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Environmental factors influencing biological rhythms in newborns: From neonatal intensive care units to home☆

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ABSTRACT

Photic and non-photic environmental factors are suggested to modulate the development of circadian rhythms in infants. Our aim is to evaluate the development of biological rhythms (circadian or ultradian) in newborns in transition from Neonatal Intensive Care Units (NICU) to home and along the first 6 months of life, to identify masking and entraining environment factors along development.

Ten newborns were evaluated in their last week inside the NICU and in the first week after being delivered home; 6 babies were also followed until 6 months of corrected age. Activity, recorded with actimeters, wrist temperature and observed sleep and feeding behavior were recorded continuously along their last week inside the NICU and in the first week at home and also until 6 months of corrected age for the subjects who remained in the study.

Sleep/wake and activity/rest cycle showed ultradian patterns and the sleep/wake was strongly influenced by the 3 h feeding schedule inside the NICU, while wrist temperature showed a circadian pattern that seemed no to be affected by environmental cycles. A circadian rhythm emerges for sleep/wake behavior in the first week at home, whereas the 3 h period vanishes. Both activity/rest and wrist temperature presented a sudden increase in the contribution of the circadian component immediately after babies were delivered home, also suggesting a masking effect of the NICU environment.

We found a positive correlation of postconceptional age and the increase in the daily component of activity and temperature along the following 6 months, while feeding behavior became arrhythmic.

1. Introduction

The circadian timekeeping system is currently considered as a network composed by multiple oscillators and has the suprachiasmatic nuclei as an important component [1]. Studies with primate models suggest that the suprachiasmatic nuclei are functionally innervated from 25 weeks of gestational age in humans and could be entrained indirectly by light/dark cycles even in prenatal life [2].

Body temperature and sleep/wake rhythms seem to develop according to a sequential pattern, in which a circadian temperature rhythm can be detected earlier in life. Reinforcing this hypothesis, circadian rhythms in rectal and skin temperature have already been detected in preterm newborns inside neonatal care units (NICUs) [3,4], while a circadian rhythm in activity/rest cycle can be identified in term newborns in the first weeks of life [5–7].

Some authors identified a similar ultradian profile of activity/rest cycle in newborns and mothers and also the presence of a circadian component with periods longer than 24 h in the first week of life [7,8]; however only one actigraphy study has been performed in preterm newborns aged less than 40 weeks of corrected age allowing for an earlier detection of a circadian rhythm for this variable [6]. MacMillen et al. [9] demonstrated an earlier emergence of a circadian rhythm of sleep/wake cycle in preterm infants compared to term babies, suggesting that the timekeeping system would be functional as early as 35 weeks of postconceptional age and the apparent delay in the emergence of the circadian rhythm described in other studies would be related to later exposure to a cyclic environment. Recently, Guyer et al. [10], using actigraphy, also demonstrated the earlier emergence of a circadian rhythm in sleep/wake parameters in preterm infants compared to term babies.

Recently, studies about temperature rhythm have also been improved with the development of a wireless system for continuous measurement of human skin temperature, allowing the longitudinal recording of peripheral temperature. Areas et al. [11] described its use in a chronobiological study, suggesting that wrist temperature measured by the thermistor exhibited a strong circadian rhythm with its acrophase occurring at night, but only one study has been performed in infants [12] and our group investigated its use in newborns [13].

Photic and non-photic environmental factors can influence the emergence of circadian rhythms. Previous studies demonstrated different behaviors, increase in weight gain and, recently, also a circadian melatonin rhythm was described in preterm newborns inside NICUs provided with light/dark cycle [14–16]. Ultradian rhythms have also been demonstrated for preterm neonates in activity, heart rate and temperature, possibly related to feeding schedule and caregiving interventions inside NICUs [17], suggesting a masking effect. Other authors, however, argue in favor of the development of circadian rhythms as a function of postconceptional age and independent of environmental interventions [18,19], as well as, suggesting independent developmental courses for sleep/wake and feeding behavior in infants [6]. Thus there remain controversial points about the development of rhythms in the first year of human life.

The aim of the present study was to evaluate the development of circadian and ultradian rhythms in newborns in transition from intensive neonatal care units to home and along the first six months of life, intending to identify masking and entraining environment factors along development.

2. Material and methods

Preterm newborns (ages ranging from 28 weeks to 36 weeks of gestational age at birth) and term babies were recruited in the Neonatal Care Unit (NICU) of the Hospital Universitário of the Universidade de São Paulo. The project was approved by the ethical committees of both the Hospital Universitário and of the Instituto de Ciências Biomédicas, according to the Declaration of Helsinki, and written informed consent was signed by parents. They were all healthy newborns, with normal Apgar scores, no evidence of perinatal asphyxia or neurological disease and not treated with sedative drugs.

Nine preterm babies and one term newborn were evaluated inside the NICU, with overall data inside the NICU previously published [13]. These subjects were followed in the first week after being delivered home and five preterm and one term infant remained in the study and were also followed until six months of corrected age for preterm babies and 6 months of postnatal age for the term infant. Corrected age refers to the age of a preterm child from the expected date of delivery, while postnatal age means the time elapsed after birth; postmenstrual age, otherwise refers to the gestational age at birth plus the postnatal age. In the present study, data of the last week inside the NICU were evaluated for comparisons with the rhythmic pattern at home.

All infants had their activity, wrist temperature and observed sleep and feeding behavior recorded continuously along their last week inside the NICU. The same parameters were recorded along the first week after being delivered home and, for the subjects who remained in the study, for fifteen consecutive days every month until six months of corrected or postnatal age.

Sleep, activities, staff interventions and feeding diaries were filled every day by hospital staff inside the NICU and by parents at home. Babies had their activity monitored by actimeters Micro-Mini-Motionlogger® – Ambulatory Monitoring Inc. (Ardsley, New York, USA), attached to their right ankle with a soft sleeve bandage and data were recorded every minute. Wrist skin temperature was recorded every 10 min with a thermistor with a data logger, Thermochron iButton® – Maxim Dallas (Dallas, Texas, USA), attached to the left wrist with Micropore 3 M®.

Activity, sleep/wake behavior (according to data extracted from diaries), feeding and wrist temperature data were grouped in 10 min blocks and divided in time series of seven days each, according to postmenstrual age, for each subject. Actograms-like graphics were constructed for all variables. The rhythmic analysis was performed using the chronobiological statistic package "El Temps" [20].

The rhythmic patterns of all variables were evaluated with the Lomb Scargle algorithm [21], scanning for all significant periodic signals in the range from 1 h to 28 h. This is a periodogram technique which fits sinusoidal curves of different periods to time series, resulting in a Periodogram value (LSP), representing the relative contribution of each periodicity for the overall oscillations, with a significance level (p < 0,05). Activity and wrist temperature acrophases were investigated through the Cosinor algorithm [22], a method based on the least square fitting of a specified period of cosine function to data series. Acrophase stabilities were tested with the Rayleigh method, an index of interdaily stability, which provides an r vector, with a length proportional to the degree of phase homogeneity for the analyzed period [12,23,24].

Wilcoxon paired test was used to compare the daily rhythm potency of activity, wrist temperature and sleep/wake behavior inside the NICU and immediately after being delivered home, using the LSP as dependent variable and the environment (NICU or home) as independent variable. The Spearman correlation test was performed to evaluate the relation of postconceptional age and the potency of the circadian rhythm for activity, wrist temperature and sleep/wake.

3. Results

Anthropometrical measurements, gestational age, Apgar score and delivery mode for all newborns are presented in Table 1.

Wrist temperature presented clearly a dominant circadian rhythm for 7 subjects in their last week inside the NICU (the other 3 subjects showed a 12 h rhythm as the most robust), while activity/rest cycle presented a circadian rhythm for 5 subjects, but dominant for only 3 babies; a 3 h rhythm (the 180 min component of Lomb Scargle
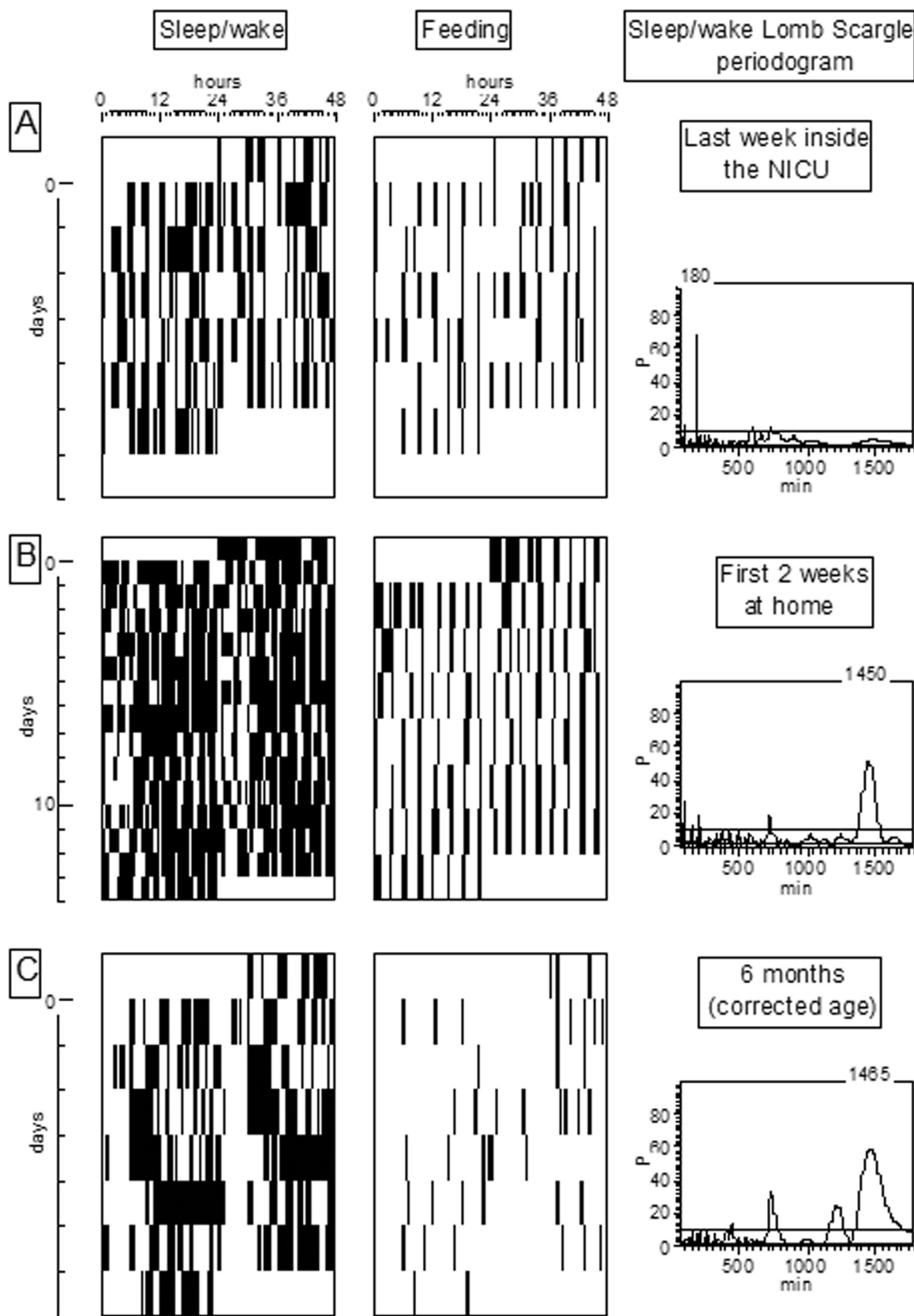
Table 1
Subject´s gestational and anthropometrical data.

ID	Sex	GA (weeks)	Delivery mode	Weight at birth (g)	Apgar 5th min	PM when delivered home (weeks)	Subjects followed until 6 months (PCA)
1	F	39 3/7	V	3450	10	41	X
2	M	34 2/7	V	2705	9	37 1/7	X
3	M	32 3/7	V	1310	9	38 3/7	
4	M	33 6/7	V	2012	9	35	X
5	M	32 6/7	CS	1625	7	39 6/7	X
6	F	30	V	1235	9	38	X
7	M	31 5/7	V	1830	9	40 4/7	
8	M	30 3/7	V	1330	7	37	
9	F	28 3/7	CS	1110	9	42 3/7	X
10	M	28	V	920	8	40 6/7	

F: female; M: male; GA: gestational age at birth; V: vaginal delivery, CS: cesarean section; PM: postmenstrual age. Subject 1 (in grey) was the only term newborn.

Fig. 1. Actogram of a representative preterm newborn (subject 2) for sleep/wake (1st column) and feeding (2nd column) behavior in the last week inside the NICU (line A), first 2 weeks after being delivered home (line B) and with 6 months of corrected age (line C). The third column represents the Lomb Scargle graphic and exhibits the significant periods of sleep/wake cycle in each represented moment (significant values of LSP range from 10 to 500).
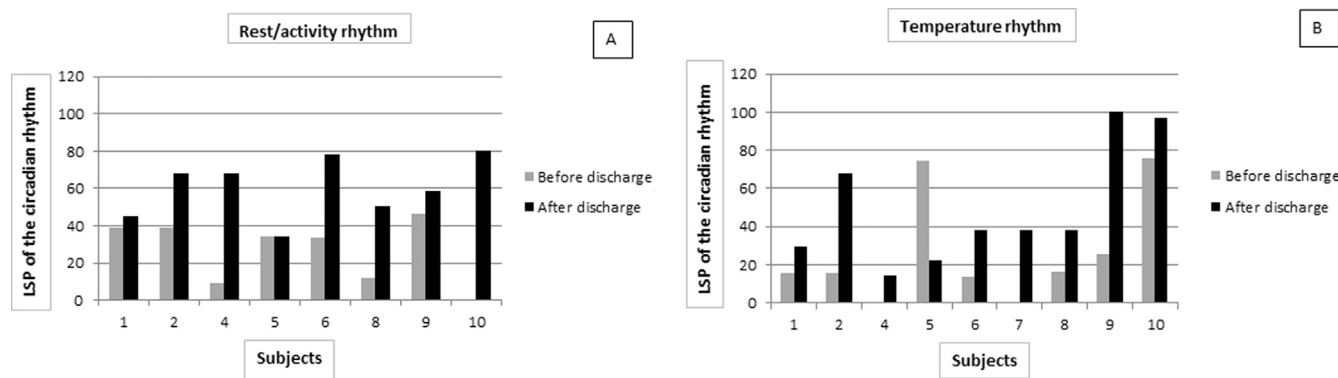
Fig. 2. Circadian rhythm before and after discharge to home. Represents the Lomb Scargle P value (LSP) of the circadian rhythm of activity/rest cycle (graph A) and wrist temperature (graph B) during the week before and the week immediately after being discharged home for all subjects (significant values of LSP range from 10 to 500).

periodogram represented in Fig. 1) in activity was present for 5 subjects. On the other hand, sleep/wake and feeding behavior had almost exclusive 3 h rhythms for almost all subjects, as shown in Fig. 1 line A, for a representative subject (3 babies showed also a circadian rhythm for sleep/wake cycle and none for feeding) and the 3 h rhythm of feeding behavior had the highest values of LSP. Acrophases of the circadian component occurred mainly from 0800 to 1400 h for activity and from 2100 to 0400 h for wrist temperature, but no grouping tendency was identified through the Rayleigh method.

A sudden increase in the circadian rhythm contribution, represented by an increase in LSP, was observed for activity/rest cycle (p < 0.05), and for temperature rhythm (p=0.027) in transition to home, excluding subject 5, as presented in Fig. 2. The circadian rhythm of wrist temperature and activity/rest cycle evolves with an oscillating pattern along the following months (Fig. 3).

We found a positive correlation between the increase in postmenstrual age after being delivered home and the LSP of the circadian rhythm (p < 0.05) for both wrist temperature (R=0.3) and activity/rest cycle (R=0.35).

A circadian rhythm emerges for sleep/wake behavior in the first week after transition to home for babies who did not present this rhythm so far (Fig. 1, line B) and a fast increase in LSP can be observed for subjects who already presented a circadian rhythm in their last week inside the NICU. Simultaneously, the 3 h rhythm, which was dominant inside the NICU, vanishes after the transition to home. Other ultradian periodicities and mainly a 12 h rhythm may be observed in the first two weeks at home.

Feeding behavior shows an ultradian rhythm, ranging from 2 to 4 h, according to medical prescription inside the NICU. After being discharged home all subjects were submitted to free feeding times with both breastfeeding complemented with artificial formulae. The rhythmic pattern in feeding behavior decreases suddenly after transi-

tion to home and 5 of the 6 babies followed until 6 months of corrected age, evolved with an arrhythmic feeding pattern along weeks (Fig. 1, line C). All five subjects had developed this arrhythmic pattern until the third month of life.

4. Discussion

Our study was characterized by the simultaneous recording of wrist temperature, activity/rest, sleep/wake and feeding parameters in newborns, most of them preterm babies, in their last week inside the NICU, in the first week of adaptation at home and six subjects were followed longitudinally along the following six months, allowing description of rhythmic patterns of several variables and their relation to different environments.

Sleep/wake and activity/rest cycle are strongly influenced by feeding schedule and staff interventions inside the NICU. This masking effect is suggested by the presence of a 3 h rhythm, which coincides with feeding timing in this environment and the sudden emergence and increase of a daily sleep/wake rhythm immediately after babies were delivered home. The sudden change of the rhythmic pattern from one week to another, without transients, suggests that the endogenous rhythms of newborns had been masked but were not entrained by the feeding schedule inside the NICU.

Although a 3 h rhythm was not detected for wrist temperature inside the NICU, we could also see an increase of the circadian component for babies in their first week at home, suggesting possibly a masking effect decreasing the potency of the daily rhythm inside the NICU.

Glotzbach at al. [17] had already demonstrated ultradian rhythms of activity, heart rate and temperature and had proposed association with feeding schedule and staff intervention inside the NICU. Once these environmental parameters had not been recorded systematically,
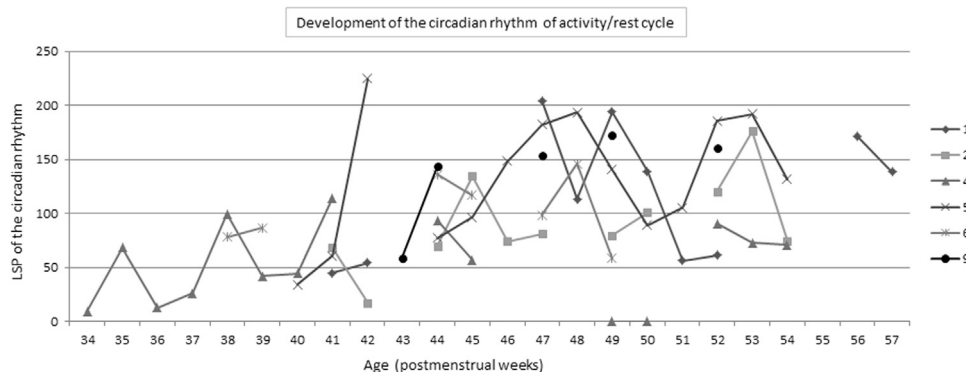

Fig. 3. Activity/rest circadian rhythm represented by LSP along 6 months (significant values of LSP range from 10 to 500).

this relation lacked stronger evidence. Our study provides simultaneous recording of these variables, strongly indicating masking among these parameters.

On the other hand, we had already demonstrated a dominant a circadian pattern in wrist temperature rhythm inside the NICU, which seemed not to be affected by environment ultradian rhythms [13]. This result is in agreement with previous studies [3,4], which demonstrated a circadian pattern for rectal and skin temperature for preterm newborns after 29 weeks of postconceptional age.

Temperature rhythm is an important phase marker for chronobiological studies, however, the use of core body temperature rhythm in longitudinal researches has always been limited by restrictions for continuous use of data recording devices, such as rectal probes. Wrist temperature, recorded by a thermistor with a data logger has emerged as an interesting alternative, since it exhibits a robust circadian rhythm in normal living conditions and also inside the laboratory [11–13,23,25]. Sarabia et al. [23] demonstrated that wrist temperature profile seems to be a mirror-like image of oral temperature, with its maximum values preceding the minimum value of oral temperature by 1 h. Zornoza-Moreno et al. [12] monitored ankle temperature with the same device, also used in our study, but they identified a significant circadian rhythm only after 3 months of age in term babies; we believe that this result is related to differences in ankle and wrist temperature pattern, being the last one more robust for chronobiological research, as also suggested by studies in adults [11,23].

Along the following months at home, we identified a positive relation of postmenstrual age and the increase of the circadian rhythm component of activity and temperature, which is in agreement with previous studies [10,26]. However, the increase in the circadian component of both temperature and activity/rest cycle evolved with an oscillating pattern, with moments of increase and decrease in its potency, a pattern that had already been described since the first classical studies for sleep/wake and skin temperature rhythms [27,28]. Interestingly, in our study, a progressive increase in the contribution of the circadian rhythm along the first 6 months of life was more evident for sleep/wake behavior recorded with diaries than for the other parameters.

Guyer et al. [10] argue in favor of an earlier emergence of a circadian pattern of activity in preterm newborns compared to term babies, but once we had only one term newborn, comparisons were not possible in our study. Wulff et al. [7], studying term infants with actimeters, found an increase in the contribution of the circadian component in relation to ultradian periodicities with a predominant circadian pattern since 7–9 weeks of age. Jenni et al. [29] described an increase of the 24 h component along the first 6 months of life according to a saturating exponential function. Although both authors studied term infants while most of our subjects were preterm neonates, even our term baby had an oscillating non-linear development of the circadian rhythm of activity. Thus, the development of activity/rest cycle in our study is similar to the one described by previous authors for the sleep/wake rhythm.

Feeding behavior, on the other hand, evolves with an arrhythmic pattern, a finding not previously described. Although feeding behavior is mentioned in some chronobiological studies, usually data results are not described. So et al. report a decrease in night-time feeds while the number of daytime feeds remains the same along the first year of life, but a rhythmic analysis is not performed. Lohr and Siegmund [30], as well as Korte et al. [6], argue for independent developmental courses for sleep/wake and feeding behavior, an idea also supported by our data. Newborns present a reflex suckling behavior that is posteriorly substituted by voluntary suckling. This voluntary suckling can be observed after the transition from the second to the third month of life [31], which coincides with the moment of emergence of the arrhythmic pattern of feeding. We suggest that reflex suckling presents an ultradian pattern, while voluntary behavior is arrhythmic.

5. Conclusions

We conclude that the environment of neonatal intensive care units has a masking effect on biological rhythms expression in newborns, inducing an ultradian pattern. This masking effect is immediately overcome when babies are delivered home and our subjects followed the same developmental pattern previously described in literature. We suggest that the masking effect of the NICU environment doesn't change the long term development of circadian rhythms in newborns.

We also described for the first time the arrhythmic pattern of feeding behavior along development and we argue in favor of independent developmental courses for feeding and sleep/wake behavior.

Acknowledgements

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