Methods in Pediatric Sleep Research and Sleep Medicine

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Abstract

Several methods are used to evaluate sleep in infants, children, and adolescents including: Questionnaires and diaries, actigraphy, polysomnography, and electroencephalography which are well established. Novel approaches such as high-density electroencephalography, simultaneous electroencephalography–functional magnetic resonance imaging and nonpharmacological methods aiming for a modulation of sleep are currently only used for research. These approaches might become valuable methods for clinical application in the future. The purpose of this review is to present an overview of current methods and their respective fields of application and to report available rules and recommendations for their use.

Keywords
- sleep
- development
- questionnaires
- actigraphy
- polysomnography
- electroencephalography

Introduction

In pediatric sleep medicine clinicians assess sleep to identify sleep problems and to diagnose sleep disorders. Sleep problems such as bedtime problems, night wakings, and poor sleep hygiene are highly prevalent in the pediatric population. It has been reported that approximately 25% of all children experience some type of sleep problem, at least once during childhood however, sleep disorder diagnoses are less common.[1] Pediatric sleep disorders include sleep-related breathing disorders (prevalence: 4–11%[2]), obstructive sleep apnea (OSA; prevalence: 1–4%[2]), restless legs syndrome (RLS, prevalence: 2%[3]), periodic limb movement disorder (PLMD, prevalence: 14%[4]), narcolepsy (prevalence: 0.05%[5]), insomnia (20–30%[6]), and parasomnias (prevalence: 14.4%[7]).

Sleep researchers assess pediatric sleep to investigate developmental changes in sleep behavior and neurobiological sleep characteristics. Clinical research aims at identifying discrepancies between clinical populations and typically developing children and adolescents.

Several methods have been developed to cover the needs of clinicians and researchers. The methods differ in terms of information source (objective vs. subjective), time and financial costs, and setting (sleep laboratory vs. habitual environment). Accordingly, they all have their specific field of application.

Questionnaires and Diaries

In a review from 2011, the authors evaluated currently used questionnaires and scales about sleep in children.[8] They found 57 instruments in which psychometric testing had been done to some extent. Best ratings for instruments assessing sleep problems in infants (1 month–2 years) were obtained by the Sleep and Settle Questionnaire (SSQ), the Maternal Cognitions about Infant Sleep Questionnaire (MCISQ), and the Parental Interactive Bedtime Behavior Scale (PIBBS). These instruments mainly focus on sleep environment and settling. In children (2–11 years) the instruments focus more on sleep–wake patterns, routines, sleep hygiene, and the screening for specific sleep disorders such as

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insomnia, sleep-related breathing disorders, or periodic limb movement disorder. Toward adolescence (11–18 years) more questions relating to sleepiness or emotional well-being are included. The authors recommend the use of the Bedtime Routines Questionnaire (BRQ), the Tayside Children's Sleep Questionnaire (TCSQ), the Children's Sleep Wake Scale (CSWS), the Behavioral Evaluation of Disorders of Sleep Scale (BEDS), the Pediatric Sleep Questionnaire (PSQ), the Sleep-related Breathing Disorders Scale (SRBD), the Sleep Disturbance Scale for Children (SDSC), and the Sleep Disorders Inventory for Students–Children (SDIS-C). The latter disposes of a specific version for adolescents (SDIS-A). The Dream Content Questionnaire for Children (ChDCQ) and the Cleveland Adolescent Sleepiness Questionnaire (CASQ) were the only self-reporting instruments with good ratings. A recent preliminary study, showed good psychometric values for a newly developed self-reporting tool for children[9]: the Children's Report of Sleep Patterns (CRSP). The authors claim that such self-reports might provide complementary information that would not be covered if only relying on parental reports.

Using these instruments, in several clinical populations the prevalence for sleep disorders was found to be increased when compared with the healthy population, that is, in children and adolescents with attention-deficit/hyperactivity disorder (ADHD), in children and adolescents with autistic spectrum disorder (ASD), in children and adolescents with cerebral palsy and in children and adolescents with Down syndrome.[10–13] The most commonly used instruments to screen for sleep disorders in these children are the Children's Sleep Habit Questionnaire (CSHQ), the SDSC, and the PSQ. The Sleep Self-Report for children and adolescents is mainly used in combination with the CSHQ for parents.[14,15] The Questionnaire for Children with Severe Psychomotor Impairment (Schlaffragebogen für Kinder mit Neurologischen und Anderen Komplexen Erkrankungen, SNAKE) is a recently developed instrument to assess sleep disorders in children and adolescents with severe psychomotor impairments.[16] It specifically takes into account impaired perception, intellectual disability, and motor impairment. Another instrument aiming at a specific patient group is the Pediatric Restless Legs Syndrome Severity Scale (P-RLS-SS).[17] However, the scale has not yet been validated.

While questionnaires and scales ask parents or children to reflect on weekly or monthly sleep behavior, diaries require a daily report of sleep and wake phases. Such diary-based reports were found to be a reliable source of information for sleep start, sleep end, and assumed sleep but not for nocturnal wake time when compared with objective measurements assessed by actigraphy.[18] In children with sleep disorders this discrepancy between parental report about nocturnal wake time and actigraphy seems to be even more pronounced.[19]

Actigraphy

Actigraphy uses a watch-like movement sensor to assess habitual sleep–wake patterns. It allows data collection over multiple days and is easily applied in the child's natural environment. At least five nights are required to obtain reliable measures.[20] The most commonly used devices are the AMI devices (Ambulatory Monitoring Inc. actigraphs: Ardsley, New York, United States), the Mini-Mitter devices (now owned by Phillips-Respironics, Bend, Oregon, United States), and the Cambridge Actiwatch actigraphs (Cambridge, United Kingdom). Across all devices epoch length is most frequently set at 1 minute, less often at 30 seconds.[21] Sleep–wake scoring algorithms, respectively, wake threshold sensitivity typically are device-specific. According to Meltzer et al,[21] the most commonly used sleep–wake scoring algorithm for the AMI devices is the Sadeh algorithm.[22] For the Mini-Mitter and the Cambridge devices the most commonly used wake threshold sensitivity level is the medium sensitivity. The authors suggest that since sleep undergoes major changes in the course of development, devices, and scoring algorithms/sensitivity levels should be selected age-specifically, based on previously published validation studies. They list 10 validation studies for different age groups which compared actigraphy to "gold standard" sleep measures such as polysomnography (PSG). A more recent validation study used different devices and scoring algorithms in children and adolescents.[21] Another recent study tested different wake threshold sensitivity levels specifically in 2 to 5 years old children.[23] Throughout all age groups, devices, epoch lengths, and scoring algorithms, studies consistently reported high sensitivity (proportion of correctly identified sleep epochs) and low specificity (proportion of correctly identified wake epochs). Thus, actigraphy accurately scores sleep periods, but is less suitable for detecting wake periods after sleep onset.

Actigraphy sleep variables such as sleep onset, wake after sleep onset, and sleep offset are determined according to time-related definitions. For example, sleep onset is commonly defined by several consecutive epochs scored as sleep. However, there are no standards for such definitions. To address this concern, Meltzer et al[9] provided a list of recommended variable names and definitions that should be considered when reporting results from actigraphy measurements (►**Table 1**). Variables such as bedtime and wake time are assessed using actigraphy markers (button press) or daily sleep logs (►**Table 1**). Furthermore, sleep logs are needed to determine artifacts such as sleeping in a car or times when the device is removed. Actigraphy has become a widely used method to objectively measure sleep over the past 20 years and has proven to be useful in assessing habitual sleep pattern in children with and without sleep problems.[18,24] In clinical research, actigraphy is used to investigate sleep and the relationship between sleep and behavioral functions in different clinical populations, for example, children with ADHD[25] or children with Down syndrome or Williams syndrome.[26] In children and adolescents with neurodevelopmental disorders the method allows to detect effects of medication on sleep.[27,28] However, actigraphy is not a suitable method for the diagnosis of disorders in which sleep is fragmented. For example, the detection of limb movement events in children and adolescents with periodic limb movement disorder is insufficiently accurate.[29] In children and adolescents with obstructive sleep apnea actigraphy fails to reliably

Table 1 Recommended variable names and definitions for actigraphy in the pediatric population

Reported variables	
Bedtime	Clock time attempted to fall asleep as indicated by either sleep log or event marker
Wake time	Clock time of final awakening in the morning as indicated by either sleep log or event marker
Sleep opportunity (time in bed)	Time between bedtime and wake time (reported in min or h)
Actigraphy variables	
Sleep onset	Clock time for first of a predetermined number of consecutive min of sleep following reported bedtime
Sleep offset	Clock time for last of a predetermined number of consecutive min of sleep before reported wake time
Sleep period	Time between sleep onset and sleep offset (reported in min or h)
TST	Duration of sleep in sleep period (reported in min or h)
Sleep onset latency	Time between bedtime and sleep onset (reported in min)
WASO	Number of minutes scored as wake during sleep period
Sleep efficiency	Percentage sleep: (TST/time in bed) $\times$ 100
Night waking	Predetermined minimal number of minutes of wake (e.g., $>$ 5 min) preceded and followed by a predetermined minimal number of minutes of sleep (e.g., $>$ 15 min)
Night waking frequency	Number of night wakings
Night waking duration	Sum of minutes scored as night waking
24 h sleep duration	Amount of sleep in a 24-h period (reported in min or h)

Abbreviations: TST, total sleep time; WASO, wake after sleep onset.
Note: Adapted from Meltzer et al, 2012.[21]

identify breathing abnormalities.[30] For such clinical populations PSG remains the best diagnostic method.

Polysomnogrphaphy

The American Academy of Sleep Medicine (AASM) manual for the Scoring of Sleep and Associated Events provides technical specifications for PSG recordings and criteria for determining sleep stages, arousals, respiratory events, cardiac events, and movement events.[31] According to these international guidelines, the electroencephalogram (EEG) should include at least eight electrodes, placed according to the international 10–20 system: bilateral frontal (F4, F3), central (C4, C3), occipital (O2, O1), and mastoids (M1, M2). Electrooculogram is recorded using two electrodes (placed 0.5–1 cm above the right outer canthus and 0.5–1 cm below the left outer canthus, depending on the children's head size). Electromyogram (EMG) is recorded using submental electrodes. Based on these parameters sleep stages are scored (wakefulness, non-rapid-eye-movement sleep stages 1–3, rapid-eye-movement sleep). The 2007 AASM manual specifies scoring rules for children. Recommended sleep variables are listed in ►**Table 2**. The scoring rules for sleep arousals are the same for adults and children. The number of arousals and the arousal index are the most currently used variables to quantify sleep disruption (►**Table 2**). Alternative measures, such as sleep pressure score, cyclic alternating pattern or computer-assisted identification of nonvisible arousals may provide complementary information.[32] For the respiratory monitoring during PSG, the 2007 AASM manual recommends to measure (1) airflow using an oronasal thermal sensor and a nasal air pressure transducer, (2) respiratory effort using esophageal manometry or respiratory inductance plethysmography, (3) oxygen saturation using pulse oximetry, and (4) hypoventilation using transcutaneous or end-tidal P_{CO_2} monitoring. In 2012 the AASM Sleep Apnea Definitions Task Force reviewed evidence for new monitoring technologies and further recommend the use of positive airway pressure (PAP) device flow signal for PAP titration PSG and the use of arterial P_{CO_2} monitoring for hypoventilation.[33] To detect snoring they recommend several sensors as options: acoustic sensor (e.g., microphone), piezoelectric sensor or nasal pressure transducer. The 2007 AASM manual provides scoring rules for respiratory events such as obstructive apnea, mixed apnea, central apnea, hypopnea, respiratory effort-related arousals, hypoventilation, and periodic breathing. All scoring rules are specified for children. The 2012 update of the AASM manual[33] adapted the pediatric scoring rules for central apnea and hypopnea (►**Table 3**), thereby improving the detection of sleep-disordered breathing in children when compared with previous standards.[34,35] Recommended respiratory variables are listed in ►**Table 2**.

PSG recordings also include an electrocardiogram. The 2007 AASM manual recommends the use of a two-lead electrocardiograph with electrodes placed on the torso. Scoring rules are the same in adults and in children. Cardiac

Table 2 Recommended variable names and definitions for polysomnography in the pediatric population

Sleep variables	
Lights out (A1)	Clock time
Lights on (A2)	Clock time
TST (A3)	Duration of sleep in sleep period (in min)
Total recording time (A4)	Time between lights out and lights on (in min)
SL (A5)	Time between lights out and first epoch of sleep (in min)
REM sleep latency (A6)	Time between first epoch of sleep and first epoch of REM sleep (in min)
WASO (A7)	Wake time during A4–A5 (in min)
Sleep efficiency (A8)	Percentage sleep: (A3/A4) × 100
Sum of sleep time for each sleep stage (A9)	(in min)
Percentage of TST for each sleep stage (A10)	(A9/A3) × 100
Arousal variables	
Number of arousals (B1)	
ArI (B2)	(B1 × 60/A3)
Respiratory variables	
Number of obstructive apneas (C1)	
Number of mixed apneas (C2)	
Number of central apneas (C3)	
Number of hypopneas (C4)	
Number of apneas + hypopneas (C5)	
AI (C6)	(C1 + C2 + C3) × 60/A3
HI (C7)	C4 × 60/A3
AHI (C8)	C5 × 60/A3
Continuous oxygen saturation (C9)	Mean value
Minimum oxygen saturation during sleep (C10)	
Occurrence of Cheyne stokes breathing (C11)	Yes/no
Cardiac variables	
Average heart rate during sleep (D1)	
Highest heart rate during sleep (D2)	
Highest heart rate during recording (D3)	
Bradycardia (D4)	Yes/no, if present report lowest heart rate observed
Asystole (D5)	Yes/no, if present report longest pause observed
Sinus tachycardia during sleep (D6)	Yes/no, if present report highest heart rate observed
Narrow complex tachycardia (D7)	Yes/no, if present report highest heart rate observed
Wide complex tachycardia (D8)	Yes/no, if present report highest heart rate observed
Atrial fibrillation (D9)	Yes/no
Other arrhythmias (D10)	Yes/no, if present list arrhythmia
Movement variables	
Number of PLMS (E1)	
Number of PLMS with arousals (E2)	
PLMSI (E3)	E1 × 60/A3
PLMSArI (E4)	E2 × 60/A3

Abbreviations: AHI, apnea + hypopnea index; AI, apnea index; ArI, arousal index; HI, hypopnea index; PLMS, periodic limb movements of sleep; PLMSArI, PLMS arousal index; PLMSI, PLMS index; REM, rapid eye movements; SL, sleep latency; TST, total sleep time; WASO, wake after sleep onset.
Note: Adapted from Iber et al, 2007.[31]

Table 3 Recommended changes to the AASM pediatric respiratory scoring rules

Scoring rules for pediatric apnea
Score a respiratory event as an apnea if it meets all of the following criteria:
There is a drop in the peak signal excursion by $\geq$ 90% of the pre-event baseline
The duration of the $\geq$ 90% drop lasts at least the minimum duration as specified by obstructive, mixed, or central apnea duration criteria
Scoring rules for pediatric central apnea
Score a respiratory event as central apnea if it meets apnea criteria, is associated with absent inspiratory effort throughout the entire duration of the event, and at least one of the following criteria is met:
The event lasts 20 s or longer
The event lasts at least the duration of two breaths during baseline breathing and is associated with an arousal or $\geq$ 3% oxygen desaturation
For infants younger than 1 y of age, the event lasts at least the duration of two breaths during baseline breathing and is associated with a decrease in heart rate to less than 50 beats/min for at least 5 s or less than 60 beats/min for at least 15 s
Scoring rules for pediatric hypopnea
Score a respiratory event as a hypopnea if it meets all of the following criteria:
The peak signal excursions drop by $\geq$ 30% of pre-events baseline
The duration of the $\geq$ 30% drop lasts for at least 2 breaths
There is $\geq$ 3% desaturation from pre-event baseline or the event is associated with an arousal

Abbreviation: AASM, American Academy of Sleep Medicine.
Note: Adapted from Berry et al, 2012.[33]

variables are listed in ►**Table 2**. According to the 2007 AASM manual the leg EMG should be recorded using surface electrodes placed longitudinally and symmetrically around the middle of the anterior tibialis muscle so that they are 2 to 3 cm apart or one-third of the length of the muscle, whichever is shorter. Both legs should be monitored for the presence of leg movements, preferably using separate channels for each leg. Recommended movement variables are listed in ►**Table 2**.

Indications for PSG in the pediatric population are: (1) diagnosis of OSA, (2) clinical evaluation after OSA treatment, (3) diagnosis of PLMD and 4) diagnosis of narcolepsy.[36,37]

According to the American Academy of Pediatrics (AAP) PSG is the current gold standard for the diagnosis of pediatric OSA.[38] The apnea hypopnea index (AHI) is a commonly used to quantify OSA severity. However, there is no consensus in terms of AHI cutoff values. The current practice is to use an arbitrary cutoff >3 standard deviations beyond the mean of the normative AHI.[39] Such normative values have been provided for infants, children and adolescents.[40,41] A recent study investigated whether results obtained with respiratory polygraphy (RP) or PSG are comparable. Although RP would be simpler and more cost-effective, the AHI is underestimated when compared with PSG, notably in children with mild and moderate OSA.[42] Novel approaches propose the use of algorithms for therapy indication. In addition to parameters derived from PSG such algorithms include factors like the severity of symptoms, risk factors, and the presence of any OSA-related morbidity.[43,44] Current treatments of pediatric OSA are adenotonsillectomy, positive airway pressure (CPAP or BiPAP), high flow nasal cannula oxygen therapy and administration of anti-inflammatory agents such as montelukast or nasal budesonide,[39] all significantly reducing the AHI. Treatment effects have been evaluated with follow-up PSG and PAP titration PSG.[45–49]

According to the AASM international classification of sleep disorders, the diagnosis of PLMD requires PSG recordings. One of the diagnostic criteria is a periodic limb movements of sleep index (PLMSI) > 5/h.[50] Normative data support the clinical periodic limb movement index cutoff of > 5/h.[51] Periodic limb movements during sleep were found to be infrequent in the typically developing children and adolescents. Positive treatment effects of oral or intravenous iron on pediatric PLMD are found in 60 to 70% of the cases.[52,53] The diagnosis of RLS in children is challenging, particularly because many young children are unable to describe typical RLS symptoms. Although not essential for diagnosis, a PLMSI > 5/h is considered supportive evidence.[54] In children diagnosed with RLS a PLMSI > 5/h has been found in 63 to 74% of the cases.[55–57]

As part of the diagnostic evaluation in patients with narcolepsy the Multiple Sleep Latency Test (MSLT) is performed. This test assesses sleep latency and sleep onset rapid eye movement sleep periods (SOREMPs) for four to five daytime naps. A mean sleep latency < 8 minute and two or more SOREMPs is considered the cutoff for narcolepsy diagnosis.[50] However, there are no specifications for children. Overnight PSG is systematically performed before MSLT, primarily to rule out other causes of excessive daytime sleepiness. Recent studies in adults and children propose to use night PSG for diagnosis.[58,59] The authors suggest short REM sleep latency or SOREMP to be diagnostic for narcolepsy.

In the absence of such findings, however, subsequent MSLT would still be required.

In clinical research, PSG is used to investigate sleep and the relationship between sleep and behavioral functions in different patient populations. For example, children with ADHD were found to have a higher arousal index and a higher PLMSI.[60] In children with Down syndrome and comorbid OSA cognitive performance was significantly lower than in those without OSA.[61] Increased sleep onset latencies and reduced REM sleep latencies were found in children and adolescents with depressive disorders[62] as well as in children with generalized anxiety disorder.[63]

For many research questions comprehensive PSG is not needed. When respiratory and movement parameters are not involved, EEG recordings are sufficient.

Electroencephalography

In basic and clinical research several sleep EEG measures have been assessed in the course of development. Discrepancies from age norms might be indicative for neurodevelopmental disorders. For example, the relative proportion of non-rapid eye-movement sleep (NREMS) and REMS changes in the course of development.[64] The percentage of REMS increases from childhood to adolescence. In children and adolescents with ASD the percentage of REMS was found to be significantly lower when compared with typically developing children and adolescents of the same age.[65]

Sleep slow waves during NREMS are a well-established marker for deep sleep. They are generated and maintained by thalamocortical and corticocortical networks.[66] The activity of these slow waves (slow wave activity, SWA: spectral power 1–4.5 Hz) is known to be regulated in a use-dependent manner, that is, SWA is increased after prolonged wakefulness in adults[67] as well as in children and adolescents.[68] In the course of development the expression of slow waves changes substantially. SWA is known to increase over the first years of life with a peak shortly before puberty and a subsequent decline throughout adolescence.[69,70]

The decay of SWA across the night has been used as a measure for the dissipation of sleep pressure in adults as well as in children and adolescents.[67,71,72]

Another sleep measure is the slope of sleep slow waves which has been proposed to reflect neuronal synchronization in adults,[73] in children and adolescents,[68] and in infants.[74] An overnight decrease in the slope of slow waves was shown to be already present in infants.[74] In children with continuous spikes and waves during slow wave sleep (CSWS) the absence of this overnight decrease was suggested to reflect non-restorative sleep[75] and to be related to neuropsychological deficits in these children.[76]

Sleep spindles are a characteristic feature of NREMS stage 2 and have been described as waxing and waning oscillations between 12 and 15 Hz. Like slow waves they are known to be related to thalamocortical and corticocortical network activity.[66] In the course of development sleep spindle activity changes in terms of frequency, amplitude, length, and density.[41,70] In adults as well as in children and adolescents sleep spindles have been related to cognitive abilities.[77–80]

Sleep characteristics cannot only be investigated globally. Interestingly, sleep regulation also shows local, experience-related changes. For example, after unilateral sensory stimulation SWA at the corresponding central electrode site over the sensorimotor cortex was found to be higher when compared with the contralateral electrode site.[81] Frontal slow oscillations (SO: spectral power < 1 Hz) were found to be related to declarative memory consolidation.[82] Recent studies investigating sleep and memory in children could show that frontal SO are correlated with declarative and emotional memory performance in typically developing children, but not in children with ADHD.[83,84]

Another measure using local information from specific electrode sites is EEG coherence. Coherence measures are supposed to reflect brain connectivity. EEG signals are correlated between two recording sites from the same hemisphere (intrahemispheric coherence) or from distinct hemispheres (interhemispheric coherence).[85] A high correlation of neural activity between two recording sites indicates that those regions are directly connected or are both connected to a common third region. Developmental changes in coherence have been assessed from early childhood to adolescence[86,87] and were suggested to reflect white matter brain maturation. In adolescents changes in intrahemispheric coherence have been related to improved cognitive abilities.[88] Alterations in coherence were found in children, adolescents, and young adults with ASD. Studies found a reduction in intrahemispheric frontocentral coherence and an increase in intrahemispheric left occipitoparietal and occcipitofrontal coherence.[89,90] In children and adolescents with major depressive disorder both, intra- and interhemispheric coherence was found to be reduced when compared with typically developing children and adolescents.[91] In a recent study, the authors calculated coherence values over 19 electrodes (placed according to the 10–20 international system) in infants, children, and adolescents, thereby obtaining topographical coherence maps for different age groups.[92] They proposed the coherence maps to represent neuronal network maturation.

Mapping EEG measures over the scalp requires a larger number of electrodes than commonly used for sleep EEG recordings. High-density EEG (hdEEG) uses up to 256 electrodes.

High-Density Electroencephalography

The high number of electrodes opens up entirely new possibilities of EEG signal analysis. Mapping the EEG activity at each electrode creates a topographical picture, visualizing the EEG activity distribution over the scalp. For example, investigating age-related differences in the topographical distribution of SWA revealed an interesting developmental trajectory (►**Fig. 1**): From early childhood to late adolescence the location of maximal SWA undergoes a shift from posterior toward anterior brain regions.[93] This pattern corresponds to the course of cortical gray matter maturation. Thus, the SWA

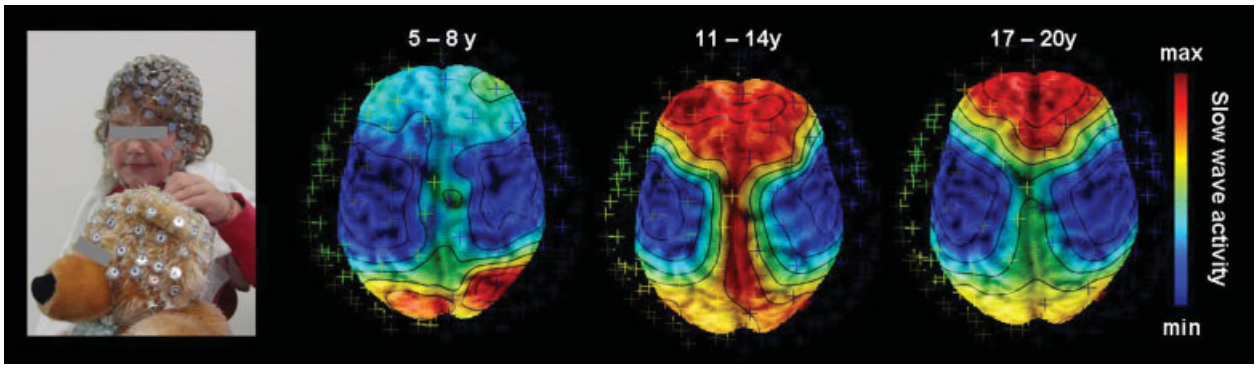

Fig. 1 (Left) A 4-year-old girl wearing a high-density electroencephalography (EEG) net (128 channels; Electrical Geodesics Inc., Eugene, Oregon) and teddy bear wearing a training net. (Right) Topographical maps of relative sleep EEG slow wave activity (1–4.5 Hz) for different age groups superimposed over T1-weighted magnetic resonance images. Crosses surrounding the brain illustrate registered electrode positions on the scalp. Slow wave activity is color coded (maxima in red, minima in blue). Values between electrodes were interpolated.

topography seems to be a marker for the maturational state of the brain. The course of developmental changes in the SWA topography has been related to skill maturation[94] and showed local gender-specific differences.[95] This mapping tool might be promising to assess regional differences in brain activity in clinical populations. For example, mapping SWA in children with an ADHD revealed increased SWA over central brain regions when compared with typically developing children and adolescents.[96] This pattern of SWA distribution in ADHD patients has been hypothesized to reflect altered or delayed brain maturation. Finally, the topographical distribution of EEG activity in other frequency ranges was also investigated. For example, a study investigated the topographical distribution of sleep spindle activity in children and adolescents.[97] The authors found region-specific positive correlations between spindle activity and cognitive abilities.

hdEEG can also be used to investigate task-related local changes in brain activity. For example, studies have investigated experience-dependent changes in SWA in adults[98] and more recently in children and adolescents compared with adults.[19] Interestingly, the task-related local increase of SWA was highest in children, suggesting a critical period of higher neuronal sensitivity to experience when compared with adolescents and adults. An experience-dependent increase in SWA was also shown after 3 weeks of working memory training in children and adolescents.[99]

An even higher spatial resolution of sleep brain activity including deep subcortical structures, for example, the thalamus, can be obtained by simultaneous EEG and functional magnetic resonance imaging (fMRI).

Electroencephalography–Functional Magnetic Resonance Imaging

EEG–fMRI combines EEG information such as sleep stages or sleep features (e.g., slow waves or sleep spindles) with fMRI network connectivity measures, that is, the coherence of the spontaneous fMRI signal between different brain regions. This potentially provides new possibilities to investigate sleep brain activity (current methods[100]).

So far, only one study used EEG–fMRI to investigate brain network connectivity during sleep in typically developing children.[101] In children with CSWS-identified networks have been suggested to reflect both spike initiation and propagation pathways.[102] The deactivations in structures of the default mode network were in line with the concept of epileptiform activity disrupting normal brain function.

The vast majority of studies presented so far involve a correlational approach. To establish causality manipulations are needed. Thus, a promising, not yet established method for future pediatric sleep research is the modulation of sleep by nonpharmacological manipulations.

Modulation of Sleep

In adults several studies provided evidence for methods successfully enhancing slow waves (review[103]). The use of transcranial oscillatory direct current stimulation at 0.75 Hz induced an increase in the slow oscillation EEG activity (< 1 Hz), which was associated with enhanced declarative memory performance, suggesting a causal role for slow waves in memory consolidation.[104] A recent study applying this method in children with ADHD reported similar results.[105]

Another study recently showed that specifically timed acoustic stimuli during slow wave sleep also induce an increase in the slow oscillation EEG activity again associated with enhanced declarative memory performance.[106] To our knowledge, only one study investigated the feasibility of acoustic stimulation during slow wave sleep in children. In contrast to previous findings in adults, the authors found no effects of acoustic stimulation on EEG activity when applying the same stimulation protocol that had been used for the adult study.[107] They hypothesize this lack of sensitivity to be due to the higher arousal threshold in children and recommend to consider increased sound levels for future acoustic stimulation studies in children.

Table 4 Overview of the current methods in sleep medicine and sleep research, limitations, and possible fields of application

Method	Properties	Field of application
Questionnaires and diaries	• Based on parental reports (or self-reports) • Subjective measures • Diaries: valid estimates of daily sleep onset, sleep offset and sleep period, however, limited accuracy of reported nocturnal wake times[18] • Questionnaires with satisfactory psychometric properties: valid estimates of general sleep behavior characteristics over extended time periods (weeks or months)[8] • Time- and cost-effective data collection and analysis	• Sleep medicine: identify sleep problems, screen for sleep disorders • Sleep research: investigate sleep behavior in typically developing children and adolescents
Actigraphy	• Based on movement • Objective measure • High sensitivity (detection of sleep) but, low specificity (detection of wakefulness)[21] • Data collection over multiple days in the natural environment • Simple data analysis using device-specific software • Moderate costs	• Sleep medicine: complementary behavioral information about nocturnal wake times • Sleep research: investigate sleep-wake patterns in typically developing children and adolescents
Polysomnography	• Based on electrical brain activity, eye movement, submental and leg muscle activity, respiration and cardiac activity • Objective measures • In-laboratory sleep recordings of single nights • Time intensive and demanding data analysis • Expensive equipment	• Sleep medicine: diagnosis of periodic limb movement disorder, obstructive sleep apnea, and narcolepsy (polysomnography and multiple sleep latency test) • Sleep research: investigate sleep characteristics in typically developing children and adolescents and in clinical populations
Electroencephalography	• Based on electrical brain activity, eye movement and submental muscle activity • Objective measures • In-laboratory sleep recordings (but also at home recordings possible, using simplified equipment) • Visual sleep scoring • Expensive equipment	• Sleep research: investigate sleep characteristics in typically developing children and adolescents and in clinical populations
High-density electroencephalography	• Based on electrical brain activity, eye movement and submental muscle activity • Visualization of brain activity over the scalp (topographical distribution) for individual nights • Objective measures • Advanced analysis techniques necessary • In-laboratory sleep recordings of single nights • Expensive equipment	• Sleep research: investigate sleep characteristics, with a focus on regional differences, in typically developing children and adolescents and in clinical populations

Conclusions and Future Perspectives

►**Table 4** provides an overview of the presented current methods in sleep medicine and sleep research. Limitations and possible fields of application are summarized.

Questionnaires and diaries are a time- and cost-effective method. Subjective parental reports provide information about their children's habitual sleep and sleep problems such as difficulty falling asleep. However, if parents are unable to reliably report or if a more accurate estimation of nocturnal wake times is needed, complementary information provided by actigraphy might be helpful. In children suspected of having PLMD, sleep-related breathing disorders or narcolepsy the gold standard for diagnosis remains PSG.

In pediatric sleep research sleep EEG is a well-established method allowing the analysis of sleep structure (sleep stages) and specific sleep characteristics such as slow waves or spindles. hdEEG additionally allows topographical analysis. fMRI–EEG and the modulation of sleep are not yet established methods. However, especially the modulation of sleep might be a very promising method for future research and clinical application.

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