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Sleep disturbances in children with attention-deficit/ hyperactivity disorder

Karen Spruyt[1] and **David Gozal**[1,†]

[1]Department of Pediatrics, Comer Children's Hospital, Pritzker School of Medicine, The University of Chicago, Chicago, Illinois, USA

Abstract

In this article, we advocate the need for better understanding and treatment of children exhibiting inattentive, hyperactive, impulsive behaviors, by in-depth questioning on sleepiness, sleep-disordered breathing or problematic behaviors at bedtime, during the night and upon awakening, as well as night-to-night sleep duration variability. The relationships between sleep and attention-deficit/hyperactivity disorder (ADHD) are complex and are routinely overlooked by practitioners. Motricity and somnolence, the most consistent complaints and objectively measured sleep problems in children with ADHD, may develop as a consequence of multidirectional and multifactorial pathways. Therefore, subjectively perceived or reported restless sleep should be evaluated with specific attention to restless legs syndrome or periodic limb movement disorder, and awakenings should be queried with regard to parasomnias, dyssomnias and sleep-disordered breathing. Sleep hygiene logs detailing sleep onset and offset quantitatively, as well as qualitatively, are required. More studies in children with ADHD are needed to reveal the 24-h phenotype, or its sleep comorbidities.

Keywords

attention-deficit/hyperactivity disorder; insomnia; limit-setting disorder; restless legs; sleep-disordered breathing

Attention-deficit/hyperactivity disorder: the basics

Attention-deficit/hyperactivity disorder (ADHD) was portrayed at least as long ago as Shakespeare:

> "…*it is the disease of not listening, and the malady of not marking*…"
>
> – King Henry IV, Act I, II

Over the past century, ADHD has been variously termed: minimal brain damage; hyperkinetic syndrome; hyperkinetic reaction in childhood (Diagnostic and Statistical Manual of Mental Disorders [DSM]-II, APA 1968); attention deficit disorder (DSM-III, APA 1980) with and without hyperactivity; and ADHD [1] with subtypes: ADHD

[†]Author for correspondence: Department of Pediatrics, Comer Children's Hospital, The University of Chicago, 5721 S. Maryland Avenue, MC 8000, Suite K-160, Chicago, IL 60637, USA, Tel.: +1 773 702 6205, Fax: +1 773 702 4523, dgozal@uchicago.edu.

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predominantly inattentive, predominantly overactive and combined type (DSM IV, APA 1994 [2]). Assessments and evaluation of children at risk for ADHD have primarily focused on observable phenomena during wake time with very little attention being given to sleep, thereby explaining the nature of the definitions used in clinical practice. Briefly, the child with ADHD characteristically manifests developmentally inappropriate symptoms of inattention, hyperactivity and impulsivity, and is diagnosed by an onset of symptoms before the age of 7 years, and presence for at least 6 months of cross-situational impaired functioning (e.g., school and home). Of note, potential changes are likely to be implemented in the forthcoming DSM-V, for instance in the subtyping categories, age at onset [3], or in the diagnostic separation towards two variants. ADHD is by far the most frequently reported developmental behavioral disorder, its worldwide reported prevalence rates varying between 5 and 12% in school-aged children, with a male-to-female ratio ranging from 4:1 to 9:1; although different incidences have been reported, potentially due to different diagnostic criteria being applied or as a corollary of cultural disparities and methodological limitations.

Attention-deficit/hyperactivity disorder is generally perceived as a neurodevelopmental condition potentially resulting from the interaction of multiple genetic and socioenvironmental factors exerting via multiple pathways symptoms marked and mediated by different phenotypes [4–7]. As such, comorbidity is not unlikely, and indeed 59–87% of children diagnosed with ADHD have at least one comorbidity, and 20% have three or more comorbid conditions or symptoms (see Box 1) [8]. Interestingly, potential links between sleep and ADHD were first published in 1957 [9] and 1971 [10].

Box 1. Synopsis of attention-deficit/hyperactivity disorder comorbid problems

Attention-deficit/hyperactivity disorder comorbidities may include:

- Learning disabilities (15–25%)
- Language disorders (30–35%)
- Social-adaptive dysfunction (e.g., 10% autistic spectrum disorders)
- Emotional lability (e.g., 15–20% mood disorder, 20–25% anxiety disorder)
- Motor coordination and balance deficits (60%) [103]
- Obesity [104,105]
- Sleep problems [106,107]
- Later in life, potential risks of oppositional deviant disorder (40%), conduct disorder (20%), substance abuse (15%) and criminal behavior [17,65,108–112

Sleep: the basics

It is widely assumed that when sleep is reduced or disrupted either acutely or chronically – that is, nonoptimal sleep – it is not without changes in the brain and behavior [11–14]. The collective evidence undoubtedly points to the vital role that sleep plays in brain ‘development’ and brain ‘performance’. The statement “sleep as a window on the developing brain” is especially pertinent [15] in the debate on ADHD as a disorder being characterized by developmentally inappropriate neurobehavior. Therefore, the most forgotten or overlooked behavior of this era is undoubtedly childhood sleep.

The sleep–ADHD interrelation

The interrelations between sleep problems and ADHD are complex and probably multidirectional and multifactorial, with significant impact on a child’s functioning (see

FIGURE 1, which will be discussed in more detail in the following sections). The ADHD symptomatology, and possible comorbidities, may disrupt sleep by increasing the probability of bedtime struggles or resistance, limit-setting sleep problems, inadequate sleep hygiene, insufficient sleep disorder or poor sleep quality, and alternatively each of them may result in ADHD-like day-time behaviors. Contrary to adults, a sleepy or sleep-deprived child may display hyperactive, impulsive, inattentive and disruptive behaviors. Overall problems with initiating and maintaining sleep may be a frequent concurrent behavioral complaint reported by caregivers of children with ADHD. Indeed, a review of the literature indicated that approximately 25–50% of parents reported sleep complaints, also in the absence of stimulant medication [16]. Conversely, the impact of sleep disorders, such as obstructive sleep apnea, snoring, restless legs syndrome (RLS) and periodic limb movement disorder, may resemble ADHD-like behaviors during the day-time, or co-occur as night-time behaviors with the day-time disorder.

Sleep–ADHD management

The guess-estimated prevalence of sleep problems in ADHD children is approximately fivefold that of healthy controls [16,17]. However, only in recent years have researchers shown increasingly more interest in sleep disorders beyond the potential (side) effects of ADHD drugs [18,19]. Methylphenidate, amphetamine, dextroamphetamine and pemoline, and even the first US FDA-approved drugs for ADHD children, are all likely to affect sleep, based on their mechanisms of action. The anticipated effects of these drugs would be: reduced total sleep time, increased sleep-onset latency and reduced sleep efficiency, and indeed, such effects have been reported in short- and long-term clinical trials [17,20–23], with sleep-onset insomnia and somnolence as the most reported complaints. Nevertheless, the effect of these drugs may also differ and be paradoxical; for instance, methylphenidate administered in the late afternoon reduced nocturnal activity and consolidated sleep, and thus improved the sleep quality [24]. Hence, methodological differences, such as dose, prescription plan, type (e.g., extended-release drugs), psychiatric comorbidities of ADHD and primary sleep problems, as well as the secondary drug effects or improvement of the comorbidity, make any firm consensus or recommendations potentially difficult, especially considering the relative paucity of well-designed pharmacological studies on ADHD-related medications that have included objective assessments of sleep in children. Future studies eliminating explicit key uncertainties (see Box 2) and that include objective assessments of sleep in ADHD children, whether as a side effect or not, may result in an improved generalizability of any of the current findings. Furthermore, there is a clear need for studies focusing on the treatment of sleep problems in children with ADHD. Improvements in sleep-onset latency and sleep duration, but not in problem behaviors, have been found for children who have stimulant-treated ADHD after treatment with melatonin at bedtime [25]. Alternatively, clonidine, diphenhydramine, cyproheptadine, trazodone, mirtazapine, guanfacine and tricyclic antidepressants have all been explored as treatment of insomniac behaviors, and have revealed mixed results [26]. Nonpharmacological treatments of sleep [27,28], particularly focusing on the initiation and maintenance of sleep in children with ADHD exhibiting problem behaviors, are increasingly attracting more interest, and thus in the near future are expected to be incorporated into multimodal intervention approaches and reflect the incremental interest and focus on sleep and ADHD (for a review see [29,30]). Regardless of the management of the child with ADHD, sleep problems should be viewed as playing a moderating and mediating role, and can be either primary or secondary (hence the gray zone in FIGURE 1).

Sleep–ADHD assessment

Whether a diagnostic hierarchy exists remains an open question, with recent studies indicating that sleep problems in children with ADHD are a significant source of stress for

both the child and family [31]. Furthermore, sleep problems in children with ADHD are common [32], and therefore, the assessment of sleep characteristics and of sleep problems in children with ADHD is highly encouraged (for a review see Cortese [32]). Subjective assessments of sleep can include parental questionnaires or interviews, self-report or surveying specific symptoms and their magnitude, such as, the presence of day-time sleepiness. We should note that nearly all behavioral parent-report questionnaires (e.g., Child Behavioral Checklist) have some sleep questions included. These could be potential 'red flags' towards the need for more in-depth history taking regarding bedtime routines, sleep hygiene, sleep duration and variability, as well as potential sleep behaviors. In addition, an advisable next step, would be a full sleep assessment [28], taken either subjectively (see Box 3) or objectively.

Objective methods for the measurement of sleep are overnight polysomnography with video (nocturnal polysomnography [NPSG]), actigraphy and multiple sleep latency testing – that is, measuring the time it takes from the start of a day-time nap period to the first signs of sleep. Although the list of objective sleep findings regarding sleep macrostructure in children with ADHD is long, they are currently inconsistent (see later and TABLE 1). Looking at the microstructure of sleep, children with ADHD showed a lower cyclic alternating pattern rate (CAP; i.e., an endogenous rhythm present in non-rapid-eye movement sleep (REM) characterized by a periodic EEG activity with sequences of transient electro–cortical activations [phase A of the cycle] that are distinct from the background EEG activity [phase B of the cycle]) and a lower number of CAP sequences, supporting the hypothesis of the existence of a hypoarousal state in these patients [33]. This is intuitively contrary to the perception that the hyperactivity–impulsivity and attention deficits or other behavioral phenomena observed during day-time reflect a 'hyperarousal state'. Nevertheless, the 'hypoarousal state' suggested by the assessment of sleep microstructure is further confirmed by the day-time multiple sleep latency testing studies that assess sleepiness, demonstrating that children with ADHD are about eight-times more likely to fall asleep in comparison with controls [34]. Increased movement and movement frequency (often perceived as restlessness) may thus assist in keeping the child awake (i.e., fighting off sleepiness). Interestingly, sleep characteristics with respect to ADHD subtypes have not been thoroughly explored. Third, even though the DSM diagnosis promotes the gathering of information from several informants and in several settings, few studies report findings of self-reports or even teacher reports. Similarly, sleep assessments and reports of sleep behaviors of the ADHD child are seldom, if ever, obtained. One of the obvious sleep-related symptoms is day-time somnolence and readers should be aware to the fact that many pathways can lead to day-time sleepiness or somnolence. In other words, the amalgamation of altered sleep, as discussed in this article, such as increased night-time motor activity, rapid eye movement differences, significant day-time somnolence, longer sleep latency, higher number of sleep cycles and many other features reported in children with ADHD [30,35], leads to the obvious conclusion that more rigorous studies are clearly needed to identify the putatively distinct night-time behavioral umbrella of ADHD (see Box 4).

Box 2. Potential issues of studies assessing links between attention-deficit/hyperactivity disorder and sleep

- Keep in mind professionally oriented bias
- Definition and diagnosis of attention-deficit/hyperactivity disorder (ADHD), or ADHD-based diagnostic paradigm
- Age and gender distribution disparities, as well as neurodevelopmental age
- Treatment or drug confounders

- Comorbidity: that is, common underlying etiology that leads to two or more different disorders, or one disorder leads to another, or where two unrelated disorders co-occur
- Respondent – that is, observer and recall bias – and subjective assessment tool
- Sleep (objective–subjective) assessment method, and consider each sleep behavior and sleep complaint, and night-to-night variability
- Sample generalizability – that is, clinical, community and referral
- Monitoring sleep when ADHD medication is given
- Time of day and night – that is, with respect to assessment and medication
- Health disparities

Behavioral sleep disorders & ADHD

From the meta-analyses performed by Cortese *et al*. (TABLE 1), which excluded medicated children and children with anxiety/depression comorbidity, it is clear that problematic behaviors at bedtime, upon awakening and, to a lesser extent, during the night, are frequently reported by parents [32]. Given that increased intra-individual day-to-day variability in children with ADHD has been suggested [29,36,37] and sleep habits are characterized by intrinsic factors attributable to the child, as well as their interface with family routines and environmental issues, the incongruence of the reported findings and the discrepancy between several objective findings and the parental complaints is not surprising. In addition, sleep may be considered as a developmentally regulated process that changes over time.

Sleep initiation problems

Poor sleep habits or those practices that promote difficulties in sleep initiation in a child with ADHD are multifactorial in the majority of cases. Indeed, increased arousal at bedtime might be due to intrinsic (e.g., ADHD *per se*, comorbidities or primary sleep problem) or extrinsic factors (e.g., parenting, parental mental health or sleep environment), as well as their interactions. To date, the contributing elements leading to the higher frequency of bedtime resistance [38,39], increased sleep-onset difficulties [32], increased instability of sleep onset [40], difficulties settling down, interruptions during bedtime routines [19,38] or anxiety, remain to be investigated. For instance, the child may be sent to bed when not yet sleepy, because of a delayed endogenous circadian rhythm potentially expressed as bedtime refusal and day-time somnolence, while on the other hand there might be a limit-setting problem, or inadequate enforcement of bedtimes by a caregiver, with resultant stalling or refusal to go to bed at the appropriate circadian clock-aligned time. Yet again, confounding factors, such as medication and comorbid status, chaotic family schedules and many others, may further obscure the interrelations between the child's ADHD and sleep behaviors. Acknowledging that the informants are typically the parents of the child being evaluated for ADHD, parental reports will probably be affected by reporting bias (e.g., a negative recall bias) or misinterpretation of symptoms. Such subjective reporting is further compounded by the perception of load and stress in parenting activities during day-time, all of which then lead to an overestimation of sleep-onset latency [41], or to an underestimation of parasomnias, the latter being considered as an intrinsic component of their child's development or as the unavoidable result of medication, ADHD itself and so on. The validity of such subjective reports therefore needs to be interpreted based on the assessment tool and setting (see Box 5). For instance, actigraphy-derived sleep-onset latency, a measure that should be objective and relatively stable, actually tends to be one of the least reliable

parameters in the context of actigraphic recordings [42]. Overall, based on the meta-analytical findings reported by Cortese *et al*. [32], the sleep latency expressed as standardized mean difference (i.e., mean of control group minus mean of ADHD group/ pooled standard deviation of the groups) would be −0.13 (95% CI: −0.35 to 0.09) for NPSG and −0.36 (95% CI: −0.56 to −0.5) for actigraphy. A review by the same group on sleep and alertness when controlling for potential confounders, such as medication, inappropriate diagnostic criteria and comorbidity, could not reveal any objective differences in sleep-onset latency or other sleep parameters besides increased motor activity and higher apnea hypopnea index in children with ADHD when compared with controls [34]. Although few studies include self-report, the study by Owens *et al*. is also indicative that children with ADHD report their own sleep to be more disturbed, particularly on items pertaining to bedtime struggles [39]. Even though the authors indicate that parents were instructed to merely help fill out the questionnaire and not answer or coerce the responses of their children, this aspect is hard to ascertain since questionnaires were filled out in the home environment. It has further been suggested that children with ADHD are more likely to wake their parents [43]. However, it remains unclear whether these children indeed disrupt the sleep in the home, whether there is a recall bias by the parents, whether delayed sleep-phase onset [44] or circadian problems are plausible causes of such reporting, and unfortunately, no information is currently available on these issues. Nonetheless, approximately one in three nonmedicated children with ADHD suffer from chronic sleep-onset insomnia [19,25]. Studies have demonstrated that melatonin administration leads to advanced circadian rhythms of sleep–wake and endogenous melatonin, and is consequently associated with enhanced total duration of sleep in children with ADHD and improvements in chronic sleep-onset insomnia, even if failing to improve problem behaviors, cognitive performance or quality of life [25,45]. However, less problematic behavior was reported by the parents, this was ascribed to the better sleep, or in other words the potential mediating role of sleep.

Box 3. Subjective sleep tools

Although few standardized sleep questionnaires, logs or diaries exist [113,114], several tools are available that have included reasonable psychometric approaches and can be administered with greater confidence. A useful sleep ‘screener’ can be one of the following, to name a few:

- Sleep Disturbance Scale for Children (SDSC) [115]
- Sleep Disorders Inventory for Students – Children and Adolescent form SDIS-C, SDIS-A [116,117]
- Cleveland Adolescent Sleepiness Questionnaire (CASQ) [118]
- Bedtime Routines Questionnaire (BRQ) [119]
- Sleep and Settle Questionnaire (SSQ) [120]
- Pediatric Sleep Questionnaire – Sleep-related Breathing Disorder scale (PSQ-SRBD) [121,122]

Problems in maintaining sleep

During the night, higher levels of nocturnal activity have commonly been described in children with ADHD. That is, these children not only move upper and lower limbs more frequently, but also for longer [46]. In fact, earlier versions of the DSM included the high nocturnal activity symptom in the diagnosis of hyperactive children, but this criterion was omitted in later revisions. Subjective [39,47–49] and objective [46,50] methods have confirmed the higher levels of activity or restlessness during sleep in childhood ADHD.

However, the precise impact, as well as the co-occurrence of day and night symptoms, such as restless legs, periodic leg movement disorders or apnea with the ADHD-symptomatology needs to be further investigated (see Box 6) (for nonbehavioral sleep problems, see Box 2). Studies have consistently reported on increased night-time awakenings [39,51,52]. Other studies have reported decreased arousal index during polysomnography [53,54], but few details are provided either by parental report or by actigraphic sleep. In the home environment, we rely heavily on parental and child reporting of their sleep, and few standardized instruments exist for assessment of night-time behavior. Therefore, we do not know how long it takes for these children to fall asleep again after an awakening or what their sleep environment is like. Sadeh and colleagues did not find any differences in the macrostructure of sleep (e.g., sleep-stage distribution and arousals) [55], yet the available meta-analyses (see TABLE 1) indicate an increased number of stage shifts, decreased sleep efficiency and increased parental reports of night-time awakenings.

Box 4. An update on the interaction between sleep and attention-deficit/hyperactivity disorder

To date, the precarious and fragmented evidence in the literature would suggest that despite high rates of parental reports of sleep disturbances in medicated and unmedicated children with attention-deficit/hyperactivity disorder (ADHD), objective sleep measurements do not seem to corroborate the extent of such disturbances as derived from parental reports [30]. Thus, these discrepant findings between subjective and objective sleep assessments in the context of ADHD further reinforce the need for extensive and in-depth characterization of ADHD subtypes in the context of their potentially distinctive sleep patterns.

Box 5. Sleep-onset latency

Mean sleep-onset latencies by actigraphy were on average 26.3 min in children with attention-deficit/hyperactivity disorder (ADHD), 18.6 min in a group of children with psychiatric morbidity but without ADHD and 13.5 min in a healthy reference group [41]. Similarly, Goraya *et al*. reported a mean sleep latency of 24 min (range: 10–39 min) when recorded by nocturnal polysomnography in a sample of medicated and nonmedicated children with ADHD [66]. A useful nocturnal polysomnography reference value of sleep-onset latency in 3–5 and 6–7 year olds is 24.1 ± 25.6 min and 23 ± 25.3 min, respectively [123].

Awakening problems

The restlessness and poor organization of sleep routines, such as those reported for bedtime, can also be present in the morning. Child diaries reported difficulty in the process of getting up from bed after sleeping, reported on less refreshing sleep and also indicated the presence of significantly more day-time sleepiness [39,56]. Furthermore, parents report these morning difficulties or the morning/day-time fatigue. Indeed, sleep disruption and insufficient sleep may lead to excessive day-time sleepiness, which could not only interfere with day-time performance, but also probably affect mood, attention and self-regulation, and subsequently impede scholastic performance [35]. Given that both sleep propensity and our need for homeostasis are regulated by biorhythms [57], the accurate assessment and interpretation of the presentation of excessive day-time sleepiness is a true challenge in children. In fact, even when a child is in a stimulating environment and is prone to learn, the overt presentation of sleepiness may not be the presence of yawning or sleepy behavior, but rather the opposite – disruptive behaviors, inattention, increased motor behaviors and so on. As previously mentioned, a shorter sleep-onset latency indicating somnolence was found in children with

ADHD [29,58,59]. However, several studies could not find an association between somnolence and poorer sleep quality or quantity [58,60], such that an intrinsic dysregulation of arousal is assumed to be present [36,58,60]. Whether this is true for all ADHD, or only for certain ADHD subtypes or comorbidities, remains unknown. In addition, most studies focus on sleep onset but not sleep offset. Sleep inertia or drowsiness when awakening might be equally informative, especially when considering the importance of our biorhythms on cognitive and behavioral performance. Similarly, it is unclear whether undiagnosed primary sleep problems are present in specific categories of ADHD, which then could be exacerbated by unstable or irregular sleep–wake patterns.

Sleep duration & variability problems

The high variability in sleep onset, and potentially in offset, found in children with ADHD undoubtedly requires careful statistical consideration. Namely, outliers could easily distort the overall week, weekday and weekend days reports. Thus, it is essential that the act of keeping an accurate diary should be implemented for a prolonged time to better depict, understand and interpret shifts in the sleep onset/offset times (see Box 7). Once again, insufficient sleep duration or poorer quality of sleep has been associated with increased psychiatric morbidity with more recent evidence indicating that short sleep duration is also associated with rule-breaking behavior and externalizing symptoms [61–64]. Similarly, it is known from sleep-deprivation studies that rebound effects can be seen in sleep macrostructure, yet we are unaware of any studies investigating this issue.

To summarize, children with ADHD with and without comorbidities may have altered sleep architecture, different sleep–wake patterns and sleep problems, which might further obscure the day-time and night-time brain–behavior interactions, and thus alter the phenotypic presentation. A generally reduced sleep efficiency and decreased sleep quality perceived by the child, as well as by the parent, are therefore one of the anticipated complaints. Sleep problems in children with ADHD are likely to be multidirectional and multifactorial in origin (FIGURE 1), ranging from psychostimulant-mediated sleep-onset delay in some children, to bedtime resistance related to a comorbid anxiety or mood disorder in others. Yet, in others, irregular schedules, primary sleep problems, parenting and several other factors may interplay with the night-time behavior of the already day-time-challenged child. Indeed, behavioral and nonbehavioral sleep problems may exacerbate or contribute to such ADHD symptomatology. Furthermore, parent-reported sleep problems may be associated with the subtypes of ADHD; for instance, the combined type is likely to be at increased risk of sleep problems, while children with ADHD-I type alone will have fewer sleep problems and in fact, have been found to be similar to healthy controls [65]. However, ADHD-I patients also suffered from more day-time sleepiness than typical controls [65]. Precise sleep profiling of the ADHD subtypes is, therefore, clearly needed (see Box 2). Notwithstanding, the quality and quantity of sleep is certainly affected in ADHD, and these children are at risk for nonrestorative sleep, which can undoubtedly impose adverse repercussions on day-time functioning, which may persist throughout adulthood. Although it remains uncertain whether the sleep problems among children with ADHD are directly related to the ADHD, the psychiatric comorbidity or to treatment, or whether ADHD children suffer from a primary sleep problem, the ‘sleep issues’ of ADHD clearly deserve extensive and thorough exploration, which unfortunately is lacking.

Box 6. Sleep and psychopathology

Given that sleep problems are not uncommon among children with psychiatric disorders – 61.5% exhibited delayed sleep onset, 63% reported nocturnal awakenings, 67.8% complained of restless sleep, 57.5% of leg jerks, 66.7% had daytime sleepiness, 49.4% of fear of the dark, 62.6% of bedtime struggles, 55.7% of snoring during sleep and 58.6%

had frequent nightmares [123] – awakenings that are the sequel of such sleep problems, or awakening that are triggered by environmental and intrinsic factors (e.g., restless legs syndrome [see later]) should be explored indepth.

Box 7. Sleep–wake schedules

Longer [19,38] and shorter sleep [39,56] duration, as well as unstable patterns or inconsistent sleep–wake patterns [35], have all been suggested. Hence, a pertinent assumption in aiming to understand the incongruence in the findings would suggest that issues with the statistical approaches, the assessment tools or other methodological aspects (i.e., subtypes, comorbidities or age) could all be contributing. More recently, studies have begun to increasingly attempt to capture the variability in sleep duration, in terms of weekday–weekend days differences, or discrepancies in sleep duration during school and holidays.

Nonbehavioral sleep disorders & ADHD

A retrospective study by Goraya *et al*. of NPSG data in 3–16-year-old children with ADHD revealed that 24% had obstructive sleep apnea, 30% had periodic leg movements during sleep (PLMS), 24% had upper airway resistance syndrome and 15% had obstructive sleep hypoventilation syndrome [66]. Furthermore, those with sleep-disordered breathing (SDB) were more obese and had more architectural sleep abnormalities that adversely impacted on the quality and quantity of their sleep. Since sleep disorders and symptoms are likely to coexist [67], both clinicians and researchers need to be attentive when facing ADHD symptomatology, since specific sleep problems that are unrelated to ADHD may be present and may contribute to the ADHD behavioral phenotype.

Insomnia & circadian rhythm

In delayed sleep-phase syndrome, no ADHD-like behaviors during the day-time have been reported, suggesting that the relationship only goes in one direction. Indeed, as previously discussed, this sleep onset/offset issue in ADHD is rather intriguing, since naturally, the propensity to sleep at a later time than normal is thought to be mediated by the biological clock located in the suprachiasmatic nucleus of the hypothalamus, allowing the child to fall asleep more easily when going to bed later. Night-time awakenings are equally problematic, and both sleep-onset insomnia and sleep-maintenance insomnia have been reported in ADHD children. Of note, sleep-onset insomnia is a component of delayed sleep-phase syndrome, and thus in some children these two conditions may coexist [68]. Given the characteristics of our biorhythms, forced ultradian cycling was apparent in unmedicated pre-adolescent ADHD boys, and has been related to alterations of brain monoamines and cortical inhibitory control accompanying the ADHD psychopathology [57]. Therefore, it is imperative to understand where sleep occurs in the 24-h cycle, if one wants to solve the problems of the day–night cycle in children with ADHD.

Parasomnias

Studies are suggestive that parasomnias manifest in seemingly independent ways, yet those affected often suffer underlying psychopathology. Children with ADHD suffer more nightmares [40] than controls and in one peculiar study [69], differences in dream content were more negatively toned, namely including misfortunes, threats, negative endings and physical aggression towards the dreamer. No differences in recall frequency or other general dream characteristics, such as length of the dream, were found. Other parasomnias [70,71] have not been consistently investigated or reported, such as, sleepwalking, sleep terrors,

sleep-related eating disorders, confusional arousals and rhythmic movement disorders (Box 8). After insomnia, enuresis is potentially the most acknowledged sleep problem. The association between ADHD and enuresis has been of interest because in enuretic children the high arousal threshold is one of three major pathogenetic factors (nocturnal polyuria and detrusor hyperactivity being the other two) [72]. Children with ADHD are at higher risk for enuresis [19,47,49,72,73] and given that arousability during REM sleep is rather variable, an overlap with REM sleep abnormalities has been hypothesized [72]. Indeed, such REM sleep abnormalities have been identified in children with ADHD, with either increased or decreased REM latency or REM sleep duration. Despite the inconsistencies in REM sleep findings in ADHD children, dysregulation of eye movements during waking hours and differences in eye movements during REM sleep have been reported in children with ADHD [74]. This provides an intriguing avenue for further exploration considering the proposed fronto–striatal comorbidities, such as autism or tics, and may also be of interest in the context of sustained attention and learning difficulties. Immature premotor and striatal circuits have been proposed to explain the association found between rhythmic movement disorders (e.g., head rocking) and ADHD [75,76]. Therefore, another interesting avenue in ADHD research may pertain to the identification of partial arousals, or arousals from stage 3 of sleep [77,78], as well as the presence of frequent sleep stage shifts [32]. Finally, differential diagnostic challenges remain given that sleep disorders such as RLS and SDB may promote ADHD-like behaviors.

Sleep-disordered breathing

Chervin *et al*. suggested that snoring and other symptoms of SDB are not only strong risk factors for future emergence of behavior problems, but might exacerbate hyperactive behaviors [79]. Hyperactivity and inattention, as well as aggressive (i.e., bullying, quarrelsome and cruel) [80] and emotional problems, such as mood disturbances [81], scholastic underperformance [82] and memory problems [83], have all been reported in the context of SDB and should alert us to their day-time behavioral phenotypes. Corroborating findings with respect to excessive day-time somnolence suggest the need to consider the potential presence of SDB in the diagnostic process of ADHD (Box 9) [84]. Of interest, children with SDB often complain about excessive sleepiness, unrefreshing sleep and insomnia. Even though neurobehavioral associations with SDB have been advanced – that is, symptoms of ADHD in children with SDB [85–89] – patterns are less definitive when examining the association between SDB severity and the magnitude of neurobehavioral problems. Continuing controversy exists regarding the frequency of SDB in children with ADHD. On the one hand, several questionnaire-based studies [39,90,91], are suggestive of increased frequency of symptoms characteristic of SDB in children with ADHD, and some objective studies have confirmed such subjective observations [32,92]. However, the Apnea Hypopnea Index (AHI) is a composite score and may not be the only parameter of interest, since the delineation of SDB requires more than just AHI [93]. Indeed, apart from intermittent hypoxemia, SDB includes fragmented sleep, such that the number of specific arousal types and arousability are also contributors to the severity of SDB, and can also impose behavioral consequences during the day-time. On the other hand, conflicting conclusions were drawn by the meta-analyses of Cortese *et al*. (TABLE 1) [32] and Sadeh *et al*. [55], whereby the former supported the association between SDB and ADHD, and the latter did not retain SDB as a risk factor in ADHD. Thus, more studies are clearly needed to assess the contribution of SDB, if any, to ADHD, its comorbidities and subtypes.

Box 8. Parasomnias

The current lack of studies on parasomnias can be ascribed to the potential misperception that such events are characteristic of normal childhood development, and are therefore unrelated to attention-deficit/hyperactivity disorder. In addition, the absence of

information on these issues can be the outcome of the limitations inherent to the majority of the tools for sleep assessment (which tool [e.g., questionnaire] and should frequency or severity be assessed?), and interpretation (e.g., other measures beyond the conventional nocturnal polysomnography parameters).

Box 9. Sleep-disordered breathing

Sleep-disordered breathing symptoms were significantly more associated with parent-reported daytime sleepiness (odds ratio [OR]: 2.2; 95% CI: 1.7–2.8), hyperactivity (OR: 2.5; CI: 2.0–3.0), inattention (OR: 2.1; 95% CI: 1.7–2.6) and aggressiveness (OR: 2.1; 95% CI: 1.6–2.6).

In otherwise healthy 3–5-year-olds, the apnea–hypopnea index is 0.90 ± 0.78 (range: 0–3.6) and in 6–7-year-olds 0.68 ± 0.75 (range: 0–6.6), while a range of 0–1.7 has been reported in children with attention-deficit/hyperactivity disorder of comparable age ranges [66].

PLMS & RLS

In the two major meta-analyses reported earlier [32,55], children with ADHD were either equally or more likely than controls to suffer from PLMS. Periodic limb movements are described as a rapid partial flexion of a limb, or periodic episodes of repetitive and highly stereotyped limb movements that occur during sleep (Box 10). Restless legs or the irresistible urge to move legs, often accompanied by uncomfortable sensorimotor sensations, is less extensively studied in children, and may even present differently than in adults. It has an incidence of 0.5% in children [94]. These sensations are worse at rest, in the evening or at night and are relieved by movement. Symptoms of ADHD and of PLMS/RLS were nearly twice as likely to co-occur [85]. Of note, growing pains may be misinterpreted as restless legs. Sleep disruption caused by the RLS/PLMS and the underlying dopaminergic pathway dysfunction ascribed to RLS/PLMS may reveal important insights into the sleep and wake behaviors of ADHD. As a potential consequence, lowered sleep quality might provoke behavioral sleep problems, such as in initiating or maintaining sleep. Furthermore, the replenishment of iron bioavailability has been proposed as a first approach in children with low ferritin levels [95] in the management of this symptomatology [96]. Furthermore, night-to-night variability has been suggested in RLS/PLMS [97], which in turn appears to exert an influence on the associations with related symptoms of mood, fatigue and inattention.

To summarize the nonbehavioral sleep disorders in children with ADHD, sleep problems are suggested to co-occur [67] and may relate to sleep duration and its variability, but also to the environment. Sleep quality might also be affected, and therefore elicit behavioral sleep disorders. Awareness to the day–night cycle of attention, hyperactive and impulsive symptoms when studying underlying pathophysiological, genetic and psychosocial pathways either in the study of sleep, in the study of ADHD or their interrelation will clearly advance our knowledge and foster evidence-based management of each of these conditions. Currently, methodological differences (see Box 2) in the aforementioned studies probably contribute to the intriguing and inconsistent findings. Owing to the preliminary stage of the scientific evidence, we can only concur with Nietzsche's quote from 1967: "There are no eternal facts, as there are no absolute truths … only interpretations".

Conclusion: pay attention to sleep

Since only a minority of children with ADHD actually present with a 'perfect' phenotype, in our article we have attempted to reproduce, an approach that resembles the approach used in

clinical practice. The main conclusion that can be drawn is that the understanding of sleep in ADHD, either as a consequence or as a contributor to the disease, is poor. More longitudinal studies are clearly needed to address the development of sleep problems in children with ADHD – that is, studies will be critical to the understanding of the night–day cycle of the brain–behavior relationship. The investigation of sleep in ADHD epitomizes the discrepant and often nonoverlapping methodological approaches taken by various disciplines. Depending on the discipline paradigm, or alternatively the wake or sleep point of view, differing opinions will emerge with respect to the mechanisms, and thereby the approaches, needed for diagnosing and treating ADHD. Commonalities and dissimilarities in findings need to be rigorously filtered, since for instance, the prefrontal and frontal cortices are suggested to play a critical role in the regulation of arousal, sleep, affect as well as attention [98,99]. Indeed, the neuromodulatory mechanisms of the sleep–wake cycle are closely associated with excitatory and inhibitory processes across the sleep–wake continuum [98,100,101]. In addition, the social environment will influence sleep. Nonoptimal sleep is unmistakably associated with decrements in neurobehavioral performance, and sleep complaints often comprise core features of psychiatric disorders. However, sleep problems are still too often perceived as part of the psychopathological symptoms, thus not as a primary disorder that then contributes to the symptoms.

Evidence-based guidelines for the management of sleep problems in children with ADHD are needed, and better understanding of the pathophysiological pathways throughout the day–night cycle will certainly emerge from future research. However, the interrelations of sleep and ADHD currently remain obscure at best. Strikingly, most of the past studies have relied on comparisons of frequencies rather than examining the severity of day- and night-time brain–behavior relationships. However, it is possible that some components of ADHD symptoms may relate to severity rather than to frequency, or relate to night- rather than day-time events. As such, day-time inattention, hyperactivity, impulsivity and night-time restless and motor activities during sleep may represent different elements of the same disease spectrum. Therefore, we advocate that day- and night-time researchers pay attention to each other, and cooperate in the delineation of an ADHD continuum within the sleep–wake cycle.

Box 10. Periodic limb movement syndrome and restless legs syndrome

Approximately 44% of children with attention-deficit/hyperactivity disorder (ADHD) have been found to have restless legs syndrome (RLS) or RLS symptoms, and up to 26% of subjects with RLS have been found to have ADHD or ADHD symptoms; of note, interpretation of results needs to factor in methodological limitations of most studies, notably the inclusion of clinical referral samples [124]. Furthermore, increased frequency of body movements during sleep has been reported in children with ADHD [58], and since RLS/periodic limb movement syndrome (PLMS) and ADHD may share neural pathways [125,126], as well as comorbidities (e.g., parasomnias, ADHD, oppositional defiant disorder, anxiety and depression are found in more than 20% of the cases with RLS/PLMS), the connection between daytime and night-time brain–behavior interchanges needs to be further explored.

Most importantly, some children with RLS/PLM disorder might complain of growing pains [127], but diagnosis of RLS is based on its clinical symptoms, such as the urge to move because of unpleasant sensorimotor sensations, which needs to be verbalized as such by the child. For a recent review see Simakajornboon *et al*. [128]. Generally, jerking legs might appear to the parent as a restless sleep. A potential clinical reference value for otherwise healthy children [123] is that for 3–5-year-old children, total PLM index will be 1.5 ± 1.4 (range: 0–4.9)/h total sleep time, and for 6–7 year olds, total PLM index will be 1.0 ± 1.3 (range: 0–4.8)/h total sleep time. Picchietti *et al*. suggested a genetic

pathway to the likely concurrence of PLMS, ADHD symptomatology and parental reports of RLS [129].

Expert commentary

To date, multiple confounders have precluded any clear statements regarding the 24-h ADHD phenotype. One of these obstacles is explored in this article in more detail and addresses sleep issues in children with ADHD. Accordingly, we advocate more rigorous filtering of the commonalities and dissimilarities at the level of the day-time and night-time symptomatology, as well as pathophysiology (e.g., neural pathways) and environmental issues (e.g., sleep hygiene) in the context of evaluating children with ADHD symptoms. In other words, decisions regarding the diagnosis, assessment and management of children with putative ADHD symptoms should incorporate frequency, severity and variability of the 24-h ADHD phenotype.

Five-year view

We anticipate that in the coming 5 years, the sleep–ADHD interrelationships, assessment and management will be more rigorously studied. For instance, increasing multimodal approaches and interventions of day and night symptoms will emerge. It is also likely that subtypes of ADHD will be associated with specific sleep complaints or with objectively measured sleep parameters, thereby allowing for refinement of treatment and potentially enabling early screening. In this realm, the motricity versus restless legs debate will surely reveal novel insights. Similarly, the potential associations with parasomnias, such as those related to partial arousal or arousal from stage 3–4 of sleep, will need to be investigated. In other words, the mediating or moderating role of sleep will surface more explicitly through the execution of studies that incorporate the key issues and the current pitfalls in the literature. Last, studies aiming at a better assessment of sleepiness in a developing child should foster pertinent insights into such sleepiness and sleep interrelations. These complex interactions could be operational in terms of neuromodulatory pathways and should shed light on relevant sleep–wake behaviors. For example, the hypoarousal state may predispose towards ‘hyperstimulatory behaviors’ in the form of nutritional or sensory content, such as eating behaviors. Therefore, day-time somnolence and night-to-night sleep variability may further exacerbate risk in these children’s health status. Finally, dysregulation by either intrisinic or extrinisic factors may exacerbate or contribute to the ADHD phenotype, as well as to its potential comorbidities [102].

Key issues

- Even though an estimated 25–50% of children and adolescents with attention-deficit/hyperactivity disorder (ADHD) experience problems with sleep, to date, the 24-h phenotype of ADHD still needs to be carefully assessed and studied.
- Recent evidence has been accumulating that the motricity and somnolence complaints should be assessed in the realm of sleep disorders, such as restless leg syndrome, periodic limb movement disorder and sleep-disordered breathing.
- Quantitative or qualitative assessment of parasomnias, such as partial arousals in sleepwalking, sleep terrors and confusional arousal, and assessment of hypersomnias and circadian rhythm disorders are advocated.
- It is crucial to query sleep–wake schedules that might be unstable or inconsistent. Sleep hygiene logs detailing sleep onset and offset could be kept.

- Sleep problems are not uncommon in children with psychopathology, and therefore comorbidity, as well as environment and intrinsic factors, should be explored in depth.
- Children with ADHD with and without comorbidities may have altered sleep architecture, different sleep–wake patterns and sleep problems, which might further obscure the daytime and night-time brain–behavior interactions, and thus alter the phenotypic presentation.
- Potential interventions are sleep hygiene training, stimulant treatment and use of melatonin. Nonetheless, referral to a pediatric sleep laboratory is advocated when a significant sleep complaint is present.

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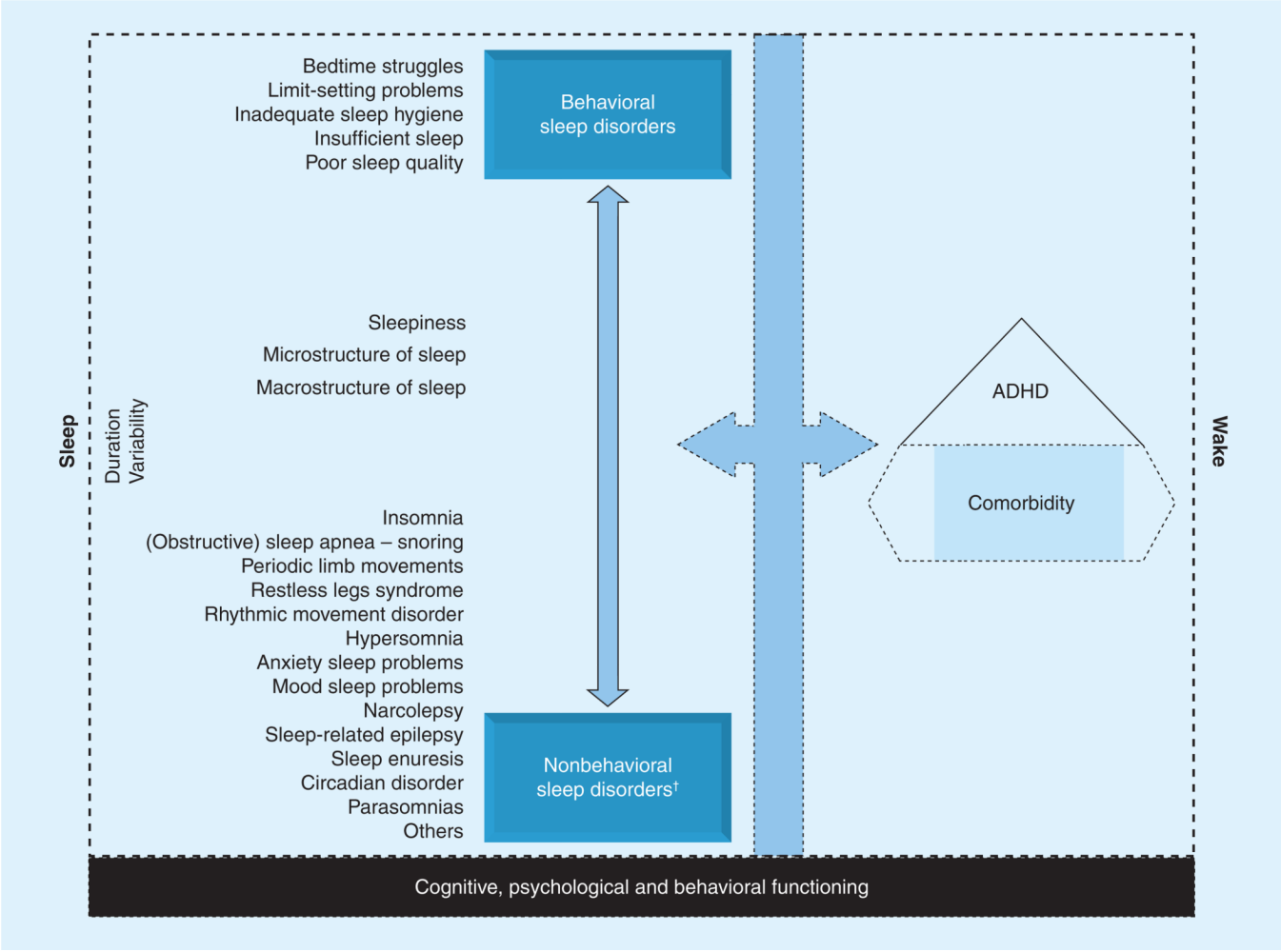

Figure 1. Conceptual model of the multidirectional and multifactorial aspects pertaining to sleep and attention-deficit/hyperactivity disorder

†Psychiatric sleep problems, respiratory-related sleep disorders, neurologic sleep disorders, developmental sleep problems.

ADHD: Attention-deficit/hyperactivity disorder.

Table 1

Simplified overview of ranked pooled effect sizes from studies (1987–2008) of sleep problems in unmedicated children with attention-deficit/hyperactivity disorder: objective and subjective measurements.

Study measurement	ADHD children versus controls	Heterogeneity in findings
Polysomnography		
Apnea–hypopnea index	↑	L
Number of stage shifts per hour sleep	↑	H
Sleep efficiency	↓	L
Actigraphy		
Sleep onset latency	↑	H
Total sleep time	↓	M
Multiple sleep latency test		
Average time to nap	↓	H
Parental report		
Sleep-onset difficulties	↑	H
Bedtime resistance	↑	H
Difficulties with morning awakenings	↑	M
Night awakenings	↑	M
Sleep-disordered breathing	↑	L
Sleepiness	↑	M
Self-report		
	Unknown	

↑ or ↓ ADHD children versus controls; L, M and H heterogeneity in findings.

ADHD: Attention-deficit/hyperactivity disorder; H: High; L: Low; M: Moderate.

Data taken from [32].