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Estimating circadian rhythm across infancy: Development of intra- and interdaily stability, and relative amplitude

Déborah Amélie Maret
Université de Fribourg – Suisse

Corresponding author : Madame Déborah Amélie Maret. Département de Psychologie. Université de Fribourg, Rue P.-A.-de-Faucigny 2 CH-1700 Fribourg. Suisse. Email : deborah.maret@unifr.ch

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Résumé

Le lien entre qualité, durée et rythmicité du sommeil chez les enfants et maturation du cerveau a été plusieurs fois relevé. Il existe cependant un manque de consensus concernant les variables et la méthodologie utilisées pour différentes tranches d'âge. Nous avons conduit une étude longitudinale avec 136 enfants en bonne santé, âgés de 3, 6 et 12 mois, dans le but de refléter la maturation du rythme de veille-sommeil. Nous avons estimé la rythmicité circadienne avec des données actimétriques (Intradaily Variability, Interdaily Stability, Relative Amplitude et Circadian Function Index). Les résultats confirment des effets significatifs pour tous les âges. L'Intradaily Variability diminue avec l'âge, reflétant un sommeil continuellement moins fragmenté et moins de transitions veille—sommeil. L'Interdaily Stability et la Relative Amplitude augmentent avec l'âge, confirmant une synchronisation graduelle avec le cycle jour-nuit. Plus globalement, le Circadian Function Index regroupant ces trois variables et nous informant quant à la maturation du rythme veille-sommeil, a révélé que le rythme circadien s'améliore entre 3 et 12 mois. Ces résultats soulignent l'évolution du sommeil durant la première année de vie et offrent de nouvelles données normatives pour le rythme de veille-sommeil. Ces données pourront être utilisées pour détecter des développements anormaux du sommeil et ainsi permettre une intervention pour améliorer le développement.

Mots clés : actimétrie, bébés, sommeil, rythme circadien, cycle veille-sommeil

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Abstract

Previous studies have emphasized the connection of sleep quality, length, and rhythmicity during infancy with brain maturation. There is, however, a lack of consensus regarding variables and methodology in relation to the diverse age periods. We thus conducted a longitudinal study with 136 healthy infants at ages 3, 6, and 12 months, aiming to capture maturation of the sleep-wake rhythm. We estimated circadian rhythmicity derived from actimetric data (Intradaily Variability, Interdaily Stability, Relative Amplitude and Circadian Function Index). Results confirm significant effects across ages. Intradaily Variability decreased with age, reflecting continuously less fragmented sleep and sleep-wake transitions. Interdaily Stability and Relative Amplitude increased with age, reflecting the gradual approaching to synchronization with the day-night cycle. More globally, the Circadian Function Index, averaging those three variables to indicate the maturation of the sleep-wake rhythm, illustrated that infants' circadian status improves significantly from 3 to 12 months. These findings highlight the first year of life as a period of great changes in sleep-wake patterns and offer new normative data regarding estimates of circadian rhythm in infancy. Such maturation curves are fundamental to detect atypical development of sleep rhythm. Furthermore, early detection allows intervention to improve negative development outcomes.

Keywords: actimetry, infants, sleep, circadian rhythm, sleep-wake rhythm

1. INTRODUCTION

Infants' sleep can be a source of sizable concern for parents, to such an extent that poor children's sleep has been reported to be the best predictor of parents' dissatisfaction (Sepa et al., 2004). Its variability and unpredictability can cause considerable struggle for parents and many believe that their infant's sleep is abnormal (Cook et al., 2020). Researchers have thus tried to grasp sleep characteristics to evaluate their impact on neural development. Two main sleep stages exist. The first one is characterized by rapid eye movements (REM sleep) and is usually associated with high-frequency brain activity. The second one does not contain rapid eye movements (non-REM sleep) and

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corresponds to a quieter state of rest and lower-frequency brain activity (Arditi-Babchuk et al., 2009). In infants, the sleep states are not as clearly distinguished, and two similar states have been outlined. Quiet sleep is comparable to non-REM sleep, while active sleep is described as an immature form of REM sleep, with a higher intensity and more phasic neuronal activity (Mirmiran et al., 2003). Whereas adults sleep is mainly composed of non-REM sleep, term-born infants spend more than 50% of their sleep in active sleep (Heraghty et al., 2008; Tarullo et al., 2011). However, by 6 months old, the proportion of active sleep is already reduced to 25%, approaching adult-like levels, while the proportion of quiet sleep increases (Arditi-Babchuk et al., 2009; Louis et al., 1997; Mirmiran et al., 2003).

Simultaneously, the human brain develops rapidly prenatally and during the first 3 months of life (Heraghty et al., 2008). Increased active sleep has thus been hypothesized to crucially support the development of learning, memory integration and consolidation that the infants experience across their first months and years (Bathory & Tomopoulos, 2017; Tarullo et al., 2011). By building a fundament of the normative patterns of sleep rhythm development, we can pinpoint perturbations in these maturational dynamics, and likely alleviate, with timely action, secondary problems of impaired daytime functioning, behavioral outcomes, central nervous system disorders or even mental diseases (Byars et al., 2012; Shimada et al., 1999; Tham et al., 2017).

Right after birth, newborns' sleep broadly lacks a sense of day-night periodicity. Only around 10-12 weeks a diurnal sleep rhythm starts to evolve, with a decrease in daytime sleep and gradual increase in nighttime sleep (Iwata et al., 2017). Slowly, the infants' sleep-wake rhythm blends with the regular light-dark 24h cycle, supported by environmental cues, such as light, maternal feeding etc. (Jenni et al., 2006). The circadian rhythm is an endogenous rhythm close to a 24h cycle. This type of rhythmicity is not only intertwined with behavioral sleep-wake patterns, but also reflected in multiple processes of human physiology, including body temperature, blood pressure, hormone secretion, or digestive secretions (Minors & Waterhouse, 2013). It is mainly regulated by the suprachiasmatic nuclei (SCN) of the hypothalamus, which acts as a biological clock that also receives contextual information from environmental elements such as light. The circadian rhythm is thus largely independent of sleep pressure.

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This supports sleeping at night, where daylight is lacking, and vice versa, staying awake during daytime (Borbély, 1982; Rivkees, 2003). Considering that infants are usually tested in their natural and unrestrained environment due to ethical reasons, we cannot access an infant's pure, non-entrained endogenous circadian rhythm. Yet, indirect estimates of circadian rhythmicity can still be extracted from actigraphy (i.e., a method to analyze rest-activity cycles) but it must be remembered that they are not direct indicators of a circadian rhythm (Van Someren, 2011).

The circadian rhythm and homeostatic processes together regulate sleep, as described by Borbély (1982) in the two process model of sleep regulation. Sleep homeostasis is dependent on the duration of previous sleep or wake. Sleep pressure increases while being awake and a neuronal recovery process takes place during sleep, reflected in a decrease of synaptic load (Tononi & Cirelli, 2012). Therefore, understanding circadian rhythmicity is key to apprehend sleep disorders, many of which underlie impaired circadian functioning or the dissociation between homeostatic and circadian regulation.

Even though studies have offered descriptive data on infant sleep, the lack of methodological consensus regarding the ages and variables measured, as well as the small sample sizes available have often hampered a continuous and rigorous description of sleep variables. To remedy this situation, we wanted to explore the longitudinal development of circadian rhythmicity across the first year of life. Our first objective was to evaluate the transition of how infants' short and numerous sleep periods evolve into longer and fewer sleeping attempts. Secondly, we intended to explore the day-to-day sleep-wake pattern stability at ages of 3, 6 and 12 months. Thirdly, our goal was to capture how infant sleep-wake patterns evolve to biphasic day-night cycle, characterized by fewer nocturnal awakenings and daytime sleep. Finally, we intended to observe the overall evolution of circadian rhythmicity of infants.

1.1. Theoretical and empirical background

To measure circadian rhythms in infants, various methods are used, depending on which rhythms are being studied. For example, melatonin and cortisol levels can be observed via salivary analyses, and temperature can be measured through

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tympanic or rectal thermometers (de Weerth et al., 2003; McGraw et al., 1999). Actimetry allows us to measure participants' movements throughout the day and night with an unobtrusive watch. This tool gives access to long periods of recordings in a natural environment. Accelerometry is then analyzed in terms of activity and inactivity states, which can be further analyzed as wakefulness and sleep states (Ancoli-Israel et al., 2003).

Although actimetry, compared to other methods, assesses less parameters and relies solely on movement, its validity has been largely proven and measures from actimetry correlate with others(Ancoli-Israel et al., 2003; Sadeh, 2011). It has been recognized as a valuable tool to detect nighttime awakenings, which usually remain unnoticed with subjective methods such as diaries. Its ability to identify day-to-day changes in sleep patterns is especially useful when investigating sleep across the first months of life, to capture rhythm variation and stability in at-home settings (Ancoli-Israel et al., 2003). Limitations of actimetry are a general lack of standardization among researchers in methodology, data processing and analysis (Berger et al., 2008), which can yet be addressed with precise methodology reporting (Schoch et al., 2021). Another limitation is the possible loss of data due to technological issues, and false interpretations of movements. For example, babies being rocked during their sleep might be misinterpreted as wakefulness. Missing data or false interpretation, can be accounted for with a combination of other assessment methods (Sadeh, 2011), i.e. daily logs (Tikotzky & Sadeh, 2001). In this study, we will thus combine actimetry, an objective measure, with sleep diaries, a subjective measure.

Several articles provide parametric and non-parametric analysis approaches for actigraphy recordings (Gonçalves et al., 2015; Portaluppi et al., 2010; Van Someren, 2011; Zornoza-Moreno et al., 2011). The parametric cosinor method is widely used to characterize sleep-wake rhythms. It entails the comparison of actigraphic data with a cosine curve, allowing the evaluation of cosine function parameters in relation to the mathematical model fit (Gonçalves et al., 2015). However, using the cosinor method implies making assumptions about the shape of the rhythm, and because the rhythm is biological, it does not typically follow a sinusoidal waveform (Luik et al., 2013). Moreover, it does not allow to observe sleep fragmentation, such as daytime sleep or night-time awakenings (Gonçalves et al., 2015). Non-parametric application is thus

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recommended to avoid assumptions about waveform shape and to analyze values not normally distributed.

The most commonly used non-parametric variables are Interdaily Stability (IS), Intradaily Variability (IV) and Relative Amplitude (RA) (Gonçalves et al., 2015; Lovos et al., 2021; Rock et al., 2014; Thomas et al., 2015; Van Someren et al., 1999). Witting et al. (1990) first introduced these variables by degrading the circadian rest-activity rhythm in patients with Alzheimer's disease. These variables are also promising to capture infants' sleep pattern development (Thomas et al., 2015; Zornoza-Moreno et al., 2011). The first variable, IS, shows day-to-day stability in sleep-wake pattern, and is a reliable indicator of how the sleep-wake rhythm matches with the 24h light-dark cycle. A high IS thus reveals a good synchronization with the 24-h rhythm and with Zeitgebers (Van Someren, 2011). IS could reflect infants' SCN development and the ability to align sleep-wake behavior with light and social cues. It also allows to observe the stability of this synchronization across days. Another interesting aspect in the development of infants' sleep is the decrease of transitions between sleep and wake states. This is expressed by the variable IV, which primarily quantifies rhythm fragmentation. In newborns, fragmentation is high due to numerous sleep periods. As their rhythm matures, IV lowers with fewer but longer sleep periods (Thomas et al., 2015). This variable is an indicator of endogenous disturbances or immaturity of the circadian rhythm (Ortiz-Tudela et al., 2010). Finally, the RA is composed of two indices that contain information about the period with the most activity and with the lowest amount of activity. The RA indicates the amplitude between daytime activity and nighttime rest, and hence approximates the robustness of circadian rhythm (Fernandez et al., 2017; Rock et al., 2014). When infant's rhythm stabilizes, less activity prevails at night and more during the day, i.e., reflected by increased RA. This variable was proposed to be influenced by light exposure and the information interpretation of the SCN to synchronize with a day-night cycle (Gonçalves et al., 2015).

IS, IV and RA are thus promising indicators for sleep-wake rhythm development. They have been used considerably to assess the status of the circadian rhythmicity in various populations, i.e., patients with Alzheimer's disease, diabetes, Down Syndrome, bipolar disorder, and also infants (Lovos et al., 2021; Rock et al., 2014; Van Someren et al., 1999; Witting et al., 1990; Zornoza-Moreno et al., 2011, 2013). For a summarized understanding

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of the circadian sleep-wake rhythm, Ortiz-Tudela (2010) created the Circadian Function Index (CFI), which averages IS, IV and RA after normalization (Bandín et al., 2014). Reliability of this index was examined with recordings of sleep activity, skin wrist temperature, motor activity, and body position in healthy adults. CFI was confirmed to be very sensitive for assessing circadian robustness, and was implemented in different populations (Bandín et al., 2014; Rodriguez-Morilla et al., 2019; Zornoza-Moreno et al., 2011, 2013). Despite being an integrated variable (combining actimetry, temperature and body position), CFI can also be calculated on these variables individually and thus suits actigraphic analysis. Taken together, CFI, IS, IV and RA are suitable descriptive tools to estimate the development of circadian rhythmicity across infancy.

There is abundant literature about the emergence of the circadian rhythm, be it regarding the sleep-wake cycle, body temperature or other measures showing circadian rhythmicity. Concerning the sleep-wake patterns, findings on the emergence of the rhythm differ from one study to another, which could partially be explained by differences in methodology. Some researchers found first signs of circadian sleep-wake rhythms already at 3 weeks old (Nishihara et al., 2002), and others only found significant results at 12 weeks (Kikuchi et al., 2020), or even 6 months (Zornoza-Moreno et al., 2011).

Nishihara and colleagues (2002) recorded actigraphy in 11 infants and their mothers during the 3rd, 6th, 9th and 12th weeks. With autocorrelation to determine if a 24-h peak could be detected in infants' sleep, they noticed a statistically significant, but weak, 24-h peak on the autocorrelogram already at 3 weeks in all infants. A clear increase in the amplitude of the 24-h peak prevailed from the 6th to the 12th week, illustrating that despite early signs of circadian rhythmicity at 3 weeks, it continued to develop and stabilize until 12 weeks old.

More recently, Kikuchi and her collaborators (2020) assessed the impact of feeding method on circadian sleep-wake rhythm in 24 infants and their mothers. Actigraphy during the3rd, 6th, and 12th week were analyzed with autocorrelograms and revealed an increase in activity during the daytime between the 6th and 12th week, and 24-h peaks already at 6 weeks in breastfed infants. However, recordings from the mixed-fed infants did not show a clear peak before the 12th week, suggesting that both groups have a circadian sleep-wake

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rhythm by 12 weeks (i.e., 3 months), yet breastfed infants show signs of circadian rhythmicity already earlier.

Zornoza-Moreno et al. (2011) assessed 10 infants' skin temperature and actimetric activity at 15 days, 1, 3 and 6 months old, for 3 consecutive days. Unlike the two studies discussed above, they analyzed IS, IV and RA. RA already increased at 3 months old, IV lowered from 3 to 6 months old, while IS increased. CFI appeared statistically significant only by age 6 months. Overall, their results revealed the apparition of both skin temperature and motor activity circadian rhythms at age 3 months for most babies, and most developmental changes happened between 3 and 6 months.

In summary, the emergence of the circadian rhythm happens between 3 weeks and 6 months old, can depend on factors such as feeding mode, and the computational approach applied.

1.2. Research question

As infants age, their sleep becomes less fragmented but shorter, and matures into a circadian rhythm (Glickman, 2010; Iwata et al., 2017; Jenni et al., 2006). This can be shown with non-parametrical variables, such as IS, IV, RA and CFI, which are particularly specific and useful to estimate circadian rhythm (Ortiz-Tudela et al., 2010; Rodriguez-Morilla et al., 2019; Zornoza-Moreno et al., 2011). IV significantly decreases with age in infants, while RA, IS, and CFI variables were shown to increase between 3 and 6 months old (Zornoza-Moreno et al., 2011). The characteristics of infant sleep thus evolves greatly during the first 6 months of life, (Burnham et al., 2002; Tikotzky & Sadeh, 2009). However, conflicting results report primary rhythm maturation from 6 months onwards (Louis et al., 1997; Sadeh et al., 2009) - which yet remains to be reported with IS, IV, RA and CFI. Moreover, there is a need for larger samples to confirm these analyses.(Zornoza-Moreno et al., 2011).

We thus conducted a longitudinal study at 3,6 and 12 months old to assess the evolution of the circadian rhythmicity in infants, expressed by the IS, IV, RA and CFI index. 136 infants were tested, representing a large sample ideal for normative values and generalization of findings.

We first hypothesized that the fragmentation of the rhythm decreases with age, and that IV gradually decreases from age 3 to 12 months. Secondly, we investigated the stability of the

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sleep-wake rhythm in a supposedly stable 24h day-night cycle and expected IS to increase as the rhythm stabilizes. Thirdly, we hypothesized increasing age relates to an increase in daytime wakefulness and nighttime sleep. This feature is portrayed by RA, which we expect to increase between 3, 6 and 12 months. Finally, the combination of these three variables in CFI is proposed as indicator of the circadian status, and will stabilize with increasing age, and thus demonstrate a higher score at 12 months compared to 6 and 3 months.

2. METHODS

2.1. Sample

136 infants (61 females) were recruited and longitudinally tested at 3, 6 months and 12 months old, with a 2 week-window prior and after the targeted age. Parents and caregivers were reached through daycares, pediatricians, maternity wards, social media, personal contacts, and flyer distribution in public places such as stores, community centers and universities. Infants were in good general health and born via vaginal birth, within 37 to 43 weeks of gestation. They also had to exceed 50% of their nutrient intake in breast milk at enrollment. The project has been approved by the cantonal ethics committee (BASEC 2016-00730), respecting the Helsinki Declaration. Parents were informed prior to the enrollment and gave a written consent. For more detailed information about the inclusion and exclusion criteria, see Schoch et al. (2022).

2.2. Measurements and procedure

At all three ages, ankle actigraphy was measured for 10 continuous days by attaching a sensor to the infant's left ankle. This was done by attaching it with a Tyvek paper strap, or with socks that had a pocket sewn onto their sides, where the sensors could be slid into. The actrigraphs were GENEActiv movement sensors (Activinsights Ltd., Kimbolton, UK, 43 × 40 × 13 mm, MEMS sensor, 16 g, 30 Hz Frequency recording resolution), with a sensitivity of +/- 8 g range and a resolution of 3.9 mg. During the assessment, parents and caregivers completed a 24-h diary, in order to keep track of the removal of the sensor during activities such as bathing or swimming. They also had to write down with a 15-minute resolution, the sleep and external movement activity of their infant (rocking, stroller, baby sling etc), feeding times, bedtimes and crying episodes that were longer than 15 minutes.

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In addition, they were also sent online questionnaires about the family background, general health, and demographics. As a compensation, they received small gifts (bodysuits, hats, etc).

2.3. Sleep analysis

Actigraphy data was processed according to in-laboratory standard protocols (Schoch et al., 2020). For statistical analyses, the version 3.6.3 of R and 2.4.1106 of RStudio were used. To generate the IS, IV and RA, we used the package "nparACT" (Blume et al., 2016), which is based on Van Someren and colleagues' (1999) description of the variables.

IV was calculated by the ratio of the mean squares of the difference between all successive hours and the mean squares around the grand mean. It ranges from 0 being a perfect sinusoidal curve to 2 for Gaussian noise.

$$IV = \frac{n \sum_{i=2}^{n} (x_i - x_{i-1})^2}{(n-1) \sum_{i=1}^{n} (x_i - \bar{x})^2}$$

IS entails the ratio between the variance of the average 24h pattern around the mean and the overall variance. It ranges from 0 (Gaussian noise) to 1 (perfect IS). Perfect score means that the sleep-wake wave repeats exactly across days (Rodriguez-Morilla et al., 2019).

$$IS = \frac{n \sum_{h=1}^{n} (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^{n} (x_i - \bar{x})^2}$$

RA is calculated with two other variables; the period of 10 hours that is the most active (M10) and the period of 5 hours with the least activity (L5). Similar to IS, it ranges from 0 to 1, with 1 representing a better adaptation to the day-night cycle, and thus a better contrast between wakefulness and sleep.

$$RA = \frac{M10 - L5}{M10 + L5}$$

CFI was then calculated by averaging IV, IS and RA. First, they were normalized between 0 and 1, meaning that IV was inverted to match the direction of maturation with IV and IS. CFI also ranges from 0 to 1, with 1 indicating maximal robustness of the circadian rhythm (Rodriguez-Morilla et al., 2019).

$$CFI = \frac{IS + (2 - IV)/2 + RA}{3}$$

Table 1
Results of the repeated-measures ANOVAs for all variables

Variable	DFn	DFd	F	p	ges
IV	2	268	169.75	p<0.001	0.43
IS	2	266	59.84	p<0.001	0.19
RA	2	268	79.09	p<0.001	0.25
CFI	2	266	174.66	p<0.001	0.41

3. RESULTS

Prior to the analysis, Kolmogorov-Smirnov normality tests were performed, to test the

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normality of the distributions. Half of variables reached significance, i.e., supposedly non-normal distribution, but as the sample was constituted of more than 50 participants, there can be a biased tendency of statistical significance to this test. We therefore inspected the boxplots and histograms of variables, and despite some slight asymmetrical distributions and some outliers, we did not notice remarkably non-normal distributions. As analyses of variances are robust tests, we therefore concluded that variables were relatively normally distributed and parametrical tests are suitable. Repeated-measures ANOVAs were performed to compare the effect of the infant's age (3,6 or 12 months old) on sleep variables (IS, IV, RA) and on their global circadian rhythmicity (CFI). Moreover, as Mauchly's sphericity tests confirmed that the assumption of sphericity was respected for all variables, we did not implement Mauchly's correction.

First, a repeated-measures ANOVA evaluated IV at each timepoint, and revealed a significant main effect of the infants age ($F(2, 268) = 169.75$, $p < .05$, $\eta_g^2 = .43$; Table 1). Infants aged 6 months ($M = 1.02$, SD = .16) had a significantly lower IV score than 3-month-olds ($M = 1.17$, SD = .018; Tukey HSD test for multiple comparisons $p < .001$; Figure 1). At 12 months ($M = 0.83$, SD = .14), infants had significant lower IV scores than at 6 months old ($M = 1.02$, SD = .16). Consequently, 12 months of age infants ($M = 0.83$, SD = .14) had significant lower scores than 3-month-olds ($M = 1.17$, SD = .018; Table 2). In other words, this data confirms the expected age-related decrease in IV, reflecting a decrease in rhythm fragmentation.

Next, a repeated-measures ANOVA compared IS of infants at 3, 6 and 12 months old. There was a significant main effect of the age on IS ($F(2, 266) = 59.84$, $p < .05$, $\eta_g^2 = .19$; Table 1). IS scores of infants at 12 months old ($M = 0.60$, SD = .10) were significantly higher than at 3 months ($M = 0.48$, SD = .09; $p < .001$; Tukey's HSD Test; Figure 1). By 12 months, infants also had significantly different IS scores than at 6 months ($M = 0.54$, SD = .09; $p < .0.001$). Finally, 6-month-olds ($M = 0.54$, SD = .09) had significantly higher IS scores than 3-month-olds ($M = 0.48$, SD = .09; $p < .001$). This confirms the expected age-related increase in day-to-day stability, expressed by an increasing IS.

Thirdly, a repeated-measures ANOVA revealed a significant main effect of the infants age on the RA scores ($F(2, 268) = 79.09$, $p < .05$, $\eta_g^2 = .25$; Table 1). RA scores were

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significantly lower in infants at 3 months old (*M* = 0.85, SD = .08), compared to both 6-month- (*M* = 0.91, SD = .05) and 12-month-olds (*M* = 0.93, SD = .04; Tukey's HSD Test; *p*< .05; Figure 1). This data highlights an age-related increase in amplitude between daytime and nighttime activity, i.e., an increasing RA.

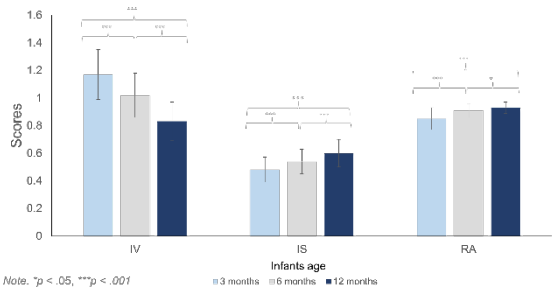


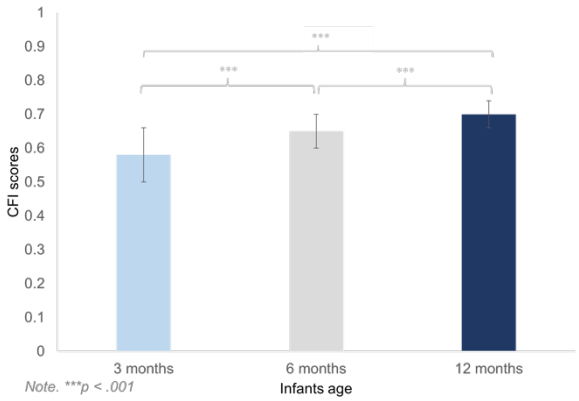
Figure 1

Intradaily Variability, Interdaily Stability and Relative amplitude scores according to the infants' age

Finally, a repeated-measures ANOVA revealed a significant main effect of the infants age on their CFI ($F(2, 266) = 174.66$, $p< .05$, $\eta_g^2 = .41$; Table 1). A significant difference between each age was found ($p< .001$ Tukey's HSD Test). Respectively, 12-month-olds (*M* = 0.70, SD = .05) had significantly higher CFI scores than 6- (*M* = 0.65, SD = .06) and 3-month-olds (*M* = 0.58, SD = .07), and 6-month-old infants had higher scores than 3-month-olds (Figure 2). This data confirms a globally age-related increase in circadian rhythm robustness.

Figure 2

Circadian Function Index scores according to the infants' age



To summarize, results confirm a general tendency across all variables towards a maturation of the sleep-wake rhythm, which is reflected by the IV decreasing with age and IS, RA and CFI increasing between 3 and 12 months old.

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Table 2

Summary of means and standard deviations for all variables and ages

Variable	Infants' age	M	SD
IV			
	3 months	1.17	0.18
	6 months	1.02	0.16
	12 months	0.83	0.14
IS			
	3 months	0.48	0.09
	6 months	0.54	0.09
	12 months	0.60	0.10
RA			
	3 months	0.85	0.08
	6 months	0.91	0.05
	12 months	0.93	0.04
CFI			
	3 months	0.58	0.07
	6 months	0.65	0.06
	12 months	0.70	0.05

4. DISCUSSION

This study explored the development of sleep-wake rhythm during the first year of life by means of longitudinal actimetry assessments in 136 infants ages 3, 6, and 12 months. The specific focus were circadian rhythm estimates: IV, IS and RA, reflecting properties of endogenous rhythm. A global index was computed that regroups these variables in a single score, representative of a person's circadian status, i.e., the Circadian Function Index. We hypothesized that IV would become significantly lower at each timepoint, as a reflection of a less fragmented sleep. IS was expected to be statistically higher at each time of measurement, indicating that the sleep-wake rhythm is increasingly coordinated with the day-night cycle. Then, as infant sleep becomes more nocturnal with age, we hypothesized that RA would also increase statistically from 3 to 6 and from 6 to 12 months. Finally, we expected the CFI to increase across timepoints.

Results demonstrate that, as hypothesized, all variables experienced significant main effects and that the differences were significant between all ages measured. In other words, maturation is clearly visible across 3, 6 and 12 months on all circadian rhythm estimates, as evidenced in a gradual and consistent increase of the day-to-day stability of sleep-wake pattern (IS), an increase in amplitude of oscillation between daytime and nighttime activity (RA) and an increasing global circadian status (CFI). There was a gradual decrease of the fragmentation of their sleep rhythm (IV), reflecting less transitions between states of sleep and wake, and therefore longer and more nighttime sleep periods.

First, we found that between 3 and 6 months old, infants' IS, RA and CFI scores increased and that IV scores decreased, which confirmed our hypothesis. This largely corroborates findings from Zornoza-Moreno et al. (2011) on infants at 3 and 6 months of age. Their actigraphic data showed that the IV, IS and CFI changed significantly between 3 and

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6 months old. They had, however, not found any significant differences between RA scores at 3 and 6 months old, whereas in our study, these results were also significant. This may be explained by their smaller sample (n=10, i.e., 7% of our sample size) that possibly prevented to capture this variation. Their use of 3-day recordings might also explain the discrepancy, as reliable sleep recordings were proposed to include a minimum of 7 recording days (Acebo et al., 1999). Our results based on a large cohort allowed to explore the natural variation in sleep-wake rhythms between 3 and 6 months, including many characteristics, yet dynamic transitions. This provides a normative reference for parents and practicians to track healthy development. Moreover, the variables used in this study (IV, IS, RA, CFI) are great tools to assess sleep-wake patterns and allow, with only few variables, accurate estimation of circadian rhythmicity easily comparable across studies. It would thus be interesting to extend this movement-based biobank across the lifespan in healthy and clinical populations.

Secondly, our results propose that changes in circadian rhythm continue to mature beyond 6 months and that IV, IS, RA and CFI scores change between 6 and 12 months. This hypothesis had been put forward by several researchers suggesting that the sleep-wake cycle continues its development after 6 months old (Louis et al., 1997; Sadeh et al., 2009; Tikotzky & Sadeh, 2009). Based on parental reports Tikotzky et Sadeh (2009) reported a decrease in nighttime awakening across the first year and a further decrease in napping (i.e. daytime sleeping) from 6 to 12 months. Our results confirm this observation by the effect of RA scores between 6 and 12 months old. Our results, however disagree with Dias et al. (2018), who report that consistent changes in sleep-wake behavior, such as the length of sleep periods, were mainly happening during the first 6 months of life. Our results also differ from Schers' (2012) findings that showed no significant change in circadian aspects of infant sleep between 8 and 14 months. This could either suggest that most of the changes occur between 6 and 8 months followed by a stabilization, or that, as they have mentioned in the limitations, their small sample might have affected the results (n=34). Our large-cohort-results offer new normative data on healthy infants' circadian rhythm estimates from 3 to 12 months and thereby extend knowledge in relation to previous data collected at older age. In a study with 8- to 12-year-old infants, IV and RA (IV: M = 0.86, SD = 0.06 / RA: M = 0.85, SD = 0.44) were comparable to those at 12 months in our

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data. We can thus suspect that the sleep-wake parameters slow down their development after 12 months old. Forthcoming studies could test this hypothesis.

Our study has the limitation that, first, by assessing ages 3, 6 and 12 months we possibly neglected changes occurring between the 6th and 12th months. It is personnel- and resource-consuming to assess infants longitudinally with multiple measurement timepoints. Further studies could, nevertheless, target the changes occurring specifically between 6 and 12 months. Then, our measure is not a direct measure of circadian rhythm. For a direct assessment, zeitgebers such as social cues and light conditions need to be controlled for (Jenni et al., 2006). Relatedly, prior findings revealed that breastmilk might be a stronger zeitgeber than formula milk (Kikuchi et al., 2020), which in turn could impact infants sleep-wake rhythmicity. In our study, we only included infants who received breastmilk for more than 50% of their food intake at 3 months, the values we presented must thus be taken with caution, as they might vary depending on infants' food intake.

In conclusion, our findings capture the development of circadian estimates based on actigraphic sleep-wake patterns during the first year of life. The large sample highlights that infants' circadian sleep-wake rhythmicity evolves considerably between 3 and 12 months. Infants become more synchronized with the 24h day-night cycle, have less fragmented sleep with less naps and instead more nighttime sleep. They wake up less at night and their rhythm becomes increasingly stable across days. This is particularly important, as the quality of sleep during the first year of life is a great predictor of later health outcomes, cognition, and behavior (Byars et al., 2012; Cook et al., 2020; Shimada et al., 1999; Tham et al., 2017). Normative data about the sleep-wake rhythm for this age period are essential for studying how sleep variables relate to neurological development. Circadian rhythm norms allow to identify evolution of infants' sleep-wake patterns in health and disease and support practitioners in detecting and diagnosing potential early risk factors before they affect the infants' development.

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