Sleep & Neurodevelopment

Sleep characterization in children may have a role in evaluation for risk of impaired development, behavior, mood, and self-regulation.

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Sleep is homeostatically regulated and development correlates well with the progression of active neuromaturation. Sleep evolves with recognized changes in number of hours needed, progressive consolidation of sleep, and changes in circadian and ultradian rhythm as a function of age and development (Figure 1).[1-3] Recognition of this intimate relationship has increased research to understand how neurodevelopment markers are related to pediatric sleep patterns and possible use of sleep-wake characteristics as a modifiable biomarker for neurodevelopment.

Mechanisms of Sleep-Wake Regulation

Sleep-wake maintenance is thought to be the response to integrated input from the circadian system and sleep-wake homeostasis. The circadian system is an innate biologic rhythm, approximately a 24-hour cycle, conducted by the suprachiasmatic nuclei (SCN) in the ventral hypothalamus. Although endogenously derived, exogenous factors (known as *zeitgebers*), such as light, medications, or even meal schedules can influence circadian rhythms. The circadian system influences more than the sleep-wake cycle and is intrinsic to multiple functions including body temperature cycle, hormone production and secretion, and blood pressure peak and nadir.[4-7]

There appears to be a developmental component to the circadian rhythm, because it also changes with age. Neonates lack circadian rhythm until age 6 to 12 weeks, after which circadian rhythm strengthens with age as greater nocturnal sleep consolidation and eventual loss of daytime napping develop.[4,8,9] Maturation of the SCN, in combination with exposure to external zeitgebers contributes to this development.[10-12] There is evidence that premature infants have an earlier emergence of the circadian rhythm than full-term infants, with longer consolidated nocturnal sleep periods and less nighttime activity.[9] In adolescence, there is a biologic delay in circadian phase that occurs in conjunction with reduced accumulation of homeostatic sleep pressure, resulting in later sleep onset.[13,14] With advancing age, circadian rhythms become less stable and more phase advanced, resulting in earlier sleep onset and possibly contributing to greater sleep fragmentation.[15] Multiple circadian clock genes that generate and sustain circadian cycles via transcriptional-translational negative feedback loops also contribute to individual variability in sleep architecture.[16-19] These genes have been replicated outside the central nervous system (CNS), within cells and organs isolated from SCN input and even grown in vitro, suggesting an ability to self-regulate activity on a circadian basis.[20,21] Thus, genetic variability in circadian-clock genes may influence not only circadian sleep-wake cycles but also the biorhythms of somatic functions, from metabolism to gastrointestinal motility.

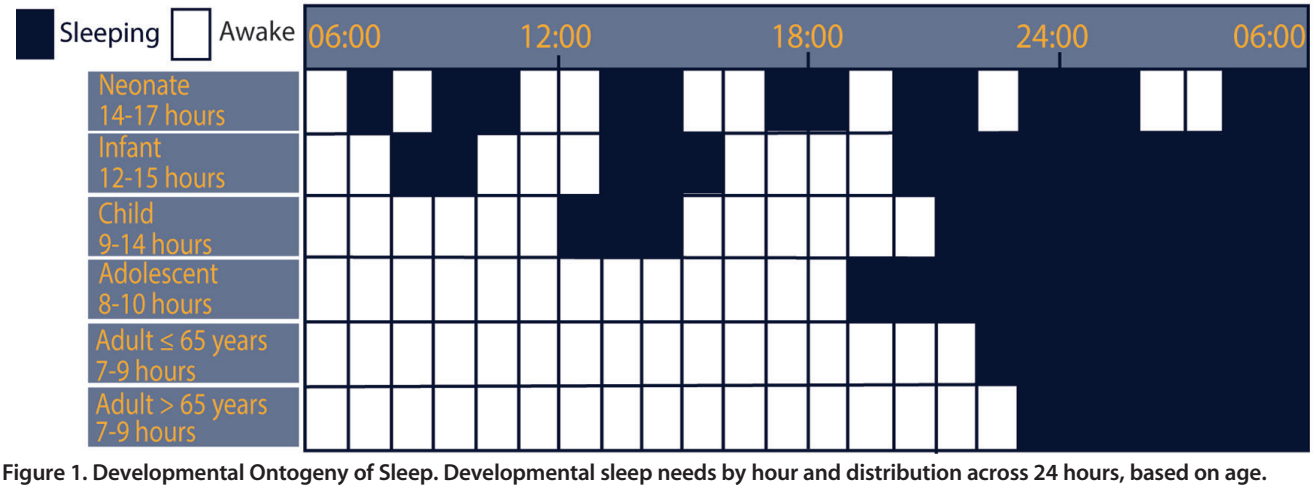

Figure 1. Developmental Ontogeny of Sleep. Developmental sleep needs by hour and distribution across 24 hours, based on age.

In contrast to the circadian system, sleep homeostasis is a process of increasing sleep debt with each waking hour, as production and accumulation of sleep-promoting substances accumulate within the CNS. These substances are then cleared with sleep "repayment." Adenosine is the principle sleep-promoting substance, produced as adenosine triphosphate (ATP) is broken down for energy production in the brain.[22] Other sleep-promoting factors include nitric oxide, tumor necrosis factor-α, brain-derived neurotrophic factor, and interleukin 1β.[23] Daily accumulation and depletion of sleep-promoting factors is thought to be driven by a need for balance between sleep and wakefulness drives, ensuring a period of quiescence that provides energy restoration, promotes cellular defense, and contributes to synaptic plasticity.[23-25]

Sleep itself has a cyclic organization, called the *ultradian*—more than daily—*rhythm* that evolves with neuromaturation. In early infancy, sleep architecture is not yet characterized as rapid eye movement (REM) and nonrapid eye movement sleep (NREM), as it lacks the defining EEG characteristics of REM and NREM sleep. Instead, infant sleep is characterized as active sleep (AS), indeterminate sleep, and quiet or nonactive (QS) sleep. Although it has EEG features similar to REM sleep, AS lacks muscle atonia and can appear restless, hence being called *active sleep*. In contrast, QS shares features with deep NREM sleep. Characteristics of NREM sleep can be seen at age 4 to 8 weeks; sleep spindles are seen first on EEG, and K-complexes typically emerge by age 6 months.[26,27] The percentage of time spent in NREM and REM sleep changes with age, as does the time spent cycling through NREM and REM sleep such that the duration of each NREM-REM cycle increases with age (Figure 2). Infants cycle between AS and QS every 50 to 60 minutes, which increases to every 90 to 120 minutes from early childhood throughout adulthood.[27,28]

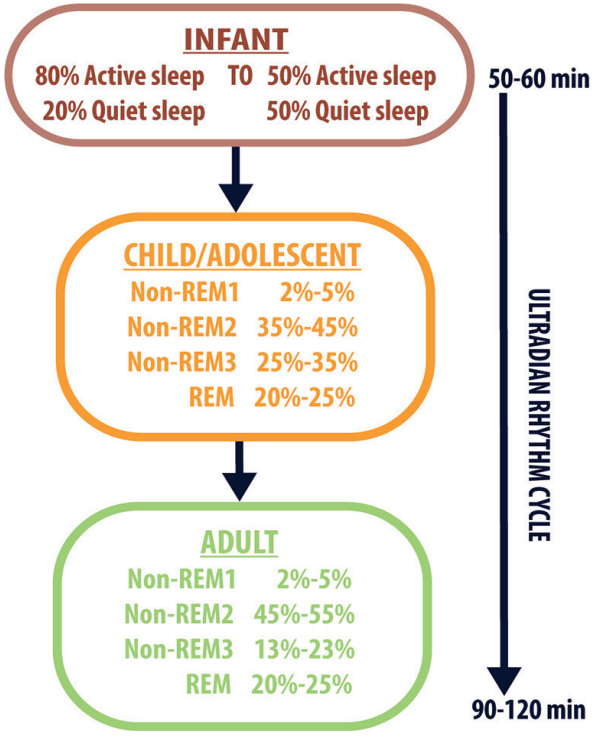

Figure 2. Ultradian rhythm cycle development shows evolution of sleep architecture and cycle length by age.

Sleep and Cognitive Development

Appropriate sleep duration and quality is needed for growth and development. Approximately 25% to 35% of neurotypical children have sleep disorders, [29] whereas 50% to 80% of children with neurodevelopmental disorders (NDD), especially neurogenetic syndromes, have sleep disorders.[30,31] Common childhood sleep problems include prolonged sleep latency, frequent and protracted night wakings with early arousal, and reduced total sleep time.[32]

Learning and Memory

Sleep influences learning, self-regulation, behavior, and mood, and this may vary with age, developmental status, and ultradian phase of sleep. There are differences in sleep-dependent learning and memory in different age groups. Infants appear to consolidate rules that can be applied more generally to problem solving. For example, in infants, the ability to apply learned rules across scenarios to negotiate understanding and outcomes was enhanced with napping immediately after initial rule instruction. In contrast, in preschoolers, sleep appears to facilitate more precise memory for encoding and recall. In a study of delayed recall (at 5.5 and 24 hours) of picture locations on a grid, preschoolers' performance was enhanced with napping and deteriorated without it.[33] These findings highlight differential effects of sleep at different development stages.[34] The infant may need first to learn and implement broad concepts to augment developmental gains, whereas the child who has already learned those concepts may need more specific attention to detail. Such differences are thought to reflect maturational changes in neurocircuitry with cortically based learning and memory predominate in infancy, and cortical-to-hippocampal connectivity prominent in preschoolers.[35]

Adolescents' cognitive performance is affected by sleep.[36] The most profound effect is with sleep deprivation that results in impaired vigilance.[36-38] Sleep directly after learning and sleep extension both benefit cognitive performance. Specifically, sleep after learning improves memory consolidation, and sleep extension shows benefit for working memory.[36]

Emotional and Attentional Stability

The ability to maintain emotional and attentional stability are specific aspects of self-regulation, foundational to a child's social and cognitive learning processes and prophetic of school adjustment and achievement.[39] Attaining age-appropriate sleep may improve mood, focus, and self-control.[40] Although

the exact role of sleep in emotional memory formation and next-day emotional reactivity is still poorly defined,[41] sufficient sleep enhances emotional stability and impaired sleep contributes to emotional fragility. A population-based cohort study of 4,109 children at 5 timepoints from infancy to age 9 years showed impaired sleep can co-occur with and even predict emotional dysregulation.[39] Emotional and attentional dysregulation were consistently and reciprocally related to sleep problems at all ages, suggesting neurodevelopmental overlap.[39]

In addition to behavioral stability, sleep enhances reaction time, which together may positively influence focus, attention, and self-regulation. Sleep deprivation, on the other hand, reduces the ability to process large amounts of information, and impairs functional connectivity between different brain regions. Attention is a complex task that requires simultaneous suppression of distracting/competing stimuli and activation of neural networks in order to focus on specific details. Thus, focus and attention may be particularly vulnerable to insufficient sleep due to impairment in ability to dynamically select and suppress stimuli.[42] This relationship is best evidenced clinically in children with disorders of attention and focus. Children with attention deficit hyperactivity disorder (ADHD) frequently have a history of sleep dysfunction that pre-existed the ADHD symptoms. Age-specific sleep reduction in early childhood across a 1-year timeframe has been identified as a significant predictor for later ADHD development.[43]

Factors Influencing Sleep and Neurodevelopment

Risk factors for sleep-wake dysfunction vary with developmental stages (Table 1)[44-49] and may influence both current and future sleep-wake patterns. For example, head circumference and ventricular size in late pregnancy and early infancy is related to longer sleep duration at 3 years and reduced risk of being a "problematic sleeper" at age 6 years.[50]

Children with sleep disorders have structural differences in brain development.[51,52] Although frequently thought to be exclusive to hypoxemia caused by sleep apnea, these morphologic findings are replicated in other causes patients with other sleep-wake problems, reinforcing the suggestion that structural differences may be related to sleep dysfunction itself (Table 2).[51,53-58] Sleep dysfunction from any cause is a serious consideration in development, as it may lead to irreversible morphologic changes and inappropriate neural organization.

Sleep and Neurodevelopmental Disorders

Sleep problems—most notably, circadian rhythm dysfunction— are frequently reported in persons with autism spectrum disorders (ASD).[59-61] This coincides with the frequent finding of intrinsic melatonin abnormalities in these individuals.[62] It has been suggested that the need to adhere to routine and difficulty adapting to change in individuals with ASD may be related to variability of their circadian rhythms and melatonin secretion.[62,63] The idea of innate circadian dysfunction as a significant contributor to ASD is reinforced when considering children with other congenital impairments that may increase their risk for developmental delay, but should not otherwise confer increased risk of ASD. For example, children with congenital vision impairment commonly have comorbid ASD (≤ 42%),[64] whereas children with hearing impairment, including complete hearing loss, less frequently have comorbid ASD (≤ 10%).[65] Thus, it is hypothesized that impaired melatonin secretion and abnormal circadian synchronization, related to a lack of light percep-

TABLE 1. POSSIBLE RISK FACTORS SLEEP DIFFICULTIES

Prenatal	Maternal depression/mood disturbances
	Maternal tobacco use
	Maternal alcohol use
	Reduced in utero head growth/smaller ventricle size
Perinatal	Prematurity
	Smaller head circumference
	Small gestational age
	Very low birth weight
	Decreased maternal sensitivity
	Challenging breastfeeding
	Impaired maternal infant bonding
Infancy	Screen time
	Developmental delay
	Daily touch screen use
	Decreased maternal sensitivity
	Neurologic comorbidity
Childhood	Screen time
	Developmental delay/autism
	Impaired self-regulation
	Daily touch screen use
	Eveningness chronotype
	Neurologic comorbidity
	Lack of bedtime routine/structure
Adolescence	Screen time
	Developmental delay/autism
	Daily touch screen use
	Psychiatric comorbidity
	Eveningness chronotype
	Neurologic comorbidity
	Lack of bedtime routine/structure

tion as a zeitgeber, may be the basis for the surprisingly high prevalence of ASD in individuals with congenital vision impairments, despite a lack of other risk factors.[64]

It may be possible to characterize neurogenetic syndromes by specific sleep phenotypes. Sleep problems in early infancy have been identified for some disorders, such as Angelman and Williams syndrome, and others later in childhood, such as Prader-Willi syndrome (PWS).[31] There may be differences not only in timing of onset but also in the chronicity and clinical features of sleep. For instance, Angelman syndrome sleep features are generally characterized by reduced total sleep time, increased sleep onset latency, disrupted sleep architecture with frequent nocturnal awakenings, increased periodic leg movements, and reduced REM sleep during early childhood that commonly improve with age.[66] In contrast, individuals with PWS frequently develop sleep symptoms later, which include hypersomnia disorders—including narcolepsy—and sleep-disordered breathing. In these individuals, susceptibility to hypersomnia is thought to be related to hypothalamic dysfunction; whereas, the risk for obstructive sleep apnea is likely a consequence of hyperphagia and obesity.[67] In these patients, sleep dysfunction is unlikely to improve, commonly persists, and can even worsen. This highlights how sleep characteristics could potentially serve as a biomarker, leading to earlier identification of the syndromes. In addition to clinical sleep features, neurophysiologic features identified on polysomnography can provide unique sleep profiles by syndrome. For example, when compared to neurotypical children, children with Williams syndrome display an atypical, but characteristic sleep pattern of decreased sleep time with reduced sleep efficiency related to increased waking after sleep onset, increased NREM percentage and increased SWS, irregular ultradian patterns, and increased number of leg movements.[68] Syndrome-specific screening and treatment protocols are needed to better identify and manage sleep problems in patients with neurogenetic disorders.

TABLE 2. SLEEP-WAKE DISORDERS AND BRAIN MORPHOLOGY

Disorder	Brain morphology abnormality
Circadian rhythm disorder	Temporal lobe atrophy[53]
Insomnia Insufficient sleep–not otherwise specified (NOS)	Reduced gray matter volume orbitofrontal cortex[55] and globally/ thinner dorsolateral prefrontal cortex[51] Reduced white matter integrity
Hypersomnia/ narcolepsy	Hippocampal CA1/amygdala centromedial atrophy[69] Reduced gray matter frontal lobe,[70] inferior temporal regions[71]
Restless legs syndrome	Multiregional brain iron deficiency[57, 72] Bilateral thalamic gray matter increase[73] Reduced somatosensory cortex gray matter[74] Reduced myelin (amount/integrity)[58]
Sleep apnea	Hippocampal,[75,76] parahippocampal,[77] and temporal cortex volume loss[78,79] Cortical thinning in multiple regions (superior frontal, ventral medial prefrontal, and superior parietal cortices)[52] Increased number and more severe nonspecific white matter changes[80]

Conclusion

Sleep is a homeostatically regulated process of elaborate, intrinsic neurocircuitry that evolves with neuromaturation. This overlap in development is reflected in the changes seen in the number of hours of sleep needed, the progressive consolidation of sleep, and the entrainment of circadian and ultradian rhythms, as a function of age and developmental status. Sleep plays a significant role in learning, memory, self-regulation, and mood that varies with both patient and sleep state. Studies evaluating the effects of sleep deprivation on learning underscore the deleterious impact of insufficient quantity and quality of sleep on neurotypical development.

A detailed characterization of sleep in infants, children, and adolescents is an important part of evaluating for risk factors for impaired development, behavior, mood, and self-regulation. In neonates, the presence of poorly organized (indeterminate) sleep is among the most predictive variables of cognitive outcome at age 12 years.[48] Children who are more vulnerable to impaired neurodevelopment, such as neurogenetic syndromes or with developmental brain disorders, are at even higher risk for sleep disorders and should receive regular sleep screening. Early identification of and intervention for individuals with inappropriate sleep-wake cycles may aid in augmenting neurodevelopmental outcomes, with benefit to cognition, behavior, mood, and self-regulation.

Further studies are needed to explore the use of sleep-wake evaluations—both objective and subjective measures—as tools to assist in earlier identification and prognostication of impaired neurodevelopment. In addition, studies evaluating sleep as an additional standardized early intervention therapy to enhance developmental outcomes should be explored in patient populations already identified as at-risk (eg, ASD). Improved characterization of genetic factors that influence risk for development of sleep disorders can provide insights into the basis of sleep-wake disorders in the general population and highlight strategies for personalized treatment in patients with genetic syndromes. In addition to considering neurodevelopmental evolution of phenotypic expression of multiomics

(genetic, epigenetic, and proteomic), studies directed at identifying the primary genes that contribute to sleep disorders and those that may indicate differential vulnerability to the detrimental effects of sleep disruption are needed. ■

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