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Early Development of Sleep and Brain Functional Connectivity in Term-Born and Preterm Infants

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Author Contributions Statement

Julie Uchitel drafted the manuscript for intellectual content, creating the figures for the manuscript, revised the manuscript for intellectual content, and prepared the manuscript for submission.

Sampsa Vanhatalo drafted major components of the manuscript for intellectual content and revised the entire manuscript for intellectual content.

Topun Austin planned the outline of the article, guided the drafting of the article, and contributed heavily to revision of the manuscript for intellectual content and preparing the manuscript for submission.

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Impact:

1. 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.

2. The connection between preterm birth, early development of brain functional connectivity, and sleep is poorly understood.

3. 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.

Abstract

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 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 littler investigation, mainly due to the challenges of studying causal links between developmental phenomena and assessing FC in newborn infants. However, 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.

I. 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), and is a possible idea that is 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 for investigating 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 even 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 FCN has been described both in term born and preterm infants, and alterations in network development associated with prematurity (40–45). Therefore, alongside developmental emergence of sleep states, the appropriate 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 (**Figure 1**). In the first part of this review we provide an overview of sleep ontogenesis, from early fetal life to birth, 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, including 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. ((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, control of sleep wake cycling, impact of preterm birth on sleep ontogenesis, and FC analysis.

II. Sleep Ontogenesis

A. 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 (**Figure 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 thalamo-cortical 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 cortex continue to develop until about the 34th week of gestation, and the 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 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, from the earliest viable preterm infants before 24 weeks GA (57). The 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 of early activity is orchestrated by deep subcortical structures (56). The growth of cortico-cortical connections (54,59) is paralleled by emergence of functional interhemispheric and intrahemispheric synchronization, which increase rapidly from about the 30^{th} to 35^{th} 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 30^{th} week GA, following growth of long-range brain connections, the EEG activity

patterns begin to fluctuate more clearly between sleep states in the preterm infant (**Figure 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 45-50wks postmenstrual age, which is about 1-2 months after term age (68). Some authors also recognize an intermediate state (66,69), which shows less clearly 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). Brainstem 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 functional connectivity networks (FCN). In infants, SWC is predominantly dominated by ultradian rhythms and brainstem 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).

B. 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 most 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, ranging from physical contact to other sensory stimulation (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 multidimensional relationships poorly understood (**Figure 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 premature.

III. Neonatal Functional Connectivity

A. Basic Principles of Measuring Functional Connectivity (FC)

Identifying FCNs

FC networks (FCN) 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). Alternatively, as stated above, EEG can measure correlations in electrical cortical activity (33–36). 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). 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). FCN can be identified during task-based studies or during rest. FCNs identified during rest are referred to as resting state networks (RSNs). Many 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 (**Figure 3**). The resulting FC matrices are then analyzed using a

variety of complex 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 in human infant studies (33). Importantly, these summarizing 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 or interpret 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).

B. 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" (see Tables 2 and 3) may not be appropriate, since newborn sleep is physiologically heterogenous and each sleep state is associated with a different FCN structure (33,50,70). In addition, FCN changes between sleep states, or network dynamics, 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 (125,126,126,127,127–129), 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.

IV. Preterm Birth and Sleep-State Related Changes in FC

A. 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 ~~(**Table 3**)~~. As such, this article will only comment on some fMRI~~notable FC~~ studies conducted during sleep to provide a reader with an idea 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 ~~healthy~~ 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 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) (**Figure 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 balance between 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 a robust FCN difference 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 effect 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 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 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. This study also represents an important step towards understanding sleep states effect and FC within the context of neurovascular coupling.

B. Current Needs and Challenges

Despite recent progress in understanding the dependency of FCNs on sleep states, several challenges prevent more detailed investigation into the immediate and long-term effects of preterm birth, impairments in FC, and disrupted sleep ontogenesis and 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 measure of neural activity with 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 asses 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 requires 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 these 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, if not impossible. 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 (Section IV).

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 (**Table 1 and 2**). Such studies are logistically challenging, yet they provide much needed insight to individual developmental trajectories. These data can overcome issues related to 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 (**Figure 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 outcome.

C. 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, while 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 the 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 where neuronal and neurovascular activity are assessed simultaneously to overcome current challenges in making comparisons across modalities. These approaches will allow for an 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, or how these transitions may change with development.

These all may prove to be important biomarkers for healthy neurodevelopment, and their assessment may thus have 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 would be to establish methodological pipelines that are i) feasible to carry out in the given target population (intensive care, vulnerable neonates, different hospitals and recording machines), ii) technically stable (i.e. show tolerable intra-session and test-retest variability) iii) with well documented open access analytical toolboxes, and iv) able to be used in a large number of subjects over time to account for biological interindividual variance and developmental trajectories.

V. 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 causal interactions between preterm birth, sleep and FC remain 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 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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Figure Legends

Figure 1. Relationship Between Preterm birth, Sleep Ontogenesis, and Functional Brain Connectivity. The relationship between these three processes is currently unclear.

Figure 2. The Parallel Development of Sleep, Functional Networks, and Structural Networks in the Developing Brain. Each row provides approximate timepoints 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 development of the other two.

Figure 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.