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Very preterm infants show earlier emergence of 24-hour sleep–wake rhythms compared to term infants

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ABSTRACT

Background: Previous studies show contradictory results about the emergence of 24-h rhythms and the influence of external time cues on sleep–wake behavior in preterm compared to term infants.
Aims: To examine whether very preterm infants (<32 weeks of gestational age) differ in their emergence of the 24-h sleep–wake rhythm at 5, 11 and 25 weeks corrected age compared to term infants and whether cycled light conditions during neonatal intermediate care affects postnatal 24-h sleep–wake rhythms in preterm infants.
Study design: Prospective cohort study with nested interventional trial.
Subjects: 34 preterm and 14 control term infants were studied. During neonatal hospitalization, preterm infants were randomly assigned to cycled light [7 am–7 pm lights on, 7 pm–7 am lights off, $n = 17$] or dim light condition [lights off whenever the child is asleep, $n = 17$].
Outcome measures: Sleep and activity behavior recorded by parental diary and actigraphy at 5, 11 and 25 weeks corrected age.
Results: Sleep at nighttime and the longest consolidated sleep period between 12 pm-6 am was longer (mixed model analysis, factor group: $p = 0.02$, resp. $p = 0.01$) and activity at nighttime was lower ($p = 0.005$) at all ages in preterm compared to term infants. Cycled light exposed preterm infants showed the longest nighttime sleep duration. Dim light exposed preterm infants were the least active.
Conclusions: Preterm infants show an earlier emergence of the 24-h sleep–wake rhythm compared to term infants. Thus, the length of exposure to external time cues such as light may be important for the maturation of infant sleep–wake rhythms.
Trial registry number: This trial has been registered at www.clinicaltrials.gov (identifier NCT01513226).

1. Introduction

In a term newborn, sleep is evenly distributed across day and night [1]. At around 6 weeks of age, 24-h sleep–wake rhythms can be detected in most infants represented by a shift of sleep periods into the nighttime and wake periods into daytime [1,2]. According to the two-process model of sleep regulation [3], the 24-h sleep–wake rhythm is dependent on the circadian rhythm (also named process C), generated by the internal clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN is already functioning at birth [4] and matures further in the following months under the influence of external zeitgebers such as light [5] and social time cues [6].

The two-process model consists of a second process – called process S – representing sleep homeostasis. According to the homeostatic regulation of sleep, sleep pressure increases during the waking period and decreases during sleep. Sleep homeostasis shows substantial maturational changes in the first months of life and still matures further on until middle childhood [7,8]. This developmental process can be seen by the consolidation of sleep period during the night and wake periods during the day occurring around the second month of life [1,7,9,10] and by the continuous decrease of total sleep duration over infancy [8]. It is suggested that the development of this process cannot be influenced by external factors, but reflects the maturation of intrinsic bioregulatory processes [8,11].

The time of emergence of a 24-h sleep–wake rhythm in *preterm* infants is still debated and is thought to develop either after a certain length of exposure to time cues [1,12–15] or after reaching a certain

Abbreviations: CA, post term corrected age; CL, cycled lighting; DL, dim lighting; GA, gestational age; LSP, longest consolidated sleep period between 12 pm an 6 am; PT, preterm; SCN, suprachiasmatic nucleus of the hypothalamus; SES, socioeconomic status; T, term.

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post term age needed for the development of intrinsic brain functions [2,16–19].

Previous studies either compared term infants to preterm infants without considering lighting condition [14,19,20], or preterm infants cared for in different lighting conditions were compared without a term control group [12,13,15,18,21–23]. The latter showed a positive effect of cycled light condition on the development of daily sleep rhythms, growth factors or state regulation such as activity measures [23], weight gain [15,21], sleep measures [13] or crying pattern [12]. As a result, cycled light regime is recommended by the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) as the standard care condition on neonatal wards since 1997 [24].

Shimada et al. [19] compared term and preterm infants and reported the occurrence of a 24-h sleep–wake rhythm at a mean age of 44.8 weeks gestational age in both groups. These authors concluded that the infant's innate biological clock needs to mature first until it is responsive to external time cues. We note, however, that the possibility of an earlier entrainment in preterm infants by cycled light during neonatal care was not addressed; preterm infants in this study were exposed to constant bright light. In contrast, Mc Millen et al. [14] found evidence that the length of exposure to environmental time cues (light–dark cycle and single caregiver) is essential. These authors showed that preterm infants exposed to environmental time cues after discharge (slightly before term equivalent age) entrained after identical time of exposure (preterm: 9.8 $\pm$ 2.2 wk, term 8.7 $\pm$ 2.7 wk), but reached entrainment at an earlier chronological age than term infants (preterm: 47.0 $\pm$ 2.2 wk, term: 48.9 $\pm$ 2.7 wk, $p < 0.05$). Also in this study preterm infants were cared for in constant bright light during neonatal hospitalization. It is important to consider that preterm infants cared for in a neonatal nursery are always exposed to various external factors influencing the development of a 24-h sleep wake rhythm. Hence, multiple caregivers and medical interventions at varying time points of the day may impair the development of a 24-h sleep–wake rhythm, while other factors such as regular infant care schedules like feeding on a 4- or 6 h interval or cycled light exposure can act as Zeitgeber for the developing rhythm [11].

With the assumption that a 24-h sleep–wake rhythm also emerges after birth in preterm infants and depends on the length of exposure to time cues, we combined both aspects and hypothesized that 1) preterm infants show an earlier emergence of a 24-h sleep–wake rhythm than term infants and 2) that this effect is more pronounced in preterm infants cared for in cycled light condition compared to dim light during their neonatal stay.

2. Methods

2.1. Population

Very preterm infants ($\leq$32 0/7 weeks gestational age) were recruited at the Clinic Neonatology of the University Hospital Zurich, Switzerland. Term infants were recruited from the postnatal wards of the University Hospital Zurich. Primary exclusion criteria were major cerebral injuries (intraventricular hemorrhage grade III [25], periventricular leukomalacia or venous infarction [26]), retinopathy of prematurity grade III and IV, congenital malformations, small for gestational age at birth, prenatal infections or intrauterine drug exposure. Secondary exclusion criteria were participation in another clinical trial or parental language difficulties. 41 preterm infants (PT) and 22 term infants (T) were recruited. Later, 7 preterm and 8 term infants had to be excluded due to various reasons: drop out after first recording (reasons: too time consuming, stressful time, moving abroad; PT n = 2, T n = 4), incomplete diary (PT n = 4, T n = 4), and excessive crying behavior (PT n = 1). Thus, a total of 34 preterm (girls = 17) and 14 term infants (girls = 7) were included for the final analysis.

The ethics committee of the University Children's Hospital Zurich and the Canton Zurich approved the study protocol. The study was performed according to the Declaration of Helsinki. Written informed consent was obtained from all parents.

2.2. Procedures during hospitalization for preterm infants and lighting conditions

Preterm infants were part of an interventional trial (see for details [12]) and randomly assigned to either cycled light condition (CL) or dim light condition (DL). CL condition was characterized by lights on between 7 AM and 7 PM and off between 7 PM and 7 AM. Every bed was equipped with curtains, which were taken away during daytime periods and overhead room lights were turned on. For the DL condition – the standard condition on the ward – bed curtains were closed whenever the child was asleep or quiet and opened only for feeding periods every 3 or 4 h for a few minutes (for infants in an incubator, green quilts were used for cover).

Enrollment took place after the transfer from intensive to intermediate care, requiring stable condition of the child and available space in the intermediate care rooms, and lasted until discharge. Randomization was performed depending on availability of free space at the time of transfer or – in case of available space in both conditions – according to a table of random numbers (for more detailed information see [12]).

2.3. Procedures at home for preterm and term infants

At 5 and 11 weeks' post term corrected age (CA), parents had to fill in the Baby's Day Diary [27], coding for sleep within 5 minute intervals over 3 consecutive days. Furthermore, actigraphs were placed on the infant's ankle, fixed with a soft sleeve bandage and recorded over 10 consecutive days. At 25 weeks' CA, parents had to fill in a sleep diary, coding for sleep within 15-minute intervals over 10 consecutive days together with the actigraph recording. For the first recording parents were personally instructed at a face-to-face home visit. The following recordings were preceded by a telephone contact and data and actigraphs were sent by mail (for further details see [12]).

In addition, the type of feeding (fully breastfed, partially breastfed, bottle fed; nominal scaled) was asked at 5 and 11 weeks CA during a telephone interview with the parents.

2.4. Sleeping variables

Based on the sleep diary, mean total sleep duration per 24 h, mean sleep duration during the day (7 am–7 pm) and at nighttime (7 pm–7 am) and sleep day/night ratio were computed using a custom made Matlab routine (The MathWorks, Inc. Natick, MA). Furthermore, the longest consolidated sleep period at night (LSP) was calculated and averaged over the number of recorded days. LSP was defined as the longest sleep period within the hours between midnight and 6 AM and expressed in percentage of these 6 h (see [20]).

2.5. Activity variables

Activity scores were measured by the Actiwatch-mini® (Cambridge Neurotechnology, Cambridge, UK) at 5 weeks CA and the Actiwatch-AW4® at 11 and 25 weeks CA in 30 seconds epochs. Mean activity counts per 24 h ("total activity"), for the night (7 pm-7 am) and the daytime (7 am-7 pm) as well as the activity day/night ratio were calculated [23]. Days were excluded when data were missing for longer than two consecutive hours. Mean number of days of recording at 5, 11 and 25 weeks respectively were for preterm infants 8.7 d, 8.5 d and 8.4 d and for term infants 9.1 d, 9.2 d and 8.4 d.