Current Sleep Medicine Reports (2024) 10:437–446
https://doi.org/10.1007/s40675-024-00307-7

REVIEW

The importance of sleep for the developing brain

Tracy Riggins[1] · Erin L. Ratliff[1] · Melissa N. Horger[2] · Rebecca M. C. Spencer[2]

Accepted: 6 June 2024 / Published online: 2 July 2024

Abstract

Purpose of review This paper summarizes recent research regarding the possible contribution of sleep to brain development. Major milestones in brain development and the methods used to track these changes are reviewed. Changes in sleep, at both behavioral and neural levels, that take place during the same developmental periods are discussed. Finally, a few empirical examples that have contributed new knowledge regarding how sleep contributes to brain development are highlighted.

Recent findings Empirical examples demonstrating associations between development of sleep and the brain include: predictive associations between SWA topography and myelin development, associations between SWS and hippocampal development, and links between sleep duration and both white matter volume and whole-brain functional connectivity in developing populations.

Summary There is evidence that sleep is important for the developing brain. However, studies utilizing longitudinal, objective measures of sleep, high-resolution brain imaging, and behavioral measures across development are critical for understanding sleep function.

Keywords Brain development · Sleep development · Sleep physiology · Electroencephalography · Magnetic resonance imaging · Neuroimaging

Introduction

The human brain undergoes significant development starting during the prenatal period and continuing through the first two decades of life. Sleep has been hypothesized to play an important role in this process [1, 2], However, identifying the precise mechanisms through which sleep contributes to brain development remains challenging, particularly during early development. This review summarizes major milestones in brain development focusing on the postnatal period through adolescence and the methods used to track these changes. We then summarize known changes in sleep (at both behavioral and neural levels) that take place during this same period. Finally, we discuss how sleep may contribute to brain development and provide a few empirical examples from the literature that have begun to address this question.

Although other reviews on sleep and brain development exist, most of these papers have focused on the co-development of sleep and the brain (as opposed to how one influences the other, e.g., [3]) or do not include direct measures of brain structure or function, but rather use changes in behavior as a proxy for brain development (e.g., [4–8]). Other reviews focus on the consequences of sleep deprivation (as opposed to normative/healthy sleep, e.g., [9]) or highlight specific populations (e.g., preterm infants, [10]). Our hope is that by summarizing research on sleep's contribution to brain development across the early lifespan and approaches used, this review will assist researchers in designing and conducting future studies to better understand the relation between brain development and sleep.

Development of the Human Brain

Human brain development begins prenatally. At the time of birth, nearly all neurons have been produced and connections between neurons have begun to form early neuronal circuits. The first year is characterized by rapid brain development [11], as the brain nearly doubles in size and, by the second year, is just 20% smaller than the adult brain [12].

✉ Tracy Riggins
riggins@umd.edu

[1] University of Maryland, College Park, USA

[2] University of Massachusetts, Amherst, USA

This remarkable postnatal growth in both gray and white matter is due in part to dendritic arborization which underlies synaptogenesis: as dendrites mature and become more densely populated with spines, they are more likely to make synapses with neighboring neurons [13]. Rates of synaptogenesis differ based on brain region, subsequently influencing the plasticity of these regions [13, 14]. Synaptogenesis peaks first in the somatosensory and sensorimotor cortices around 4 months, followed by the auditory and visual cortices between 4–12 months. Synaptogenesis has been shown to peak much later in the prefrontal cortex with estimates around 15–18 months [13, 15].

Synaptogenesis is accompanied by cell death (apoptosis) and synaptic pruning. At its peak, synaptic density in specific regions can be over 1.5 times the synaptic density in the same region in an adult brain [13, 16]. Thus, synaptic pruning and apoptosis are developmentally normative regressive events allowing for greater efficiency and specificity of neuronal networks [17]. These processes accelerate during the first two years of life, decline during childhood and adolescence, and are thought to be complete in early adulthood [18, 19]. Rates and timing of synaptic pruning and apoptosis are region-dependent with high rates in sensory and motor cortices seen following birth, in the visual cortex at approximately 8 months, and in the frontal cerebral cortex around 24 months [13]. Following this early period, additional pruning is predominantly experience driven. In the visual and auditory cortex, pruning is typically complete by early childhood, whereas pruning in regions involved in higher order cognitive function may continue through adolescence [20, 21].

Myelination also occurs rapidly in early life with the highest rate between 3 weeks and 1 year postnatally [22]. Myelination has been found to move from the back to the front of the brain, starting with the cerebellum, pons and internal capsule, proceeding to the corpus callosum around 3–4 months, to the occipital and parietal lobes around 4–6 months, and ending with the frontal lobe around 6–8 months [23], with all major white matter tracts defined by the end of year 1 [22]. Following the first year, the rate of change in myelination is much lower, increasing gradually through childhood and adolescence (see Fig. 1, upper panel). Myelination in sensory and motor regions is typically complete around 3–5 years; whereas regions involved in higher order cognitive function may not be fully myelinated until early adulthood [21].

Most brain development following the second year is focused on efficiency and fine-tuning of the established

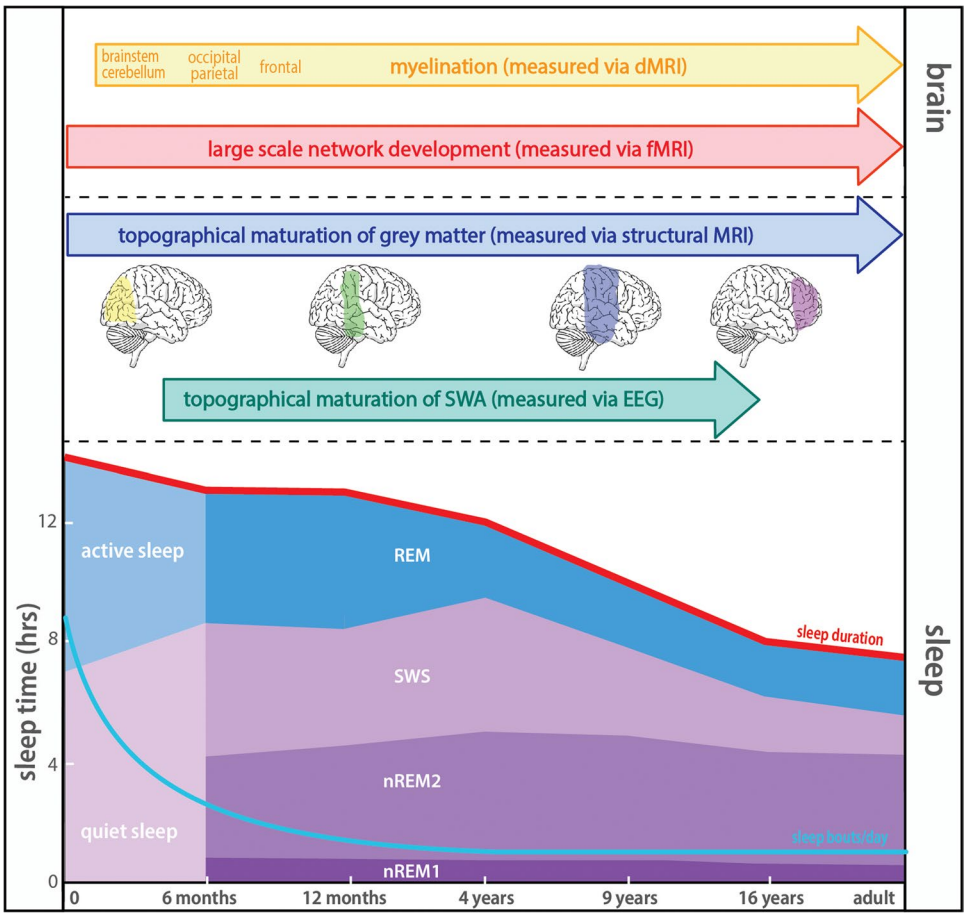

Fig. 1 Summary of reviewed components regarding both brain maturation and neuroimaging methods (upper panel) and sleep physiology (lower panel). Note multiple shifts in terms of sleep duration, type of sleep, and number of naps (i.e., from many naps a day at birth to 1 sleep bout by about 4 yrs of age). One distinct parallel between sleep and brain development is highlighted in the middle panel—the posterior to anterior developmental trajectory of SWA and gray matter maturation

networks. Global measures show gray matter increases at a more rapid pace than white matter by 2 years [24]. After this, increases in gray matter are almost negligible and begin to decrease in adolescence [25], whereas white matter steadily increases into young adulthood [26]. These changes are reflected in measures of cortical thickness and surface area, which have been shown to continue to increase into late childhood followed by regionally variable decreases during adolescence [27]. Age-related linear increases in white matter connectome development from birth to 13 years contribute to functional specialization and maturation [28, 29]. In addition, although functional brain networks begin forming at birth, reconfiguration and dynamic pruning driven by experiences and biological changes continue to shape and refine large-scale functional networks through adolescence [30, 31]. In sum, after basic building blocks are in place, the brain continues to change based on experience and environmental input (i.e., experience-dependent plasticity, [14]). These changes include subtle variations in gray and white matter, as well as development of functional connectivity reflecting networks of the brain. Trajectories are broadly summarized in Fig. 1.

Measurement of Human Brain Structure and Function Across Development

Diverse neuroimaging modalities allow researchers to explore changes in structural and functional brain development in vivo. Here we briefly review the most commonly used techniques to explore links between sleep and brain development.

3.1 Electroencephalogram (EEG) Provides a direct measure of neuronal activity with high temporal resolution and can provide insight into the developmental timing of cognitive processes. Strengths of EEG include that it is typically more affordable and more robust to motion compared to most other forms of neuroimaging, making it particularly useful when working with developmental populations [32]. However, EEG has relatively poor spatial resolution as it is a summation of neuronal activity across the cortex and cannot capture or differentiate subcortical activation. EEG measures collected during sleep are informative regarding the temporal dynamics, frequency, and magnitude (or power) of brain activity – both at specific sites and connectivity between sites. EEG is the most commonly used neuroimaging technique during sleep as it can largely differentiate sleep stages, is reasonably comfortable for sleeping, and can measure continuously across a sleep bout.

3.2 Structural magnetic resonance imaging (MRI) Provides static anatomical information and can discriminate between white and gray matter in the brain as well as cerebrospinal fluid. Structural data obtained with MRI can be used to assess size, shape, and integrity of white and gray matter [33]. Due to folding of the cortex, variations in gray matter are assessed via cortical thickness (i.e., the distance between the gray and white matter cortical boundary) and/or surface area (i.e., the area of the boundary). Strengths of structural MRI include its regional specificity and its ability to assess both cortical and subcortical regions. As structural imaging is subject to motion artifact, particularly in young children, conducting scans on children when asleep provides a solution to this problem at least for those under 3 years [34]. However, structural MRI does not capture the specific mechanisms underlying developmental changes in gray matter in vivo in humans and may result from changes in cell number or size or the extent of dendritic branching [35] (for elaboration see [36]). Studies have linked measures of sleep with metrics obtained from structural MRI in an attempt to shed light on the association between sleep and structural brain changes (e.g., [37–41]).

3.3 Functional MRI (fMRI) Can be used to explore functional brain development through the measurement of changes in the blood-oxygen-level-dependent (BOLD) signal [12, 42]. This approach also allows researchers to explore changes in functional connectivity, or temporal synchronization of neural signals from distinct brain regions [42]. In the absence of a task paradigm, this approach is referred to as resting state fMRI. Functional connectivity can provide insight into how functional interactions between brain regions change over development [31, 43]. Advantages of fMRI include its regional specificity and the ability to examine functional brain networks. Similar to structural MRI, studies have linked measures of sleep with metrics obtained from fMRI in order to shed light on the association between sleep and functional brain changes [44–46]. However, like structural MRI, fMRI is sensitive to motion making it difficult for early developmental studies.

3.4 Diffusion-weighted MRI (dMRI) Provides information about the microstructure of brain tissue [47]. Two primary types of diffusion-weighted imaging include diffusion tensor imaging (DTI), which allows for examination of the integrity of white matter tracts, and neurite orientation dispersion and density imaging (NODDI), which assesses the microstructural features of dendrites and axons [48, 49]. Developmental changes in white matter are driven by changes in axon thickness and retraction, oligodendrocyte development, myelination, and synaptic pruning [12, 50]. These changes support advances in neural signaling between brain regions [28]. Studies have aimed to link measures of sleep with metrics obtained from diffusion-weighted imaging to explore associations between sleep and changes in the brain. These

measures can be obtained concurrently, or measures of sleep can be used to predict future changes in the brain. Relating changes in sleep with development of tissue microstructure can inform the role of sleep in plasticity and skill refinement [51, 52].

Each of these methods assesses a different aspect of brain development, has its own advantages and disadvantages, and captures unique ways brain development may be impacted by sleep. With advances in technologies, these measures are being more readily applied to developmental populations, although challenges remain.

Developmental Changes in Sleep

4.1 Developmental Changes in Sleep Timing and Duration

In the first month of life, infants sleep an average of 14 h in 1–3-h intervals [53]. Sleep time declines little over the first year; however, sleep becomes more efficient, consolidated into one longer sleep bout during the night with 1–2 naps during the day [54]. Large individual differences in sleep time are common during this developmental period, with total sleep time ranging from 9–20 h in the youngest infants [53].

Between 2 to 6 years, sleep duration is generally stable [55]. Yet, inter-subject variability still remains pronounced, with sleep times ranging from 9–15 h [56]. Most children also transition out of daytime sleep at this time, typically between 3–5 years. From 6–10 years, sleep time steadily decreases by several minutes per year, from 10.5 h to 9 h [53, 56]. Inter-subject variability in sleep time continues to decline as well. By adolescence, average sleep time stabilizes to around 8–9 h per day, which remains similar into early adulthood [57].

Many external factors contribute to sleep duration and timing, including caregivers' schedules, breast vs. bottle feeding, maternal depression, and sociocultural expectations [58–61]. Moreover, bedtimes and waketimes are subject to external pressures; bedtimes move later due to social and extracurricular activities while waketimes are often dictated by school/childcare start times. As a result, observed average sleep duration and timing may not reflect actual child sleep need.

Developmental Changes in Sleep Physiology

4.2.1 Sleep Macrostructure

In early infancy (< 6 months gestational age), sleep is broken into 2 stages: active and quiet sleep. Active sleep is the precursor to REM sleep and shares many of the same behavioral characteristics including increased and more variable cardiorespiratory rates, twitching, and eye movements [62–65]. Neonates spend about 50% of sleep in active/REM sleep and the proportion rapidly decreases to about 30% by the end of the second year [64]. Quiet sleep is the precursor to NREM and is demarcated by more regular respiration and limited movement with occasional twitching. Time spent in quiet/NREM sleep, as displayed in Fig. 1 (lower panel), has a comparatively inverse developmental trajectory, increasing throughout infancy [63].

REM and NREM continue to change through toddlerhood and childhood. Transitions between the states are cyclical; early on, the duration of a single cycle is approximately 60 min and by school-age this lengthens to over 90 min [64, 66]. Within the ultradian cycle, NREM can be further broken down into the adult-like three substages (NREM1, NREM2, NREM3/SWS) by 5–6 months. While young infants begin a nighttime sleep bout with REM sleep, older populations experience their first REM episode within the first hour after sleep onset, at the end of a sleep cycle and throughout the night, duration of REM sleep increases [64].

The proportions of time spent in each state vary with whether it is a day or nighttime sleep bout as well as the accumulated sleep pressure, or time since last sleeping [67]. Midday naps in 2–5-year-olds are predominantly composed of NREM2 (roughly 40% of the total nap time) and SWS (roughly 50% of the total nap time; [68]). Regarding overnight sleep bouts, the beginning of the sleep period largely includes NREM1, making up 2%-5% of the child's total sleep time. Subsequently, children enter NREM2 sleep. Characterized by reduced muscle tone and eye movements, this stage typically constitutes one half of the total overnight sleep time. Stage 3 or SWS, in contrast, makes up 20% of total sleep time, primarily taking place in the first half of the sleep interval. Arousal during this stage is difficult and if roused, the child will appear perplexed and disoriented [69]. REM sleep constitutes about 20%-25% of the sleep period by the age of 5 years [70].

4.2.2 Sleep Microstructure

Spectral analysis of the sleep EEG shows the largest developmental shifts in the prototypical sleep spectrum – delta (slow wave activity (SWA)), sigma, and theta – with little change in alpha and beta. Theta power and SWA decrease from 2 years through adolescence. Notably, SWA also shows a distinct topographic shift along the posterior–anterior axis (see Fig. 1, middle panel). It is concentrated in the occipital regions until 5 years when it begins peaking more centrally. By 14 years, most SWA is found in central regions with some in the frontal and by adulthood, most SWA activity is concentrated in the frontal area [71].

Sigma power is uniform in the first year of life, averaging approximately 13 Hz. By 2 years, power spectra display two distinct peaks within the sigma range. Activity in the sigma band reflects sleep spindles and these two peaks reflect the emergence of fast spindles (~ 13–16 Hz, centrally located) and slow spindles (~ 10–12 Hz, frontally located) similar to adults [72]. The most rudimentary iteration of sleep spindles can be observed as early as 2 weeks post-term (though this is earlier in premature infants) and they become more differentiated and easily observable from 3–9 weeks [73]. In infancy, sleep spindles are often asynchronous across brain hemispheres and even unilateral. By 2 years, spindles appear bilaterally. While bilateral spindles often lag early in development, this lag decreases across childhood and stabilizes around age 11 years [72]. Spindle duration decreases over the first two years [64] and then increases again across early childhood and adolescence [72]. Spindle density follows a similar U-shaped trajectory, decreasing from infancy to toddlerhood then increasing across childhood [73].

Linking Changes in the Brain and Sleep

Given parallels in the development of the brain and sleep, studies have begun to examine these relations and point to theoretical underpinnings. For example, it has been proposed that because the trajectory of SWA topography matches the course of cortical gray matter maturation [74], moving posterior to anterior, sleep slow waves may actually contribute to cortical maturation [75]. Individual variability in topographical changes and the extent of SWA maturity, calculated via the ratio of activity in frontal versus occipital regions, has been linked to long-term outcomes [71, 76–78]; for exception, see [79]. Another hypothetical model suggests that REM sleep is linked to basic brain development processes, such as laying the groundwork for brain morphology and early neural circuitry, whereas NREM sleep provides a refinement of those basic processes by regulating synaptic homeostasis [63]. It has also been argued that limb twitches during active sleep not only provide direct brainstem activation of the cortex but also sensory feedback arising from discrete activation of somatosensory cortex, which may contribute to the refinement of sensorimotor neural circuits [80]. Finally, our group has hypothesized that maturation of the hippocampal-dependent memory network results in more efficient memory storage, which reduces the buildup of homeostatic sleep pressure (as reflected by slow-wave activity), and eventually contributes to nap transitions [67]. Each of these theories suggests a specific link between sleep and brain development that is ripe for empirical investigation.

Dutil and colleagues [81] systematically reviewed the literature linking brain development and sleep in 2018. Although their initial goal was to characterize the influence of sleep on developing brain structure and function via a meta-analysis, this was not possible due to the disparate measures used across papers both in terms of brain development and in terms of sleep. Thus, they were restricted to a narrative synthesis. They concluded that the literature clearly showed the importance of sleep for the developing brain. However, they also called for harmonization of measures not only reflecting sleep but also reflecting outcomes at the neural level [81].

Since then, more research has been done although methodological approaches continue to be highly variable. However, a few key studies are important to highlight in this regard.

LeBourgeois and colleagues [82] explored relations between topographical distribution of SWA during childhood and brain development. High-density EEG was collected from 13 children between 2.4 to 8 years. Approximately 3 years later, MRI was used to assess myelin water fraction and cortical morphology. EEG findings at time 1, comparing EEG power at frontal versus occipital electrodes, strongly predicted whole brain myelin water fraction at follow-up. These results support the hypothesis that sleep supports brain development and, specifically, that processes occurring during sleep physiology may contribute to brain myelination.

A relation between SWA and hippocampal development has also emerged from our recent work. Specifically, we examined relations between nap habituality (assessed via actigraphy and parent-report), sleep physiology (assessed via EEG), and hippocampal volume (assessed via structural MRI) in 56 3- to 5-year-old children [83]. Sleep physiology and hippocampal volume differed based on nap habituality. Habitual nappers had more SWA in the nap than intermediate nappers and smaller hippocampal head volumes than non-nappers. Additionally, across participants, SWS was positively associated with hippocampal volume. Given this latter result, it is possible that SWS-dependent mechanisms support hippocampal development [67, 84].

Other recent studies suggest that sleep duration is critical to brain development. Pittner and colleagues [40] examined infant sleep trajectories across the first year of life based on maternal reports at 1, 3, 6, 9, and 12 months. Structural MRI was then conducted at 12 months. Infants whose sleep duration decreased less during the first year of life had, on average, greater white matter volume. Furthermore, average sleep duration across the first year and sleep duration specifically at 6 and 9 months were positively associated with white matter volume. There were no associations between sleep and gray matter volumes (see also, [52]).

Sleep duration continues to be important to early-adolescent brain development. Mummaneni and colleagues [46] used fMRI to examine relations between sleep duration and whole-brain functional connectivity in adolescents aged 11–12 years.

Average sleep duration was extracted from Fitbits worn for an average of 24 days. Brain development was assessed via whole-brain functional connectivity patterns derived from n-back task (n = 786) and resting-state (n = 1274) fMRI data. Connectome-based predictive modeling was used to predict mean sleep duration from functional connectivity patterns. Large-scale functional connectivity patterns were positively related to sleep duration. This trend showing associations between aberrant functional connectivity and sleep duration has been replicated in large samples of 5–11-year-old children [85–87].

These four exemplary cases have rigorous sleep and imaging methods. However, there is additional literature speaking to other facets of sleep. Sleep disturbances (i.e., longer sleep onset latencies, timing irregularities and higher levels of daytime sleepiness) interacted with depression in early childhood (3–5 years) to predict later gray matter volume and trajectories of change [88]. In adolescence, later sleep timing, poorer sleep continuity, and shorter sleep duration were related to greater cortical thinning and, in some regions, this relationship was unique to early adolescence [89]. Similarly, disrupted sleep negatively impacted topological characteristics, specifically stability and efficiency, of multiple functional networks suggesting shorter sleep duration may impact information processing and transmission across the entire brain [86].

Collectively, these studies support a role for sleep in brain development. These studies suggest that the more time spent asleep – particularly consistent, uninterrupted sleep – across early and later development, the more the brain is able to mature. This may not be mutually exclusive from findings regarding SWA, as longer sleep duration would generally come with more SWA-rich SWS. Alternatively, sleep may serve multiple functions that support brain development. Note that sleep may not play an active role in brain development per se but, rather, protect it from interference from other ongoing processes that happen during wake.

Finally, studies in clinical populations might be useful in providing insight into whether sleep has causal role in brain development. Specifically, children with obstructive sleep apnea (OSA) have disrupted sleep relative to their healthy peers. Notably, children with OSA show reduced white matter volume across hemispheres [90], more cortical thinning [91], and abnormal functional connectivity [92]. Results regarding gray matter are mixed; one study found greater gray matter volume in the middle frontal gyrus (ages 8–13 [93]), whereas another study found reduced gray matter volume in the frontal region [90]. Likewise, childhood insomnia is linked to smaller brain surface area [94]. Taken together, these studies provide further evidence for the inferred active role of sleep documented in correlational work with imaging outcomes.

Conclusions and Suggestions for Future Research

Taken together, recent research provides evidence supporting the role of sleep in brain development. However, further research is needed. First, additional data is needed on normative brain development, especially longitudinal data in samples representative of the populations to which one hopes to generalize. More work is needed across development, however data during infancy and early childhood is particularly critical, as reviewed above and illustrated in Fig. 1, changes in both sleep and brain are most dramatic during these periods [66]. Second, given some of the limitations of the methods reviewed, future work may benefit from functional near-infrared spectroscopy (fNIRS), a non-invasive, optical neuroimaging technique which is less subject to noise from movement, portable, and a newer, more sleep-friendly technology. Researchers studying neonates have demonstrated the feasibility of using fNIRS in combination with sleep EEG to examine the influence of sleep state on the presence of observable resting state networks [95]. Third, improved theoretical motivation for brain and sleep measures are needed in future studies. When possible, regional predictions should be made, or justification for exploration across the whole brain provided. Likewise, theoretical motivation for sleep measures, for example SWA or sleep duration, is important and may guide decisions in the methodological approach to sleep measurement (e.g., polysomnography versus actigraphy). Such specifications also improve the overall power of the experimental design, a critical consideration when working with challenging populations such as infants and children. Fourth, as both brain and sleep change, so does behavior; including assessments of cognition (memory, executive function, emotion processing, language) or mental health (such as psychopathology and adaptive functioning) may allow for meaningful translation to improve lives. Related, development does not occur in a vacuum; as such, assessing the role of environment on sleep-brain relations will be important as well (e.g., [96, 97]. Finally, the above literature does not clearly disentangle the contribution of sleep to brain development from the contribution of brain development to sleep. This is a limitation and a call for more research aimed at disentangling the direction of these effects, perhaps with the use of longitudinal data, more advanced statistical modeling or the inclusion of clinical comparison groups. Such clarification will be critical in the future.

In sum, despite all that is known about the development of the brain and sleep, linking these developmental changes is in the early stages. Critical to understanding sleep function, are longitudinal objective measures of

sleep, high-resolution brain imaging, and behavioral and psychological measures across the developmental lifespan. This work establishing basic sleep function is an essential first step to understanding the impact of sleep disruption or dysfunction in early childhood.

Human and Animal Rights and Informed Consent

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Author Contributions T.R. and R.M.C.S. secured funding and conceptualized the paper content. All authors contributed to text for the main manuscript text and R.M.C.S. and M. H. prepared the figure. All authors reviewed the manuscript.

Funding This work was supported by National Institute of Health, R01HL164628.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of Interest The authors have no conflicts of interest to disclose.

Competing Interests The authors declare no competing interests.

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