

# Sleep and Early Brain Development

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## Key Messages

- Sleep pattern changes dramatically in early childhood.
- Establishing a healthy sleep pattern in early life is very important for child development.
- Sleep plays a critical role in learning and memory, emotional regulation, and related brain structure development.

## Keywords

Brain development · Early childhood · NREM and REM sleep

## Abstract

The early years of life are characterized by dramatic developmental changes. Within this important time period lies the transition from newborn to childhood. Sleep is one of the primary activities of the brain during early development and plays an important role in healthy cognitive and psychosocial development in early life. This paper will first review the normal sleep characteristics and their development in neonates and children, including architecture of sleep, development of a healthy sleep rhythm in early childhood, sleep recommendations and cultural disparity, as well as important factors for establishing a healthy sleep pattern during the first years of

life, such as regular and consistent bedtime routine, safe and comfortable sleep environment, and appropriate sleep onset associations. This paper then provides recent updates of evidence of the effects of sleep on early brain development, particularly on learning and memory, emotional regulation, and general cognitive development through behavioral and neurophysiological studies. As regards the mechanism, many experimental sleep deprivation studies in animals and adults have attempted to explain the underlying mechanisms of sleep on cognition and the emotional brain. Future studies are expected to delineate the effects of sleep on brain structural and functional networks in the developing brain with the marked development of image acquisition approaches and the novel analysis tools for infants and young children in recent years.

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The early years of life are characterized by dramatic developmental changes. Within this important time period lies the transition from newborn to childhood [1]. Sleep is one of the primary activities of the brain during early development and also plays an important role in healthy cognitive and psycho-

social development in early life [2]. This paper will first review the normal sleep characteristics and their development in neonates and children, followed by recent updates of the evidences of the effects of sleep on early brain development, particularly on memory functions and emotional control.

## Normal Sleep and Its Development in Neonates and Children

### *Definition and Architecture of Sleep*

Sleep is defined as a behavioral state characterized by reduced motor activity, decreased interaction with the external environment, a specific posture (e.g., lying down, eyes closed), and easy reversibility. The architectural organization of sleep refers to the coordination of independent neurophysiologic systems into 3 distinct functional states: non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, and wakefulness. Each state is distinctly associated with a discrete pattern of brain electrical activity [3].

NREM sleep is believed to function primarily as a restful and restorative sleep phase. NREM sleep also represents a time period of relatively low brain activity during which the regulatory capacity of the brain continues to be active and body movements are preserved. Using electroencephalogram, NREM sleep is conventionally subdivided into 3 stages (stages 1, 2, and 3), which roughly parallel a depth of sleep continuum, with arousal thresholds generally the lowest in stage 1 and highest in stage 3 sleep (stage 3 sleep is also called slow-wave sleep [SWS] or deep sleep). NREM sleep is usually associated with minimal or fragmentary mental activity.

REM sleep, also called “dream” sleep, is characterized by desynchronized cortical activity with low-voltage and high-frequency electroencephalogram. REM is typically thought to play a role in consolidating and integrating memories as well as in the development of the central nervous system – both maintaining and establishing new connections particularly during the time period of early brain development [4]. The mental activity of human REM sleep is associated with dreaming. The other important characteristic of REM sleep is the absence of skeletal muscle tone, meaning that people cannot move their body and limbs when they have vivid dreams.

NREM and REM sleep alternate in cycles throughout the night, which is called ultradian rhythm [4]. The relative proportion of REM and NREM sleep per cycle changes over night, and stage 3 NREM sleep (known as deep sleep) dominates the first 1/3 of the night, while REM sleep dominates the last third. In other words, the percentage of deep sleep declines and REM sleep increases over the course of the night.

### *The Development of a Healthy Sleep Rhythm in Early Childhood*

The sleep patterns change with age during the first years of life. The characteristics of sleep-wakefulness states during early development originate from the rest-activity cycles in the fetus and the early months after birth. Sleep states are categorized as active sleep, quiet sleep, and indeterminate sleep in very young babies. By the second half of the first year, quiet sleep gradually transitions into NREM sleep, which could be further divided into 3 stages as outlined above. Meanwhile, the active sleep characterized by frequent muscle twitches and grimaces turns into REM sleep. After 6 months of age, the electrical patterns of NREM and REM sleep progressively resemble those seen in adults [5].

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Early childhood life is a critical time period when normative transition of sleep-wakefulness patterns occurs, which is characterized by nighttime sleep consolidation and daytime sleep discontinuation. Starting from newborn babies to pre-school children, 24-h sleep duration declines dramatically by decreasing both daytime and nighttime sleep amounts. Particularly, diurnal sleep gradually declines, while the extent to which nighttime sleep decreases is less remarkable during this period of time. Newborns (0–3 months) do not have an established circadian rhythm, and day/night reversal is common in the first few weeks after birth [6]. The regular rhythm of periods of sleepiness and alertness emerges by 2–3 months of age and becomes more nocturnal between the age of 4 and 12 months [7]. While children continue to take daytime naps between 1 and 4 years of age, the number of naps decreases from 2 naps to 1 nap by 18 months on average, and this typically stops by the age of 5 years [8].

Not only sleep duration but also sleep architecture and sleep cycle change with age. The proportion of REM sleep dramatically decreases from birth (50% of sleep) through early childhood into adulthood (25%). The proportion of deep sleep peaks in early childhood and then decreases over the lifespan. The ultradian cycle, which means the nocturnal cycle of sleep stages, is about 50 min in infancy and gradually increases to an adult level, about 90–110 min, by school age [5].

**Table 1.** The recommended amount of sleep and sleep quality for children under 5 years old by the National Sleep Foundation in the USA [10, 11, 15]

Age category	Sleep duration per 24 h			Sleep quality		
	recommended	may be appropriate	not recommended	sleep latency <sup>a</sup>	awakenings (>5 min) <sup>b</sup>	Sleep efficiency <sup>c</sup>
Infants (4–12 months)	12–15 h	10–11 h 16–18 h	less than 10 h, more than 18 h	less than 30 min	na	85%
Toddlers (1–2 years)	11–14 h	9–10 h 15–16 h	less than 9 h, more than 16 h	less than 30 min	less than 2 per night	85%
Preschool children (3–5 years)	10–13 h	8–9 h 14 h	less than 8 h, more than 14 h	less than 30 min	less than 2 per night	85%

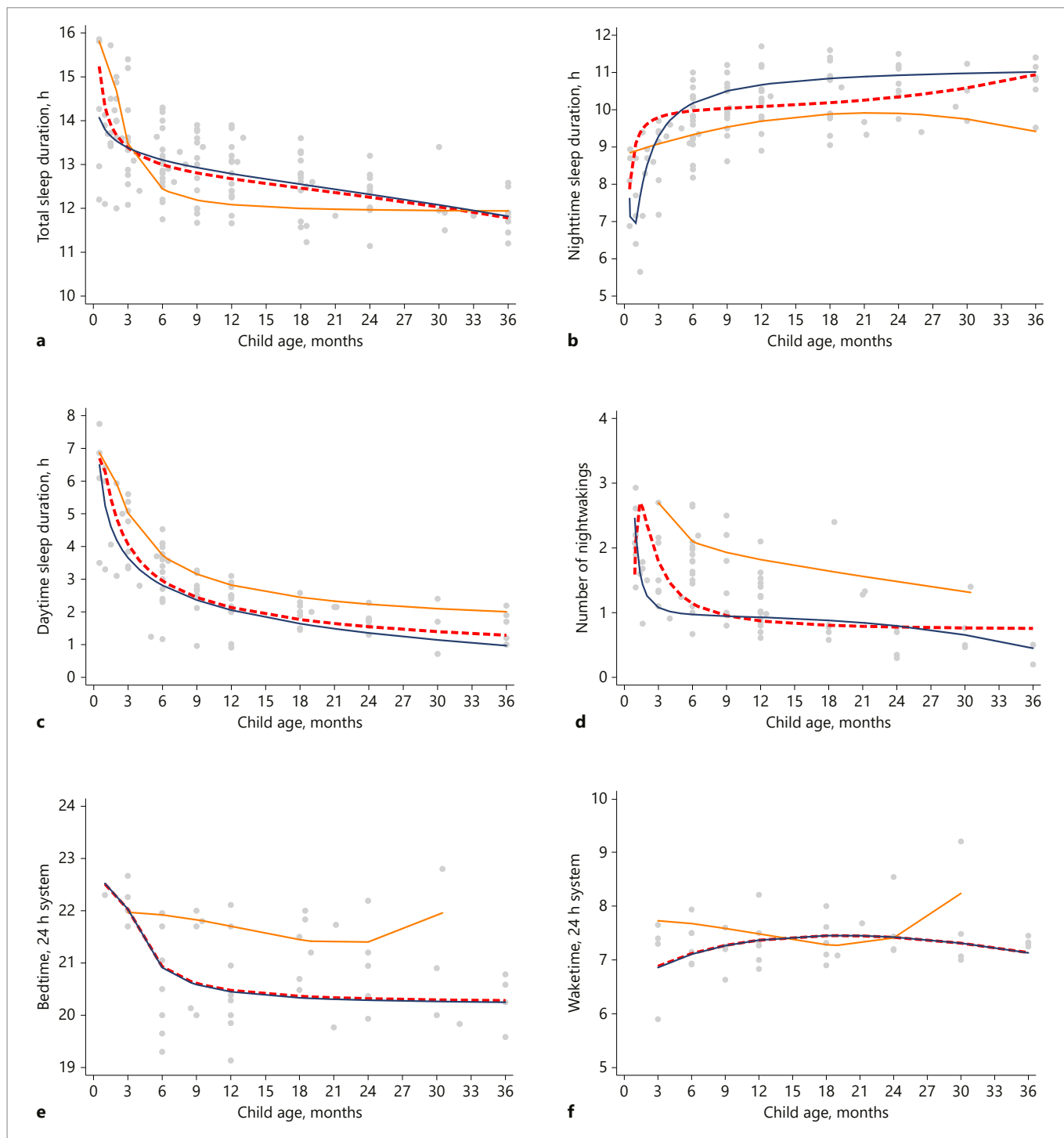
<sup>a</sup> Sleep latency: length to time, in minutes, it takes to transition from wakefulness to sleep. <sup>b</sup> Awakenings (>5 min): number of episodes, per night, in which a child is awake for more than 5 min. <sup>c</sup> Sleep efficiency: ratio of total sleep to time in bed.

### *Sleep Recommendations and Cultural Disparity*

In a clinical setting, one of the most common questions from parents is “what is healthy sleep for children?” Generally, healthy sleep requires adequate duration, appropriate timing, good quality, regularity, and absence of sleep disturbances or disorders [9]. Although genetics plays an important role in the individual variability of sleep need, many healthy sleep practices can help children to achieve age-appropriate amounts of sleep with good quality from the very beginning of their life. To develop scientifically sound and practical recommendations for sleep duration, the National Sleep Foundation (NSF) in the USA convened a multidisciplinary expert panel to evaluate the latest scientific evidence, including a consensus and voting process in 2015 [10, 11]. Later, the American Academy of Sleep Medicine and American Academy of Pediatrics (AAP) issued similar recommendations for sleep duration in the pediatric population [12, 13]. The only difference of the recent guideline is that the 2 organizations did not include recommendations for infants younger than 4 months old owing to a wide range of normal variations in duration and patterns of sleep and insufficient evidence of their associations with health outcomes. In 2017, the NSF published evidence-based recommendations and guidance to the public regarding indicators of good sleep quality for children under 5 years of age [14], which are summarized in Table 1. Nevertheless, it is worth noting that even though the normative sleep duration values are helpful and inform what constitutes the norm and what is considered outside the norm for a given age, these references provide norms at the population level standpoint and need to be individualized for each patient in the clinical setting [15].

The culture milieu is of importance for the understanding and evaluation of child sleep duration and patterns [16]. We recently systematically reviewed 102 studies with 167,886

children aged 0–3 years from 26 different countries across the world. Our results indicated that an apparent cross-cultural disparity of the sleep parameters already exists in early childhood [17]. Specifically, the predominantly-Asian (PA) toddlers had a shorter sleep duration and more frequent night wakings when compared to their predominantly-Caucasian (PC) peers under 3 years of age. But the cultural difference of total sleep duration is not exactly the same across age groups. The total sleep duration of the PA cohort was more than that of the PC samples in the first 3 months of life but dropped below the PC samples beyond 3 months of life. More importantly, it seems that the PA children are not born with a shorter sleep duration and the intersection of the sleep duration trajectories between the PA and PC children occurs around 3 months old (Fig. 1a, b). We believe that parental sleep-setting behaviors contribute largely to the observed disparity of the sleep parameters between the PA and PC children. For example, parental nighttime involvement and nightly bedtime routine will play a major role in a baby’s sleep [18–20]. Mindell et al. [19, 20] studied cultural differences of parental sleep settings for many years and indicated that children from the PA regions were much more likely to be engaged with their parents, to partake in maladaptive activities (for example, inappropriate sleep associations including rocking, nursing, and swinging) and were less likely to have a consistent bedtime routine than those from the PC regions. Trends of nighttime sleep duration for the PC regions showed rapid changes over the first 3–6 months before stabilizing to a plateau, whereas nighttime sleep duration for the PA regions exhibited a slight change across different states in early life with an increase initially, followed by a decrease. The cross-cultural disparities of the age-related trends for sleep parameters over the first 3 years of life can be found in Figure 1.



**Fig. 1.** Cross-cultural disparities of the developmental trajectory (weighted by sample size) for sleep parameters over the first 3 years of life. Grey dots represent the samples. The orange line represents the trajectory curve fitted by the data from the Asian region samples; the dark blue line represents the non-Asian region samples; and the

red dashed line represents all samples. **a** Total sleep duration. **b** Nighttime sleep duration. **c** Daytime sleep duration. **d** Number of night wakings. **e** Bedtime in the evening. **f** Waketime in the morning [17].

### *Important Factors for Establishing a Healthy Sleep Pattern during the First Years of Life*

Positive sleep practices (known as “sleep hygiene”) are essential for establishing a healthy sleep pattern during the first years of life. Thus, it is recommended that parents start promoting good sleep hygiene by establishing a safe and comfortable sleep environment, a regular bedtime routine, and an appropriate sleep onset association starting from infancy, and throughout childhood [21].

#### Regular and Consistent Bedtime Routine

Having a regular and consistent bedtime routine is one of the critical steps to achieve good sleep hygiene and yield health benefits to young children. It provides them a sense of predictability and security and helps with activity transitions. Bedtime routines deliver external clues to children that sleep is coming and assist them in preparing for sleep mentally by being both predictable and calming. A bedtime routine should involve the same 3–4 calming and relaxing activities every night in the same order, e.g., warm bath, reading stories, singing lullabies, and listening to soft music. A pictorial representation of the bedtime activities is recommended for children at a younger age or developmentally delayed.

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#### Safe and Comfortable Sleep Environment

Maintaining a safe and comfortable sleep environment could promote adequate sleep quantity and quality. Usually, a comfortable sleep environment should be calm, quiet, dark, and with cooler temperatures. Prevention of accidental suffocation and strangulation are key considerations, especially for young babies. The crib mattress should provide a firm sleeping surface and fit tightly in the crib. Removal of all pillows and stuffed toys from the crib is recommended. The AAP recommends that the baby should be placed on his or her back to sleep at night and during naptime as evidence has shown that sleeping in a prone position significantly reduces the risk of sudden infant death syndrome [21]. In addition, the sleep environment around babies should be a “smoke-free zone.”

#### Appropriate Sleep Onset Associations

Sleep onset associations are those conditions that are present at the time of sleep onset as well as in the night following nighttime arousals. The “inappropriate” or problematic sleep onset associations refer to the conditions where infants require parental interventions, e.g., being rocked or fed. Infants with inappropriate sleep onset associations have been shown to be vulnerable to developing frequent night wakings. In order to avoid developing inappropriate sleep onset associations, the most important sleep behavior for a given infant to learn is the ability to self-soothe and fall asleep independently [22]. Specifically, putting infants to bed when they are drowsy but still awake and leaving them to go from drowsy to asleep on their own is a recommended approach for infants to develop appropriate sleep onset associations. Transition objects, such as blankets, dolls, and stuffed animals, could also help young children to foster independence and self-soothing to fall asleep.

#### Avoiding Media Exposure

It has been widely reported that young children have been exposed to significantly more media over the past few decades, and media exposure can negatively impact children’s sleep duration and quality and may lead to sleep difficulties [23, 24]. Media (such as smartphones, iPad, and desktop and laptop computers) will not only interfere with a relaxed state required for sleep initiation, but also suppress the normal evening surge in melatonin and alter the sleep-wake cycle via light exposure. Parents are strongly encouraged to remove TVs and electronic devices from the child’s sleeping environment.

#### Regular Daily Schedule of Activities with Appropriate Stimulations

Babies should be encouraged to develop a consistent age-appropriate schedule of sleep, outdoor activities, and mealtime to help regulating the internal clock and synchronize the sleep-wake cycle. For example, getting daily exposure to the sun especially in the morning and avoiding direct light exposure in the evening could appropriately regulate melatonin secretion to further promote sleep regulation. Evidence accumulated during recent years suggests that mealtimes can also affect the sleep-wake cycle [25].

### **Sleep and Early Brain Development**

#### *Learning and Memory*

Sleep has been implicated to play a critical role in memory functions of the adult brain and is thought to favor the “off-

line" processing of new memories [26]. Two types of sleep have been shown to be associated with different memory processing. The role of NREM sleep, especially SWS, is reactivation of the hippocampal-neocortical circuits activated during a waking learning period, while REM sleep is responsible for the consolidation of the new learning into long-term memory [27]. While the aforementioned information is informative about our understanding of the roles of sleep in adult memory function, how sleep benefits children's memory remains largely unknown.

It is explicit that the means through which children learn are very different from those of adults. Children rely more on rote learning other than knowledge-based learning, which is common in adults [28]. Wilhelm et al. [29] found that school-age children showed greater sleep-dependent extraction of explicit (or declarative) knowledge of the rules that govern an implicit procedural task than do adults. They further suggested that at least some of the differences in how children and adults process newly acquired information result from age-dependent differences in the forms of sleep-dependent processing applied to such memory. Pisch et al. [30] investigated whether the particularly high inter-individual differences in infant sleep duration and fragmentation are indicative of cognitive developmental trajectories examined by eye-tracking over a prolonged time period. They found that children spending less time awake during the night in early life were associated with better performance of a working memory task. Although several physiological explanations could account for the observed improved performance, it is highly plausible that the increased deep sleep (SWS) duration during the night in children is one of the main reasons.

Not only the whole night sleep but also daytime nap is related to declarative memory performance. The benefit of daytime nap on memory was also observed in infants and toddlers. Hupbach et al. [31] found that 15-month-old infants who had napped within 4 h of language exposure remembered the general grammatical pattern of the language 24 h later, while the infants without napping showed no evidence of remembering anything about language. More importantly, their results were confirmed by another research team which reported that nap facilitated generalization of word meanings, as indicated by event-related potentials [32]. Another study by Seehagen et al. [33] found that having an extended nap ( $\geq 30$  min) within 4 h of learning a set of object-action pairings from a puppet toy enabled 6- and 12-month-old infants to retain their memories of new behaviors over a 4- and 24-h delay. These findings support the view that infants' frequent napping may play an essential role in establishing long-term memory.

Two studies examined the effects of daytime nap on recognition tasks and generalization of word meanings in pre-

schoolers and confirmed the positive role of sleep in explicit memory consolidation [34, 35]. However, these results were not consistent with those reported by another study, which found that wakefulness (not sleep) promotes generalization of word meanings in children 2.5 years old [36]. Horváth et al. [35] speculated that the contrasting findings from these studies could be explained by 2 reasons. One possible reason is the developmental changes in the preferred sleep-dependent memory consolidation across early childhood. However, many studies in adults have also reported sleep-dependent generalization. Thus, it is plausible that other factors may have contributed to the observed inconsistent results, including, but not limited to, the change in background color and texture, the requirement of pointing in Werchan's task, or the circadian effects. Additional studies focusing on the potential benefits of daytime nap on cognitive development in children will be needed.

Sleep does not only play important roles in learning and memory, but it can also stimulate creative thinking. It is widely believed that sleep plays a role in the flashes of insight, for example. The Nobel Prize winner Loewi reported that he woke up with the essential idea for an experiment confirming the principle of chemical neurotransmission. The famous German chemist Kekule spoke of his great creation of ring-like structure of benzene and said that he had discovered the ring shape of the benzene molecule after having a daytime nap. Nevertheless, the hypothesis of sleep stimulating creative thinking was not proven until a well-designed study was conducted by a German group, which showed that sleep, by restructuring new memory representation, facilitates extraction of explicit knowledge and insightful behavior [37]. Since then, a few studies have further explored the association between sleep, especially REM sleep, and creative behaviors [38–40]. Nevertheless, in contrast to the ample evidence linking sleep and memory function, the relationship between sleep and creative thinking has not been widely studied and confirmed, most likely attributed to the challenges of a well-defined method of investigating insight/creative thinking [41], especially in young children.

#### *Emotional Regulation*

Sleep plays a critical role in mental health and psychosocial adjustment across the lifespan. A growing body of research has suggested that inadequate sleep leads to more negative and less positive emotions [42]. In addition, the impact of sleep on next-day mood/emotion is thought to be particularly affected by REM sleep [43]. During REM sleep, a hyperlimbic and hypoactive dorsolateral prefrontal activation and a normal function of the medial prefrontal cortex may explain its adaptive role in coping with emotional events [43].



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## The impact of sleep on next-day mood/emotion is thought to be particularly affected by REM sleep

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Actually, the effects of sleep on emotional regulation could be traced back to the neonatal period. It is noteworthy that active (or REM) sleep accounts for the biggest portion of a child's sleep, and it is likely to subserve crucial emotional function [44]. It was observed that the neonatal smiles, particularly Duchenne smiles, which involve lip corner raising with cheek raising, tend to predominate in active sleep compared to during wakefulness or other sleep states, suggesting a potential tie to early constituents of emotion [45]. An imaging study of 3- to 7-month-old infants revealed specific brain regions responding to emotional human vocalizations during sleep, including the orbitofrontal cortex and insula [46]. Not only REM sleep, but also sleep structure and quiet sleep (NREM sleep) contribute to children's emotional function. A longitudinal cohort study of premature infants found that premature infants with sleep state transitions characterized by shifts between quiet sleep and wakefulness at gestational age 37 weeks exhibited the best emotional and cognitive development in later childhood, contrary to other two-state transition patterns [47]. We recently used eye-tracking technology to study the association between sleep and circadian rhythm characteristics with waking social cognitions in 12-month-old infants, particularly face processing – an important predictor for social-emotional functions. We found that infants' face scanning patterns were related to several sleep- and circadian-related parameters, such as sleep quantity, sleep quality, circadian stability, circadian amplitude, and circadian phase [48].

A systematic review has examined the association between sleep duration and a broad range of health indicators in children aged 0–4 years, where emotional regulation was one of the important outcomes [2]. Overall, a shorter sleep duration was associated with poorer emotional regulations (13/25 studies), and among these studies, 2 randomized studies (both randomized cross-over trials with high quality of evidence) showed better self-regulation strategies and emotional responses in the routine sleep versus the sleep restriction conditions [44, 49].

Many experimental sleep deprivation studies in animals and adults have attempted to explain the underlying mechanisms of sleep on the emotional brain [42, 43, 50]. In particular, noninva-

sive imaging approaches have been widely employed to potentially shed light on our understanding of the underpinnings linking sleep and emotional control. Neuroimaging studies in adults reported that sleep deprivation was associated with a 60% greater magnitude of activation of the amygdala and a 3-fold greater amygdala activation volume between groups [51]. The diminished amygdala-prefrontal connectivity was also found after sleep deprivation, suggesting a lack of cognitive control over emotional brain areas [51]. Finally, a functional magnetic resonance imaging study investigating the effect of sleep loss on the emotional brain network found that sleep deprivation amplifies reactivity throughout the mesolimbic reward brain network in response to positive emotional pictures [52].

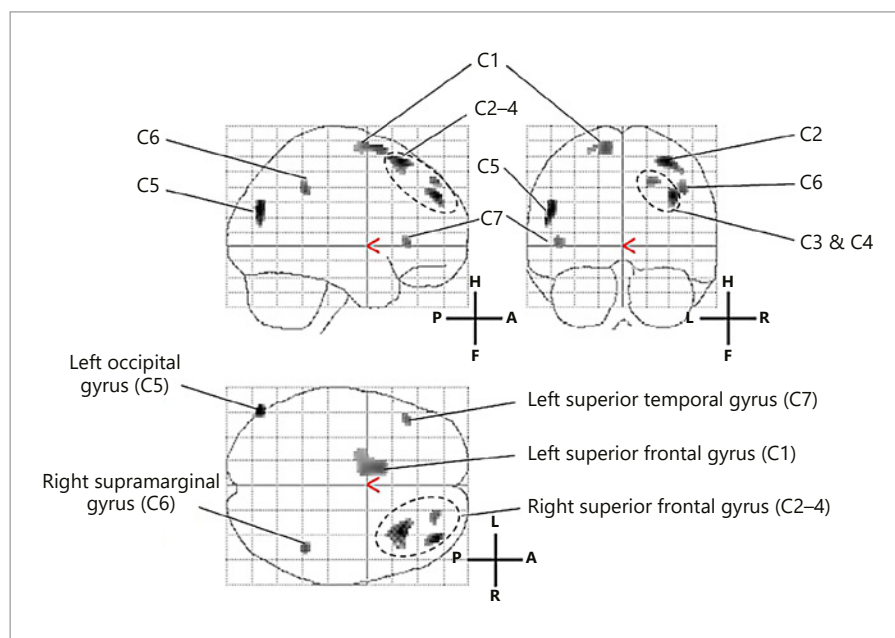
### *General Cognitive and Brain Structure Development in Children*

Apart from the studies focusing on sleep and memory and emotional development in young children, several studies have examined the relationship between sleep and general cognitive development or language development in infants and toddlers. One study revealed that a greater number of awakenings after sleep onset measured via sleep actigraphy recordings amongst 10-month-old infants were negatively correlated with the scores of the Bayley Scales of Infant and Toddler Development second edition (BSID-II) Mental Development Index (MDI) [53]. Gibson et al. [54] also found that 11- to 13-month-old infants who had either greater sleep efficiency or longer proportions of sleep at night measured by sleep actigraphy data were associated with better cognitive problem-solving skills as measured by the Ages and Stages Questionnaire. Recently, we examined the association between nighttime awakenings and cognitive development in a large-scale community sample of infants and toddlers from 8 provinces across China and found that frequent nighttime awakenings reported by caregivers are associated with a lower MDI in BSID-I in toddlers between 12 and 30 months [55]. A longitudinal twin study assessed the association between sleep-wake consolidation at 6, 18, and 30 months and language skills at 18, 30, and 60 months and found that a poor sleep consolidation during the first 2 years of life may be a risk factor for language learning in later childhood [56].

In adults, many studies have reported that sleep patterns and problems are associated not only with brain functions but also with structural properties of the brain, especially the gray matter volumes [57–59]. But very little is known about how sleep affects the developing brain from the structure perspective, and the only few studies all collected imaging data from children older than 5 years old [60–64].

Recently, one study investigated the prospective associations between sleep disturbances throughout early childhood

**Fig. 2.** Maximum intensity projection (MIP) of the statistical map showing areas of grey matter deficits in patients with moderate-to-severe obstructive sleep apnea. The MIP is projected on a glass brain in 3 orthogonal planes. Corresponding brain regions: C1, left superior frontal gyrus; C2–4, right superior frontal gyrus; C5, left occipital gyrus; C6, right supramarginal gyrus; C7, left superior temporal gyrus [61].



and brain morphology at 7 years of age [60]. They found that sleep disturbances from age 2 years onwards were associated with smaller grey matter volumes. The global trend of this phenomenon also showed meaningful regional specificity. Children with sleep disturbances were associated with thinner cortex in the dorsolateral prefrontal area, which may reflect effects of sleep disturbances on brain maturation [60]. However, one of the major limitations of this study is the use of a cross-sectional design, making it difficult to rule out reverse causality. That is, rather than being a consequence of sleep disturbances, brain morphology may underlie childhood sleep problems. Two studies explored the relationship between gray matter density and obstructive sleep apnea (OSA), which is one of the most common sleep disorders in childhood [61, 62]. Chan et al. [61] found that children with moderate-to-severe OSA had a significant grey matter volume deficit in the prefrontal and temporal regions (Fig. 2). A similar finding was also reported in Philby et al.'s [62] study where significant grey matter volume reductions were observed in OSA children throughout regions of the superior frontal and prefrontal, and superior and lateral parietal cortices. Even though these 2 studies of OSA children could further support the effects of sleep on brain structural development, the mechanisms of OSA and general sleep disturbance, for example dyssomnia, on cortical development might be very different. Reduction of grey matter volume in pediatric OSA children could be the result of sleep fragmentation as well as hypoxic damage to the brain [65].

Not only sleep problems but also sleep duration could impact cortical maturation. Taki et al. [64] analyzed the correlation between sleep duration and cortical development in 290 school-aged children and adolescents, which are the most vulnerable populations suffering from sleep deprivation. They found that the regional gray matter volumes of the bilateral hippocampal body as well as the right dorsolateral prefrontal cortex were positively correlated with sleep duration during weekdays. It has been speculated that children with more sleep problems could be delayed in reaching peak cortical thickness or advanced on the maturation curve of the prefrontal cortex [66].

Although there is abundant evidence from behavioral and neurophysiological studies suggesting that sleep affects infants' cognitive and emotional development, there is lack of evidence from imaging studies in this population, largely limited by the difficulties of imaging nonsedated children and the lack of analysis tools tailored to very young children. Nevertheless, with the marked development of image acquisition approaches and the novel analysis tools for infants and young children [1], we can expect more studies delineating the effects of sleep on brain structural and functional networks in young children.

## Disclosure Statement

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