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REVIEW ARTICLE

Early development of sleep and brain functional connectivity in term-born and preterm infants

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The proper development of sleep and sleep-wake rhythms during early neonatal life is crucial to lifelong neurological well-being. Recent data suggests that infants who have poor quality sleep demonstrate a risk for impaired neurocognitive outcomes. Sleep ontogenesis is a complex process, whereby alternations between rudimentary brain states—active vs. wake and active sleep vs. quiet sleep—mature during the last trimester of pregnancy. If the infant is born preterm, much of this process occurs in the neonatal intensive care unit, where environmental conditions might interfere with sleep. Functional brain connectivity (FC), which reflects the brain's ability to process and integrate information, may become impaired, with ensuing risks of compromised neurodevelopment. However, the specific mechanisms linking sleep ontogenesis to the emergence of FC are poorly understood and have received little investigation, mainly due to the challenges of studying causal links between developmental phenomena and assessing FC in newborn infants. Recent advancements in infant neuromonitoring and neuroimaging strategies will allow for the design of interventions to improve infant sleep quality and quantity. This review discusses how sleep and FC develop in early life, the dynamic relationship between sleep, preterm birth, and FC, and the challenges associated with understanding these processes.

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IMPACT:

- Sleep in early life is essential for proper functional brain development, which is essential for the brain to integrate and process information. This process may be impaired in infants born preterm.
- The connection between preterm birth, early development of brain functional connectivity, and sleep is poorly understood.
- This review discusses how sleep and brain functional connectivity develop in early life, how these processes might become impaired, and the challenges associated with understanding these processes. Potential solutions to these challenges are presented to provide direction for future research.

INTRODUCTION

Sleep is essential for life. It serves multiple purposes for ensuring brain health, including memory consolidation, emotional processing, and most importantly, maintaining neural networks and synaptic plasticity.[1–4] Sleep begins to develop in early fetal life, during which it is described as an alternation in behavioral states.[5–7] Poor quality sleep in the fetal and neonatal period is associated with lifelong developmental consequences. Sleep in early life is not only physiologically crucial,[8–14] but also may be used as a contextual framework to understand the early organization of brain networks, and even the effects of medical adversities on later neurodevelopment.

Sleep and brain development may be disrupted in early life if infants are born preterm. Preterm infants are often admitted to neonatal intensive care units (NICUs), where they are exposed to environmental conditions that interrupt sleep.[15–21] As such, disrupted sleep in this period can be both the cause and the effect of neurodevelopmental impairments,[10,14,22,23] as supported by studies of neonatal sleep deprivation in animal models.[24–26] Moreover, preterm birth has a significant impact on neurodevelopment across the life span.[27–30] Studying sleep development (sleep ontogenesis) in preterm infants, therefore, provides a unique opportunity to investigate the relationship between disrupted sleep and potential impairments in early neurodevelopment.

Early brain development and relative maturation can be investigated by studying functional brain connectivity (FC), which reflects the functional integration of different brain regions.[31,32] Formally, FC is defined as a type of statistical relationship (usually a correlation) between brain areas that describes their related activity. These related areas are therefore described as functional brain networks, or functional connectivity networks (FCNs).[33–36] Large-scale correlations in FCNs are associated with all cognitive functions,[37,38] including sleep,[33] and are also tightly linked to sleep states.[33,39] It is, therefore, essential in the study of the development of large-scale functional brain networks to understand sleep ontogenesis and its disturbances. The presence of FCNs has been described both in term-born and preterm infants, and alterations in network development are associated with prematurity.[40–45] Therefore, alongside the developmental emergence of sleep states, the appropriate

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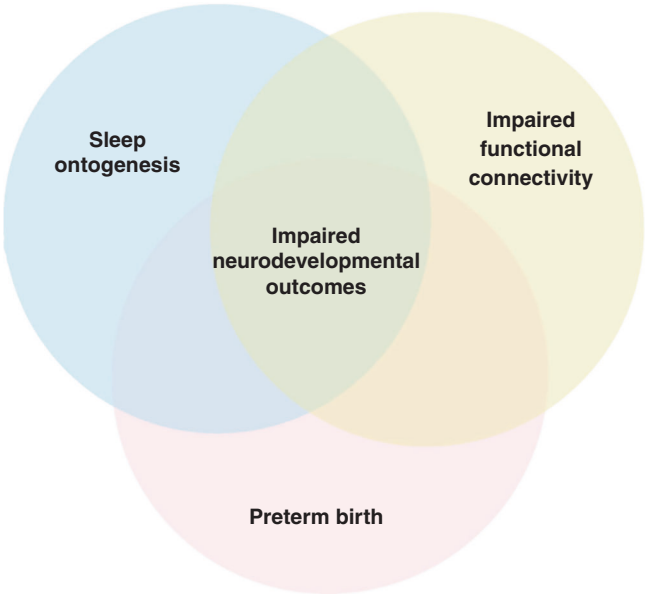

Fig. 1 Relationship between preterm birth, sleep ontogenesis, and functional brain connectivity. The relationship between these three processes is currently unclear.

development of their neuronal underpinnings, such as FC patterns, in early life appears important for later neurocognitive outcomes.

In recent years, several technological advances in neurophysiological brain monitoring and functional neuroimaging have allowed for more detailed investigations into neonatal FC and early sleep development.[33,34,46–51] As pointed out in this review, it is challenging to study the causal relationships between preterm birth, sleep impairments, and development of brain FC (Fig. 1). In the first part of this review, we provide an overview of sleep ontogenesis, from early fetal life to birth, and the impact of preterm birth on this process. We then go on to discuss neonatal FC development within the context of sleep states and its associated challenges, before describing studies that have specifically investigated neonatal FC in the context of sleep and/or preterm birth. Finally, current research challenges are discussed, as well as new technological and methodological innovations that hold promise for future research.

This review article is a systematized review, which includes elements of the systematic review process without meeting all of the standards, given the broad nature of this topic. To identify studies relevant to this topic, we used the following search strategies in PubMed and SCOPUS. (1) ((functional connectivity) OR (resting-state functional connectivity)) AND ((newborn) OR (neonate) OR (preterm)) AND ((sleep) OR (sleep state)); (2) (fMRI) AND ((resting-state functional connectivity) OR (functional connectivity)) AND (infant) AND (sleep); (3) (fNIRS) AND ((resting-state functional connectivity) OR (functional connectivity)) AND (infant) AND (sleep). All resulting EEG and fNIRS studies were included in Tables 2 and 3. fMRI studies were not included as nearly all infant fMRI studies are conducted during sleep, yet none take into account the effect of sleep state. The text includes the findings of the most relevant studies that are exemplary of the current state of the literature. Additional literature is also presented to provide background for the reader on the development of sleep states, the control of sleep-wake cycling, the impact of preterm birth on sleep ontogenesis, and FC analysis.

SLEEP ONTOGENESIS

Basic principles

Development of brain networks to support sleep. Sleep ontogenesis coincides with structural and functional brain development. Structural brain organization is an activity-dependent process where neuronal function shapes the growth, organization, and survival of brain structures.[52] Therefore, neuronal interactions, or functional connections, evolve together with the growth of brain networks (Fig. 1). From the 24th week of gestational age (GA) to term-equivalent age of 40 weeks GA, the major events in neural network development are (1) growth of thalamocortical connections, (2) growth of long-range cortico-cortical connections, (3) growth of short cortico-cortical connections, and (4) pruning of connections based on initial endogenous, and then subsequent exogenous activity.[53] Ascending thalamic afferents penetrate the subplate and deeper cortical layers at around 24–26 weeks GA,[53,54] reaching their final destinations in cortical layer IV during the following month. The six cytoarchitectonic layers of the cortex continue to develop until about the 34th week of gestation, and long cortico-cortical connections, including interhemispheric callosal projections, are mostly established by 35 weeks GA.[53]

These major events in structural development are intimately linked to functional brain development.[52] Endogenous activity, or spontaneously occurring brain activity, provides the temporal and spatial cues needed to link fibers from distant brain areas.[55,56] For instance, during the primary organization of thalamocortical circuitry, spontaneous activity in the sensory organs, such as the retina or cochlea, provides input to sensory cortices. This activity-dependent, but experience-independent period differs from later experience-dependent fine-tuning of cortical networks, whereby sensory organ responses to environmental stimuli drive cortical activation.[55]

Very early cortical activity can be detected by electroencephalography (EEG), which measures spontaneously occurring electrical signals via scalp electrodes, even from the earliest viable preterm infants younger than 24 weeks GA.[57] This early cortical activity is discontinuous (*tracé discontinue)*, characterized by periods of relative quiescence interspersed with self-organizing, locally generated bursts (spontaneous activity transients, SATs).[56,58] Early SATs are crucial for neuronal survival and for guiding the activity-dependent/experience-independent growth of brain networks, both *in utero* (endogenous activity) and *ex utero* (exogenous activity).[56,58] In preterm infants around 30 weeks GA, brain-wide synchrony in bursting activity can be detected via EEG, before the emergence of cortico-cortical connections, suggesting that the occurrence of brain-wide bursts is orchestrated by deep subcortical structures.[56] The growth of cortico-cortical connections[54,59] is paralleled by the emergence of functional interhemispheric and intra-hemispheric synchronization, which increase rapidly from about the 30th to 35th week GA.[60] However, the relative maturity or functional brain age[61] can be affected by many events, including the process of birth itself[62] and medical adversities.[61,63]

Development of sleep states. Sleep states in the human fetus are expressed as different behavioral states during the very earliest weeks of development,[6,7,64] driven by activity from deeper brain structures.[35] Over time, vigilance states become behaviorally and on EEG more distinct (Table 1). From the 30th week GA, following the growth of long-range brain connections, EEG activity patterns begin to fluctuate more clearly between sleep states in the preterm infant (Fig. 2).[57,65]

In the newborn, infant sleep is divided into two distinct states, active sleep (AS) and quiet sleep (QS).[66,67] These are often thought of as precursors to REM and non-REM sleep, respectively, and are characterized by a constellation of EEG and behavioral patterns.[66] After birth, newborn EEG phenomena persist for only a few weeks. First, the intermittent EEG activity of QS is replaced by a slow-wave activity, and then sleep spindles emerge. The phenomenology of neonatal EEG lasts up to about 45–50 wks post-menstrual age, which is about 1–2 months after term age.[68] Some authors also recognize an intermediate state,[66,69] which shows less clearly

Table 1. Comparative timeline of sleep, structural brain, and functional brain development.

Gestational age (weeks)	Behavioral characteristics[53,54]	EEG during sleep state	Structural development	Functional development
24–26	Periods of REM and non-REM	During REM: less discontinuous, higher amplitude activity During non-REM: discontinuous, IBIs up to 30 s, lower amplitude	Thalamic afferents accumulate in the cortical subplate[36]	Spontaneous activity transients (SAT)s present at 24 weeks (EEG)[169] Functionally active neural networks identifiable via fMRI at 26 weeks[96]
27–28	Periods of REM and non-REM	During REM less discontinuous, higher amplitude During non-REM: discontinuous, long intervals between bursts (~30 s) lower amplitude	Thalamic afferents penetrate cortical plate, first synapses appear (deepest > most superficial) in the somatosensory, auditory visual, and frontal cortices[36] Synapses appear in the deep part of the cortical plate[170]	Evoked potentials can be recorded from the somatosensory, visual, and auditory frontal cortices[42,171]
29–30	REM predominantly occurs during AS, motion and limb movement begins to occur during AS	AS: semi-continuous activity QS: bursts ~3 s, relative quiescence between bursts ~20–30 s		Fetal pain pathways functional in the somatosensory cortex (fNIRS)[172,173] Bilateral occipital networks detectable (DOT)[137]
31–32	REM predominantly occurs during AS, motion and limb movement occurs during AS	AS: semi-continuous activity, micro-arousals QS: bursts ~3 s, relative quiescence between bursts shortens, ~15-20 s	Intra-cortical thalamocortical fibers elaborate, establish synapses with cortical layer 4 and become sensory driven[36] Primary gyri and sulci develop[36] Cortical plate divides into 6 cytoarchitectonic layers[36]	SATs start to become coincident between hemispheres (EEG)[42]
33–34	REM predominantly occurs during AS, motion and limb movement occurs during AS	AS: semi-continuous activity QS: bursts ~3 s, relative quiescence between bursts shortens, ~10–15 s	Primary gyri and sulci develop[36] Cortical plate divides into 6 cytoarchitectonic layers[36] Callosal connections begin to develop[42]	
35–36	REM during AS, motion during AS, no REM during QS	AS: high amplitude continuous QS: interburst interval shortens to <10 s, amplitude and duration of bursts increases	Interhemispheric connectivity increases, corpus callosum cross-section thickens, and subplate gradually resolves[36]	Consistent, temporally synched SATs across hemispheres[42] Intrahemispheirc networks identifiable via fMRI[96]
38-term (birth)	REM during AS, motion during AS, no REM during QS	AS: high amplitude continuous activity QS: tracé alternant	Long intra-hemispheric and interhemispheric cortico-cortical connectivity matures[36]	Temporally synched SATs across hemispheres, smaller in amplitude and longer[42] Default mode network (DMN),[94,96] frontoparietal network,[94] executive control network[94] identifiable in term infants (fMRI)

REM rapid eye movements, *AS* active sleep, *QS* quiet sleep.

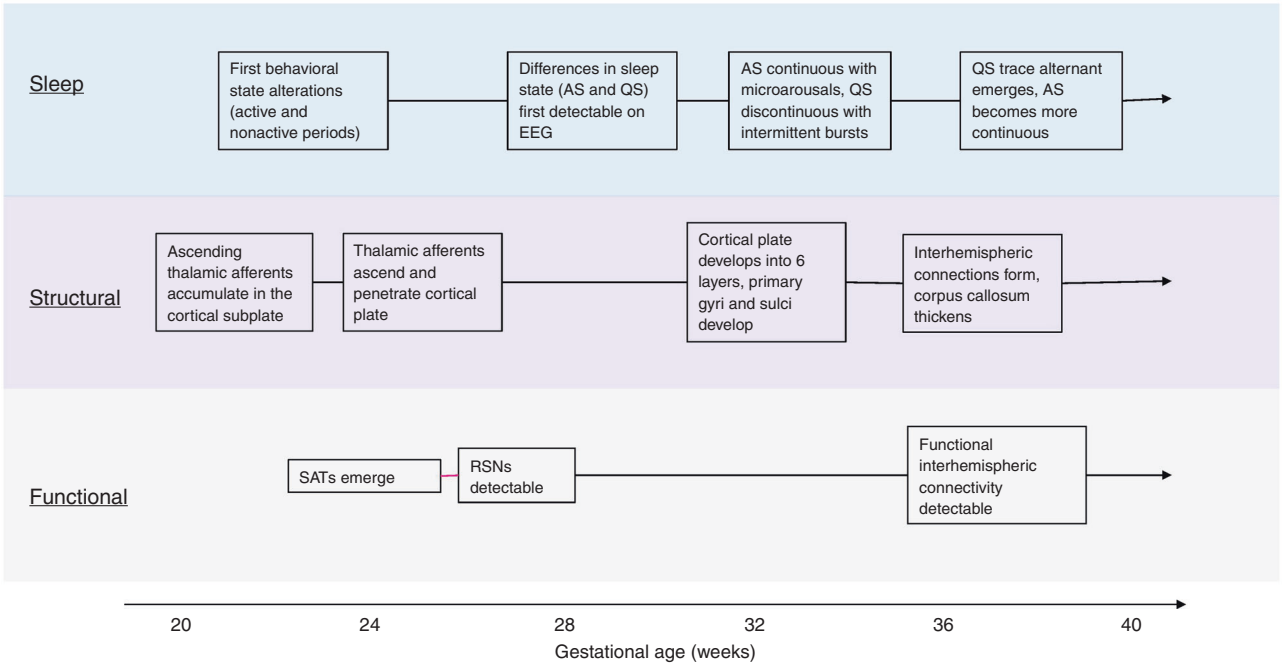

Fig. 2 The parallel development of sleep, functional networks, and structural networks in the developing brain. Each row provides approximate time points of major markers in sleep, structural, and functional development. These three processes develop concurrently and interdependently, such that impairments in any one of these processes may potentially affect the development of the other two.

differentiated patterns of either sleep state. AS and QS are primarily used to describe behavioral features of sleep, but they are less well understood from the perspective of brain network dynamics.[33,70]

Control of sleep-state cycling. Sleep-state cycling (or sleep-wake cycling, SWC) refers to the natural fluctuations between the wake and sleep states. SWC is controlled by three major systems in the brain: (1) the circadian rhythm,[71] (2) sleep pressure from adenosine buildup in the basal forebrain,[72] and (3) brain stem-based mechanisms that drive ultradian fluctuations in vigilance states.[73,74] Circadian rhythms emerge with the development of the suprachiasmatic nucleus (SCN), the site of the circadian pacemaker[57], and clock gene oscillations.[75] Brain stem structures, particularly in the upper pons,[76] are fundamental for SWC via their brain-wide projections, which in turn also make them important for the dynamics of large-scale FCNs. In infants, SWC is mostly driven by ultradian rhythms and brain stem regulation, as circadian rhythms only develop during the first few months after term age.[77] Brain stem-based regulation of infants' SWC have been previously investigated as a measure for assessing global brain function.[65,78]

The impact of preterm birth on sleep ontogenesis

Studies suggest that preterm birth is independently associated with impaired structural brain development.[79–82] Preterm born infants also demonstrate impaired sleep architecture, decreased sleep efficiency, and abnormal sleep patterns relative to their term-born counterparts at birth,[83] at comparable post-conceptual ages,[84] as older infants,[8,85,86] and as children.[11,87–89] However, one study has reported no difference in sleep behavior over time.[90]

These observed impaired sleep patterns in preterm infants may be due to a variety of factors. These infants often spend their earliest days of life in NICUs, where stressful conditions may interfere with spontaneous fluctuation through sleep states.[15] Procedures in the NICU, such as changing light or sound levels, and medical testing (e.g., line insertion, blood sampling, clinical examination, and radiological procedures) can all affect infant sleep.[15,18] Handling of infants can lead to arousal and disturb respiration, particularly during AS.[16] Some NICUs have implemented clustered care protocols to minimize these burdens,[91,92] and others have aimed to provide various kinds of sensory enrichment, such as physical contact.[15] Moreover, pathology associated with prematurity, such as bronchopulmonary dysplasia or severe intraventricular hemorrhage, may also affect sleep behavior.[93,94]

It is clear that prematurity impacts both sleep architecture and neurodevelopment, but the nature of their causal or multi-dimensional relationships is poorly understood (Fig. 1). Studies of FC in the newborn brain have shed some light on how sleep states may influence brain function, and how this process may differ for infants born prematurely.

NEONATAL FUNCTIONAL CONNECTIVITY

Basic principles of measuring functional connectivity

Identifying FCNs. FCNs are identified from temporal correlations of neurophysiological events between spatially remote regions of the brain. Functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS) can be used to measure fluctuations in regional brain blood flow and oxygenation.[32] fMRI assesses changes in regional blood flow via changes in the blood oxygen level-dependent (BOLD) signal,[95] while fNIRS relies on near-infrared light (650–950 nm) and the wavelength-dependent absorption characteristics of hemoglobin to measure regional changes in cortical oxygenation levels.[96,97] Alternatively, as stated above, EEG can measure correlations in electrical cortical activity.[33–36] FCNs are well documented in adult fMRI studies and are named according to their functional entities: motor function, visual processing, executive functioning, auditory processing, memory, and the default-mode network (DMN).[98–100] fMRI studies have also highlighted the emergence of primary functional systems very early on in utero,[101–106] in term-born and preterm infants[40–45] as well as the development of some higher-order functional systems (e.g., the DMN) after birth.[107] FCNs can be identified during task-based studies or during rest. FCNs identified during rest are referred to as resting-state networks (RSNs). Many

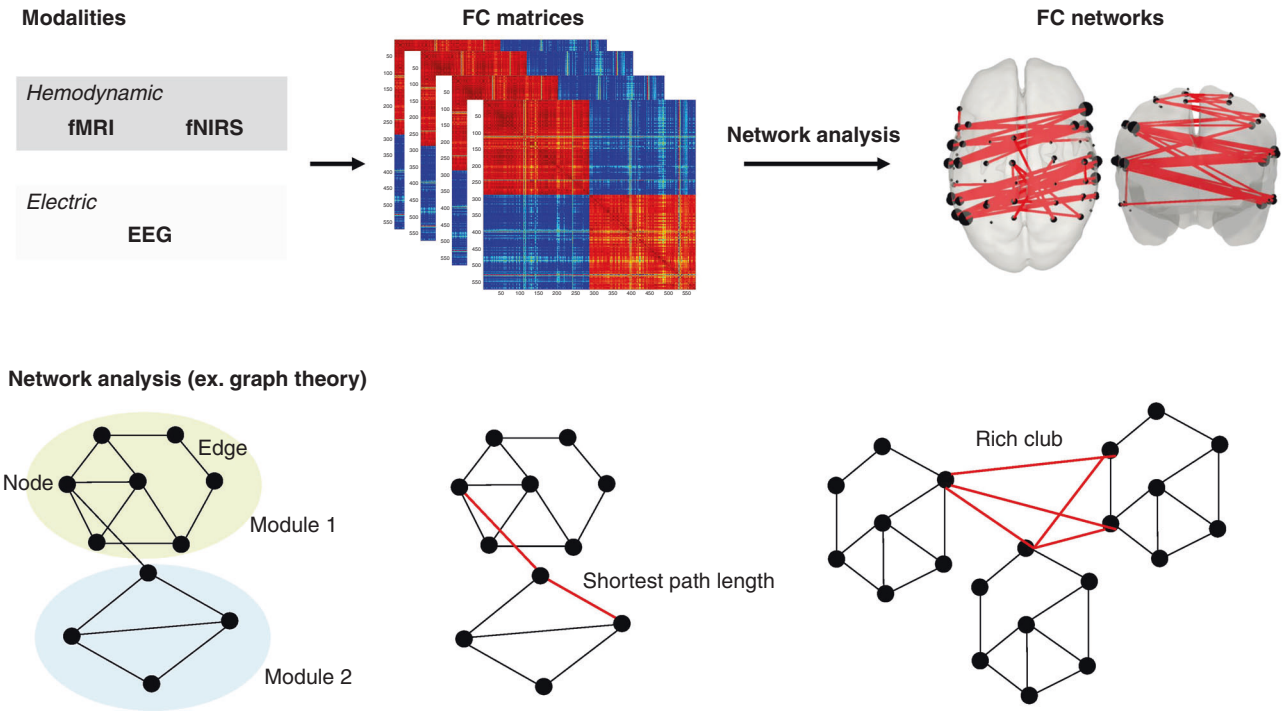

Fig. 3 Identifying, analyzing, and interpreting FCNs. The choice of modality determines whether a hemodynamic or an electrical response will be recovered. From recordings, functional connectivity matrices are computed from statistical relationships between each possible pairwise combination of signals. Network analysis can then be performed to describe statistical relationships between brain areas in terms of networks.[33,108,116] Graph theoretical modeling is shown here as an example. In this method, each brain region/cortical area is considered a *node*, and the relationship between regions (i.e., EEG phase coherence) is considered an *edge*.[108] More highly weighted edges represent stronger functional connections. All nodes and edges in the brain together form a topological network that can be characterized in terms of local and global attributes.

infant fMRI studies use the term RSNs or resting-state functional connectivity (RSFC) to describe infant FC, given that infant fMRI can only be performed during sleep.

Analyzing and interpreting FCNs. At the most basic level, FCNs are obtained by computing statistical relationships between all pairs of time-series signals (Fig. 3). The resulting FC matrices are then analyzed using a variety of higher-level statistical techniques to summarize network information. One recently popular approach to compress various aspects of network structure is graph theoretical measures,[31,108,109] as previously applied to neuroimaging/EEG studies involving infants.[50,108,110–112] However, it is often difficult to interpret their results physiologically,[113,114] particularly given the maturational changes in physiology and anatomy in the newborn.[115] Other network metrics have been recently introduced,[116–118] and have been shown to provide novel insight into human infant studies.[33] Importantly, these network metrics make network neuroscience clinically useful as they allow comparison to brain structures, physiological states, or clinical information.

There are many complex challenges in the analysis and interpretation of FCN results: First, the choice of neuroimaging modality (EEG vs. fMRI vs. fNIRS), as well as the analysis pipeline applied to the data, will significantly impact the results.[119,120] As such, FCNs identified with different modalities or different analytic pipelines are difficult to compare physiologically. Second, an FCN typically consists of thousands of interactions in an individual, and a large number of co-existing networks can be identified within an individual (e.g., different coupling modes, and different frequencies[33]). It is therefore often useful to reduce the dimensions of information by extracting summary metrics, which may, however, reduce the importance of certain features in the data. Third, FCNs are usually reported as static phenomena, yet studies suggest that they are highly dynamic, changing at a sub-second scale and with multiple different networks ("multiplex networks") concurrently active.[121–124]

Challenges to studying FCNs in newborns

In the newborn, FCNs are most commonly studied during sleep, as data obtained during wakefulness is usually corrupted by movement artifacts. Recent evidence shows, however, that the typical practice of recording infants during "natural sleep" or "unsedated sleep" (Tables 2 and 3) may not be appropriate, since newborn sleep is physiologically heterogeneous and each sleep state is associated with a different FCN structure.[33,50,70] In addition, FCN changes between sleep states might represent a developmentally important marker in itself,[33] perhaps reflecting the brain's flexibility, or ability, to switch network configurations between sleep states. FCN structure is also affected by prematurity,[125–129] and these changes are further dependent on sleep state.[33]

For studies that do consider the effects of sleep, studies often differ in the criteria they use to characterize sleep. For instance, some EEG studies rely on purely behavioral criteria,[46,49,130,131] while others use more comprehensive approaches of polygraphic channels (EEG, EMG, ECG, EOG).[51,70] fNIRS studies have used EEG to distinguish between sleep states,[34] but other studies have also assessed infants during "natural sleep" or described infants as "behaviorally inactive".[132–134] To date, no fMRI studies have distinguished between sleep states.

PRETERM BIRTH AND SLEEP STATE-RELATED CHANGES IN FC

Review of studies

fMRI studies. To date, all newborn fMRI studies have examined FC during the physiologically heterogeneous state of "natural sleep" or "unseated sleep", rather than considering AS and QS separately. As such, this article will only comment on some fMRI studies

Table 2. EEG studies assessing infant FC during sleep.

Author	Population	Methods/aim	Parameter(s) of interest	Separately analyzed AS and QS (y/n)	Method to discriminate between AS and QS	Longitudinal, cross-sectional, neither	Results/conclusions
Tokariev et al. [70]	38 healthy full-term-born infants	EEG, characterize healthy newborn FC, identify the changes in connectivity related to vigilance states and to maturation	FC quantified via PPC, AAC, and phase-amplitude correlations at 2 neonatal time points: 1 at first few days after delivery second at 42 weeks conceptional age	Yes	EEG and polygraphic channels	Longitudinal	All FC measures changed significantly between vigilance states and matured rapidly after birth. Changes were frequency-specific, most salient in AAC coupling, and their development was compatible with the known development of structural cortico-cortical connectivity
Toth[130]	139 healthy full-term infants	EEG, analyze functional brain networks in healthy term infants during quiet sleep within 1–6 days from birth	Neural synchrony during QS	Yes	Behavioral criteria	Neither	Infant cortical networks were significantly more hierarchical and had a more cost-efficient organization compared with random control networks. Frontal and parietal sites acted as the main hubs of these networks. Topological characteristics were associated with GA. Individual differences in network topology are related to cortical maturation during the prenatal period when functional networks shift from strictly centralized toward segregated configurations
Gonzalez,[176]	7 preterm 7 junior-term and 7 senior-term neonates	EEG, study how FC of neonatal EEG during sleep is assessed by different interdependence indices. Analyze its dependence CA and GA	8 cortical regions; coherence function (its magnitude (MSC) and it's imaginary part (IMC)) and the phase lag index (PLI)	Yes	Polysomnography	Neither	EEG inter- and intra-hemispheric FC in neonates during sleep changes with the CA and GA in delta and beta frequency bands
Myers et al. [131]	105 preterm infants	EEG, assess the impact of Family Nurture Intervention (FNI) on cortical function in preterm infants at term age. 49 neonates in standard care, 56 in Family Nurturing Intervention	Coherence between all pairs of electrodes in 10 frequency bands. Grouped electrodes into 12 regions. Assessed AS vs. QS	Yes	Behavioral criteria (Stefanski et al.[182])	Neither	Coherence levels were negatively correlated with PMA age in both groups. As compared to SC infants, FNI infants showed significantly lower levels of EEG coherence within and between frontal regions. FNI may accelerate brain maturation particularly in frontal brain regions, which are involved in the

Table 2. continued

Author	Population	Methods/aim	Parameter(s) of interest	Separately analyzed AS and QS (y/n)	Method to discriminate between AS and QS	Longitudinal, cross-sectional, neither	Results/conclusions
							regulation of attention, cognition, and emotion regulation
Burroughs,[177]	28 infants, 12 with infantile spasms with hypsarrhythmia (West Syndrome), and 16 healthy term-born infants	EEG, assess FC in infants with hypsarrhythmia	Coherence and spectral power	Yes	Healthy infants: eyes closed and sleep spindles and vertex sharp waves present. Infants with IS: eyes closed and there was no muscle or movement artifact	Neither	During sleep, increases in delta, theta, alpha, and beta coherences were noted, particularly at long inter-electrode distances while at short inter-electrode distances coherences were decreased in the theta and beta range, particularly in the frontal region. Enhanced coherences at long inter-electrode distances suggest that during sleep in children with infantile spasms widely spread cortical region do not have functional differentiation whereas in the frontal lobe there is reduced FC and integration of local cortical regions
Grieve,[178]	8 ELBW infants and 8 healthy full-term infants	EEG, determine whether electrocortical functional connectivity ELBW infants, measured at term post-menstrual age, had regional differences from that of full-term infants	Regional spectral power and coherence (intra-hemispheric and interhemispheric)	Yes	Behavioral criteria (Myers et al.[183], Sahni et al.[184], Stefanski et al.[182])	Neither	ELBW infants had significantly reduced interhemispheric coherence (in frontal polar and parietal regions) and intra-hemispheric coherence (between frontal polar and parieto-occipital regions) in the 1–12 Hz band but increased interhemispheric coherence between occipital regions in the 24–50 Hz band. ELBW infants at term post-menstrual age manifest regional differences in EEG functional connectivity as compared to term infants
Grieve et al. [49]	12 healthy term-born infants 2- to 4-month-old infants	EEG, investigate whether infant cortical regions activated by a head-up tilt exhibit increased FC	Coherence and electrocortical synchrony (local and long distance)	No	n/a	Neither	Newborn infants had significant increases in local coherence in the activated left frontal, right frontal-temporal, and occipital cortical regions; long-distance coherence increased between the right frontal-temporal and

Table 2. continued

Author	Population	Methods/aim	Parameter(s) of interest	Separately analyzed AS and QS (y/n)	Method to discriminate between AS and QS	Longitudinal, cross-sectional, neither	Results/conclusions
							occipital regions. In contrast, infants at 2–4 months old had no significant changes in coherence
Scher,[179]	18 preterm infants at term-equivalent age, 18 healthy full-term infants	EEG, determine potential differences in state-specific EEG spectral values preterm and full-term neonates at term-equivalent ages	Spectral power correlations between 91 channel pairs (regional, interhemispheric, and intra-hemispheric channels)	No	n/a	Neither	Preterm infants had significantly higher correlation values in 27 of the 91 pairs of channels, 14 interhemispheric, 8 intra-hemispheric, and 5 sagittal combinations, while 3 intra-hemispheric combinations were higher in the term group.
Milde,[180]	6 healthy full-term-born infants	EEG, investigate time-variant directed interactions between brain regions during the interburst-burst EEG pattern (tracé alternant), characteristic QS in healthy infants	Time-variant partial directed coherence (PDC) analysis	Yes	EEG segmenting by a "trained physician"	Neither	Strongest degree of interaction between 0.5 and 4.5 Hz (as quantified by the total mean of PDC values [0.5–4.5 Hz, 0–10 s]) were observed between the frontal electrodes,[3] interhemispheric interactions occur between the frontal, central and occipital electrodes and intra-hemispheric interactions occur to a much lesser extent
Nghiem et al. [46]	55 healthy term-born newborns with mothers from dioxin contaminated areas in Vietnam	EEG, investigate the effects of maternal dioxin exposure on fetal brain development	Relative powers and coherence	Yes	According to the criteria based on infant behaviors regardless of EEG patterns[49]	Neither	Delta powers were significantly decreased in right frontal and parietal regions, and relative alpha and beta powers were significantly increased with increasing dioxin exposure. Increases in delta power and decreases in alpha power on the right frontal and parietal regions were associated with an increase in language scores at 2 years of age. Results suggest that prenatal dioxin exposure affects neuronal activity and functional connectivity between brain regions, and may lead to poor language development
Rasanen,[181]				Yes		Neither	

Table 2. continued

Author	Population	Methods/aim	Parameter(s) of interest	Separately analyzed AS and QS (y/n)	Method to discriminate between AS and QS	Longitudinal, cross-sectional, neither	Results/conclusions
	33 healthy full-term and 25 preterm infants	EEG, develop a quantitative measure of interhemispheric (a) synchrony in the neonatal EEG, called activation synchrony index (ASI)	Interhemispheric synchrony (ASI)		EEG trace alternant for QS, trace continue for AS		ASI values are sensitive to sleep stage and correlate with age in preterm infants

FC functional connectivity, *ASI* activation synchrony index, *PPC* phase–phase correlations, *AAC* amplitude–amplitude correlations, *CA* conceptional age, *GA* gestational age, *ELBW* extremely low birth weight, *ASI* activation synchrony index.

conducted during sleep to provide a reader with an overview of the current state of the field.

Prior fMRI studies carried out during "natural sleep" or "unseated sleep" have reported weaker FCN strength (i.e., lower spatial correlations between brain areas) in preterm born infants compared to term-born controls. Brain areas that were reported to have weaker FCNs are diverse, ranging from areas involved in motor function,[44] to regions associated with motor, cognitive, language, and executive functions,[126] or frontal cortex and basal ganglia.[127] These findings may be linked to the motor or other impairments observed in preterm infants without structural brain lesion,[135–137] or linked to changes in microstructural connectivity in the preterm brain.[138,139] Network analysis using graph-theoretical measures[108] (Fig. 3) have shown many additional effects of prematurity. For instance, studies have shown that prematurity may affect functional segregation (which reflects local information processing and amount of nodal clustering),[140] small-world topology (a measure of the balance between the segregation of nodes into distinct clusters vs. integration of nodes into more globally efficient networks),[126,128] modular organization (modules consist of functionally related nodes that serve similar roles, modular organization implies dense intra-modular and sparse intra-modular connectivity),[128] and rich club measures (highly connected regions of the brain are more highly connected to one another).[106,126] However, there is a notable spatial diversity in the reported findings, and even opposite effects have been reported.[141] This suggests that more studies are needed to fully establish the effects of prematurity on fMRI-derived networks, and perhaps investigate the effect different sleep states may have on these networks.

EEG studies. Infant FCN studies using EEG have shown robust differences in FCN structure between sleep states,[33] irrespective of coupling mode (phase synchrony vs. amplitude correlation) or level of inspection (sensor vs. cortex level signals). Comparison of infants born preterm vs. term have shown a development-dependent shift from functionally integrated networks to functionally segregated networks,[50,112] frequency-specific effects on coherence,[49] and changes in frontally projecting FCNs as a result of prematurity[142] or NICU care interventions (Table 3).[131] Studies employing graph measures to summarize infant FCNs have shown a relationship between network organization and GA or brain injury,[110] as well as the later neurodevelopmental outcome.[110] More advanced methods of network-based statistics have shown that prematurity affects the FCN dynamics in a frequency-specific and spatially selective manner, and the sleep state-related dynamics of these networks also correlate with later neurodevelopmental outcomes.[33]

fNIRS studies. Several prior studies have used fNIRS to investigate infant FCNs.[129,134,143–145] Of the three prior studies that assessed for the effects of sleep on FCNs using fNIRS, two did not distinguish between AS and QS.[132,134] Only one study assessed for the effects of neonatal sleep states on FC, using a used a combined fNIRS-EEG system with fNIRS to assess FC and EEG to assess sleep state.[34] Stronger interhemispheric FC was observed during AS than QS, whereas within hemisphere short-range FC was enhanced during QS relative to AS.

Current needs and challenges

Despite recent progress in understanding the dependency of FCNs on sleep states, several challenges prevent a more detailed investigation into the immediate and long-term effects of preterm birth, impairments in FC, and disrupted sleep ontogenesis, as well as how they relate to each other.

Challenges in methods to assess sleep. All recording modalities have their own significant drawbacks.[146] While EEG is a direct

Table 3. fNIRS studies assessing infant FC during sleep.

Author	Population	Method, aim	Parameter(s) of interest	Distinction between AS and QS	Longitudinal, cross-sectional, neither	Notable findings/ conclusions drawn
Bulgarelli[185]	Single case study, 6 mo old healthy term-born infant	Proof-of-principle study for the application of dynamic casual modeling (DCM) method to infant fNIRS data, and for using a simultaneously recorded fMRI-fNIRS	fMRI: regions of interest in the inferior frontal gyrus, superior temporal sulcus, and temporo-parietal junction fNIRS: 9 channels over the temporal lobe, correlations between all channel pairs. DCM-estimates the coupling between brain regions and how this might be modulated by changes in experimental conditions. Applied to fNIRS and fMRI data	No, "during natural sleep"	Neither	Demonstrated converging results between both the fMRI and fNIRS methods, demonstrates both the feasibility and validity of applying DCM to infant fNIRS data
Fuchino et al. [134]	25 preterm born infants (includes 6 ELBW infants) and 24 healthy term-born infants	fNIRS, compare cortical RSFC between preterm infants at term-equivalent ages and full-term neonates without any anatomical abnormality risk during natural sleep using optical topography	Optical topography system (94 measurement channels). Changes in the concentration of oxygenated hemoglobin, calculated correlation between the time course of a single channel and the time course of all other measurement channels for each infant	No, "during natural sleep"	No	On comparing the bilateral temporal regions, and bilateral parietal regions, RSFC was enhanced in preterm infants compared with full-term neonates. Moreover, on comparing the left temporal and left parietal regions, RSFC was enhanced in full-term neonates compared with preterm infants. Also, there were noted differences in developmental changes of RSFC related to PMA on comparing the preterm and full-term groups. Results suggested that preterm infants and full-term neonates follow different developmental trajectories during the perinatal period
Imai et al. [133]	15 early-preterm born infants GA < 34 weeks, 12 term-born or late infants (GA ≥ 34 weeks and birth weight >1700 g), 5 infants with Down Syndrome (DS)	fNIRS, investigate the spontaneous brain activity of sleeping infants who were admitted to a NICU unit at term-equivalent age	Multichannel fNIRS (10 channels) covering the frontal, temporal, and occipital regions. Temporal correlations of the changes in hemoglobin signals for both oxy- and deoxy-H were calculated between all pairs of channels. 4 types of connectivity: (i) short-range, (ii) contralateral-transverse, (iii) ipsilateral-longitudinal, and (iv) control. Also calculated the phase differences between the oxy- and deoxyhemoglobin signals	No, "in natural sleep"	Neither	Development of the FC of cortical networks did not differ between term-or-late-preterm infants and early-preterm infants around term-equivalent ages, while DS infants had alterations in their FC development and local hemodynamics at term age
Taga et al. [132]	91 healthy term-born infants, 2-10 months age	fNIRS, investigate cortical hemodynamic responses to auditory and visual stimuli during wakefulness and sleep	48 channel fNIRS. Auditory, visual, or no stimuli presented asynchronously while awake and asleep. Temporal correlations of the changes in hemoglobin signals	No, "when their eyes were closed and behaviorally inactive"	No	Asynchronously presented auditory and visual stimuli during wakefulness induced focal responses in the corresponding sensory regions of the occipital

Table 3. continued

Author	Population	Method, aim	Parameter(s) of interest	Distinction between AS and QS	Longitudinal, cross-sectional, neither	Notable findings/ conclusions drawn
			for both oxy- and deoxy-H were calculated between all pairs of channels. Also calculated the phase-locking index of the two signals			and temporal cortices, the responses to the same stimuli during sleep were markedly different. The FC among the cortical regions was generally higher during sleep than during wakefulness. The hemoglobin phase of oxygenation and deoxygenation (hPod) and the phase-locking index of hPod (hPodL) showed general developmental changes and behavioral state-dependent differences but no significant differences were seen between the stimulus types
Lee et al. [34]	20 healthy term-born neonates	fNIRS and EEG (fNIRS to assess FC and EEG to assess sleep states), monitor sleep state, and investigate RSNs in a cohort of healthy term-born neonates	69 channel fNIRS and 11 channel EEG	Yes, via EEG	Neither	During AS and QS, neonates show functional connectivity patterns spatially consistent with previously reported RSN structures. Stronger interhemispheric connectivity during AS than during QS was noted. Within hemisphere short-range functional connectivity was enhanced during QS

FC functional connectivity, *AS* active sleep, *QS* quiet sleep.

measure of neural activity with a high temporal resolution, it suffers from lower spatial resolution, although this may be improved by increasing electrode count and transforming signals into cortical sources.[33,142] The blood flow-dependent measures fMRI and fNIRS have higher spatial resolution than EEG, but their temporal resolution is lower, as their signals reflect the slower vascular response.[147] Both methods assume that regional blood flow is consistently linked to neuronal activity (neurovascular coupling, NVC), an assumption that may not hold in early infancy.[148–150] Physiological measures have also been employed to assess sleep states, including heart rate-based indices, breathing patterns, and motion.[151–153] However, very few studies have attempted to validate these methods in classifying preterm infant sleep in NICU environments.[154] Moreover, behavioral measures to assess sleep states require significant human resources and also have limited feasibility in longer-term sleep monitoring. Polysomnography may provide a more cohesive picture of sleep states, yet it requires long periods of time and is often difficult to perform in vulnerable populations. Overall, there is no consensus or gold standard for assessing sleep states in the NICU, and studies tend to consider what measures are most appropriate to their unique circumstances.

Methodological challenges unique to infants. Additional practical challenges arise within the infant population. First, FCN studies require long-duration recordings, which may not be feasible using fMRI in vulnerable neonatal populations. Second, subject motion, which often occurs in infants, even while sleeping, can make data interpretation difficult.[155] In some cases, light sedation may be used,[156] but these may have unknown effects on sleep networks. EEG is more feasible in infants, but primarily for low-density systems, which cannot fully capture whole-brain functional interactions. Finally, the varied neurovascular response in the developing brain presents a particular challenge to interpreting FCN results from infant fMRI or fNIRS studies.[41–44,157] Preterm infants demonstrate altered relationships in neurovascular coupling,[148,149] especially when affected by brain injury,[158,159] making it difficult to draw inferences from results.

Challenges in comparability across methods. As noted above, the lack of comparability across modalities, and even across studies using the same recording modality, presents major challenges. The fundamental difference in brain mechanisms underlying EEG and fMRI/fNIRS-based FCNs makes their direct comparison difficult. Moreover, the analytical pipelines in generating FCNs are convoluted, and changes in analytical parameters may have impact results. Such technical instability might be a source of significant variability across studies (see the section "Preterm birth and sleep state-related changes in FC").

Challenges to longitudinal studies of FCN and natural sleep. There is currently a limited number of longitudinal and cross-sectional studies assessing FCNs and sleep in preterm and term-born infants (Tables 1 and 2). Such studies are logistically challenging, yet they provide much-needed insight into individual developmental trajectories. These data can overcome issues related to the high interindividual variability of FCN studies, while also allowing for an improved understanding of the long-term clinical course of abnormalities in sleep behavior and their related FCNs.

Challenges in defining causal links between sleep, FCN, and early development. It is clear that the development of sleep and FCNs, and the effects of prematurity are related (Fig. 2). The results of current studies suggest that this relationship poses a "chicken-and-egg" problem, where one cannot exist and develop without the other, but studying such causal links is not possible by using standard experimental paradigms. For clinicians, it is perhaps more important to focus on studying how these co-existing developmental processes may become derailed during early life medical adversities, how these impairments can lead to long-term problems in neurocognitive development, and how improving sleep in NICU settings may improve outcomes.

Needed research and future prospects

Techniques to detect and classify infant sleep states. Continuous long-term EEG monitoring is a feasible method to monitor SWC in intensive care units, particularly when using amplitude-integrated EEG (aEEG).[78,160–163] SWC patterns in aEEG trends can be recognized from just a single EEG channel when clearly expressed in a term age infant. However, aEEG cannot be used to distinguish AS from wake, even though it is effective in distinguishing QS from the rest, or for recognizing SWC.[164] Additional challenges arise when examining the aEEG of early-preterm infants or infants with acute neurological problems.[165] Moreover, measuring cyclicity in EEG by visual inspection is difficult,[166] although quantitative tools have been recently introduced to assist in measuring cyclicity.[167] Recently, several studies have described machine learning-based and deep-learning-based methods to classify epochs of EEG into AS and QS states.[111,168,169] Automated sleep-state detections can also be achieved using computational features of respiration,[154] ECG,[170,171] or their combination.[33,70]

Multimodal techniques. Future investigations should consider multimodal approaches, in which neuronal and neurovascular activity are assessed simultaneously to overcome challenges in making comparisons across modalities. These approaches will allow for an improved understanding of how sleep states concurrently affect both rapid neuronal effects and slower hemodynamic effects. For example, this could include a combination of fNIRS and EEG. fNIRS has previously been used in conjunction with EEG in neurologically compromised infants,[172] and high-density fNIRS systems (known as diffuse optical tomography) have demonstrated applicability to infant populations.[173] Another possibility to consider is fMRI-EEG, which has been previously been demonstrated to be safe and feasible in newborn infants.[174,175]

Sleep states as a contextual framework. Overall, the current literature suggests that studies investigating infant FCNs must control for both age and sleep state, even if the main purpose of the study is not to investigate infant sleep. Future investigations are also needed on the transition between sleep states,[33] how FCNs change during transitions, and how these transitions may change with development. These all may prove to be important biomarkers for healthy neurodevelopment, and their assessment may thus have a significant clinical impact.

Integrating into clinical practice. In order to make FCN studies part of evidence-based medicine, the key tasks for future studies to address these challenges are to establish methodological pipelines that (i) are feasible to carry out in the given target population (intensive care, vulnerable neonates, different hospitals and recording machines), (ii) are technically stable (i.e., show tolerable intra-session and test–retest variability), (iii) possess well documented open-access analytical toolboxes, and (iv) are able to be used in a large number of subjects over time to account for biological interindividual variance and developmental trajectories.

CONCLUSIONS

The development of sleep and the FC networks supporting it are crucial for healthy brain development. These processes are often disrupted in preterm infants, yet the nature of the relationship between preterm birth, sleep, and FC remains poorly understood. Research in this area is in its infancy; gaps in our current knowledge include the best method to assess sleep states

in newborns, the best method to compare term and preterm infant brain networks, and the best method to link measures of FC to measures of neurodevelopment. Nonetheless, the literature suggests that there are indeed differences in FC between sleep states, and that preterm-born infants differ from their term-born counterparts in brain FC patterns, as well as sleep-state dynamics. More mixed methodological techniques are needed that account for both cortical hemodynamic and neuronal activity. Future studies need to understand the limitations of modalities and how this affects the interpretation of results, further explore how brain network dynamics themselves may be developmentally important markers, and consider sleep state as a context for analyzing and interpreting infant FCNs.

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AUTHOR CONTRIBUTIONS

J.U. drafted the manuscript for intellectual content, creating the figures for the manuscript, revised the manuscript for intellectual content, and prepared the manuscript for submission. S.V. drafted major components of the manuscript for intellectual content and revised the entire manuscript for intellectual content. T.A. planned the outline of the article, guided the drafting of the article, and contributed heavily to the revision of the manuscript for intellectual content and preparing the manuscript for submission.

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