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Chapter 4

CIRCADIAN SLEEP-WAKE RHYTHMS IN PRETERM INFANTS

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ABSTRACT

Knowledge is recently building regarding the factors that affect the development of an optimal sleep-wake cycle. Fetuses near term experience arousal fluctuations and sleep episodes already in the darkness of the womb. Yet, the factors that allow for a smooth emergence of an optimal sleep wake cycle are the conditions that place newborn at higher risk to develop sleep disorders are not yet fully understood. The current chapter proposes an integrative model for the development of circadian sleep-wake rhythms in preterm infants. This model is based on a comprehensive review of the basic science literature as well as clinical work with at-risk preterm infants. This integrative model proposed a three source risk source: 1) infant dependent neurobiological vulnerability risk, such as brainstem mediated functional disability; 2) a familial source that entails genetic predispositions, parental style and support resources; and 3) an environmental stimulation source, such as excessive NICU related stimulation and handling. These three realms act as main effects and interact with the infants' prenatal and postnatal age and with the infants' self- regulation mechanisms. The manner in which these sources operate and interact lead to directions of interventions that ameliorate the development of circadian sleep-wake rhythm deficit in infants born at-

risk for sleep disorders. The chapter details each component of the model and illuminates the complexity of the interactions involved in it to deepen the understanding the mechanisms involved in early organization of sleep-wake rhythms in infants.

INTRODUCTION

Sleep-wake rhythms serve as a basis for the modulation of arousal (Feldman et al., 2002; Feldman et al., 2004), which in turn provides the foundation for emotion regulation (Kopp, 1999; Feldman, Weller, Sirota, & Eidelman, 2002), social competencies (Feldman, 2006) attention shifting and maintenance (Aston-Jones, 2005), sustained exploration (Feldman et al., 2002) and cognition (Sadeh, Dark, Vohr, 1996; & Mayes, 1999; Scher, Amir & Tirosh, 2000), by providing a global organizing framework of arousal. The development of circadian sleep – wake rhythms is therefore of central importance in securing adaptive development across infancy.

Noradrenergic locus coeruleus (LC) neurons provide a circadian regulation of the sleep-wake cycle, and the maintenance of LC function depends on light exposure. Studies have shown that noradrenergic LC neurons exhibit a circadian rhythm in impulse activity, which peaks during the active period. This is mediated by an indirect circuit projection from the suprachiasmatic nucleus (SCN) to the LC, via the dorsomedial and paraventricular hypothalamic nuclei, as well as medial and ventrolateral pre-optic areas (Aston-Jones, Chen, Zhu, & Oshinsky, 2001).

Light deprivation induces a loss of noradrenergic fibers, which in turn decreases the amplitude of the sleep-wake rhythm (Gonzalez & Aston-Jones, 2006). The effects of excessive light exposure on sleep wake rhythmicity were recently described in a case study (Doljansky, Kannety & Dagan, 2005). Modifications of this exposure were shown to yield normalization effect of the sleep wake cycle within days. Effects of excessive light exposure, particularly during night hours on the neonatal circadian sleep-wake cycle are presently debated.

FETAL ENTRAINMENT

In recent years, experimental data shows that among the significant developmental changes occurring in the 2nd half of pregnancy, sleep related

structural and functional developments are among the most central. Recent findings present intriguing findings that fetal endogenous system is capable of generating increasingly differentiated fetal behavioral states and transitions between them in association with fetal development, such clearly defined non-REM and REM conditions (Frank et al., 2006). These differential bio-behavioral states are increasingly evident by short epochs of heart rate acceleration and deceleration that define differential regularity patterns (Kuhnert, Hellmeyer, Stein, Schmidt, 2006); Van Leeuwen, Cysarz, Lange & Gronemeyer, 2006)

Halpern and colleagues in their review (Halpern, Maclean and Baumeister ,1995) noted that the chronological age at which binary sleep – wake states first appear are reported to occur at different phases, depending upon methodological differences. Studies conducted in the 70s noted that active sleep emerges at about 32-35 weeks gestation (Dreyfus-Brisac, 1970;Parmelee, Wenner, Akiyama, Schultz & Stern, 1967) and quiet sleep emerges a bit later at about 32-35 weeks of gestation (Dreyfus-Brisac, 1970; Prechtl, 1974). However, studies conducted in the 90s showed that both active and quite sleep can be reliably detected in both healthy and medically vulnerable preterm infants that are 28-31 weeks old (Curzi-Dascalova et al., 1988; Holditch-Davis, 1990; Stefanski, Schulze, Bateman, Kairam, Pedley, Masterson, & James, 1984).

Yet more recent studies from the last 5 years indicate that cyclicity of neonatal sleep behaviors emerges for most at 25 to 30 weeks' post-conceptional age, reflecting an ultradian biologic rhythm during the early perinatal stage of brain development (Scher, Johnson, Holditch-Davis, 2005).

It has been recently shown that the fetal sleep-wake system is also capable of producing in vivo intrauterine circadian rhythms during the third trimester (Frank et al., 2006). This development is to some degree endogenously driven (Mirmiran, Baldwin, Ariagno, 2003). It is also operating via responding to maternal entrainment signals of day-night rhythms. This circadian rhythmicy is measurable via recordings of fetal heart rate fluctuations in human fetuses for various periods of times. This capacity is not an expression of a free running internal clock, despite the relative darkness, typical of uterine environment. It represents effects related to fetus' capability of sensing the maternal diurnal rhythm, through reception of rhythmic auditory changes, bowel movement changes, HR changes, and more. Analysis of the results is indicative of some preliminary rhythmicity.

In primates, maternal melatonin has been suggested as a candidate to entrain fetal circadian rhythms, including the SCN rhythms of metabolic activity. Recently maternal melatonin has been indeed shown to be a Zeitgeber for the fetal supra charismatic nucleus of the hypothalamus, but probably not for the adrenal

gland (Torres-Farfan, Rocco, Monso, Valenzuela, Campino, Germain, et al., 2006).

NEONATAL ENTRAINMENT

McGrow and colleagues (1999), following the emergence of entrainment of a healthy male infant in Texas from birth to 6 months of age in conditions of a household with a fixed schedule and natural light environment showed that the circadian rhythm of temperature appeared first, during the first week of life. The wake circadian rhythm appeared second, attaining significance at day 45; approximately at the same time that increased melatonin concentration began to occur at sunset. The sleep circadian rhythm appeared last, attaining significance after day 56. Ninety to 120 minute zones of sustained wakefulness first appeared in the second month of life subsequent to awakening and prior to sleep onset. The infant's nocturnal sleep-onset was coupled to sunset before day 60 and subsequently to family bedtime, giving evidence of initial photic entrainment followed by social entrainment. McGraw and colleagues concluded that Circadian rhythms appeared much more rapidly in this infant than previously reported; their rapid appearance was probably facilitated by maximal exposure to sunlight, and presence of social routine cues, such as schedules of family meals, bath time and such, that were closely tied to daylight cyclicity. Thus McGraw's work underscores the importance of exposure to artificial light and irregular handling schedules as risk factors that delay normal circadian rhythm attainment (McGraw, Hoffmann, Harker & Herman, 1999).

An Integrative Model for the Development of Circadian Sleep-Wake Rhythms in Preterm Infants

Based on reviewed literature that will be discussed in detail below, we hypothesize an integrative model that integrates neurobiological vulnerability, maturation and stimulation factors that eventually pattern circadian sleep-wake rhythms in neonates. This model is based on an extensive literature review of both basic science models as well as on clinical studies with normally developing and at-risk human neonates.

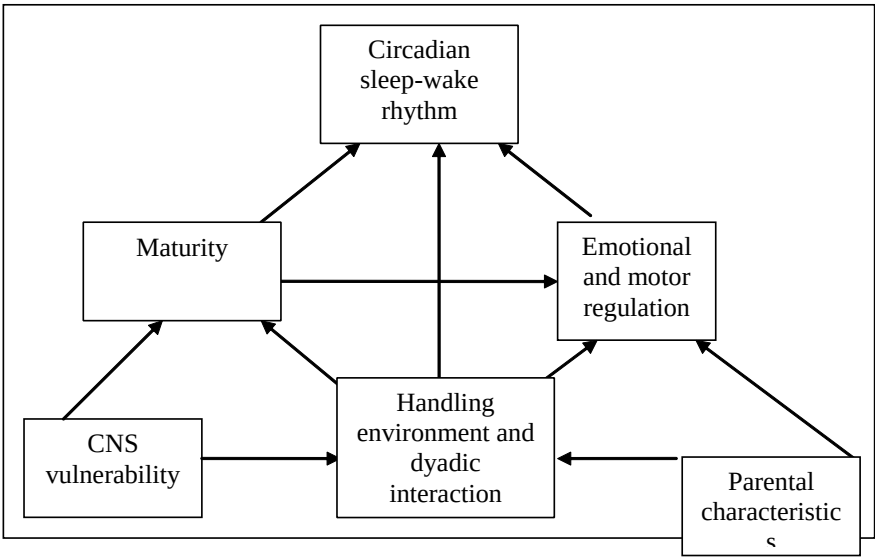

Figure 1. An integrative model for the development of circadian sleep-wake rhythms in preterm infants

This integrative model proposed a three source risk source: 1) infant dependent neurobiological vulnerability risk, such as brainstem mediated functional disability; 2) a familial source that entails genetic predispositions, parental style and support resources; and 3) an environmental stimulation source, such as excessive NICU related stimulation and handling. These three realms act as main effects and interact with the infants' prenatal and postnatal age and with the infants' self- regulation mechanisms. The later then mediate the development of infants' circadian sleep-wake rhythm. Further understanding of the manner in which these sources operate and interact would lead to development of proper interventions to eliminate the development of circadian sleep-wake rhythm deficit in infants born at-risk for sleep disorders. In the following we detail each component of the model

Prematurity - A Unique Window to Study Preliminary Circadian Rhythm Development

Maternal illness and premature birth adversely affect the development of circadian rhythms (Mirmiran & Ariagno, 2000). These effects seem to be strongest around the developmental mile stone at which the adverse process, .i.e.,

preterm birth, occurred (Mirmiran & Ariagno, 2000). The authors note this process disrupts the initial mother-infant process which is also vital for proper entrainment.

Prematurely born infants offer a unique window to study the circadian rhythm related developmental progressions. However, studies on sleep patterns of preterm infants at the age of expected birth have shown a fairly variable pattern of results (Ingersoll & Thoman, 1999). For example, on some patterns, preterm neonatal measures appeared to be precaucial relatively to neonates born at term, while on other parameters, an opposite direction was apparent (Booth Thoman & Leonard 1980; Holditch-Davis & Thoman, 1987). So that around birth, preterm neonates showed a higher frequency of REM in active sleep, and their sleep was characterized by longer quite sleep episodes.

It is worth noting that some similarities in circadian behaviors occurred in the development of sleep-wake cycle in preterm infants in the extra-uterine environment and full-term infants in the intrauterine environment (de Vries, Visser, & Prechtl, 1982; Diambra & Menna-Barreto, 2004; Olischar, Klebermass, Kuhle, Hulek, Kohlhauser, Rucklinger, Pollak & Weninger, 2004). However, recent data point to a vital transitional milestone that occurs around 31 weeks of gestation. This milestone, points to a possible additional risk related to preterm birth prior to 31 weeks of gestation. Following the development of sleep-wake cyclicity in premature infants born at 25 to 29 weeks gestation, we found that a developmental leap in the organization of the sleep-wake cycle occurred at 31 weeks gestational age and that those infants who did not show a timely maturation of the biological clock showed deficiencies in social interactions and arousal modulation capacities in later infancy (Feldman, 2006).

Overall, as noted in Halpern, Maclean & Baumeister's review (Halpern et al., 2006) the variability in sleep parameters in preterm infants is much greater than that reported in infants born at term. This tendency holds also in preterm infants born extremely early and or with extremely small weights (Leitner, Bloch, Sadeh, Neuderfer,Tikotzky, Fattal-Valevski et al., 2002). Researchers thus continue to search for additional risk factors that would explain significant portions of this large variability. Among the variables recently explored both infants factors and environmental measures are studied.

CNS Perinatal Susceptibility as a Risk Factor

Brainstem structures regulate and modulate sleep and arousal (Losier & Semba, 1993). Structures in the brainstem influence higher brain structures in the

midbrain and cortex. The ascending reticular activating system that transverses through the brainstem stimulation to the thalamus, hypothalamus, and basal forebrain, results in excitation of the cortex. Its cholinergic, glutamic and catacholinergic neurons are stimulated by afferent sensory input, such as audition and vision (Harris, 2005). Wakefulness is manifested by an active cortex that exhibits a characteristic pattern of desynchronized EEG

Mechanisms related to the nucleus tractus solitarius, which project on to midbrain and forebrain structures, inhibit activity in the reticular system, resulting in activation of inhibitory thalamocortical projections to the cortex. During a state of decreased activation, the cortex exhibits a pattern of synchronized EEG that is manifested as various forms of Non-REM and REM sleep (Harris, 2005).

Other brainstem structures regulate activities known to affect sleep and arousal indirectly, such as arousal and attention (Lai, Shalita, Hajnik, Wu, Kuo, Chia, et al., 1999; Wong & Wong, 1991; McNamara, Wulbrand & Thach, 1999; Karmel, Gardner & Freedland, 1996) and the processing of sensory information (Anthony & Graham, 1997; Nattie, 2000), such as visual and auditory perception (Larson & Yajima, 1994; Jiang, & Wilkinson, 2006; Aitkin, 1986; Davidson & Bender, 1991). Still, direct effects of brainstem dysfunction on sleep and arousal regulation early on in development are not yet fully understood.

Neonatal brainstem dysfunction has been suggested as a risk factor for various neural-developmental deficits (Karmel, Gardner, Zapulla, Magnano & Brown, 1988; Darnall, Ariagno, Kinney, 2006): neurobehavioral deficits (Karmel, Gardner, Zappulla, Magnano, & Brown, 1988), orodigestive and cardiorespiratory difficulties (Abadie, Morisseau-Durand, Beyler, Manach & Couly, 2002; Darnall, Ariagno, Kinney, 2006), and neurological dysfunction (Yilmaz, Degirmenci, Akdas, Kulekci, Ciprut, Yuksel, et al., 2001). We propose that brainstem dysfunction may be directly related to an aberrant development of sleep- wake cycles, particularly in preterm neonates for whom the maturation of higher-order structures is still under way. For such infants, the sensitive circadian system may have been compromised by the pre-term birth.

It has been shown that Cholinergic and aminergic brainstem neurons can concurrently modulate the activity of neurons in the thalamus and basal forebrain during cortical arousal, through dual projections (Losier & Semba, 1993- in the rat model). Structural damage in brainstem structures, specifically in the ventral mesencephalon and rostroventral Pons have been shown to results in deficits in sleep- wake organization (Lai, Shalita, Hajnik, Wu, Kuo, Chia & Siegel, 1999- in the cat model). It is thus hypothesized that brainstem-related neonatal dysfunctions would result in abnormalities in the development of the sleep-wake circadian rhythms.

NICU Environment as a Risk Factor

The environment of the NICU presents ample demands on the preterm infants (Field, 1990). The NICU's great life-saving potential comes often at some cost. The NICU environment is different from maternal uterus in numerous fashions, some of particular importance to circadian rhythm development.

The NICU presents various levels and types of lights that are significantly different from natural lights. Solar lights are presented un-baffled by uterine wall and artificial light, at various wave lengths, are often intense and are presented at prolonged phases, way beyond characteristics of solar light phase (Niessen, 2006).

The NICU environment also presents the infant with excessive noise (Kent, Tan, Clarke & Bardell, 2002; Byers, Waugh & Lowman, 2006; Niessen, 2006). It is fraught with multiple noises, monitor beeping, ventilator alarms, low spectrum noises of wheeling incubators and various carts during the day and the night and stuff activity related noises. Some are fairly constant through the day and the night, some are impulsive and unexpected. Overall activity levels are higher than other environments to which infants are brought to. Still, recent measurements of sound pressure levels at NICU indicated the highest levels were recorder at 6-7 AM and around noon (Kruege, Wall, Parker, & Nealis, 2005). Activity at NICU is maintained at relatively high levels during the day and also is significantly high during the night, though typically lower than that of the day.

The effects of loud noise on the preterm infants are evident on a physiological level by increased heart and respiratory rates and decreased oxygen saturation (Bremmer, Byers, & Kiehl, 2003). Its effects on sleep –wake rhythms are not yet fully understood. However, animal models have demonstrated via simulating continuous lights and sounds of a typical nursery and exposing newborn animals to these conditions, showed that this constellation of stimuli schedule results in permanent damage to the biological clock, in differences in sensory processing of stimuli, and in immature habituation to stimuli in the young animal (Hao & Rivkees, 1999- in a baboon's model; Philbin, Ballweg, & Gray, 1994 and Sleigh & Lickliter, 1998- in chicks models). The studies point to the potentially damaging effects of nursery conditions on the developing infant in general and have a potential harmful effect on its developing systems that regulate circadian activity.

Experimental light manipulation has shown, that the circadian sleep-wake rhythm in the preterm infants entrained after a similar time of exposure to an environment with daily time cues but at an earlier post-conceptional age when compared with the term group (McMillen, Kok, Adamson, Deayton & Nowak, 1991). While McMillen's group in Australia has concluded that maturity of the

premature infant is less of a determinant in attaining circadian sleep, but rather that the length of time spent in a cycles day-night environment is vital for this purpose (McMillen, Kok, Adamson, Deayton & Nowak, 1991).

Environmental variability at the NICU is often less directly related to the status of the infants, but rather to necessary management of neighboring infants and the fixed routine procedures of the NICU, irrespective of the infants' current status. This factor is also very different from uterine environment where by the uterine environment is almost solely responsive to the mother-infant dyad capacity, changes and needs. It may very well be that a chaotic, non-circadian environment of the NICU adversely affects initiation and stabilization of circadian rhythms of the preterm infants (Mirmiran & Ariagno, 2000).

Attempts to support this hypothesis were so far only partly successful, since circadian and sleep development in preterm infants occurs independently from the influences of environmental lighting (Mirmiran, et al., 2003). Entrainment of preterm infants using a different lighting environment during the night (a day-night cycled room), seem to be not effective or at least not sufficient to differentially effect entrainment during the first 3 months of the preterm infants post natal life (Mirmiran, et al., 2003). Similarly, phototherapy at the NICU has been shown to have no short-term effects, on neonatal sleep-wake cycles when compared with preterm infants who have not received photic intervention. Nor does it effect sleep-wake rhythms or saliva cortisol levels at two years of age (Shimada, Segawa, Higurashi, Kimura, Oku, Yamanami et al., 2003).

At the same time, analysis of activity levels recorded by Actiwatches, cycled light (7PM-7AM use of crib covers) has been shown to affect activity levels during the first month post preterm birth (Rivkees, 2003; Rivkees, Mayes, Jacobs & Gross, 2004). Exposure of premature infants to low-intensity cycled lighting, rather than to a fixed dim light level, in the hospital nursery induces distinct patterns of rest-activity that are apparent within 1 week after discharge. The data thus shows that day-night rhythms in activity patterns can be detected shortly after discharge to home in premature infants and that the circadian clock of developing infants is entrained by cycled lighting.

Harris (2005) in his review summarizes that the amount of time spent sleep changes throughout the life span. Such, that at the neonatal-period the infant sleep most of time. Sleep periods of 1-4 hours are distributed evenly during the circadian cycle. By 6 months of age well defined sleep-activity states appear. Sleep episodes lengthen and the proportion of REM sleep declines (Harris, 2005)

Birth Mode as a Risk Factor

Effects of specific risk factors, which typically accompany preterm birth on circadian sleep wake rhythms is yet significantly understudied. Of the various significant risk factors for which some preliminary data has been collected, one can find: Delivery mode, that seem to be of no consequence on the amount of sleep but rather has an effect on the development of circadian rhythms in neonates (Korte, Hoehn & Siegmund, 2004). It was found that the majority of vaginally born neonates showed a distinct circadian frequency in their spectra, which is characterized by more sleep during the night. In contrast, both groups of neonates born by C-section showed significantly less distinct circadian frequencies in their spectra. The authors did not find these differences in infants born preterm.

Others find that c-section deliveries are related to differences in sleep- wake organization during the first few days post birth.

In Finland, postnatal adaptation after c-section was found to be related to changes in sleep organization, and increases in oxyhaemoglobin saturation and frequency of body movements in the first few days after birth (Nikkol, Kirjavainen, Ekblad, Kero & Salonen, 2002). Similar findings were reported in the US, where by full term neonates born via vaginal delivery had more wakefulness, shorter mean sleep periods and shorter longest-sleep periods during the daytime on the first two days post birth (Freudigman & Thoman, 1998) . Thus, perinatal interventions such as stress and pain (Nikkol, Kirjavainen, Ekblad, Kero & Salonen, 2002) and surgical birth (Freudigman & Thoman, 1998) seem to disrupt neonatal circadian rhythm of full term neonates. The mechanism/s of these effects is not yet understood.

Prematurity as a Risk Factor

Effects of prematurity of sleep-wake rhythms seem to be complex. On the one hand one may hypothesize greater vulnerability of a younger system in handling excessive interventions. At the same time greater plasticity to aberrations is to be expected under certain conditions. Generally, preterm infants exhibit more active sleep and indeterminate sleep states than full-term infants (Curzi-Dascalova, Peirano, & Morel-Kahn, 1988; High & Gorski, 1985; Holditch-Davis, 1990; Holditch-Davis & Edwards, 1998; Parmelee, Wenner, Akiyama, Schultz, & Stern, 1967). At the same time, there is a significant debate regarding indications of sleep-wake rhythmicity in preterm neonates.

Following these robust findings, some presume a greater weight for prematurity than to its related complications, such as illness severity and medical treatments, handling and hospitalization (Holditch-Davis, Scher, Schwartz, Hudson-Barr, 2004). Indeed, large scale studies, such as that performed by Sadeh, show that sleep of infants born at later gestational ages is characterized of greater organization levels, indicated by increased percent of quiet and motionless sleep (Sadeh, et al., 1996). Yet, it is not know whether the effect of prematurity on sleep-wake rhythms is a main effect one, or rather that risk factors interact with gestational age to affect sleep-wake cycles during the neonatal period. An example for such an interaction effect is maternal glucose values during pregnancy (Sadeh, et al., 1996) - which is related to sleep-wake patterns in preterm infants, but not in the controls. Another factor recently discovered that interacts with prematurity to affect sleep characteristics in preterm infants is administration of antenatal magnesium sulfate and corticosteroid therapy (Black, Holditch-Davis, Schwartz & Scher, 2006). It was found infants exposed to magnesium sulfate had more active sleep without rapid eye movement, indicating poorly organized active sleep. Investigators seem to concur that the mechanism involved in the majority of these processes is some subtle affect on CNS in these vulnerable infants.

The Development of Circadian Sleep-Wake Rhythm in Preterm Infants as a Factor of Parenting and Environmental Stimulation

Postnatal entrainment goes through marked changes during the first few weeks of life. Entrainment to maternal schedule occurs irrespective of prematurity around the post conceptual age of 45 weeks in 75% of infants (Shimada, Takahashi, Segawa, Higurashi, Samejim & Horiuchi, 1999). During the transition periods infants go through either ultradian of irregular sleep-wake cycles (Shimada, Takahashi, Segawa, Higurashi, Samejim & Horiuchi, 1999).

Neonatal cyclicity measures are reported to be negatively related to indices of advanced perinatal status as well as 6-month mental scores; however, at 6 months, the cyclicity measures from infant born preterm were positively related to perinatal and neonatal measures as well as mental scores (Borghese, Minard & Thoman, 1995; Feldman, 2006). These seemingly contradicting results may indicate the necessity for different interpretations of periodicity at the preterm and later age (Borghese, Minard & Thoman, 1995).

Sleep disorders have been reported in children born preterm as they grow up. A study conducted at 20 months corrected age has shown that the quality of night-

time sleep of preterm toddlers is more disrupted on average than that of toddlers born at term (Gossel-Symank, Grimmer, Korte, Siegmund, 2004). The daytime rest duration of preterm infants at 20 months is significantly shorter than that of full-term infants. The sleep quality of preterm infants is significantly lower than that of full-term infants, since the preterm infants have a larger percentage of less restful nighttime sleep (Gossel-Symank, Grimmer, Korte, & Siegmund, 2004).

A theoretical framework that may account for the complex circadian sleep-wake rhythm of neonates proposes an interaction between components that are more directly related to CNS vulnerability and other components that are more prone to handling and stimulation effects (Anders, Keener, Kraemer, 1985)

Literature cited by Halpern (Halpern et al., 1995) shows that during the 90s it was thought that the first 6 months of life are not yet accompanied by changes in the awaked state during nighttime (Anders & Keener, 1985). Halpern summarizes reports of observational studies of infants during the day time during the first 6 months of postnatal life, in which a non-linear increase in the percent of day time wakefulness, and longer periods of wakefulness during the day (Halpern, 1995; Wolff, 1984). Comparisons of wakefulness at daycare settings and in the home revealed that wakefulness in the home setting was maintained at earlier ages and for longer periods of times (Wolff, 1984) This difference was attributed to the level of stimulation provided in the home relatively to relatively lack of it at the day care setting (Thoman & Whitney, 1989). Stimulation effect on wakefulness was also found as a factor of maternal company, parental co-sleeping (Thoman, 2006); as opposed to a lonely setting.

The age of early marks of circadian influences on sleep-wake patterns is still in debate (Halpern, 1995). Some reported on first appearance between 6-8 weeks of age (Thoman & Whitney, 1989), even though gradual increase in daylight wakefulness emerges earlier, at around 4-5 weeks of age in the home setting (Thoman & Whitney, 1989). Significant sleep episodes during the night are typically fairly common at 3 months of age (Coons & Giullenault, 1984).

Effects of Touch Interventions for Preterm Infants on Sleep-Wake Circadian Rhythmicity

The development of sleeping and waking behaviors in preterm infants is reactive to handing and to social encounters right from the neonatal period (Ingersoll & Thoman, 1999). Nursing care affects sleep states already at the nursery and during the first three months of post natal life (Brandon, Holditch-Davis & Beylea, 1999).

Of special interest are the effects of touch-and-contact interventions on sleep-wake rhythmicity in neonates.

Among the central benefits of touch-and-contact intervention to the fragile premature infant is the organization of the biological clock. Animal studies point to the important role of the mother's physical proximity and specific body cues for the maturation of the biological clock in the pup during the first post-birth days (Hofer, 1995). In addition to their immature CNS, premature infants are deprived of the soothing, regulating, and organizing presence of the mother's body and closeness (Feldman, 2004). Two types of touch-and-contact interventions were found to have an impact on sleep-state organization; Kangaroo Care and massage.

Kangaroo Care (KC), a method developed in Bogota, Columbia during a period of incubator shortage, involves skin-to-skin contact between mother and her premature infant. Several studies showed both concurrent and long-lasting effects to the KC intervention on state organization and sleep-wake cyclicity. During contact, infants spent more time in quiet sleep, heart rate was lower and more stable, apnea and bradycardia decreased, body temperature was maintained, and oxygenation improved. Moreover, the effects of skin-to-skin contact seemed to persist even after contact was ended. Following kangaroo contact premature infants slept longer and sleep was more restful and organized. Interestingly, KC improved not only sleep states but also infant alertness, as shown by the findings that infants spent longer periods in alert states after KC. It is thus possible that KC organizes the biological clock by increasing the time infants spend in the two ends of the arousal continuum—quiet sleep and alert wakefulness—while reducing transitory states and active sleep. An addition contribution of kangaroo contact to state organization was the decrease in transitory, indeterminate sleep states among infants born preterm who underwent KC as compared to matched controls (Feldman & Eidelman, 2003).

Kangaroo care similarly contributed to the organization of sleep-wake rhythmicity. Following two weeks of daily kangaroo contact, we found that the amplitudes of sleep-wake cyclicity as measured in 10-second epochs over four consecutive hours were higher for treated infants compared to controls (Feldman et al., 2002). Better organization of the biological clock, in turn, was related to improved arousal and emotion regulation capacities across infancy and up to age five. Infants with better sleep-wake organization had higher thresholds to negative stimuli, were better able to modulate arousal, and showed more exploratory behavior across the first year. During the toddler and preschool age, these children scored higher on neuropsychological tests that required attention shifting and maintenance and displayed higher executive functioning at age five. In the social-emotional domains, children with better organization of the biological clock were

more able to show restrained and self-regulation during social and nonsocial tasks that requires inhibition and regulation of anger and frustration (Feldman, 2007).

Massage therapy, active stroking of the premature infants following a specific regime similarly showed that premature infants who received massage therapy spent more time in alert wakefulness and less time in active sleep states, were discharged earlier from the hospital, and showed more mature neurobehavioral profiles (Field, 1995).

Overall, recent developments demonstrate intervention effects of stimulation, on sleep-wake state organization and the development of sleep-wake circadian rhythms of infants born prematurely, via careful modifications of infant's exposure to light, sound, and touch in early phases of development. Developing multi-modality intervention protocols that are more closely tied to circadian mechanisms of the infant and its CNS capacities may re-direct development of infants born at risk into more adaptive sleep-wake circadian rhythms.

CONCLUSION

We reviewed and critically tested the primary issues affecting the development of sleep-wake circadian rhythms in infants: 1) CNS vulnerability, as indexed by specific brain structures known to be involved in regulation of sleep-wake functions, such as *perinatal brainstem dysfunction*; 2) *Aberrant maturation caused by premature birth*; and, 3) *Suboptimal environmental conditions*. This topic relates to the unnatural neonatal environment and excessive exposure to light sound and touch in early development.

We propose that an integrative view that takes into account the vulnerability of autonomic system, neonatal neural maturation, and environmental conditions provide the foundation for the emergence of circadian sleep patterns in early development. Finally, this source has been proposed as a valuable intervention tool, in the forms of specific message and KC in ameliorating the adverse effects of CNS related vulnerability, and excessive stimulation early on in development and redirecting a more optimal development of neonatal circadian sleep-wake cycles.

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