Neurocognitive Function and Learning in Children with Sleep-Disordered Breathing

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Abstract

Developmental neuropsychologists address cognitive, behavioral, and emotional disorders within an integrated model or a developmental brain–behavior paradigm embedded in an extrinsically and intrinsically dynamic environment. Yet despite the abundance of studies aiming at the understanding of a variety of brain–behavior disorders, and their treatment, the vast majority of such studies focuses on daytime behavior, that is, as a start point and as an end point. Hence, the impact of disrupted sleep in the developing child is tremendously underrated. Mental processing difficulties and executive dysfunctioning, for especially verbal material, suggestively form the sleep disordered breathing profile, yet few studies have reached a level of evidence succinct to funnel studies or practice, and a clear need for them is evident. Thus, sleep in a child is a public health issue of utmost importance and healthcare providers should always reflect on sleep.

Introduction

Although sleep is "of the brain, by the brain and for the brain" (J.A. Hobson), findings on neuropsychological outcomes of sleep-disordered breathing (SDB) are surprisingly found within the sleep medicine literature and not within the developmental neuropsychology research. Developmental neuropsychologists address cognitive, behavioral, and emotional disorders within an integrated model or a developmental brain–behavior paradigm embedded in an extrinsically and intrinsically dynamic environment. Yet despite the abundance of studies aiming at the understanding of a variety of brain–behavior disorders, and their treatment, the vast majority of such studies focuses on daytime behavior, that is, as a start point and as an end point. For example, symptoms of attention deficit and hyperactivity disorders are observed during the day and consequently are assessed and treated during the day; but what happens at night? What is the nighttime phenotype of such neurodevelopmental (daytime) symptoms or disorders? Or conversely, what are the daytime phenocopies of sleep disorders? Animal studies consistently suggest an adverse impact on health by sustained

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sleep loss [1]; for instance, sleep loss may trigger generalized inflammatory and stress responses in the brain. Although substantive causative relationships between sleep loss and end-organ dysfunction are missing in children, it is widely assumed that when sleep is reduced either acutely or chronically, it is not without changes in brain and behavior [1–3]. The collective evidence points to the vital role that sleep plays in brain "development" and brain "performance." Unfortunately, the most forgotten, overlooked, or even actively ignored behavior is undoubtedly childhood sleep.

The implications of compromised sleep such as occurs in SDB in children are thought by sleep researchers to be multifaceted and potentially complex. Furthermore, as might have become clear throughout this book, if left untreated, or if treated late, pediatric SDB may lead to substantial and multifaceted morbidities. Indeed, SDB may induce cardiovascular and metabolic impairments, in addition to neurocognitive and neurobehavioral dysfunction. For example, manifestations of hyperactivity, inattention, poor concentration, poor impulse control, disruptive behavior problems, emotional lability, and poor school performance have been associated to non-optimal sleep such as SDB in childhood [4, 5]. Although the literature focusing on inadequate sleep in children is constantly and rapidly increasing, being a rather new pediatric discipline, it is plagued by the lack of consensus in the assessment of SDB, resulting in disparities in research findings, their interpretations, recommendation for treatment, and outcome assessments. For example, only recently neuropsychological findings are being associated to snoring and OSA separately, such that interest in the poles of the spectrum of SDB in children (see Chap. 18) will hopefully lead to accrual of divergent findings relevant to other SDB-spectrum symptomatologies along the spectrum and maybe even for other sleep problems in general. In fact, the SDB fragmented or disrupted sleep might be a good working model toward other sleep problems and their neurodevelopmental impact.

This chapter highlights our current understanding on the cognitive and learning consequences of SDB and aims at indicating cognitive and learning impairments evaluations that should alert the health-care provider.

A Developmental Neuropsychology Viewpoint

Before discussing the cognitive and learning impact of SDB, a synopsis of the intricacy of this young field will be provided and will underline why the study of the brain–behavior relationship is particularly versatile in children. In fact, when concluding upon the interrelation of brain–behavior such as in SDB in children, the factors discussed in this chapter need to be entered in such brain–behavior equation.

First, collective findings support the interrelation between brain and behavior; i.e., such an interrelation is studied by correlating structural changes in the developing brain with behavioral or functional changes, by investigating behavioral changes and making inferences about the structural maturation of the brain, and lastly, by studying the brain dysfunction and its relationship to behavioral disorders [6]. This interrelation can be qualitatively observed, quantitatively measured through lengthy and elaborative assessments, or visualized, for example, by imaging techniques. The study of this brain–behavior interrelation is especially important where a normal developmental process is being disrupted by an insult or injury, particularly because the impact of such disruption will be at the time of the interruption itself but additionally also in the longer term since the brain is a rapidly evolving system. Indeed, ongoing organic (i.e., neurological), cognitive, behavioral, and psychosocial development will likely be influenced, and it is the developmental neuropsychologist's challenge to capture the degree of impact on each of these evolving dimensions and reveal their interrelation in such a dynamic context. In fact, a child might "grow into its deficit." Thus, any developmental neuropsychologist considers and integrates *the age at time of insult, the age at time of testing, the time since the insult, the nature and severity of the insult, the state of brain development, and the*

level of cognitive ability (premorbid functioning) of the child in the profile equation.

Secondly, cerebral development follows a genetic code, e.g., proliferation, migration, metabolic and electrical activity, myelination, pruning, etc. Although psychological theories express "growing up" in terms of a preset series of developmental stages, individual variation is widely acknowledged with respect to timing of the stages and the level of mastery of the function. However, the stages themselves and the need to pass through each of them have been considered invariant. Alternatively, sleep is regarded as a window on the developing brain; i.e., sleep and sleep cycles begin at around 26–28 weeks' gestational age and are essential for the development of the neurosensory and motor systems in the fetus and neonate [7, 8]. For instance, the rapid eye movement (REM) sleep is thought to play a vital role in somatesthetic, kinesthetic, proprioception, chemosensory, auditory, vision, limbic (thus emotion), and hippocampal systems (thus [social] learning), while non-REM (NREM) sleep has been associated to creation of memory and long-term memory circuits. Maybe more importantly, sleep is considered essential for the maintenance of brain *plasticity* throughout our life span, and thus, considerable importance should be given to sleep and its problems, such as disordered breathing, in developmental neuropsychology. Relationships are bound to be multidirectional and presumably not always advantageous.

Thirdly, there is growing evidence that disruption to the brain during development may impose irreversible consequences. In contrast to adults, during childhood such disruptions are more likely of a generalized nature or affecting the brain as a whole. Furthermore, the equation of recovery profiles needs to include plasticity not only at the *neuronal level* but also at the *behavioral or functional levels*. Hence, the difficulty will remain to determine: *what is normal, variation of normal (*i.e., *delayed or deviating), or abnormal*. In fact, considering the trial-and-error nature of the adaptive brain–behavior relations, the brain–behavior equation should include the *environmental* factors at any stage of development by either placing the child at increased risk or conversely by protecting the child.

Finally, there is a need to acknowledge the *limitations* of evaluating immature (i.e., emerging), establishing, or developing skills when seeking evidence of impairment or dysfunction. For example, although executive skills develop from infancy, they are not fully measurable until late childhood. Conversely, it is still a misconception that the child's brain is a mini-version of the adult's brain, as such extrapolations from adult SDB impairments to pediatrics might be misleading. In other words, the test performance of the child unequivocally needs interpretation in such neurodevelopmental context. As a consequence, the core of each developmental neuropsychological assessment, interpretation, and treatment warrants full appreciation of an adaptive brain–behavior relationship profile of (dys)function.

As a last note, with respect to cognition and learning the neurodevelopmental functions discussed in this chapter, several paradigms can be chosen. Although it is neither our aim to discuss such neurodevelopmental paradigms nor to adhere to an ability–achievement discrepancy viewpoint, cognition and learning assessments may evaluate comparable behaviors. However, in spite of such a potential overlap, I would like to emphasize that each test assesses functions based on its underlying paradigm, and hence, interpretation of findings is limited to the underlying paradigm. Commonly, achievement tests are used to assist in diagnosing learning disabilities (e.g., dyslexia, dyscalculia) and are useful adjuncts to neuropsychological assessment. A neuropsychological assessment, which goes well beyond intellectual testing or a neuropsychological interpretation of psychological tests, requires a good working knowledge of test standards and of the specific psychometric characteristics of each test used in the realm of brain–behavior development. For instance, to list a few, does reaction time play a role in scoring, or how are omission and commission errors incorporated in the score, which norms are available, etc. For simplicity, we will subdivide the two functions—cognition and learning—discussed herein as nonacquired knowledge and acquired knowledge, respectively.

In summary, when practitioners continue to overlook sleep or nighttime behavior in their

professional activities, a long list of potentially misleading conclusions can be drawn. We therefore advocate an increased awareness for the commonalities and dissimilarities in behavior throughout a day–night cycle.

The Cognition: Nonacquired Knowledge

There are diverse concepts of cognition and how it should be measured and interpreted. Some have emphasized the importance of a general factor, *g*, representing what all the (sub)tests have in common and what determines our performance on each task, such as intelligence and global cognitive ability. Others have theorized multiple cognitive dimensions, such as verbal "abilities," nonverbal "abilities," memory, information processing, reasoning, abstraction or concept formation, or even awareness of strategies and methods of cognition or metacognition. Results from a myriad of (sub)tests, ages, and SBD criteria have been disseminated, and in what follows, we attempt to technically argue the impact of SDB on cognition from a sleep and from a developmental neuropsychological perspective (Table 33.1).

Given the history of pediatric sleep medicine and the interest in the assessment of sleep problems [9, 10], potentially the first neurodevelopmental associations regarding SBD were behavioral (see chapter on SDB and behavior). To date, behavioral reports likely precede any comprehensive neuropsychological assessment, or alternatively they are more feasible and readily studied, and as a result, they still prevail within the sleep literature. Alternatively, could they be observable phenomena of a *g*-effect or cognitive malfunctioning?

Pre-1990

Pre-1990 studies regarding SDB recruited subjects from clinical settings, either through ear–nose–throat (ENT) or psychiatric clinics, and relied heavily on parental report of behavior and academic performance [11–13]. Only gradually did true neuropsychological assessments find their way with a substantial heterogeneity in methodology (Table 33.2). Early studies [14–16] were suggestive of reduced nonacquired knowledge, with a potential reversibility after treatment. More interestingly might be the reaction time-error pattern of these children. In the Ali et al. [15] study, performance on both non-IQ (intelligence quotient) tests, a reapproximation of such ratios is suggestive that snorers performed worst of all, namely, fast with many errors, which would corroborate their vigilance findings.

Early 2000 and Onwards

In 2000, some norm-referenced studies were published suggestive of mild cognitive deficits. That is, while further "slicing" of the sample [17] during analyses into SBD severity categories (i.e., apnea–hypopnea index [AHI] ranged from 2 to 37); being 2.9 ± 0.9 for the mild group ($AHI \leq 4$; $n = 9$) and 16.8 ± 12.5 for the moderate ($AHI \geq 5$) group, the diminished performance even in the mild group was supported. A critical look at the results, however, shows that about 40% of the subjects fell in the clinical range regarding the global cognitive functioning (McCarthy Scales of Children Abilities, 1972) and on the quantitative subscale (note, $n = 5$), or mathematical abilities, while for about 30%, a time or error underperformance pattern might be assumed. Similarly, another norm-referenced approach [18] concluded executive dysfunction. Despite the conclusion of these studies, none of the averaged cognitive scores fell in the clinical range. Results may therefore reflect the normal distribution, yet alternatively, even though sample sizes remain small, an association between SDB and cognitive dysfunction was further supported.

Toward the mid-2000s, a tremendous boost in the number of more elaborate assessments of intellectual, verbal, and also memory, attention, and executive functions occurred, combined with a shift toward community-based recruitments and focused on treatment outcomes. Blunden et al. [19, 20] showed masked overall performance, even when allowing socioeconomic status (SES)

Table 33.1 Flags regarding cognition and learning of SDB in children

To keep in mind regarding		Despite the heterogeneity in methodology and mostly within normal range		
Sleep	Developmental neuropsychology	Red flag	Orange flag	Green flag (?)
SDB criteria	Not a mini-adult brain	"Learning"	Verbal (auditory)	Pictorial
NPSG parameters	Immature, developing, emerging skills	Vigilance	Motor	"General intelligence"
SDB assessment	([Mal]adaptive) plasticity	Achievement	Maths	
Recruitment setting	"Growing into deficit"	Processing	Memory	
Small samples	Age at time of insult	Attention	Mental flexibility or multimodal integration	
Intervention studies	Age at time of testing			
Sleep duration	Time since the insult			
Sleep behavior/problems	The nature and severity of insult			
	State of brain development			
	Level of cognitive functioning			
	Normal variation of normal–abnormal			
	Intrinsic and extrinsic environment			
	Risk–protective factors			
	Profile of (dys)functioning, hence comorbidity			
	Paradigm			

Table 33.2 The nonacquired knowledge

Research Team	Group 1	Group 2	Group 3	Group 4	Age	Function	(Sub)test	Result
Pre-1990								
Rhodes et al. [14]	5 OSA (AHI, 32.8 ± 35.2)	9 without OSA (AHI 1.9 ± 1.5)			Average of 13 years	Learning†	{Wide Range Assessment of Memory and Learning, ?}	Without-OSA children scored in the 90s range, the OSA children had scores <80, while no potential disparities regarding sociodemographic aspects were discussed
						Memory†	Especially verbal memory	
						Vocabulary†	{Wechsler Intelligence Scale for Children-III, ?} [normative score 100 ± 15]	
Ali et al. [15]	12 OSA (median>4% SaO_2 dip rate, 2.9/h)	11 snorers (1.0/h)	10 control (1.1/h)		5.8–12.5 years	Vigilance	{Continuous Performance Test, adapted from a program kindly supplied by Dr. E. Taylor of the Institute of Psychiatry for use on a laptop personal computer (Zenith Data Systems, St. Joseph, Michigan)}	Relief of mild to moderate SDB improved vigilance
						Reflection-impulsivity	{Matching Familiar Figures Test, revised version 1978}	No statistical differences
						Intelligence (IQ)	{Wechsler Intelligence Scale for Children-Revised, UK 1974 short version; by multiplying Similarities, Vocabulary, Block Design and Object Assembly subscales with 2.5} [normative score, 100 ± 15]	No statistical differences, but for instance, the SDB children's IQ was about 100, whereas the control's average was 113
Harvey et al. [16]	24 undergoing surgery NPSG obstructive event index (the sum of obstructive apneas, obstructive hypopneas, mixed apneas, and mixed hypopneas divided by total sleep time in minutes then multiplied by 60 ≥1)	15 without intervention or waiting list NPSG obstructive event index (the sum of obstructive apneas, obstructive hypopneas, mixed apneas, and mixed hypopneas divided by total sleep time in minutes then multiplied by 60 ≥1)			32.8 ± 17 months	General quotient†	{Griffiths Scales of Mental Abilities, 1970}[normative score is 100 ± 13]	At time 1, the mean total group general quotient was 96 ± 21, whereas 6 months later, the children that underwent surgery showed a nonsignificant 2.0-point difference and the nonsurgery children a significant 3.6 When the researchers excluded the neurologically impaired children from the follow-up testing, they concluded intervention did not improve mental ability (neither did the IQ of the nonsurgery children change)

2000 onwards

Owens et al. [17]	18 children with an AHI of 9.8 ± 11.2	Norm-referenced		5–12 years	Global cognitive, language, executive/attention, memory, visual perception/visual–motor, motor functioning areas	Conglomerate of tests {about 23 (sub)test administered during a 2-h assessment session}	Mild deficits in executive functions and motor skills were concluded based on the modest improvements in the same neuropsychological domains posttreatment
Archbold et al. [18]	12 children scheduled for adenotonsillectomy; mild SDB diagnosed when the AHI was ≥1 and < 10, and minimum oxygen saturation level (min O_2) remained at or above 90%	Norm-referenced		5–13 years	Executive functions	{Integrated Visual and Auditory Continuous Processing Test, requiring rapid response, 1995}, {Children's Memory Scale, 1997}, {Children's Category Test, 1993}, {Wechsler Abbreviated Scale of Intelligence, 1999}, and {Wechsler Individual Achievement Test WIAT, 1999}	Children with mild SDB display impaired levels of cognitive executive functions including sustained attention, vigilance, and mental flexibility, as measured by the timed, rapid-response pattern Other cognitive functions, including general intelligence and general reading ability, showed no impairment
Blunden et al. [19, 20]	16 children referred to ENT for snoring	16 matched controls		Mean age of 7.2 years	Full assessment of intelligence, in addition to memory and attention	{Wechsler Preschool and Primary Scale of Intelligence-Revised, 1976 and Wechsler Intelligence Scale for Children-III, 1974}; 4 memory subtests: picture memory†, verbal learning†, design memory†, and story memory† resulting in a screening index {Wide Range Assessment of Memory and Learning, 1990}; Auditory Attention† {Auditory Continuous Performance Test, 1994} measuring auditory selective and sustained attention	This study is suggestive of "protected" pictorial functioning, and potential masked overall performance
Lewin et al. [21]	12 severe OSA (RDI > 10 and nadir arterial oxygen saturation, nadir SaO_2 < 90%)	16 mild OSA (RDI between 0.5–10 and nadir SaO_2 > 90%)	10 Control (<–1 score on the Brouillette Apnea Symptom Scale)	4–12 years	Cognition	{Differential Abilities Scale, 1991}	All "ability" scores were within normal range

(continued)

Table 33.2 (continued)

Research Team	Group 1	Group 2	Group 3	Group 4	Age	Function	(Sub)test	Result
Friedman et al. [22]	39 ear–nose–throat surgery mean RDI was 6.5 ± 4.3, and the 9 children who did not undergo adenotonsillectomy had a lower RDI (4.3 ± 2.6) as compared with the 17 other children who did undergo adenotonsillectomy (7.5 ± 5)	20 communities			6.8 ± 0.2 years and 7.4 ± 1.4 years, respectively	Intelligence	A process-oriented test containing mental processing scales, i.e., sequential and simultaneous, and an achievement scale (note: this was not administered), each comprising several subtests{Kaufman Assessment Battery for Children, 1996}	Impaired neurocognitive functions are almost reversible at least 3–10 months following adenotonsillectomy
Kurnatowski et al. [23]	87 children and 34 children OSA defined as OAI >1 and oxygen desaturation SpO_2 <92%				6–9 years and 10–13 years, respectively	Sensorimotor coordination, perception, memory, learning ability, concentration, focused attention, and language reception	The Token Test including tasks with progressively longer and more complex instructions and abstract concepts {Token Test, 1978}, the diagnosis test of brain dysfunction {DCS-test, ?}, Luria auditory verbal learning test {LAVLT, 1976}, and the Rey complex figure test {RCFT, 1995}	Memory problems, concentration of attention deficits, learning disability, language dysfunction, lower sensorimotor integration, and perception, whereas the older children with adenotonsillar hypertrophy had memory problems and learning disabilities
Tucson Children's Assessment of Sleep Apnea Study or TuCASA [24]	77 OSA (AHI > 5) with home-based NPSG	71 controls (AHI < 5); group would currently not be interpreted as controls			6–12 years	Immediate recall, full-scale IQ, performance IQ, and math achievement	Conglomerate of tests	Weaker learning and memory were found, though differences between groups decreased when arousals were taken into account
Boston Study [25]	A composite SDB variable indicating the presence of any of the following three SDB symptoms: snoring ≥3 nights per week, loud or noisy breathing, witnessed nocturnal apnea, and analyses were rerun in a subsample of AHI ≥4 (being the 95th percentile of AHI in the sample)				5 years	Attention, planning, memory, and general cognitive ability Measure of sustained attention Full assessment of intelligence Attention, planning, and efficiency	NEPSY Attention and Executive Core Domain† (Tower†, Auditory Attention†, Visual Attention†) and the NEPSY Memory Core Domain† (Memory for Faces†, Memory for Names†, and Narrative Memory†) {NEPSY, 1998} 12-min visual Continuous Performance Test called Catch the Cat† [65] {Wechsler Preschool and Primary Scale of Intelligence, revised, 1989} Animal Pegs test†	Full-scale IQ and scores on the continuous performance tasks were well within normal range A group difference was found for attention and executive functioning even though results are visibly in normal range (i.e., >95)

Cleveland Children's Sleep and Health Study [26]	164 SDB categorized by OAHI ≥ 5 and/or OAI ≥ 1, and loud snoring during the past month, occurring at least 1–2 times per week; the OAH of the SDB group was 2.4 ± 5.6	671 controls; OAH of the non-SDB was 0.3 ± 0.4	8–11 years	Comprehension of spoken words and the ability to selectively attend to the response choices	{Peabody Picture Vocabulary Test, revised, 1985}	Overall scores were in normal range; verbal comprehension was 100.5 versus 103.6, mental processing was 99.9 versus 100.9 and so forth for the other subscales, and the continuous performance was nearly identical
				Mental processing and written language and mathematical skills	A set of 13 subscales and resulting in 5 composite scales {Kaufman Assessment Battery for Children, 1984}	Moderate group differences were observed for almost all cognitive measures, and the attenuation effects of confounders such as socioeconomic status need to be considered
				A 14-min computerized test of sustained attention and response inhibition	{Conner's Continuous Performance Test, 1995}	
Louisville preschool as well as school-aged study [22, 27–31, 66]	Various approaches regarding the SBD criteria		6–9 years	Cognition and learning	6 core subtests resulting in a General Cognitive Ability† Score {Preschool Form of the Differential Ability Scales, 1990}, i.e., verbal and nonverbal cluster scores interpretable as IQ with addition of the Matching Letterlike† forms and Recall of Digits† diagnostic tests, and five functional domains: Attention/Executive functions†, Language†, Sensorimotor functions†, Visuospatial Processing†, and Memory and Learning† in combination with the Design Fluency and Sentence Repetition subtest {NEPSY, 1998}	Although scores fell in normal range, masked performance was noted on General Conceptual Ability, Attention/Executive function (e.g., Tower, Visual Attention), while Design Fluency and Phonological Processing subtest scores were at the lower boundary
			Preschoolers and infants	Mental Development Index†	{Bayley Scales of Infant Development-II, 1993}	Lower mental scores

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Table 33.2 (continued)

Research Team	Group 1	Group 2	Group 3	Group 4	Age	Function	(Sub)test	Result
Other perspectives								
Carvalho [37]	79 children with questionnaire based-SDB	468 children with nonrespiratory sleep disorders (i.e., disorders in initiating and maintaining sleep, arousal, sleep–wake transition, and excessive somnolence derived from questionnaire scores)	633 normal control children		7–10 years	Visuomotor integration	{Bender Visual Motor Gestalt Test, 1999}	Cognition was not shown to be different between the normal children and the children with sleep disorders
Blunden et al. [67]	11 snorers	13 behavioral sleep problems	9 combined sleep problems (i.e., snoring and behavioral sleep problems)	13 controls	6.2–16.8 years	Neurodevelopment	{Wechsler Abbreviated Scale of Intelligence, 1999};{Children's Memory Scale, 1997}; {Test of Everyday Attention, 1999}; {Auditory Continuous Performance Test, 1994}	Reduced intelligence and attention
Kohler et al. [40]	48 OSA with an OAHI > 1	44 matched controls			3–12 years	Intelligence, cognitive functioning	Verbal† and nonverbal† IQ and composite IQ†, Fluid Reasoning† being inductive and deductive reasoning, Knowledge† or general information, Quantitative Reasoning† or numerical ability, Visual–Spatial processing† or ability to process spatial information and Working Memory† or the capacity to use short-term memory in problem solving{Stanford–Binet Intelligence Scale 5th edition, 2003}, as well as neuropsychological tests to measure auditory and visual attention, planning and problem solving, inhibition, language development, sensorimotor function, and memory and learning {NEPSY, 1998}	Verbal, nonverbal, and full-scale IQs are lower albeit in normal range preoperatively compared to controls The Fluid Reasoning, Knowledge, Quantitative Reasoning, Visual–Spatial, and Working Memory composite scores are reduced at any time point when compared to control but fall in normal range, and likewise, composite scores of the NEPSY for Attention/Executive† functioning, Language† development, Sensorimotor† function and Memory† were significantly reduced

Calhoun et al. [41]	AHI < 1	≥1 AHI < 5	AHI ≥ 5	6–12 years	Intelligence	{Wechsler Abbreviated Scale of Intelligence, 1999}
					Verbal and nonverbal reasoning ability	Verbal fluency {Animal Naming Test, 2003} or verbal learning and memory {California Verbal Learning test, 1994}
					Attention	A continuous performance test {Gordon Diagnostic System Vigilance and Distractibility, 1983} and via Digit Span† {Wechsler Intelligence Scale For Children-III, 1991}
					Executive functioning	{Stroop Color and Word Test-children's version, 2003} {Wisconsin Card Sorting Test-64 Card version, 2000}
					Memory	(i.e., also by Digit Span)
					Processing speed	Coding† {Wechsler Intelligence Scale For Children-III, 1991}
					Visual–motor skills	{Developmental Test of Visual-Motor Integration, 1997}

Reference to the neurodevelopmental function assessed, the test or test battery expressed as {…} and subtest or subscale as †

and IQ to covary in the analyses. Although limited by the fact that not all children underwent an overnight polysomnography (NPSG) and group definition was based on the mean respiratory disturbance index being <1, Blunden et al. should be commended for tabulating subscale scores, which clearly aid toward "clinical profiling." In fact, out of the 12 Wechsler subtests, the snorers/OSA group scores were comparable on three of them (performance subtests: picture arrangement,[1] object assembly,[2] and symbol search[3]), whereas for the remaining, albeit visibly within normal range, scores tended toward the lower boundary of the applied verbal as well as nonverbal subtests. A similar trend was found for memory functioning but was substantially outspoken for selective auditory attention performance. With respect to the latter, an important note might be that nearly all assessments rely on verbal instructions, but more importantly, our behavior in school and home environments equally depends on this function. Subsequent studies with a primary focus on intervention [21, 22] concluded that impaired, albeit in normal range, neurocognitive functions are almost completely reversible at least 3–10 months following adenotonsillectomy. Friedman et al. [22] focused on whether the stimuli are manipulated one at a time or simultaneously, regardless of item content, and these authors concluded that mental flexibility might improve with treatment. An equally interesting test approach was applied in Poland [23]. In contrast to the more Anglo-Saxon-oriented studies, these investigators included assessments of sensorimotor function and perceptual ability (Table 33.2). From a neuropsychological perspective, it would have been interesting to subanalyze the error patterns in performance since scores are suggestive to be within normal range.

Over the last 5–6 years, four major research projects have focused on the interrelation of SDB and neurodevelopment. These teams include the Tucson Children's Assessment of Sleep Apnea Study or TuCASA [24], the Boston Study [25], the Cleveland Children's Sleep and Health Study [26], and the Louisville preschool as well as school-aged study [22, 27–31]. The first group concluded that weaker learning and memory were found among children with SDB, although differences between groups studied decreased when arousals were taken into account and suggested that sleep fragmentation adversely impacts learning and memory and that hypoxemia adversely influences nonverbal skills. Similarly, the Boston group [25] concluded that SDB symptoms are associated with poorer executive function and memory skills and lower general intelligence in 5-year-old children. In the Cleveland-based study [26], analyses were adjusted for potential confounders (e.g., SES, weight, prematurity), and subanalyses were pursued, for instance, in the preterm group. More importantly, only the subanalyses based on snoring history revealed group differences on each of the (sub)tests except for mental processing and continuous performance. These findings support the presence of diminished (but within the normal range) performance among SBD children, whereas the subanalyses regarding snoring history, or parent report of loud snoring over the past month occurring 1–2 times/week or more, suggest that such mediating or moderating effect needs to be further explored. The Louisville assessments with respect to cognition and learning have been suggestive toward processing difficulties.

More recently, studies from the Gozal's lab are suggestive that the degree of hypoxemia correlates preferentially with deficits in executive function [32], whereas the magnitude of sleep fragmentation, as expressed by the number of arousals during sleep in response to respiratory events, appears to account for changes in attention and memory deficits [27, 33–35]. Similar findings were reported by the TuCASA group. In addition, Gozal and colleagues have explored other "direct and indirect" pathways that contribute to the cognitive phenotype, by examining markers of inflammation such as high-sensitivity C-reactive protein (hsCRP) levels, which were found to be higher in children with OSA and particularly in those who develop neurocognitive deficits. These studies

[1] Assessing planning, logical thinking, social knowledge.

[2] Assessing visual analysis and construction of objects.

[3] Visual–motor quickness, concentration, and persistence.

suggest that the magnitude of the inflammatory responses elicited by OSA is a major determinant of increased risk for neurocognitive dysfunction [36] (see other chapters). In other words, gradually separate attention is being given to snoring independently but also to other PSG-based parameters on how they contribute to neurocognitive outcomes. As a result, an overarching neuropsychological profile in terms of cognitive "executive" dysfunction is gradually emerging.

Other Perspectives

Incorporating other sleep behaviors may yield important insights. For example, Carvalho et al. [37] showed that an interaction between grade and starting time to school significantly increased the odds for cognitive dysfunction among those children with SDB. The merit of this study is the reflection on the mediating or moderating effect of SDB (albeit assessed by questionnaires), with respect to daytime but also nighttime functioning. Indeed, sleep problems are found to co-occur [38], and their comorbidity as well as their interrelation to sleep duration needs to be included when interpreting results. The combination of sleep problems and snoring has shown reduced intelligence and attention scores [37], and although analyses were considered exploratory in nature, these findings might further underpin the complexity of sleep problems, their assessment, and overall impact. Giordani et al. [39] indicated that their counterintuitive findings, being that worse outcomes were not clearly demonstrated for the children with OSA, may in fact reflect a combination of factors including age, daytime sleepiness, features of sleep-disordered breathing too subtle to show on standard polysomnography, and academic or environmental factors not collected in their study. We might add to this list the nighttime behavior. We also advocate the importance of applying more sophisticated methodologies to better understand the pathophysiology of childhood sleep-disordered breathing. Alternatively, the ongoing quest toward treatment benefits [40], questioning the neurocognitive gain, remained. In general, studies are suggestive that it is as if a veil covers the SDB children's performance. A potential "unveiling" answer to the questions on cognition and SDB may be provided by the multicenter Randomized Controlled Study of Adenotonsillectomy for Childhood Sleep Apnea (a.k.a. CHAT). Namely, children receive NPSG before enrollment to confirm an OSA diagnosis (OAI>1 or AHI>2), and researchers monitor their growth, blood pressure, neurocognition, learning, and behavior through a lengthy assessment. A second sleep study is conducted at the end of the 7 months, and researchers compare the results to the subjects' initial scores.

Contrary to previous findings, Calhoun et al. [41] expressed the relation between mild SDB ($1 \leq AHI < 5$) and neuropsychological performance as a noncausal but rather comorbid one, based on a 9-h NPSG recording of 571 children aged 6–12 years who underwent a 2.5-h neuropsychological evaluation *prior* to NPSG. Analyses of the three AHI groups (Table 33.2) were covaried for race. In contrast to previous studies, the range of scores was normal with a trend toward the lower boundary in the first two groups, i.e., except for Stroop Color–Word subtest, which measures the ability to shift cognitive inhibition and ability to inhibit an overlearned dominant response in favor of an unusual one. However, given their sample size, this is what you would expect in a large sample (i.e., the Gaussian curve), and this should have been addressed statistically. The authors should, though, be commended on their elaborative and precise selection of tests. Furthermore, this Stroop effect is rather fascinating in our cognition–learning quest of SDB.

Finally, Beebe et al. [4, 42, 43] studied and subsequently reviewed neuropsychological and achievement findings extensively up until 2006 and proposed in collaboration with Gozal an executive dysfunction or prefrontal cortex heuristic model. Lately, the same prefrontal cortex regions generating slow oscillations during NREM sleep, which are the main components of the A1 subtypes of the so-called cyclic alternating pattern (CAP) and map over the frontal and prefrontal regions of the scalp are being studied with respect to SDB. Indeed, reflecting upon the previous results, it is very tempting to hypothesize a

dysfunction in the prefrontal cortex, which controls executive functions and contains the brain areas that mature last, but notably, they also depend upon intact lower structures and circuits. This would corroborate with the Spruyt et al. [31] hypothesis, namely, the presence of slower information processing, or secondary memory problems, in the absence of retrieval or recall impairments among a subset of children with obstructive sleep apnea; i.e., inefficient/insufficient encoding may account for the primary deficit (see further). In fact, to date, such primary and secondary deficits have not been discussed thoroughly.

In conclusion, even though the heterogeneity in findings does not allow for a straightforward conclusion, they should be further filtered and contrasted. When performance of children with SDB is compared to otherwise healthy children, a masked profile of nonacquired knowledge emerges. In addition, (sub)tests applied and developmental functions assessed need to be further disentangled in terms of type I and type II errors and by their neuropsychological communalities and dissimilarities. As stated before, neuropsychological assessments are lengthy and elaborate, as several inferences need to be pursued in order to decipher convergent and divergent findings into a clear-cut impact of SDB, preferably embedded in a neurodevelopmental paradigm. Nonetheless, given the ongoing brain development, morbidity of SDB can be expected, and future studies will undoubtedly elucidate the degree. In search for the "*g*-effect" of SDB, we may conclude that morbidity along the spectrum can be anticipated; the question to what extent from a brain–behavior perspective remains to be vigorously studied.

The Learning: Acquired Knowledge

A child's main task is to energetically learn, and coincidently during that period in our life span, we sleep the most; i.e., it is the period during which neurogenesis, synaptic activity, neuronal activity as well as emotional, cognitive, and behavioral development occur at peak activity. Children's neurological circuits are particularly receptive to acquiring information. In parallel, substantial amount in REM and NREM sleep can be registered; that is, studies have indicated that the NREM plays a substantive role in homeostatic balance, while the REM sleep is presumed to be vital toward neuronal development. Contrary to the previous section, acquired knowledge in our childhood vastly results from our school or classroom environments, but also through our home environment, and intrinsically depends upon overall cognitive capacities.

Early Studies

In 1976, in a case-series report on apnea, Dr. Guilleminault reported that five out of seven children aged 5–14 years old had learning difficulties, with the older children having a general decrease in intellectual performance [44]. Ten years later, Weissbluth et al. [11] compared 71 children with parental report of "behavioral, developmental or academic problems" versus 355 control children at age 6, and found associations with signs of airway obstruction during sleep but reported also later bedtime hour, briefer duration of total sleep, longer night awakenings, and increased latency to sleep in them, hence compromised sleep. In 1998, Dr. Gozal focused on children that performed poorly at school, defined as performing in the lowest tenth percentile of their class ranking, and found a six- to ninefold increase in the expected incidence of SDB of these "failing" first-grade children.

These three studies form the basis of the need for studies focusing on academic achievement. In other words, is there a potential "learning debt" in children suffering from SDB?

More Recent Studies

As opposed to cognition, fewer studies have shown interest in school achievement and school performance. In addition, the construct of "school or academic performance" can be variously defined and measured, for instance, a low grade is not necessarily the same everywhere or perceived

similarly by everyone, something that we should keep in mind when reading and interpreting studies on achievement results. Ferreira et al. [45] surveyed parents of 988 children aged 6–11 regarding their child's sleep and behavioral patterns, and concluded that the "loud and frequently or constantly snoring" children did not differ from their "never snoring" classmates in terms of school achievement, but it is not clear if this conclusion reflected parental or teacher ratings. Richards et al. [46] retrospectively surveyed from ear–nose–throat (ENT) clinic 45 randomly selected parents of children with mean age of 6 years at time of surgery, and found that 10 of the 26 children (i.e., of those children >5 years old) had poor school performance. Of particular interest is a survey-based study that compared top versus bottom quartile performers of the class at ages 13 and 14 years when matched for age, gender, race, school attended, and socioeconomic status of children [47]. These investigators found that early childhood snoring was more frequently reported among bottom quartile performers. As stated before, the subanalyses performed in the Cleveland [26] study were similarly supportive of reduced cognition and achievement, albeit scores fell within the normal range for mental processing and written language, while mathematical skills were blunted (Kaufman Assessment Battery for Children, 1984). In a survey followed by in-home sleep study for children that were reported to snore always, Brunetti et al. [48] identified 710 (79.3%) nonsnorers, 141 (15.8%) occasional snorers, and 44 (4.9%) habitual snorers in the age range 3–11 years old. Poor school achievement was significantly more likely to be reported in SDB children, that is, 16.48–32.62% and 34.09%, respectively. As stated before, the TuCASA research group [24, 49–51] has reported findings in 6- to 11-year-old Caucasian and Hispanic children with SDB (e.g., RDI ≥ 1) being diagnosed by unattended home polysomnograms and questionnaires. Although learning problems appeared to be a single item collected through parental report resulting in a pooled average of approximately 5.6% and odds ratios ranging from 1.37 to 6.45, only Kaemingk et al. [24] reported academic achievement tests. The letter and single-word reading and math skills (Letter-Word Identification test, Applied Problems and Dictation form of the Woodcock-Johnson Psychological Educational Battery-Revised Tests of Achievement, 1989 and 1990) assessment did not reveal group differences between AHI < 5 ($n = 72$) versus AHI ≥ 5 ($n = 77$), though note the applied AHI cutoff. As stated in the cognition part, negative relationships between AHI and immediate recall, full-scale IQ, performance IQ, and math achievement were found. In Germany, reports of frequent snoring (in the absence of hypoxemia as assessed by pulse oximetry at home) were associated with twice the risk of poor performance in mathematics and spelling [52–54], i.e., poor academic performance equaling a grade 4–6 on a 6-point scale (i.e., approximating the lowest quintile) in mathematics, science, or spelling based on last school report, which was also reevaluated after 1 year (odds ratios ranged from 1.1 to 4.3). The sample was further analyzed in a stratified fashion, and habitual snorers (i.e., frequently to always snoring) with poor academic performance had a significantly increased risk of behavioral problems. The authors proposed a dose-dependent relationship between SDB and performance, albeit others suggest that confounders, mediators, and moderators might be in play [39, 55]. As an example, Montgomery-Downs et al. [56] explored in preschoolers the relationship between socioeconomic status, SDB, and learning through a survey. The "at risk" SDB (22% of the 1,010 sample) were more likely to be African-American, exhibited more daytime sleepiness and hyperactivity, as well as lower academic performance. Non-American studies such as Arman et al. [57] reported in a sample aged 7.2–13.5 years old of 96 habitual snorers (i.e., snoring often and always by questionnaire) learning disabilities (21.1%), and academic underperformance (3.3%) but failed to find group differences when compared to otherwise healthy children. Sogut [58] in a large epidemiological study of 3- to 11-year-olds found increased odd ratios of poor school achievement as reported by parents for nonsnorers (2.5%), occasional snorers (7.3%, i.e., snore twice a week), and habitual snorers (7.7%; i.e., three or more times snoring during the week), which

translates into an increased risk for occasional snorers by 3.05 (95% CI, 1.57–5.94) and for habitual snorers by 3.22 (95% CI, 0.92–11.22). Habitual snorers were subsequently invited for sleep study, and based on these stratified analyses by NPSG classification (AHI>3), the 15 OSA children had a 4.36 (95% CI, 0.95–20.01) increased risk for scholastic underperformance. Such morbidity accompanying nonoptimal sleep, even at the earliest stages of life and worldwide, undoubtedly supports the critical need for continued research in this area.

Other Perspectives

Visualizing what happens in the brain when we think or learn is certainly a hot topic, as stated in the cognition section, the importance of CAP, which "visualizes" the sleeping brain is rapidly growing. Likewise, event-related potential study (ERP), which is a procedure for studying brain–behavior relations when the brain is performing a task, is gaining territory within sleep research [59–61]. ERPs are changes in ongoing brain activity induced by environmental events such as auditory or visual stimuli. The amount of activation and how the activation is distributed across brain regions is currently being pursued in children with sleep problems, such as SDB. Given the neuronal and behavioral plasticity that characterizes childhood, this might reveal new insights regarding the *g*-effect, especially, if a learning debt is being caused by SDB. ERPs might thus be a more subtle and sensitive approach to capture the relatively masked performance issues of children with SDB, i.e., error-time profile patterns, processing (especially of verbal information), mathematical difficulties, and executive dysfunctions. It was shown recently that [60] brain indices of speech perception and discrimination (i.e., N1/P2), or auditory processing, are sensitive to individual differences in the quality of sleep. The same group also found that basic sensory processing in snoring children is longer than in controls, suggesting that delayed frontal activation requires more effort in snorers [59]. These findings might further corroborate the potential Stroop effect. More research is clearly needed to determine mechanisms underlying SDB, its impact, and its consequences, and in fact new measures such as these should be applied and closely examined to further elucidate the relationship(s) between nonoptimal sleep and neurocognitive morbidity.

In summary, the acquisition and the achievement of knowledge is undoubtedly cardinal for a child. Despite the conversed expeditions by sleep researchers in this chapter, aptitude is different from achievement, and thus, far only a few studies in children with SDB have included such achievement assessments. Indirectly this might hamper awareness of the SDB impact among teachers, remedial teachers, and educators, as well as the readily referral toward sleep studies. Nonetheless, most of the neuropsychological studies discussed within our part of the nonacquired knowledge incorporated to some extent (sub)tests, which assess learning and memory, or "acquiring" knowledge. The studies discussed in this section unfortunately depend on parental or teacher reports and vastly lack actual assessment. Furthermore, nearly all studies sampled snoring children. Independent from the critiques pertaining to the various studies over the years, it is fair to conclude that lower level of school performance in pediatric SDB is highly likely [44, 62, 63], even if the question on the presence of a learning debt remains unanswered.

The Brain–Behavior Equation: The Whole Is More than the Sum of Its Parts

Difficulty breathing during the night is suggested to elicit sleep fragmentation, which in turn may presumably affect nighttime behavior and ongoing brain processes. The documentation of the *g*-impact or cognitive malfunctioning effect as well as the potential longer-term consequence in terms of susceptible achievement will continue to expand. Alternatively, sleep is indisputably a complex behavior, both in its manifestations and regulation. Given the auxiliary evidence that sleep loss is associated to neuronal and cognitive

loss, the potential short-term and long-term consequences of SDB, more specifically regarding the history of snoring, call for more studies embedded in a developmental neuropsychology paradigm with precise interest in nonacquired and acquired knowledge. Indeed, contrary to the vast amount of readily observable phenomena or behavioral findings in SDB children, which are discussed in other chapters, the precise cognitive and learning effects of SDB are potentially being "overlooked." Moreover, literature potentially fraught by type II errors, publication biases, or outcome reporting biases might partially account for such discrepancy in neurobehavioral versus neurocognitive findings. However, in the realm of a neurodevelopmental paradigm, or the neuropsychological inference of an interactive brain, such discrepancy should be rather minimal. Studies within the field in fact support the clustering of learning and behavioral problems in children, in the short term and longer term [64]; hence, given a "developing" brain comorbidity is more the rule than the exception. Unfortunately, the task ahead of us is even more challenging by the diversity of SDB criteria and assessments, as well as the potential unequal weight of sleep parameters in the equation, for instance, hypoxia, fragmentation or arousals, and sleepiness. While from a developmental neuropsychological perspective, the version of tests applied, reference to normative scores, subtest scores or profiles, detailed information regarding functions being tested, qualitative observations, and the underlying paradigms of (sub)test applied are often lacking, yet prerequisites to better profiling a brain–behavior relation. So are test order, length of assessment, timing of assessment, and level of sleepiness, to name a few, needed when interpreting test results of children that had a nonoptimal sleep. Likewise, reports of ethnicity or race, socioeconomic status, or surrogate measures such as parental education are missing in several of the analyses. Finally, many studies potentially lack statistical power.

If indeed executive functions are affected by SDB (or nonoptimal sleep), researchers should incorporate considerations related to the maturational stage during assessment and also allow for the fact that executive functions cannot be considered as a unitary concept. It would be a tremendous understatement of how our brain develops and performs by not incorporating subcortical circuits. Several important questions emerge from this such as: what is the neurodevelopmental trajectory of a history of snoring, does SDB alter the neuronal circuitry irreversibly, how severe does the SDB need to be captured at the neuronal or neurobehavioral or neurocognitive level, and which skills will be most affected in the short term and longer term? Alternatively, it is highly tempting to ascribe blunted performance found in a wide range of sleep problems to the observable phenomena such as sleepiness, inattentiveness, impulsiveness, or hyperactivity of the child. However, each of these behaviors can be ambiguous and may be perceived differently by various observers, and as such, we obviously advocate multidisciplinary, multiraters, and multisetting approaches. This is especially the case since mechanisms through which sleep and its problems influence daytime performance are yet to be revealed. It is therefore important to note that many sleep problems may co-occur and that they are a source of stress for the child as well as any member of the family.

Summary

In conclusion, methodological differences among the published studies currently obscure the view on the precise impact that SDB may potentially have on cognition and learning. Mental processing difficulties and executive dysfunctioning, for especially verbal material, suggestively form the SDB profile, yet few studies have reached a level of evidence succinct to funnel studies or practice, and a clear need for them is evident. On a critical note, even though treatment effects need to be evidence-based, and "cure" might help in elucidating pathways, the overreliance on treatment studies, i.e., adenotonsillectomy, may create a substantial bias, such that, combined with a polarization along the SDB spectrum, it might further enhance type III and type IV errors in scientific findings. Hopefully, in due course, multicultural findings could further help elucidating the

presumed multifaceted and complex implications of nonoptimal sleep since they may further validate the brain–behavior equation throughout the day–night cycle.

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