Sleep and Brain Development

The Critical Role of Sleep in Fetal and Early Neonatal Brain Development

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Sleep and sleep cycles begin at around 26 to 28 weeks' gestational age. They were originally recognized by observing infant behaviors. This observation of behaviors and changes in physiology has now added electoenchephalography (EEG) and continuous electoenchephalography (aEEG) to the studies of sleep and sleep cycles. Sleep partitions from indeterminate sleep EEG patterns to quiet sleep or non–rapid eye movement (REM) sleep, REM sleep, and quiet awake intervals. The REM sleep follows the quiet or slow wave sleep in the cycles. Sleep and sleep cycles are essential for the development of the neurosensory and motor systems in the fetus and neonate. They are essential for the creation of memory and long-term memory circuits, and they are essential for the maintenance of brain plasticity over the lifetime of the individual. The importance of sleep and preservation of sleep cycles in infants has been known for more than 40 years. They are critical for the fetus in utero and the preterm infant in the newborn intensive care unit (NICU). The infants' state and sleep-wake cycles have been studied as part of developmental care since the 1980s. A major part of the implementation of developmentally appropriate care involves using the infant state and cues to plan care and interventions. This is also essential for the preservation of sleep and sleep cycles that are essential for early neurosensory development. Interference with sleep and disruption of sleep cycles can significantly interfere with the early processes of sensory development. Parents are playing an increasingly important role in supporting early development.

Keywords: Sleep; REM sleep; Sleep cycles; Fetal development; Infant development; Non REM sleep; Brain plasticity

The existence of brain electrical activity was first described in 1936,[1] but sleep cycles were not described until the 1950s.[2,3] Sleep was still considered a time of brain rest. The interpretation of dreams and problems of sleep deprivation were the major subjects of sleep studies. The description of sleep states and sleep cycles was established in 1968.[4] In humans, sleep states and cycles are distinct and unlike any other animal. Animal models are primarily useful to study individual processes that have similarities to humans. This is particularly relevant to understanding visual and auditory development. It has become evident in the past 20 years that sleep and sleep cycles are essential for sensory system development in the fetus and young infant, as well as for preservation of brain plasticity and for creation of long-term memory and learning. Sleep deprivation in the fetus and young infant has a profound effect on early sensory development and the creation of permanent neural circuits for the primary sensory systems. Systems that require sleep and sleep cycles for development in the fetus and newborn are shown in Table 1.[5]

This explains the importance of protecting sleep and sleep cycles in the fetus and young infant. Sleep and sleep cycles are vital for early development of the sensory systems.[6]

All of these systems in Table 1 require rapid eye movement (REM) sleep for development beginning at 28 to 30 weeks' gestational age. Rapid eye movement sleep and sleep cycles are crucial for the endogenous stimulation needed to form long-term circuitry. This forms the basic architecture of the sensory cortex and brain stem nuclei that relay the signal from the sensory organ (ie, ear, eye, etc) to the appropriate site in the neocortex.

Between 20 and 28 weeks' gestation, the human fetus has irregular electrical activity that is characteristic of the immature brain. There are periods of rest and periods of electrical activity as well as intermittent ganglion cell electrical activity during this stage of development. It is an indeterminate or immature electrical pattern. The ganglion cell activity is required for axon growth and targeting as an early phase of building the

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Table 1. Sensory Systems That Require REM Sleep for Normal Development

1.	Somatesthetic	(Touch)
2.	Kinesthetic	(Motion)
3.	Proprioception	(Position)
4.	Chemosensory	(Smell and taste)
5.	Auditory	(Hearing)
6.	Vision	
7.	Limbic	(Emotion)
8.	Social learning	
9.	Hippocampus	(Memory)[5]

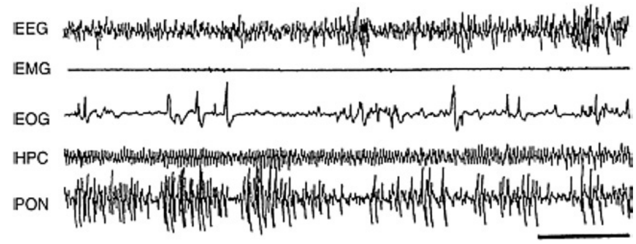

Fig 1. REM sleep signal patterns. The REM sleep signal patterns include the cortex (EEG), the postural muscles (EMG), the eye lid movement (EOG), the hippocampal waves (HPC) and the P waves from the pons (PON). Reprinted from Graven S. Sleep and brain development. *Clin Perinatol. 2006;33:696 with permission © Elsevier.*

connection between the sensory receptors (ie, retina) and the midbrain, as well as between the midbrain and the cortex. As the fetus or preterm infant approaches 28 weeks' gestation, the ganglion cell firing becomes regular and then occur as synchronous waves.[7]

At approximately 28 weeks' gestation, the distinct electrical patterns associated with the different sleep states begin to emerge. Between 28 and 30 weeks' gestation, the sleep patterns are discontinuous with interspersed periods of little electrical activity.[8] By 30 weeks' gestation, the encephalographic (EEG) patterns of REM and non-REM (NREM) sleep appear but are not continuous. They still alternate with periods of quiet. The sleep cycles and the EEG patterns become continuous by 36 to 38 weeks' gestational age.

There are two basic forms or types of sleep. The first is NREM or also referred to as *slow wave sleep* based on the EEG wave pattern; and the second is REM or *paradoxical sleep* based on the EEG pattern and the motor movement, especially the eyelid movement (Table 2). The NREM sleep has a high amplitude, synchronized slow waves on the EEG pattern with very little muscle movement or activity, and regular heart and respiratory rate patterns with little variability. It is divided into four stages or depths of sleep. Stage 1 is the drowsy stage that is between wakefulness and sleep. Stage 2 NREM sleep is the onset of true slow wave sleep as well as the initiation of the slow wave sleep brain activity. Stages 3 and 4 are the deep sleep level of NREM or slow wave sleep. These stages are crucial to the creation of long-term memories and learning.

Rapid eye movement sleep or paradoxical sleep is characterized by rapid eyelid movement as well as muscle movement and, by 2 to 3 months' postnatal age, will have atonia of the spine or postural muscles (Fig 1).[9] Rapid eye movement sleep is the critical component of the sleep cycle associated with the development of the sensory systems. In the fetus and young neonate, the REM sleep part of the sleep cycle is a period of maximal brain activity. When REM sleep patterns first appear between 28 and 30 weeks' gestational age, most of the sleep cycle is REM sleep, with little NREM or slow wave sleep. By term at 40 weeks, the sleep cycles are about equal REM and NREM. By 8 or 9 months of age, the sleep cycle is 80% NREM and only 20% REM. The EEG patterns for NREM and REM sleep are near adult-like patterns by 5 to 8 months of age.[10]

Table 2. Sleep Phases

NREM	Stage 1	Drowsy
	Stage 2	Light
	Stage 3	Deep slow sleep
	Stage 4	
REM		Paradoxical sleep

Sleep and sleep cycles are not a passive process as was believed for many years. Just as the awake state in infants is maintained by active stimulation from aminergic cell groups in the brain stem, sleep is driven or stimulated by cholinergic cells. These cells stimulate sleep as an active process that can be inhibited by depressant drugs. Different cell groups in the brain stem activate different components of REM sleep. Each of the specific EEG waves that occur during REM sleep plays a specific role in visual, auditory, or touch system development. Rapid eye movement sleep has a direct effect on the formation of the nine systems listed in Table 1. Rapid eye movement sleep deprivation between 30 weeks' gestational age and 4 to 5 months postterm results in delayed or disordered development of any or all of the systems listed above. The best-studied effects of sleep cycle and REM sleep deprivation involve the visual, auditory, somaesthetic (touch), and limbic (emotions) systems.

Preservation of Brain Plasticity

In addition to the essential role of REM sleep and sleep cycles in early development of the sensory systems, sleep cycles with REM and NREM sleep are critical for the preservation of brain plasticity. Brain plasticity is the preservation of the capacity to change, adapt, and learn in response to environmental experiences and new needs. This involves the continual activation and preservation of three cellular components: nerve growth factor, brain-derived neurotropic factor, and ubiquitin. These processes depend on sleep cycles for the lifetime of the individual and start in response to REM sleep in late fetal and early neonatal life. These cell components respond to the stimulation and activate Cyclic AMP-Responsive-Element-Binding Protein (CREB) that alters the DNA of the cell. This results in the synthesis of a synapse-specific protein that is responsible for the maintenance of long-term memory.

Learning and Memory

Learning and long-term memories are created in three phases. The first phase is the acquisition phase where an individual creates short-term memory circuits from objects, events, or other sensory input (ie, reading etc) while awake and attending to the object or event. These short-term memory circuits are in the neocortex as well as different areas of the brain. If these short-term memory circuits are reinforced or repeated, they may last longer. To become long-term learning or memory circuits, a consolidation phase that occurs during NREM, slow wave sleep, or quiet sleep must take place. The hippocampus communicates with the neocortex with electrical waves called θ *waves* or *oscillations*. As these oscillate, the short-term memory circuits are transferred to the hippocampus. When the sleep cycle progresses to REM sleep, the hippocampus organizes the memory circuits and, with different θ waves, transfers the memories back to the cortex in various locations. With the continued θ oscillations, a permanent connection to memory is created. These pattern and process are illustrated in Fig 2.[9] To create a long-term memory or retained learning, it must be processed through a complete sleep cycle including wakefulness, NREM sleep, and REM sleep. Without the sleep cycle, the sensory experiences remain a short-term memory, most of which is ultimately lost. Recent studies have demonstrated that sleep deprivation interferes with the acquisition of material for new memories, both episodic and declarative. During sleep, the hippocampus processes the information, reinforcing the important material with emotional content and dropping the unimportant. It then sorts and files this important or significant material as permanent memory circuits.[11,12]

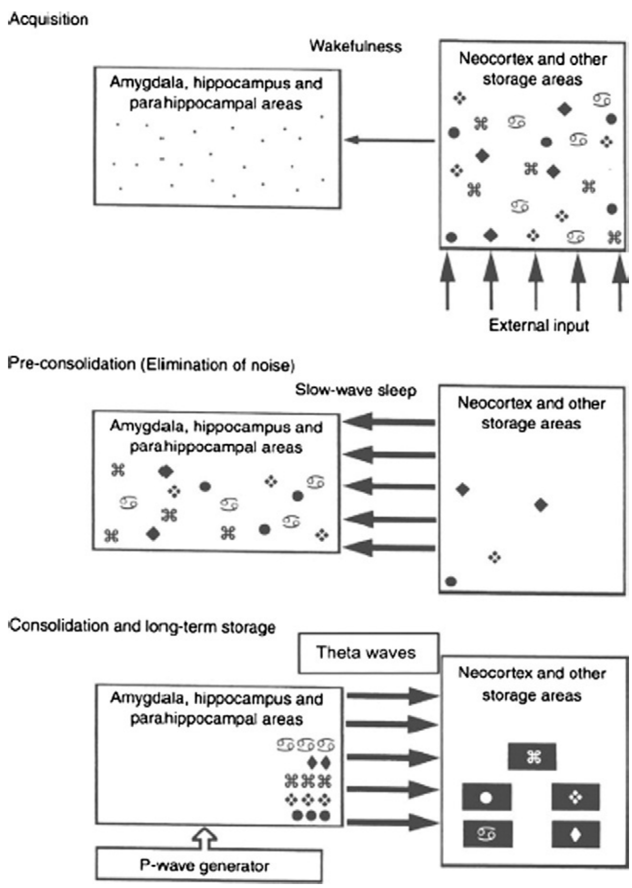

Fig 2. Model of sleep-dependent memory consolidation and long term storage. The aquisition phase occurs when external information (vision, hearing etc) is input into the brain and stored in the neocortex and other storage areas. In the preconsolidation phase during slow wave sleep, redundant and/or unrelated information are eliminated. This is followed by the consolidation phase when during REM sleep the P waves from the pons activates the hippocampus, amygdala and parahippocampal areas to organize the information acquired during wakefulness. When the information is consolidated the theta-frequency waves from the hippocampus binds the consolidated information in long term memory storage in the neocortex and other storage areas. Reprinted from Graven S. Sleep and brain development. *Clin Perinatol.* 2006;33:702 with permission © Elsevier.

Thus, preservation of sleep cycles in infants is essential to building the sensory systems, preservation of brain plasticity, and creation of long-term memories and learning. It is necessary for the building of the sensory systems (Table 1) between 28 weeks' gestation and 3 to 4 years of age.

The fetus in utero, the preterm infant in a newborn intensive care unit (NICU), and the infant in the early months of life all need to have their care organized so that most sleep cycles and especially REM sleep are preserved. This is an aspect of early brain development that can be facilitated or inhibited by the care they receive and the maintenance of an environment that protects sleep.

Support for Sleep Development in the NICU

Sleep organization in the newborn has been related to developmental outcomes[13-15] and may be shaped by early interactions between infant and the physical and caregiving environment.[16] The caregiving environment for early-born and medically fragile infants may produce arousal, interfere with sleep-wake transitions, and disrupt sleep.[17-19] Attention to appropriate timing of caregiving according to the infant's sleep and arousal thus becomes essential, as better sleep organization has been correlated with improved outcomes.[20]

Sleep state identification plays a primary role in determining neurobehavioral organization in the newborn. Studies of EEG sleep recordings have been done for more than 50 years and have been considered important for identification of sleep in newborn infants.[21] Periodicity of arousal behavior in sleep from early gestational ages has been identified in both the fetus and infant.[22-24] Borghese et al initially demonstrated sleep cycling in preterm infants at 36 weeks' postconceptional age; and more recently, Scher et al[25] identified cyclicity of sleep behaviors in 25 to 30 week gestational age infants. Development of technology to monitor cerebral functioning at the bedside has offered clinical application of EEG technology to determine effects of drugs and caregiving on state organization.[26-28] However, for the bedside clinician, neither EEG nor continuous electroencephalography (aEEG) technology is typically available to assist with sleep state identification to guide timing of caregiving.

Behavioral state identification can be accomplished clinically through observation of an infant's respiratory efforts as well as body and eye movements. Both physiology and behavior must be considered in relation to the state of sleep or wakefulness in which they occur, particularly in preterm infants.[29] The infant's level of arousal or consciousness ranges from sleep to drowsy, to awake and crying. Categories of sleep can be further identified to include REM sleep, which is essential for brain development, and diffuse sleep, which is particularly characteristic of preterm infants. Several reliable classification systems have been developed for term and preterm infants for use in both clinical situations as well as research.[30-33]

Motor and physiologic organization, embedded in infant sleep and arousal, is the main means that infants have to communicate with their caregivers. Recognition of behaviors that are associated with state organization and transition from one state to another can guide both initiation and provision of caregiving. However, application of state-related information does not appear to be consistently used in planning NICU caregiving.[34,35] Peters[36] discusses how handling interventions in the NICU have historically been and continue to be frequent with more than 100 interventions within a 24-hour period. When considering the frequency of these handling interactions, their provision must be without regard to infant states. Understanding not only the importance of identification of sleep states but also the utilization of the information in clinical practice needs to be a priority for professionals caring for high-risk infants. Furthermore, assisting parents to identify sleep organization to appropriately interact with their fragile infants should be considered for all parents.

Early-born infants have proportionately more REM sleep than quiet sleep and, as they approach term gestation, decrease the time they are in REM and increase the time they are in deep sleep. Similarly, they have increases in wakefulness as they approach term.[37-40] Infants have marked stability in the overall development of sleep-wake state organization with only minor effects of infant characteristics, illness severity, and medical treatments.[30,40-43] The exception appears to be those infants with chronic lung disease where they show less active sleep, more frequent arousals, and more body movements.[44] Infants on supplemental oxygen have increased quiet sleep and total sleep time.[45] Care practices that focus attention to supporting sleep in infants with chronic lung disease, in particular, are warranted.

Preterm and fragile infants have difficulty in organizing and maintaining consistent robust sleep and wake states. They are extremely sensitive to stimulation from the environment, including light, sound, and handling, which often precipitates state change and arousal from sleep[19,46,47] Studies of infant state organization typically focus on periods of time when the infant is not being handled,[40] yet several studies have documented arousal and physiologic disorganization with intrusive environments and routine caregiving.[47-54] Research that explored the impact of nursing care on the development of preterm infant sleeping and waking behavior revealed that both the presence and type of caregiving the nurse provided influenced state organization. Waking states increased over time when infants were with caregivers, with greater behavioral response to caregiving as they matured. The most intrusive caregiving resulted in more negative facial expressions and sleep-wake transitions. Alternatively, sleeping increased when infants were left alone.[55]

Although there are few solid studies to inform practice, several caregiving strategies such as positioning, swaddling, rest periods, and nonnutritive sucking may facilitate state organization.[55-61] Clustering of care was thought to be a caregiving strategy that would respect the infant state availability and provide longer times for recovery and sleep. However, recent studies of clustered care reveal that infants can become aroused and have poor ability to modulate their heart rate to an invasive procedure when it is preceded by routine tactile caregiving. Adverse responses were more significant in earlier-born as compared with later–gestational-age infants.[62,63] Individualized cue-based care, including identification of infant state, was recommended in contrast to clustered caregiving for fragile preterm neonates.

Kangaroo mother care (KMC) has been shown to increase sleep time[64] and the amount of quiet sleep[65] and to improve sleep-wake cyclicity.[66] During KMC, the mother's body not only supports the physiologic and behavioral organization for the infant; it facilitates the mother's state and psychologic well-being, contributing to the attachment relationship.[67,68] Liberal use of KMC can facilitate sleep organization and synchrony in the dyad.

As early as the end of the first trimester, fetuses begin to show circadian rhythms of heart rate, respiratory efforts, rhythmic hormone production, and periods of rest and activity (sleep-wake states). Daily oscillations are regulated by the mother and reflect activity of the biological clock located in the suprachiasmatic nucleus of the anterior hypothalamus.[69] After birth, these processes are entrained by the day-night lighting that the infant experiences and may be responsive as early as 25 weeks' postmenstrual age.[70] The question of appropriate cycled lighting in NICUs for circadian rhythmicity and development of sleep-wake states has been addressed by several investigators.[71-73] Although more studies are needed to determine optimal light environments for sleep development in premature infants, it appears that there are several recommendations that can be considered. Day-night cycled lighting, if used, should be low rather than bright during the day and dim at night. This is often accomplished by having incubator or crib covers pulled back during the day and pulled down at night. The infant's eyes should never be exposed to direct light (see article on visual development, this issue). Lighting should be kept low enough that the infant will comfortably open their eyes when interacting with their parents and caregivers. Nighttime interruptions in sleep should be minimized, and lights should continue to be kept low when the infant wakes for caregiving or feeding.

Encouraging the mother to be present and to provide breast milk can support the establishment of circadian rhythmicity. The mother should be able to be with her infant as much as possible to continue the familiar rhythms and physiologic entrainment that were afforded in utero. Breastfeeding provides the rhythmic and predictable activities of holding and feeding and supports sleep-wake organization. Breast milk composition also includes hormones such as melatonin[71] that entrain circadian rhythms.

Predictable sleep-wake cycles are not well established until well after term and are further delayed if the infant was born preterm. Sleep disorganization can be one of the most frustrating behaviors that parents encounter upon discharge. Education for parents before going home is essential to help them understand how sleep develops over the first few weeks and months, how to determine the best timing for interaction, how to support awakening for social interaction, and how to enhance night sleeping.[74]

Intrusive environments and caregiving arouse infants, result in interrupted sleep, and potentially influence development. No one caregiving or environmental modification strategy appears to result in producing better sleep organization and cycling in preterm infants. Caregiving practices that provide restful, nurturing, noninvasive environments; identify when the infant is available for interaction; and facilitate appropriate arousal and state change should be encouraged. To facilitate rest and reduce physiologically disorganizing arousals, an individualized cue-based approach that is based on the infant's availability, uses the mother as a regulator of behavior, and limits intrusiveness appears to provide the best overall developmental outcomes.[75]

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