

CLINICAL REVIEW

Development of fetal and neonatal sleep and circadian rhythms*

Majid Mirmiran^{1,2}, Yolanda G. H. Maas³ and Ronald L. Ariagno¹

¹Department of Pediatrics, School of Medicine, Stanford University; ²Netherlands Institute for Brain Research and ³Department of Visual System Analysis; University of Amsterdam, Amsterdam, The Netherlands

KEYWORDS

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Summary The origin of sleep and circadian rhythms development is found during the fetal period. Both quiet (NREM) and active (REM) sleep are distinguishable during the last 10 weeks of gestation. Comparable to fetuses, low risk preterm infants recorded at 30–40 weeks postconceptional age, had a similar development of sleep i.e. an increase in quiet sleep and a decrease in indeterminate sleep. A further development in sleep organization characterized by increased slow wave and spindle activity during quiet sleep and coupling with circadian rhythm takes place during the first 6 months of life in both term and preterm infants.

Circadian rhythm of fetal heart rate synchronized with maternal rest-activity, heart rate, cortisol, melatonin, and body temperature rhythms is present during the last 10 weeks of gestation. Although maternally influenced, circadian rhythm antenatally becomes ultradian at birth. Both preterm and term infants show a significant increase in circadian body temperature rhythm amplitude during the first 3 months of life.

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DEVELOPMENT OF SLEEP

The emergence of different behavioral states, i.e. quiet sleep (QS or NREM), active sleep (AS or REM), and wakefulness (W) is one of the most significant aspects of early brain maturation in infancy [1]. These behavioral states are characterized by a number of state specific criteria which emerge coherently in time [2]. A certain degree of brain maturation is required before the behavioral states can be classified. Early in

development a large amount of time is spent in indeterminate sleep (IS). Nijhuis *et al.* [3], using fetal ultrasound behavioral observations of the fetus and continuous fetal heart rate monitoring, were among the first to describe well organized sleep states in humans. Mulder *et al.* [4] and Visser *et al.* [5] demonstrated that, as early as by 32 weeks gestation, QS and AS could be differentiated although a large percentage of time was spent in IS. Two hour longitudinal studies of fetal behavioral states development between 32 and 40 weeks postconceptional age have shown significant increase in QS and decrease in IS with no significant change in AS [4]. These results were in agreement with the earlier studies in preterm infants [6, 7]. Neonatal sleep states are usually defined by behavioral (direct observation and/or video recording), cardiorespiratory, and EEG criteria.

Correspondence should be addressed to: Majid Mirmiran, M.D., Ph.D., Department of Pediatrics, Division of Neonatal and Developmental Medicine, School of Medicine, Stanford University, 750 Welch Road, Suite 315, Palo Alto, CA 94304, USA. E-mail: mirmiran@stanford.edu

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The polysomnographic characteristics of sleep states are detailed in the following sections.

Active Sleep (AS)

EEG: Continuous mixed (theta with some delta, alpha, and beta) activity; 40–80 μV amplitude.

EOG: Slow and rapid bursts and isolated eye movements.

EMG: Low amplitude superimposed with twitches and phasic jerky movements.

ECG: Variable beat-to-beat interval.

Respiration: Variable.

Quiet Sleep (QS)

EEG: Until 36 weeks PCA, discontinuous EEG with bursts of delta activity. After 37 weeks PCA in preterm infants as well as in term infants at birth, *tracé alternant* (TA) or continuous 50–150 μV delta. TA is defined with 3–8 s bursts of high amplitude slow wave separated by 4–10 s low voltage mixed EEG; this pattern disappears by 46–48 weeks PCA. After 3 months of age Stage 2 of QS is defined with 1–3 s bursts of spindle activity (12–15 Hz) and less than 20% of epoch occupied with delta waves ($> 150 \mu\text{V}$); Stages 3 and 4 (combined) are defined with more than 20% delta. After 6 months of age Stage 3 is defined by 20–50% delta and Stage 4 by more than 50% delta in a given 30 s epoch.

EOG: No eye movements; although infrequent eye movement can be seen.

EMG: Low amplitude; can be difficult to differentiate tonic EMG activity during QS from atonia during AS until approximately 10 weeks of age (50 weeks PCA).

ECG: Predominantly regular with some acceleration during, e.g. startle.

Respiration: Predominantly regular.

Indeterminate Sleep (IS)

Defined when the above state criteria are not met.

Wakefulness (W)

Characterized with open and moving eyes; high muscle tone superimposed with general body movements; high rate and irregular heart and respiratory patterns; and low voltage, irregular, mixed pattern of EEG with frequent movement artifacts.

Arousal

Can be defined using at least two of the following 4 criteria based on baseline sleep state.

EEG: Decreased amplitude and increased frequency; reduction in delta and/or spindle activity.

ECG: Heart rate acceleration; increased beat-to-beat variability.

Respiration: Increased respiratory variability and respiratory pause, including sigh.

EMG: General body movement including but not limited to startle. Durations vary from 3 s to as long as 1 min. Events longer than 1 min are “awakening”.

For further details on methods of recording and analyzing infant sleep states see [8–13].

Preterm infants offer an excellent opportunity to study brain development extra uterine and compare these results with *in utero* fetal studies. Such comparison will shed light on endogenously regulated neuronal systems in the brain that regulate sleep-wakefulness independent of environmental factors. Most of the earlier sleep studies in human development were cross-sectional and showed large individual variability in behavioral states. We have completed a large longitudinal study on the development of behavioral states in 96 very low birth weight (VLBW) preterm infants < 30 weeks gestational age at birth. We asked if the post conceptional age (brain) maturation of these infants studied longitudinally would be correlated with the development of behavioral states. Two hour observations and polygraphic recordings were made as soon as the infant’s clinical condition was stable and then were repeated every 2 weeks until term corrected age. All recordings were done in the neonatal intensive and intermediate care nurseries in the early afternoon between two feedings. The infants were observed in an incubator or under a radiant warmer and were dressed in only a diaper. They were placed in supine or semi-lateral position and allowed to settle before recording in a well controlled thermal environment. Polygraphic recordings were made of respiration, instantaneous heart rate variation, and EOG and EMG. Direct behavioral observation and synchronous time-lapse video recording were performed. In addition, the following state dependent criteria were noted on the polygraph paper: (a) eyes open or closed, (b) eye movements present or absent, (c) respiration regular or irregular, (d) gross body movements, (e) twitches and jerky body movements, and/or (f) crying.

The combination of behavioral observation and polygraphic recording was used to determine behavioral

states [12]. Five separate behavioral states were scored: (1) QS, (2) AS, (3) quiet W, (4) active W and (5) crying. The remainder of each recording session in which the state criteria were not fulfilled was scored as IS.

We obtained a total of 372 2-hour recordings from 96 infants. The observations were done every 2 weeks; thus 30–31, 32–33, 34–35, 36–37, and term (38–42 weeks PCA) were used in a repeated measurements analysis. Our findings, during the 2 hour observations at 30 weeks PCA and at corrected term age, were: QS amount significantly increased with age ($P = 0.018$) (Fig. 1); AS amount was not significantly different with age ($P = 0.73$) (Fig. 2); IS amount significantly decreased with age from an average 64 min (59–70, 95% CI) to 23 min (19–27, 95% CI) ($P = 0.0007$); and W (active and quiet) increased from an average 5.8 min (3.4–8.2, 95% CI) to an average of 26.5 min (19.1–33.9, 95% CI) ($P = 0.001$).

A separate analysis was performed to see whether a significant relationship between abnormal cerebral ultrasound findings and behavioral state development could be found. A grade 3 or 4 hemorrhage and/or a grade 2 or 3 ischemia and/or a grade 2 or more ventricular dilatation in weekly ultrasound were considered abnormal. Differences were found in QS ($P = 0.045$) and IS ($P = 0.077$) for the infants with an abnormal outcome ($n = 12$) compared to the infants with a normal ($n = 42$) cerebral ultrasound outcome. In contrast to controls, abnormal infants did not show the gradual increase in QS and decrease in IS from 30 weeks till corrected term age.

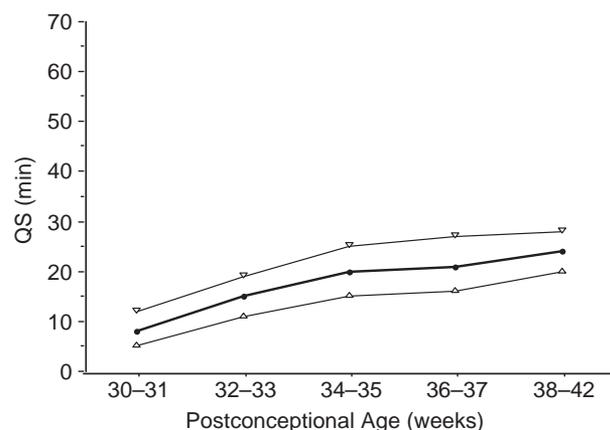


Figure 1 Development of quiet sleep (QS) as a function of age in preterm infants born at < 30 weeks gestational age are shown. Data are presented as mean and 95% confidence interval of 2 h longitudinal recordings of 96 infants.

In accordance with our hypothesis postnatal brain maturation in low risk preterm infants born before 30 weeks gestational age, as measured by behavioral state development, showed a significant age effect. Preterm infants spent more than 50% of the recording time in IS at 30–31 weeks PCA and less than 20% by corrected term age. This was mainly due to the development of QS and wakefulness. This developmental change and the pattern of sleep-wake found in this longitudinal study in preterm infants was reminiscent of observations in fetal and neonatal studies [4, 5, 14–17].

The time course of development of QS and IS in our low risk preterm infants between 30 and 40 weeks PCA was remarkably similar to findings in a comparable study in the low risk fetuses [4]. A decrease in time spent in IS was more remarkable between 32 and 34 weeks PCA in both Mulder's fetal studies and our own work in preterm infants. This supports earlier cross sectional studies in preterm infants by Curzi-Dascalova *et al.* [6, 7, 12]. At present we can only speculate that there is a neuronal network developing at this age which is responsible for a progression from relatively random chaotic patterns to more well defined predictable, organised, behavioral states of sleep and wakefulness. Preterm birth per se does not seem to change the time course of this development which suggests an endogenous brain mechanism. This finding supports the thesis that the development of sleep-wakefulness is a measure of brain maturation [1, 18, 19].

Sleep development encompasses not only the relative amount of each sleep state, but also consolidation of sleep and wakefulness over the 24 h day. Using a movement sensitive mattress, 12 preterm infants were continuously recorded for two consecutive days at

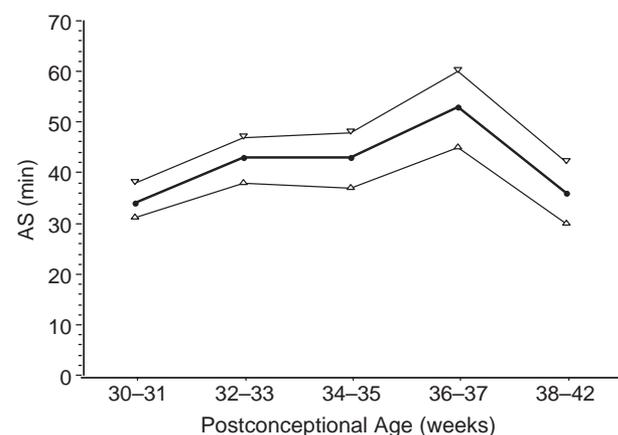


Figure 2 Development of active sleep (AS) in preterm infants (see also Fig. 1).

36 weeks PCA (before discharge) and at 3 months corrected age. At 36 weeks PCA, these infants slept as much during the day (65%) as during the night (71%); but by 3 months of age the same infants showed a clear day-night rhythm of sleep [20, 21]. At 3 months of age the percentage of recording time asleep during the day was $18 \pm 12\%$ versus a more consolidated $65 \pm 11\%$ at night ($P < 0.001$).

In another longitudinal study of 40 low risk preterm infants with mean gestational age of 30 weeks (birth weight range 751–2280 g) we have examined the development of night-time sleep before discharge from hospital as well as at 1 and 3 month corrected age at home. For each long term unattended recording, Anders's time-lapse video technique was used for recording and scoring sleep states (see [22] for more details). We have measured the amount of time spent in QS and AS from 7 p.m. until 7 a.m. We found a significant increase in QS from 36 weeks PCA till 3 months of age ($P = 0.001$) (Fig. 3). This was accompanied by a significant decrease in AS ($P = 0.03$) (Fig. 4).

Sleep organization undergoes further developmental changes during the first year of life [9, 23]. This includes increase in proportion of QS and increase in sleep cycle length [24]. A longitudinal 24 h home polygraphic study of 15 term infants at 3, 6, 9, 12, 18, and 24 months of age showed a decrease in total sleep time, AS, and IS with an increase in QS and waking time in addition to the development of circadian rhythm of sleep-wake activity [25]. Similar results have been found by Salzarulo and his colleagues [9, 23, 26].

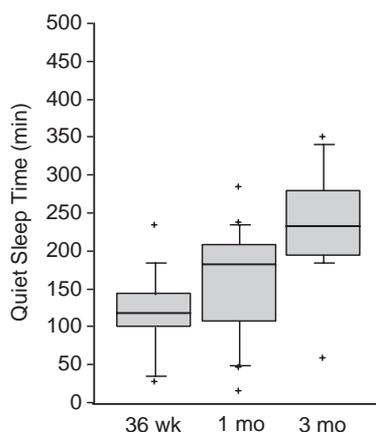


Figure 3 Development of QS in low risk preterm infants before discharge (36 weeks postconceptional age) and at 1 and 3 months corrected age. Data are presented as medians, quartiles, 10th and 90th percentiles, and outliers.

Other developmental aspects of sleep include changes in EEG activity particularly during QS [27]. Although during the first week of life power spectrum analysis of EEG shows higher delta activity during QS compared to AS, it is not possible to classify different stages of QS (i.e. Stages 1 and 2 and Slow Wave Sleep (SWS) Stages 3 and 4) [28]. By 6 months of age, similar to adults, Stage 2 (sleep spindles) and Stages 3 and 4 of SWS during QS can be classified [29]. Using spectral analysis of 12 h EEG recordings, Scher *et al.* were able to show significant maturational changes in EEG total power density, power density during QS, and % EEG discontinuity in preterm infants from 28–43 weeks PCA [30]. Although EEG power spectra in theta, alpha and beta frequencies were lower in preterm infants at corrected term age compared with term infants, delta activity was comparable [30]. The development of SWS is the principal component for lengthening the duration of QS in infants between 1 and 54 weeks of age [31]. Sleep spindles rapidly develop during the first 3 months of life, most probably reflecting developmental changes in thalamo-cortical activity [32]. A new aspect of sleep which has not been systematically studied in infancy is sleep homeostasis and coupling between the so called “process S” (decrease in the amount of slow wave activity after sleep onset) and circadian rhythm of the body temperature “trough” at night. A study comparing infants (up to one year of age), children, and adults showed SWS decreased during subsequent sleep cycles in the night sleep of adults and children, but not in infants [33]. In a more recent study these investigators found, as in adults, a negative correlation between the rate of process S diminishing and prior wakefulness in infants during the 1st year of life. However, delta latency was

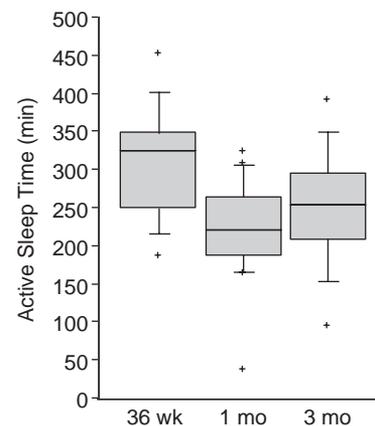


Figure 4 Development of AS in preterm infants (as in Fig. 3).

not correlated to prior wakefulness [34]. Although more studies are required before definitive comparisons can be made, one reason for differences found in infants may simply be due to their relatively frequent daytime naps. Future sleep studies should include continuous rectal temperature monitoring and must control for naps, feedings, and bedtimes.

INFANT SLEEP, AROUSAL, AND SIDS

The majority of Sudden Infant Death Syndrome (SIDS) deaths occur during a narrow developmental window of 1–4 months postnatal age, a period when significant changes occur in sleep organization and in the modulation of brainstem and cortical centers involved in cardiovascular/respiratory and arousal state control. There is consensus that SIDS typically occurs during sleep periods, but it is unclear whether SIDS occurs during sleep itself, within transitions between sleep and waking, or between sleep states. Nevertheless, the link between the peak occurrence of SIDS and the period of major sleep developmental changes suggests that SIDS is state-related and involves abnormal interactions between the state-modulated arousal threshold and central regulatory mechanisms of cardiovascular/respiratory control. It is also generally agreed that infants who are at risk for SIDS may have central nervous system abnormalities at birth that may be too subtle to detect clinically. Nevertheless, most of the SIDS pathology data show abnormalities in the brainstem and hypothalamus, areas involved in sleep, arousal, and central cardiovascular/respiratory control. Among the most notable changes in sleep occurring between 1 and 4 months of age, both in term and preterm infants (corrected age), are: (a) an increase in the percentage and episode length of QS, (b) sleep onsets switch from AS onset to QS onset, and (c) the longest sleep period begins to occur most frequently during the nighttime hours. Differences in temporal patterning of slow wave EEG activity (delta power) may indicate differences in the depth of sleep and may provide objective measures which could be used to define the “failure to arouse” hypothesis of SIDS.

In California, although the risk of SIDS is less than 1 per 1000 for full-term babies, the incidence increases sharply with declining birthweight (BW) in preterm infants; 3.8 for 2000–2500 g; 6.4 for 1500–2000 g; and to 7.5 for less than 1500 g BW babies. Furthermore,

the median postnatal age (PA) at death increases with decreasing gestational age (GA) and BW [35]. Infants > 2500 g BW had a peak age of SIDS at 83 days PA; those with BW between 1500 and 2500 g at 92 d PA, and those with BW < 1500 g at 127 d PA. It appears that when a correction is made for prematurity, the age at death occurs at an age similar to that of full term infants.

The number of low birthweight (< 2500 g) preterm infants born in the United States is estimated at 298 202 infants per year (7.6% of all live births) and modern advancements in neonatal care have led to survival rates exceeding 90% in infants with birthweights > 1000 g. Sleep periods for infants during hospitalization in the Neonatal Intensive Care Unit (NICU) are frequently disrupted by clinical interventions. These infants may have less sleep due to the nature of the care they require and we therefore anticipate that preterm infants have higher arousal thresholds for life threatening stimuli. Furthermore, perinatal insults may adversely influence neonatal sleep organization. It is interesting to note that Scher and co-workers found fewer and shorter arousals during nighttime sleep in preterm (< 32 weeks gestational age) infants recorded at corrected term age compared with full term infants [30]. In recent studies, overall, very low birth weight infants are at 3–4 times higher risk of SIDS compared with low birth weight infants [36, 37].

Most of the literature describes the development of the arousal response in relation to different respiratory, tactile, and auditory stimuli. These data clearly show a higher arousal threshold at 1–4 months of age that is further increased when the infant is sleeping prone. Spontaneously occurring arousals have been studied less during infancy and there are few studies in preterm infants. Since preterm infants have a higher risk for SIDS, studies of arousal mechanisms in this group would be important. It has been assumed that there is, in most cases, a close temporal association between the SIDS event and sleep, suggesting that wakefulness or arousal provides protective mechanisms for survival. Arousal thresholds for respiratory, tactile, thermal, and visual stimuli during sleep in infants presumably at risk for SIDS are higher (for a recent review see Ariagno and Mirmiran, 2001 [38]), thus spontaneous arousal from sleep to waking, or the infant's ability to make a transition from one sleep state to another when confronted with a life-threatening challenge is decreased. The number of arousals in term infants from 2–3 months of age is greater than in children at a mean age of 4.6 years. Spontaneous

arousals occurred every 3–6 min in infants compared to every 6–10 min in children. The spontaneous arousals were not associated with apneic events. These results suggest that there may be a basic protective mechanism of arousal and a lower arousal threshold in normal infants during the period of SIDS vulnerability.

FUNCTION OF SLEEP IN EARLY DEVELOPMENT

Although the amount of both QS and wakefulness in our very low birth weight preterm infants increased as a function of age, the time spent in AS remains high throughout this critical period (30–40 weeks PCA) of brain maturation. Fetuses who were recorded during the last 10 weeks of pregnancy showed similar results. Indeed the amount of AS in the womb as well as during the early neonatal period (both in term and premature infants) parallels the period of rapid brain maturation.

REM sleep predominates the sleep time during early brain development [39]. In the altricial mammal, such as the rat in which the brain mainly develops postnatally, the high amount of REM sleep declines to a low level during the first month of life. In the precocial mammal fully developed by birth such as guinea pig, on the other hand the high levels of REM sleep seen prenatally decline to low (adult) values at birth. In both species the amount of REM sleep declines to a low adult level [40] as the brain matures. At birth, human newborns spend 16–18 h a day asleep, more than half of this is occupied by REM sleep [41]. The human brain develops rapidly during the last trimester of gestation and the first 3 months of life with slower development thereafter. Both prenatal recording in the fetuses and postnatal studies in preterm infants showed a large proportion of time spent in REM sleep between 30–40 weeks postconceptional age [1, 4]). The decline in REM sleep as a function of brain development is much slower in humans and does not reach low levels till preschool years [39, 41]). Nevertheless, the time course of REM sleep development in human like other mammals corresponds well with the period of brain maturation.

The high level of endogenous neuronal activation during REM sleep makes this state a good milieu for promoting brain development during a period in which environmental experiences are very limited [39]. It is not only the amount but also the intensity of phasic neuronal activity during REM sleep which is high in

early development and diminishes as rapid brain maturation is completed [1, 42]. Eye movements during REM sleep are good indicators of phasic neuronal activity in the brain. We have studied the development of eye movements during REM sleep in rats from 10–25 days of age. At approximately 15–18 days there is a peak in the mean frequency of eye movements, burst density, burst duration, and the mean number of eye movements within the burst. Since rat pups reared in constant dark showed similar increase in eye movements, this change seems to be part of an endogenous developmental timetable of REM sleep which is necessary for brain maturation rather than an association with an increase in visual stimuli [43]. Similar developmental changes in eye movement density during REM sleep are also found in utero in the human between 30 and 40 weeks postconceptional age [44, 45].

REM sleep and brain development

Although correlation studies indicating a relationship between REM sleep and the degree of brain maturation are interesting in their own right, the most straightforward experimental approach to study the function of REM sleep in brain development is to deprive the rapidly developing mammal of its normal quota of REM sleep. Accordingly, the consequences of this deprivation on later brain function in adulthood can be elucidated. Since long term instrumental deprivation or lesion studies are not feasible we and other investigators have used a pharmacological approach [46–52]. We have suppressed REM sleep during the 2nd and 3rd weeks of postnatal development in rats using an antidepressant drug such as clomipramine or an antihypertensive drug clonidine. In adulthood, the neonatally REM sleep deprived animals showed increased anxiety, reduced sexual activity, and disturbed sleep [46, 47, 53, 54]. Other investigators found similar results which included despair behavior, reduced pleasure seeking, and increased alcohol preference when using clomipramine or other antidepressants in rats [48, 55–58]. Subsequent regional brain measurements showed a significant reduction in the size of the cerebral cortex and brainstem in adult rats who were REM sleep deprived during neonatal development. In addition a proportional reduction of tissue protein was found in the affected brain areas [46].

We have pursued these structural changes at the functional level and found, in adulthood, changes in the

neurotransmitter circuitry of neonatally REM deprived animals. In the cerebral cortex the magnitude of the GABAergic depression of the glutamate induced single cortical neurons responses was greater in the neonatally REM deprived rats [59, 60]. In the hippocampus there was a supersensitivity of the pyramidal cells to noradrenaline [61]. Based on these results we hypothesized that during the homeostatic adaptation of receptor sensitivity to a persistent change in the intensity of incoming neuronal stimulation, individual neurons establish "set-points", which are determined by the amount of synaptic activation in early development, most probably during REM sleep [59].

REM sleep and brain plasticity

Environmental enrichment in rats has been shown to increase the size of the cerebral cortex, the number and efficacy of synapses and the problem solving ability of the animal. When our neonatally REM sleep deprived rats were subjected to a standard or an enriched environment after weaning, no significant plasticity effect was found [62]. The kindling phenomenon in rats has been used to assess hippocampal plasticity. In this model kindling causes a prolonged decrease in latency and an increase in sensitivity for epileptogenesis by electrical stimulation in the hippocampus. However, in the case of neonatal REM sleep deprivation an increase in latency was induced from the end of the kindling stimulation to the initiation of the epileptic activity (i.e. after discharge latency). Additionally, there was a reduced excitability ratio in these neonatally REM sleep deprived kindled rats compared with the kindled controls [61, 63].

Ponto geniculo occipital (PGO) waves are endogenous phasic activity in the visual system which are characteristic of REM sleep. Depriving one eye of stimulation (monocular deprivation) reduces the size of the lateral geniculate nucleus (LGN) contralateral to the deprived eye only during a critical period of brain development. Bilateral lesions of the brainstem generator of PGO waves in kittens has been shown to amplify the brain plasticity induced by monocular deprivation [64–66]. Selective suppression of REM sleep by manually keeping the kittens awake during the critical period of development induced similar results [67]. Amplification of plasticity induced by monocular deprivation with concomitant sleep deprivation has recently been demonstrated at the single cell level [68].

Taken together, these results indicate that neonatal REM sleep deprivation not only impairs brain development but it also interferes with later plasticity of the brain in adulthood. If one views memory processes as a sort of brain plasticity present throughout life, recent studies support the important role sleep may play in consolidation of these processes [69–74].

REM sleep and depression

Neonatal suppression of REM sleep induced several long lasting behavioral changes reviewed above. Vogel hypothesized that these behavioral changes can be interpreted as symptoms of endogenous depression [51]. He and his group carried out a number of studies to support this hypothesis [52, 55, 56]. First of all they found reduced shock-induced aggression and enhanced defensive responses in adult rats neonatally treated with clomipramine. Second, sexual activity in these neonatally REM sleep deprived males showed fewer mountings, intromissions, ejaculations, and longer mount latencies and postejaculatory pauses. Third, in an open-field activity test these rats showed increased activity mainly in the outer part of the chamber, indicating a motor restlessness associated with the fear or stress of an open, exposed environment. Fourth, in an experimental pleasure-seeking behavior paradigm (hypothalamic self stimulation), neonatally REM sleep deprived rats showed reduced pleasure seeking. Fifth, these rats also showed increased voluntary alcohol consumption and despair behavior [48, 57, 58]. Sixth, sleep studies showed reduced REM latency, frequent sleep onset REM and an abnormal temporal course of REM rebound after REM sleep deprivation in adult rats neonatally treated with an antidepressant drug. Last, administration of antidepressant drugs to these animals in adulthood ameliorated several of these behavioral consequences of neonatal REM sleep deprivation. These findings suggest that neonatal REM sleep deprivation induces adult depression in rats.

The function of QS during development has not been systematically studied. However, given the results of adult studies, sleep as a whole serves a vital function [75]. Given the enormous research (reviewed above), there is no doubt that sleep serves an important role in brain maturation in utero and extra uterine. Our brain function in childhood, adulthood, and even during aging is maintained as a result of the complex interactions with the environment during wakefulness. Although sleep throughout life serves an

important role in consolidation of our waking experiences and removal of unwanted experiences, endogenous neuronal activation during sleep in early life serves as the main source of input for brain maturation [39]. Although neuronal development is genetically preprogrammed, neuronal connections and stabilization of these connections is a function of input to the brain. Sleep provides endogenous input for human fetuses, preterm, and term infants that have limited waking experiences.

DEVELOPMENT OF CIRCADIAN RHYTHMS

The origin of circadian rhythms development can be found during the fetal period [76, 77]. A fetal biological clock responsive to maternal entraining signals is already oscillating by the last trimester of gestation in primates [78–80]. A clear day-night rhythm of fetal heart rate synchronized with maternal rest-activity, heart rate, cortisol, melatonin, and body temperature rhythms is found in humans [81, 82]. A recent study showed the presence of circadian rhythm in fetal plasma cortisol production at term gestational age [83]. We have recorded 24 h fetal heart rate in a discordant anencephaly twin pregnancy and compared these data with three normal twin pregnancies. Although circadian rhythm was present in the intact fetus and all other twin pregnancy fetal heart rate recordings, no circadian rhythm was found in the anencephalic fetus despite day-night rhythm in the maternal heart rate [84]. The lack of circadian rhythmicity in the anencephalic fetus despite the presence of this rhythm both in the mother as well as in the intact twin fetus, supports the notion that the fetal brain (most probably the fetal biological clock) is necessary for appearance of this endogenous rhythm. These observations also support the notion that, during fetal life and long before birth, the mother entrains the developing circadian rhythm of the infant to the light–dark cycle.

Most of the earlier studies in human infancy have shown little or no evidence of circadian rhythm at birth. We have studied the development of circadian rhythms in a group of 40 preterm infants born at mean gestational age of 30 weeks (birth weight range 751–2280 g). Rectal temperature was continuously recorded over 1–3 days as an endogenous marker of circadian rhythm. We have recorded these infants at 36 weeks PCA (before discharge from nursery) as

well as at 1 and 3 months corrected age at home. The amplitude of the circadian rhythm was determined by calculating the magnitude of body temperature change (maximum minus minimum) for each infant at each age. These longitudinal studies in preterm infants showed a significant maturation in circadian rhythm of body temperature. The amplitude of this rhythm increased, by 3 months of age, to a level very similar to 6 months or older children (Fig. 5).

A nocturnal trough of body temperature, which is a good marker of human circadian rhythms, is already present at 6–12 weeks of age in term infants [85]. Many factors including feeding (scheduled versus on demand, mother's milk versus formula milk), environmental lighting (indoor versus outdoor, regular versus irregular light–dark cycle) and chronological/postconceptional age of the infant influence the experimental outcome [9, 26]. Moreover, short recordings and other methodological pitfalls (including sampling every 4 h versus continuous recording; averaging all infants versus analysis of each individual's data) may have, indeed, resulted in earlier negative findings. For instance, in Lodemore *et al.* study [86] some infants showed circadian rhythm of body temperature as early as 8 weeks and others not until 16 weeks. Breast fed infants, girls and first born infants showed earlier rhythm development. Recio *et al.* [87] have discussed a number of important issues influencing the development of circadian rhythm, especially during the first 3 months of postnatal life. They indicated that newborns are often kept in a dark room during the day so that they can sleep and may also be exposed to bright light during nightly feeding periods. This unusual environmental light–dark cycle may conflict with the infant's endogenous rhythm. Human milk contains

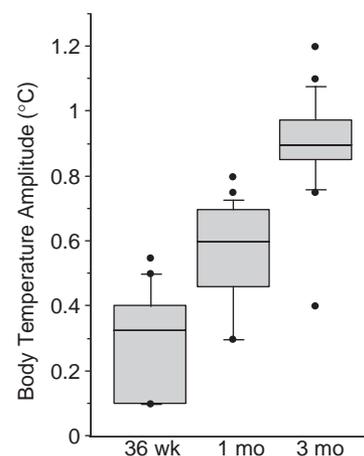


Figure 5 Median and quartile of body temperature amplitude is shown as a function of age.

melatonin. The change from breast milk to commercial milk may affect melatonin levels in the infant. Furthermore, mothers usually provide breast milk which has been pumped during the day, and therefore would also lack melatonin, for night-time feedings. In both cases the newborn is deprived of the maternal melatonin signal since melatonin peak in maternal milk is between midnight and 4 AM [88].

Recently, McGraw *et al.* [89] carefully studied a term infant from the moment of birth. They recorded hourly body temperature, daily sleep-wake patterns and weekly 24 h melatonin. The infant was fed only on demand and left undisturbed by the mother, who was the first author herself. Careful attention was paid to have outdoor daytime lighting and dim light at night. Even during feeding at night no extra lighting was used, to avoid disturbing the circadian rhythm of the infant. These investigators found a clear circadian rhythm in body temperature within one week of life. Circadian rhythms of sleep-wake and melatonin emerged by 6 weeks of age. Their study clearly demonstrates that the results from earlier circadian research in human infancy were confounded by maternal/environmental factors as well as by only recording sleep-wake or rest-activity cycle [90]. These results are in accordance with several other investigators and our own data [20, 91, 92] which demonstrate that the inherent functional fetal biological clock is able to continue oscillating after birth if not disturbed by interfering ex-utero environmental factors (including scheduled feeding every 2–4 h and night-time bright light). We have recently shown in newborn baboons, reared in the absence of mother in a continuous dim light condition from the moment of birth, an endogenous circadian rhythm in body temperature by one week of age [93]. The amplitude of this rhythm significantly increased as a function of age.

Kennaway *et al.* [94] found no evidence of circadian rhythm in melatonin before 9–12 weeks of age in term infants. They also found a delay of 2–3 weeks in development of melatonin circadian rhythm in preterm (corrected for age) versus term infants. However, in a study of phototherapy in term infants with high bilirubin, it was demonstrated that covering eyes during the artificial light exposure induces a surge in plasma melatonin level [95]. These results suggest some features of the biological clock development and responsiveness to light. In another study in very low risk preterm infants (33–36 weeks gestational age) recorded during the first week of life the investigators showed that pineal gland actively secretes melatonin [96, 97]. However exposing these infants for two successive days to day-night cycle (using eye pads at

night) does not show similar increase in melatonin at night in contrast to what has been found in term infants. A study in term infants showed the development of cortisol circadian rhythm by 8–12 weeks of age [97]. Another longitudinal study in preterm infants (gestational age 31–34 weeks) showed circadian rhythm in salivary cortisol level in more than half of the infants at 2–8 weeks of life [98]. The group as a whole developed circadian rhythm of cortisol between 8 and 12 postnatal weeks similar to the above study in term infants.

Many investigators have also indicated individual differences in development of circadian rhythms in infants [90, 99, 100]. To what extent these individual differences are the results of differences in prenatal circadian rhythms and/or postnatal environmental condition is yet to be studied. For example, in our own studies in preterm infants before discharge from the nursery [20], it was found that although no day-night differences were present in body temperature at < 14 days postnatal age, a small but significant rhythm of body temperature emerged in infants older than 14 days of age. The presence or absence of circadian rhythms in preterm infants is also influenced by their intrauterine growth. Although we were not able to find significant differences in presence of fetal heart rate between intrauterine growth retarded fetuses and controls [82], our postnatal studies showed that the percentage of preterm infants with circadian rhythms of body temperature and heart rate was significantly greater in the appropriate for gestational age group compared with the small for gestational age infants [20]. Postconceptional age (maturational effect) is important to consider in the development of circadian rhythms. In our postnatal studies, infants with post-conceptional ages of 35–37 weeks had much higher amplitudes of body temperature rhythm compared with 32–34 weeks PCA infants [20, 99, 101]. Although preterm infants before discharge from the hospital at 36 weeks post-conceptional age, slept as much during the night as during the day, by 3 months corrected age the same infants showed a clear day–night rhythm of sleep; see sleep development above [20].

An important function of maternal entrainment during the perinatal development may be to prepare the fetus' circadian timing system for later independent adaptation to the light–dark cycle. It is possible that the postnatal development of human circadian rhythms may be hampered by maternal, fetal, or perinatal disturbances. This is observed clinically when the intimate mother-fetus relationship is dramatically altered by premature birth or by maternal illness.

Furthermore, preterm infants are exposed to continuous or unpredictable light illumination for several weeks or months in the Neonatal Intensive Care Unit (NICU) and intermediate nursery [20]. Preterm infants are deprived of several potentially important maternal entrainment factors. This lack of maternal entrainment and random/unpredictable environmental condition in the nursery may induce disturbances in sleep, body temperature, feeding, and other rhythms in preterm infants. For instance, Mann [100] reported increased sleep and growth in preterm infants subjected to a regular light–dark cycle in the nursery but this finding was not evident until 6 weeks post discharge. Tenreiro *et al.* [102] found some beneficial effect of light–dark cycle in the nursery on development of circadian rhythms of heart rate and skin temperature before discharge. Kennaway *et al.* [94] also found that the delayed development of the melatonin rhythm in some preterm infants could be advanced by home cycled light. Hao's recent study [80] is important because it shows that the biological clock is responsive to light as early as 125 days in prematurely born baboons (normal baboon gestational age is 180 days). When extrapolated to human this means that as early as 28 weeks, preterm infants might be responsive to the biological effects of light on the circadian system.

McMillen *et al.* [103] found that circadian rhythm of sleep adaptation, in a group of infants discharged home, occurred after 6–10 weeks, whether they were preterm or term. However, this was true in her study with a regular day–night cycle, a single care giver, and “on-demand” feeding. Since the preterm infants were discharged home around 35 weeks PCA in their study, the entrainment to light–dark cycle took place at significantly earlier postconceptional age (47 weeks) in these infants compared with the term group (49 weeks PCA). Interestingly, they also found an inverse relationship between gestational age and the postnatal age at which the entrainment occurred in preterm infants. They interpreted this postnatal delay in entrainment of the younger preterm infants to be due to the longer period of non-entraining stimulation in the neonatal nursery environment. Their results suggest that regular environmental entraining factors are more important than preterm/term delivery in later adaptation of the infant to a light–dark cycle. It is also interesting to note that one infant in this 4 month study never developed a sleep circadian rhythm. This term infant was fed at night with full, bright light. McMillen's findings suggest that early exposure of preterm infants to a cycled light would result in earlier development of

circadian rhythms. However, in our studies in which we compared the effect of several weeks in a cycled light nursery on development of circadian rhythms, with those in a continuous dim nursery we did not find significant differences between the two groups [20]. Shimada *et al.* [104, 105], in a large study, found no differences between term and preterm infants in the circadian rhythm of sleep, duration of day and night sleep, or the time of onset of the longest sustained sleep time after home discharge when corrected for age. Preterm infants (low risk 28–36 weeks GA) in their study were exposed to continuous light ranging from 420–500 lux in the NICU. On the other hand the light intensity at home was similar for both groups and varied substantially during day versus night: ranging from 650–3000 lux during the day to 10–100 lux at night. There were also no significant differences between the two groups regarding the frequency of on-demand versus scheduled feeding or the time of parents' bedtime. Both groups showed entrainment to day–night rhythm by 48 weeks PCA. Contrary to McMillen, they concluded that environmental factors (both entraining and perturbing) are not able to influence the endogenous time course of circadian rhythm maturation. The exposure of preterm infants to continuous lighting for several weeks before discharge home does not appear to retard the development of sleep–wake circadian rhythms if an appropriate lighting regime is experienced at home. In their later report [105] they studied home sleep habits of 44 preterm and 40 term infants longitudinally from birth for more than 16 weeks. Seventy-five percent of the infants initially showed either ultradian or irregular sleep–wake patterns. Only 7% of the infants showed a free-running sleep–wake rhythm before entrainment. The mean age of the entrainment to light–dark cycle was 44.8 weeks postconceptional age, much earlier than in their earlier publication and very similar to our own data in preterm and term infants [20]. There were no significant differences in either the frequency of each pattern or the mean age of the entrainment between preterm and term infants [105].

Although an earlier onset of circadian development did not result from using a relatively short cycled lightening in our neonatal nursery, there are sufficient data [20] to state that there is no rationale for continuing a chaotic non circadian environmental approach in the neonatal nursery for the care of the prematurely born infant. Lack of circadian rhythmicity, not only in light but also in the pattern of noise, parental care, may subject the infant's developing circadian rhythm to conflicting temporal cues [20].

Furthermore, if the suprachiasmatic nucleus (SCN; Biological Clock) is responsive as early as 28 weeks gestation, cycled light at this time until discharge home may influence circadian organization. Introducing a regular day–night cycle into the NICU and intermediate nursery has been recommended in the recent Guidelines for Perinatal Care by the American Academy of Pediatrics and The American College of Obstetricians and Gynecologists [106]. Continuing such regular day–night rhythm at home as well as maximizing the day–night differences by minimizing night time care-giver intervention (including feeding) may benefit the development of preterm and term infants. Achievement of such a regimen would also have great practical implications for mothers with young infants, especially working mothers.

Practice Points

1. The origin of sleep and circadian rhythms development can be found during the fetal period.
2. The fetal/neonatal brain endogenously generates sleep and circadian rhythms and responds to maternal and environmental time cues.
3. Although sleep and circadian rhythms are coupled, they are generated by different neuronal mechanisms, their time course of development is not necessarily comparable.
4. The abundant amount of sleep in early fetal and neonatal life serves an important function in brain maturation and plasticity.
5. Fetal and early neonatal circadian rhythms prepare the neonate for later adaptation to the environmental light dark cycle.

Research Agenda

Future research is needed to study:

1. The functional significance of sleep for brain maturation and plasticity in the human fetus/neonate.
2. The time course of process S and its relationship to circadian phase of body temperature in preterm and term infants.
3. The development of SWS and sleep spindles in high risk preterm infants, compared with low risk preterm and term infants, as an indication of the degree of cortical-thalamic maturation.

4. The neuronal network (most probably in the hypothalamus) develops around 32–34 weeks gestation. This network is responsible for orchestrating more well defined, predictable, organized behavioral states of sleep-wakefulness from relatively random chaotic patterns.
5. The effect of a long-term environmental light–dark cycle in the neonatal intensive care unit (NICU) on maturation of circadian rhythms in very low birth weight preterm infants.
6. The influence of the maternal circadian rhythm during gestation and lactation on maturation of fetal and neonatal circadian rhythms.
7. The pattern of arousal during sleep over 24 h during the 1st year of life and differences in sleep microstructure in victims of sudden infant death syndrome (SIDS).

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