleep disturbance in children with OSA compared to those with PS. Whether the current assessment techniques are sensitive enough to detect sleep disturbance in milder forms of SDB is a topic often debated and is discussed in more detail below.

Cognitive and behavioural differences between primary snoring and OSA

Table 4 provides a summary of the differences in cognitive and behavioural outcomes between children with PS compared to those with more severe OSA and/or non-snoring controls.

Cognition

In the pioneer study by Blunden and colleagues [19], IQ measures showed up to a 13 point mean difference between the PS group and non snoring controls. This unexpected finding resulted in a cautious discussion, with the authors acknowledging that although children with PS were impaired compared to controls, mean scores were within the normal range. Indeed, criticisms were raised regarding the control group, as mean scores for that group were above standardised normative values. However, the 10 point difference in IQ measures between groups and the higher mean scores of control children in Australian samples has since been replicated in other studies [22,54], confirming these initial results.

While many studies have supported these original findings [22,25,26,28,29], the observation of cognitive deficits in children with PS is not universal. Two studies by Beebe et al. [20,21], conducted with different cohorts six years apart, did not find any group differences on the majority of cognitive measures. There was a group effect on the outcome of verbal fluency in the earlier study [21], however analysis of individual group differences was not reported. In the later study [20], there was a group effect in self-reported academic grades, however group differences failed to reach statistical significance on post-hoc testing. While these findings appear to provide contrary evidence, comparison between studies is difficult due to potential confounders. The first study included children with diagnosed attention deficit hyperactivity disorder, and it was reported that all children within the study taking stimulants were in the PS group. The latter study contained only overweight children, and overweight and obesity have been shown to be associated with cognitive deficits independent of SDB [55].

Ting et al. [30] also found little difference in academic measures between children with increasing severity of SDB, although one possible explanation for this could be in the study design. The subjects in that study were recruited through schools as part of a SDB education campaign which offered free PSG for interested or

Table 3
Difference in sleep parameters across SDB severity groups.

1st author	Group (*n*)	TST[h] (min)	SOL[h] (min)	SE (%)	%N1	%N2	%SWS	%REM
Blunden 2000 [19]	Control (13)	NR	NR	NR	2.7(0.5)	45.0(2.0)	27.4(1.7)	24.7(1.0)
	PS (13)				4.4(1.4)	46.0(1.9)	23.3(1.2)	26.2(1.1)
Beebe 2004 [21]	PS (17)	402(41)	NR	90.4(7.9)	4.1(2.1)	49.5(9.6)	30.5(7.9)	15.9(6.0)
	Mild OSA (9)	378(49)		87.8(11.5)	6.7(3.4)	49.1(9.4)	29.7(7.3)	14.6(5.0)
	MS OSA (6)	365(31)		81.3(10.7)	7.4(4.2)*[f]	46.7(11.5)	34.0(12.4	11.9(4.8)
O'Brien 2004 [29]	Control (31)	481(37)	21(20)	90.7(7.5)	NR	NR	21.1(5.3)	27.1(5.4)
	PS (87)	472(45)	27(30)	89.2(8.3)			22.6(5.3)	23.4(5.6)[a]***
Honaker 2009 [26] [g]	Control (76)	476(35)	22(22)	90.7(6.2)	6.1(4.6)	45.9(8.4)	25.9(8.3)	21.2(4.9)
	PS (76)	486(37)	18(17)	90.4(8.7)	8.0(8.1)	45.4(7.4)	25.9(6.7)	21.3(8.1)
	OSA (76)	481(43)	16(15)	91.1(7.2)	8.0(6.7)	44.2(7.7)	27.8(29.8[h])	22.9(16.7)
Beebe 2010 [20]	Control (37)	438(56)	NR	89.4(8.0)	2.9(1.3)	53.8(9.1)	23.5(7.3)	14.8(5.0)
	PS (26)	468(39)		89.9(6.4)	3.3(1.6)	54.5(8.8)	23.3(6.7)	16.7(4.1)
	Mild OSA (58)	429(62)		88.3(8.5)	3.8(1.8)	53.2(9.2)	21.5(7.2)	15.3(4.7)
	MS OSA (42)	442(62)		86.3(10.0)	3.5(2.1)	50.8(11.4)	20.6(10.1)	14.7(5.7)
Ting 2011 [30]	Non-SDB (10)	323(12)	12(8)	90.1(4.7)	1.4(0.8)	53.7(13.3)	24.4(12.0)	11.5(3.9)
	Mild SDB (21)	325(14)	12(8)	91.2(5.2)	1.8(1.4)	51.2(12.7)	26.9(12.6)	15.3(5.7)
	Moderate SDB (80)	323(19)	13(9)	90.8(4.7)	1.9(1.7)	53.9(12.8)	22.6(10.9)	14.2(6.1)
	Severe SDB (27)	331(12)	12(9)	92.6(3.6)	1.7(1.5)	56.9(14.0)	18.3(13.0)	16.2(5.5)
Miano 2011 [28]	PS (13)	420(57)	25(21)	85.9(12.5)	8.6(3.6)	31.7(6.8)	35.5(5.1)	18.8(4.2)
	OSA (31)	424(44)	26(16)	87.0(7.6)	9.3(4.1)	34.3(9.7)	30.1(7.4)[b]*	19.3(5.9)
Bourke 2011 [22,23]	Control (35)	415(7)	NR	86(1)	9(1)	48(2)	25(1)	18(1)
	PS (59)	395(6)		83(1)	9(1)	49(1)	24(1)	17(1)
	Mild OSA (24)	395(9)		81(2)	12(1)	44(1)	27(2)	17(1)
	MS OSA (18)	363(15)		79(3)	14(2)[c]*	45(1)[d]*	24(1)	16(2)
Jackman 2012 [27]	Control (37)	453(5)	28(5)	88.3(1.1)	8.6(0.6)	42.0(0.9)	26.7(0.9)	22.7(0.7)
	PS (60)	440(5)	23(3)	88.8(0.8)	9.0(0.5)	40.9(0.9)	30.2(1.2)	19.9(0.5)
	Mild OSA (32)	440(9)	28(6)	88.3(1.2)	10.0(0.7)	41.5(1.2)	28.3(1.4)	20.2(0.7)
	MS OSA (24)	431(10)	25(5)	88.0(1.5)	12.6(1.0)[c]***	40.8(1.3)	26.9(1.2)	19.8(0.8)[e]**

%N1 = minutes of N1/TST × 100; %N2 = minutes of N2/TST × 100; %SWS = minutes of slow wave sleep(N3 or Stages 3&4)/TST × 100; %REM = minutes of REM sleep/TST × 100; MS OSA = moderate–severe OSA; OSA = obstructive sleep apnoea; PS = primary snoring; SE = Sleep Efficiency; SOL = Sleep Onset Latency; TST = Total Sleep Time.
***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.
All data expressed as mean ± SD, except Blunden [20], Bourke [23,24] and Jackman [28] which are mean ± SEM.
[a] Control > PS.
[b] PS > OSA.
[c] Control = PS < MS OSA.
[d] Control = PS > Mild OSA.
[e] Control > PS = MS OSA0.
[f] Significance based on model difference. No between group differences reported.
[g] Values rounded to whole numbers where one or more decimal place given.
[h] Standard deviation is reported at 29.84 in original manuscript.

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Table 4
Differences in cognitive outcomes across SDB severity groups.

1st Author	Cognitive assessment	Domain	Result ↓ indicates poorer performance compared to control unless otherwise stated
Blunden 2000 [19]	WPPSI-R (5 y), WISC-III (6–10 y)	Verbal IQ, performance IQ, global IQ	PS ↓ on all domains
	WRAML	Memory	PS ↓
	ACPT	Attention	PS ↓
Beebe 2004 [21]	WISC-III	Verbal IQ, performance IQ, global IQ	No group difference
	WRAML	Memory	No group difference
	Stroop Test	Processing speed	No group difference
	GDS	Visual vigilance	No group difference
	NEPSY	Visual attention, verbal fluency	Significant group effect for verbal fluency. No post-hoc but mean scores higher in all SDB groups
	WCST	Executive function	No group difference
O'Brien 2004 [29]	DAS	Verbal ability, non-verbal ability general conceptual ability	PS ↓ on all domains
	NEPSY	Attention/executive function, language, visuospatial ability, memory and learning	PS ↓ on language and visuospatial ability
Hamasaki Uema 2007 [25]	RAVLT	Verbal memory	PS ↓ OSA = control, except for first recall
Honaker 2009 [26]	DAS	Verbal ability	Preschool: no group difference Primary school: PS and OSA ↓ OSA ↓ compared to PS
	NEPSY	Phonological processing, speeded naming, comprehension of instructions	Preschool: OSA ↓ on comprehension of instructions Primary School: No group difference
	PPVT-III	Receptive vocabulary	No group difference
	EVT	Expressive vocabulary	No group difference
Beebe 2010 [20]	WISC-IV	Vocabulary, block design	No group difference
	CVLT-C & CMS	Memory	No group difference
	GDS	Attention	No group difference
	Grooved pegboard task	Motor coordination	No group difference
	School grades	Grades A–F	Significant group effect for self-report grades. Post-hoc testing did not reach significance
Ting 2011 [30]	School grades	Chinese, English, mathematics, society, nature and science technology, arts and humanities	No group difference
Miano 2011 [28]	WISC-R	Verbal IQ, performance IQ, total IQ	PS & OSA ↓ on all domains. No difference between PS and OSA
Bourke 2011 [22]	WASI	Verbal IQ, performance IQ, full-scale IQ	PS, Mild OSA & MS OSA ↓ on verbal IQ and full-scale IQ. No difference between SDB groups
	WRAT-3	Spelling, reading, arithmetic	No group difference on mean scores, however proportionally more PS displayed impairments in reading than other groups. Proportionally more PS and MS OSA displayed impairments in arithmetic.
	COWAT	Verbal fluency	No group difference
	RCFT	Organisation ability	No group difference
Brockmann 2012 [24]	School grades	Mathematics, science, spelling	PS ↓ on all subjects OSA ↓ on science
Jackman 2012 [27]	Stanford-Binet	Verbal IQ, performance IQ, full-Scale IQ	No group difference on mean scores. Proportionally more MS OSA displayed impairments in all domains.
	NEPSY	Visual attention, phonological processing, comprehension of instructions, design copy, visuomotor precision	No group difference
	RBMT	Memory	No group difference
	Shape school, delayed alternation, spatial reversal	Executive function	No group difference

ACPT = auditory continuous performance test; CMS = children's memory scale; COWAT = controlled oral word association test; CVLT-C = California verbal learning test for children; DAS = differential abilities scale; EVT = expressive vocabulary test; GDS = Gordon diagnostic system (visual vigilance); IQ = intelligence quotient; MS OSA = moderate–severe OSA; NEPSY = neuropsychological assessment; OSA = obstructive sleep apnoea; PPVT = Peabody picture vocabulary test; PS = primary snoring; RAVLT = Rey auditory verbal learning test; RBMT = Rivermead behavioural memory test for children; RCFT = Rey complex figure test; Stanford Binet = Stanford Binet intelligence scales for early childhood; SDB = sleep disordered breathing; WASI = Wechsler abbreviated scale of intelligence; WCST = Wisconsin card sorting test (mental flexibility and visual reasoning); WISC = Wechsler intelligence scale; WRAML = wide range assessment of memory and learning; WPPSI-R = Wechsler pre-school and primary scale of intelligence; WRAT = wide range achievement test (academic functioning).

concerned parents. It is possible that the comparison group, labelled non-OSA, of which there were only 10 subjects, included primary snorers as participating parents were likely to have a vested interest in accessing the PSG.

Bourke et al. [22] found no group difference in mean scores of academic ability when assessed via univariate analyses. However, when the data were examined as the proportion of children within each severity group to display clinically significant impairment, it was found that a significantly higher proportion of children with PS were impaired in reading and arithmetic, compared to non snoring control children. A significantly higher proportion of children with moderate/severe OSA also were impaired in arithmetic compared

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to control children. In all SDB groups, a greater proportion of the cohort was impaired in both spelling and reading compared to what would be expected in the general population (16%). This suggests that although mean scores are within the normal range and there might be no statistical difference between groups, children with SDB, and particularly those with PS, are at greater risk of impairment.

The highest prevalence of SDB in children occurs during the pre-school years, yet there is a paucity of research conducted in this age group, with only one study specifically targeting pre-school children [27]. In that study, pre-school aged children with SDB were reported to have intact cognitive function, with no differences between SDB severity groups on any cognitive outcome measure. It was postulated that this may be a direct reflection of the duration of the condition [27]. That is, primary school children are likely to have had SDB longer than pre-school children, and it may be that the plasticity of the brain at the younger age is protective and the cumulative effects of SDB are not yet evident. The authors also suggested that it may be that deficits as measured by psychometric matrices are not evident until academic milestones are met.

It must be acknowledged that although children with PS show reduced cognitive functioning compared to non snoring children, the majority of their scores still fall within normative limits. It has been suggested that children with PS are not actually impaired at all, and the group differences are simply a reflection of high functioning control groups. It is true that in many cases, the control group mean scores are above average, however when one examines the percentage of children who would be considered to have a clinical impairment [22,23] or those who are carefully matched to control children [26], it is clear that some children with PS are negatively affected. It may also be that there is a yet to be determined phenotype which places certain children with SDB at risk of dysfunction regardless of severity. Indeed, previous studies have demonstrated that even in children with OSA, only approximately 50% show clinical impairment [22,56]. It has been proposed that morbidity is the result of a combination of OSA severity, genetic susceptibility and environmental factors [57], which will be discussed in more detail below.

Behaviour

Studies have consistently shown behavioural impairment in children with PS, although the manifestation of these differs (Table 5). Hyperactivity, inattention and somatic complaints are the most commonly reported deficits, although not universally so. As all behavioural measures in these studies are parent-reported, cultural differences in the perception of whether a child's behavioural trait is considered a problem will differ. For example, hyperactivity is not reported as a concern for Australian or Taiwanese cohorts, but is common in American cohorts, which may reflect community awareness of conditions like attention deficit hyperactivity disorder [58].

What is most surprising about the behavioural outcomes is that for the most part, children with PS have been shown to exhibit poorer behavioural functioning compared with those with more severe OSA. For example, in the study of pre-school children by Jackman and colleagues, deficits observed in the majority of the behavioural domains were greatest in the PS group, followed by the mild OSA group. In most behavioural domains, there was no difference between the non snoring controls and the moderate/severe OSA group [27]. In older children, Bourke et al. [23] reported that proportionally more children with milder forms of SDB had clinically significant scores (>65) on behavioural measures than children with moderate/severe OSA. Brockman et al. [24] also reported that children with PS had a higher risk of inattentive behaviour than those with OSA, and compared to the control group, children with PS had a 10 fold increase in daytime tiredness, whereas those with OSA had only a five fold increase.

Thus, if cognitive deficits in children with PS are, for the most part, no different to those in children with more severe OSA, and if behavioural deficits are worse, should we be questioning whether PS is simply a milder form of OSA or if it has its own phenotype? Indeed, while the mechanistic theories linking SDB with daytime deficits fit well within the model of OSA, they are not well applied to PS.

Proposed mechanistic pathways

In a comprehensive review, Beebe and Gozal [59] proposed a model linking sleep disruption, hypoxia and executive dysfunction via insult to the prefrontal cortex. In this model, arousal and gas exchange abnormalities result in disruption of the restorative features of sleep and/or disrupt cellular homeostasis. This interacting hypoxia/arousal model is the most widely accepted mechanistic explanation for cognitive and behavioural deficits in children with SDB. The conundrum is that children with PS do not, at least by current definition, experience intermittent hypoxia or increased arousals when compared to control children (Tables 1 and 2). However, there are some questions as to whether our current recording techniques and definitions are in fact sensitive enough to detect gas exchange abnormalities or sleep disruption in these children.

Hypoxia

There is compelling evidence from animal models that hypoxic insult to the developing brain results in long term cognitive deficits [60,61], however this relationship is not as clear in paediatric studies. Although SpO_2 is generally reported in studies examining daytime effects of SDB in children, very few have directly analysed the association between the two. In a population based oximetry study which included over 1000 children, Urschitz et al. [62] showed a dose response relationship between mild hypoxia (defined as a SpO_2 nadir of 91–93%), moderate hypoxia (defined as a SpO_2 nadir $\leq$90%) and level of mathematical impairment. Of note, being a habitual snorer was not predictive of mild or moderate hypoxia, with equal proportions of snorers and non-snorers in each category. In the 13 studies included in this review, only four examined the correlation between SpO_2 and cognitive and behavioural outcomes, and none found a significant association [21,22,27,28]. However, Kennedy et al. [63] examined the association between oxygen desaturation and neurocognitive performance in a sub-set of the Blunden et al. [19] cohort, and found the number of SpO_2 dips $\geq$3% per hour of total sleep, during REM sleep and when associated with arousals were negatively associated with working memory, attention and global IQ. Desaturation following a hypopnoea was related to performance IQ, global IQ and attention.

Determining the level of impairment of brain development caused by intermittent hypoxia is difficult in human subjects. Inducing repetitive hypoxic insults, similar to those carried out in animal models, measuring naturally occurring hypoxic insults intracranially, or dissecting the brain following a period of hypoxic insult, are not viable options when it comes to studies in children. As such, our current assessment methods may not be sensitive enough to determine the effects of such a complex interaction. Indeed, oxygen levels are predominantly measured at the periphery and it is unknown whether this is an accurate reflection of desaturation at a cortical level. Measures of cerebral oxygenation in response to a respiratory event such as snoring may provide a stronger association with cognitive deficits, with

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Table 5
Differences in behavioural outcomes across SDB severity groups.

1st Author	Behavioural assessment	Domain	Result ↑ indicates poorer behaviour compared to control unless otherwise stated
Blunden 2000 [19]	CBCL	Internalising, externalising, total problems	No group difference
Beebe 2004 [21]	BASC	Hyperactivity, aggression, conduct problems, anxiety, depression, attention	Significant group effect on all domains except anxiety, depression and attention. No post-hoc but mean score higher in all SDB groups compared to control
	BRIEF	Inhibition, shift, emotional control, initiation, working memory, planning, organisation of materials, self-monitoring	Significant group effect on all domains. No post-hoc but mean score higher in all SDB groups
O'Brien 2004 [29]	Connors'	Oppositional, inattention, hyperactivity, anxious, perfectionism, social problems, psychosomatic, ADHD index, DSM-IV inattentive, DSM-IV hyperactive, DSM-IV total	PS ↑ on hyperactivity, social problems, DSM-IV hyperactive, and DSM-IV total
	CBCL	Withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention, delinquency, aggression, internalising, externalising, total problems	PS ↑ on withdrawn, anxious/depressed, social problems, attention, delinquency and internalising problems
Beebe 2010 [20]	BASC	Hyperactivity, aggression, anxiety, depression, attention problems, atypicality, leadership, social skills	PS, mild OSA, and MS OSA ↑ on anxiety and depression PS & mild OSA ↑ on hyperactivity Mild OSA ↑ on aggression MS OSA ↑ on attention problems
Ting 2011 [30]	CBCL	Withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention, delinquency, aggression, internalising, externalising, total problems	Severe SDB ↑ compared to non-SDB (PS) on somatic complaints and attention problems
Miano 2011 [28]	ADHD Rating Scale	Hyperactivity, inattention, total ADHD rating	PS & OSA ↑ on all domains. No difference between PS and OSA.
Bourke 2011 [23]	BRIEF	Inhibition, shift, emotional control, initiation, working memory, planning, organisation of materials, self-monitoring, behavioral regulation index, metacognition index, global executive function	PS, mild OSA & MS OSA ↑ on behavioral regulation index, metacognition index, global executive functioning, shift, initiate, working memory and planning PS & mild OSA ↑ on self-monitoring On all indices, mild OSA had the highest mean score and the greatest proportion of children with impairment.
	CBCL	Withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention, delinquency, aggression, internalising, externalising, total problems	PS, mild OSA & MS OSA ↑ on internalising, externalising, total problems, withdrawn, somatic complaints, thought problems and attention problems Mild OSA & MS OSA ↑ on rule-breaking behaviour and aggression Mild OSA ↑ on social problems PS, mild OSA & MS OSA had significantly greater impairment on internalising, externalising and total problems
Brockmann 2012 [24]	Author devised questions	Hyperactivity, inattention, daytime sleepiness	PS ↑ on all measures OSA ↑ on inattention
Jackman 2012 [27]	BRIEF	Inhibitory self-control, flexibility, emergent metacognition, global executive function	PS & mild OSA ↑ on all domains. PS ↑ compared to MS OSA on flexibility and global executive composite PS showed highest proportion of impairment on all domains except inhibitory self-control
	CBCL	Internalising, externalising, total problems	PS, mild OSA, MS OSA ↑ on internalising PS ↑ on externalising PS & mild OSA ↑ on total problems PS showed highest proportion of impairment on all domains
	ABAS	Conceptual composite, social composite, practical composite, general adaptive functioning	PS ↑ on all domains. Mild OSA ↑ on practical composite PS showed highest proportion of impairment on all domains
Tripuraneni 2013 [31]	BASC-2	Hyperactivity, aggression, depression, withdrawal, externalising problems, internalising problems	Obese OSA ↑ compared to PS and non-obese OSA on depression, withdrawal, internalising.

ABAS = adaptive behavior assessment system; ADHD = attention deficit hyperactivity disorder; BASC = behavioral assessment scale for children; BRIEF = behavior rating inventory of executive function; CBCL = child behavior checklist; Connors' = Connors' parent rating scale-revised long form; MS OSA = moderate–severe OSA; OSA = obstructive sleep apnoea; PS = primary snoring; SDB = sleep disordered breathing.

one study showing differences in cerebral blood flow velocity obviating group differences in cognitive function between children with mild SDB (AHI < 5 events/h) and non snoring controls [64].

Without evidence to assume that there is no effect of intermittent hypoxia on the developing brain would be misguided. Research has recently shown that with the improvement in OSA following treatment, including increases in oxygen saturation, there are concomitant improvements in electroencephalogram (EEG) slow wave activity (SWA), the quantification of delta power during slow wave sleep [65]. As EEG SWA is a marker of cortical development [66], it may be that the effects of repetitive hypoxia are better observed through the impact on developmental markers.

Arousal

Comparatively more literature exists regarding the mechanistic links of repetitive arousal from sleep in the association between SDB and daytime deficits. An arousal is defined as an increase in EEG frequency for three or more seconds (excluding spindles), which in REM are accompanied with an increase in submental EMG

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amplitude [67]. The underlying theory is that repeated arousals related to respiratory events lead to sleep disruption or fragmentation, which is then manifest as excessive daytime sleepiness, in turn resulting in daytime functional deficits. However, as can be seen from Table 2, sleep parameters, as currently defined, are primarily conserved in children with SDB, regardless of severity. In fact, the lack of differences in sleep parameters, particularly those relating to sleep quality, such as sleep efficiency, led to an early suggestion that excessive daytime sleepiness was not a usual feature of the disorder [39]. This contention has been supported by research indicating that daytime sleepiness was not a prominent concern of parents with snoring children [68]. More recently, through studies of objective assessments of sleepiness via a multiple sleep latency test, it has become understood that sleepiness may be present in children with SDB, particularly if it is severe or the child is obese [69,70], but this is manifest differently than in adults. Rather than experiencing lethargy, a sleepy child is more likely to become overactive, emotionally labile and oppositional [71], the very behaviours consistently observed in children with SDB.

The evidence that there is relatively little sleep disruption in children with SDB has led many authors to speculate whether the current definitions for arousal are sensitive enough to detect sleep fragmentation, particularly in children with milder forms of SDB [27,29,72]. The current definition for scoring arousals does not allow for slow high-voltage changes in EEG during delta activity and as such cyclic alternating pattern (CAP) analysis has been used as a measure of more subtle sleep instability in children with SDB [73,74]. This analysis consists of examining the EEG during non-REM sleep and identifying the transient events from the background rhythm. CAP can be affected by events such as snoring which do not create enough disturbance to warrant detection using traditional scoring criteria. An increase in sleep instability is reflected in an increase in CAP rate, which is the percentage of CAP time to NREM sleep time [75].

Lopez et al. [74] examined CAP in a group of primary snorers (AHI < 1, $Sao_2 > 92\%$ and RDI < 1.5 events/h), clinically referred for a range of sleep and behavioural complaints, and compared them to age matched non snoring control children. No difference was found between the two groups on the traditional measures of PSG including AHI, sleep efficiency or arousal index. The PS group however showed a significant increase in CAP rate and CAP during slow wave sleep when compared to controls. These results suggest that sleep disruption is indeed a factor in PS. Additionally, a positive correlation was found between children who had presented with behavioural complaints and CAP rate, suggesting that an increase in sleep instability is related to behavioural problems. CAP rate differences have also been shown in children with mild OSA (AHI ≥ 1 but <5) [73].

While these studies show that CAP may identify more subtle arousals and sleep disruption not detectable on current scoring methods, the analysis is labour intensive and, although automatic scoring software has been developed, it is not widely utilised clinically. Tauman et al. [76] developed a simple tool to measure sleep pressure as an indicator of sleep disruption in children with SDB. The sleep pressure score is calculated as: (respiratory arousal index/total arousal index)/(1 − spontaneous arousal index/total arousal index). A threshold score of 0.25 was derived as the cut-off for increased sleep pressure. They showed that sleep pressure score increased as a function of increased AHI, levelling off at an AHI of between 30 and 40 events/h in primary school-aged children. Thirty three percent of the children in the study also underwent neurobehavioural testing following their PSG [77]. The results from that subset demonstrated that children with SDB who had a sleep pressure score greater than 0.25 had impairments in aspects of memory, language, verbal comprehension and visuospatial abilities. Of note, it was reported that a sleep pressure score of 0.25 corresponded to an AHI of approximately 7 events/h. This suggests that this measure may only be applicable to children with moderate to severe OSA and not sensitive enough to determine increased sleep pressure in children with PS, however more studies are required.

Power spectral analysis of the EEG signals has also shown evidence of more subtle sleep disruption in children with SDB. Bandla and Gozal [78] showed that obstructive events were associated with changes in EEG patterns despite not being associated with clinically defined arousals. In that study, the authors examined EEG power across the delta, theta, sigma and beta frequencies directly prior to, during and immediately following obstructive events without arousal in eight children aged 2–8 years with OSA (mean AHI $= 9.8 \pm 2.2$ events/h). They found that there was a significant decrease in delta and increase in theta power during an event. Immediately following the event, delta rebound was observed with a corresponding decrease in theta power. The authors concluded that important dynamic changes in EEG were being missed with current measurement techniques and it may be these changes that play a role in neurocognitive dysfunction.

One factor that may be missed using current sleep scoring techniques are sub-cortical activations, defined as a combination of increased heart rate, increased activation on submental EMG, or distortion of respiratory belts [79]. It has previously been reported that only 50% of obstructive events in children are terminated by a cortical arousal, yet over 80% of events result in sub-cortical activation [1]. More recently, it has been reported that over 60% of REM related events in primary school [80] and pre-school [81] children were terminated with a sub-cortical activation. Specific examination of sub-cortical activation and whether there are any associations between these activations and neurocognitive and behavioural impairments in children with PS is yet to be conducted.

Therefore, while it can be argued that current techniques may not be sensitive enough to detect subtle dynamic shifts in brain activity in children with PS, an appropriate alternate method which can be used clinically is yet to be found.

Alternate mechanistic pathways and confounders

Inflammation, oxidative stress and obesity

Two alternate mechanistic pathways are those of systemic inflammation and oxidative stress. Both animal models and human studies show that intermittent hypoxia associated with SDB results in increased systemic markers of oxidative stress and inflammation, which subsequently correlates with cognitive and behavioural morbidity. These studies have been comprehensively reviewed in a number of publications [57,82–84] so will not be discussed here. However, it is worth noting that in children there appears to be a dose effect in the inflammatory response with SDB severity [56]. Moreover, Gozal and colleagues [56,85] demonstrated that markers of inflammation were higher in children with SDB who also displayed cognitive dysfunction, than in those with SDB alone, irrespective of severity. This dose effect in the inflammatory response highlights the likelihood that genetic or environmental factors are the underlying mechanisms behind morbidity in children with PS, suggesting that perhaps what we are missing, or what is yet to be discovered, is the ability to phenotypically identify those most at risk.

The association between SDB and daytime deficits is further confounded by obesity, which has independent effects on inflammation [86] and behaviour and cognitive functioning

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[87,88]. Tripuarneni et al. [31] recently reported that obese children with OSA had significantly poorer quality of life and behavioural outcomes than normal weight children with OSA, who were not significantly different from children with PS. As overweight and obese children are over-represented in more recent studies of children with SDB, this co-morbidity represents an important confounding factor in the relationship between SDB and daytime functioning.

Referral bias

It is possible that children with PS may present to their health provider due to ongoing behavioural concerns, rather than concerns primarily about sleep. Indeed, anecdotally, many clinicians report an increase in SDB related consultations following popular media coverage of the potential association between OSA and problematic behaviour. Beebe et al. [21] reported that in their cohort, all the children who had been prescribed stimulants fell into the PS group, with unmedicated children in the more severe OSA groups. In addition, many children presenting to clinical sleep services with snoring have concomitant behavioural disorders of sleep [89] which may contribute to their daytime problems. If there is a referral bias in children with PS, it may be that the cognitive deficits observed are mediated by their concomitant, although possibly unrelated, behavioural problems.

Inter-relationship between behaviour and cognitive functioning

Beebe et al. [20] tested the mediating role of behaviour on school performance in children with SDB. They showed that the group differences in academic grades were only marginally attenuated by demographic and sleep factors, but were markedly attenuated by behavioural outcomes, with group differences in academic grades no longer significant after the effect of behaviour was controlled for. Biggs et al. [90] also recently postulated that cognitive performance in children with SDB is mediated by behavioural deficits. In a four-year longitudinal study, children who underwent treatment for SDB, the majority of whom had moderate to severe OSA at baseline, showed improvements in Performance IQ but not verbal IQ or any academic measures. No improvements were seen in behaviour in either the treated or untreated groups, the majority of whom had PS at baseline. Both groups were reported to have significantly poorer behaviour than non snoring children at baseline and four years later. This is contrary to previous treatment studies which have reported improvements, sometimes dramatic, in behavioural outcomes in children after treatment of SDB [54]. These differences in outcome may reflect the duration of follow-up and/or the lack of untreated children or children with PS as a comparison group. It may also be that the improvements in behaviour reported in the short term studies are an acute response to improvements in sleep for both the child and parent, rather than a sustainable change in behaviour.

Biggs and colleagues [90] suggested that the lack of improvement in verbal IQ may be related to the different aspects of intelligence targeted by verbal and spatial abilities. Verbal IQ is a measure of crystalised intelligence, which describes the cognitive skills highly influenced by formal learning experiences. Performance IQ assesses fluid intelligence, which are the cognitive skills reliant on one's ability to adapt to new situations. Fluid Intelligence is reflective of incidental learning [91]. As research indicates that schooling has a larger impact on verbal IQ than Performance IQ [92], it may be that the behavioural problems reported in children with SDB result in poor attention in formal learning settings, particularly during crucial periods of development and maximal brain plasticity [93]. Indeed, the most consistently observed area of cognitive deficit in children with PS is verbal knowledge and language development (Table 3).

In support of this theory, Biggs et al. [94] examined group differences in the dissipation of EEG SWA as a marker of homeostatic regulation [95], in the Jackman et al. [27] pre-school cohort. The results showed that children with PS displayed significantly higher SWA at the beginning of the night compared to the other groups, yet dissipation across the night was not impaired. Conversely, children with moderate/severe OSA had similar SWA to controls at the beginning of the night, however showed impaired dissipation, with significantly higher SWA at the end of the sleep period. The authors concluded that children with PS may be sleepier at sleep onset, but have intact homeostatic regulation, whereas children with moderate/severe OSA have impaired recovery of sleep debt. This suggests that sleepiness related behavioural concerns may be affecting cognitive performance in children with PS, but as slow wave sleep is associated with neuronal development and memory consolidation [66,96], the attenuated brain activity during sleep may underlie the cognitive dysfunction in children with OSA.

Environmental factors

It may also be that environmental factors are playing a larger part in functional outcomes than is currently recognised. Although many studies co-vary for maternal education and socio economic factors which are often higher in the control group and ensure that there are no demographic differences between clinical groups, these factors may be causing inherent effects that cannot be statistically controlled for [97]. For example, Honaker et al. [26] demonstrated a dose–response relationship in deficits of verbal fluency in a study where all children were recruited from the community, rather than from clinical referral and were tightly matched on maternal education, ethnicity, age and gender. A recent randomised control trial examining, among other things, the effect of treatment on cognitive and behavioural morbidity in children with mild OSA, showed that African American children and obese children were less likely to show improvements in AHI with time, irrespective of treatment [98]. For the most part, due to the recruitment protocols of the studies, it is unlikely that environmental factors would be different in PS compared to OSA, which may provide some explanation as to the similarity in cognitive and behavioural outcomes. However, it is impossible to control for all environmental confounders completely, and more longitudinal and randomised controlled trials are needed to determine the true effects of these confounders.

Conclusions

PS is currently viewed as the minimum anchor point for the continuum of SDB, yet despite the absence of recognised intermittent hypoxia or repeated arousal, children with PS experience similar cognitive and often heightened behavioural deficits compared to children with OSA. As children with PS constitute up to 70% of children with SDB and are rarely treated for their condition, there is an urgent need to understand what we are missing in regards to the mechanisms involved in their cognitive and behavioural morbidity. It may be that a level of hypoxia or arousal exists in PS but is undetectable using our current assessment techniques. More controversially, it may be that PS is part of a more complex phenotype and not simply a milder form of OSA. If this is the case, then a paradigm shift regarding the potential mediating factors of daytime morbidity is needed. Whatever we are currently missing, recent research suggesting that deficits continue over time in children with PS necessitates further specific investigation into

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both the mechanistic pathways and treatment options that directly address the morbidity of PS.

Practice points

- Children with PS experience similar cognitive and behaviour morbidity as children with OSA
- Cognitive and behavioural deficits in children with sleep disordered breathing are most commonly attributed to intermittent hypoxia or increased arousal, yet children with PS do not, by definition, have these problems
- While it may be that our current assessment techniques are not sensitive enough to detect subtle changes in oxygen saturation or sleep disturbance in children with PS, the association between PS and cognitive and behavioural morbidity may also be due to alternate mechanisms such as inflammatory response or environmental influences
- Obesity, referral bias and the inter-relationship between cognition and behaviour may also confound this relationship

Research agenda

To further understand the mechanisms behind the conundrum of cognitive and behavioural morbidity in children with PS, future research needs to:

- Provide and utilise more sensitive measures of oxygen desaturation and arousal
- Determine the independent effects of behaviour on cognition
- Consider that PS may not simply be a milder form of OSA, but be one element within a phenotypic profile that places children at risk of daytime dysfunction

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