Reference Values for Amplitude-Integrated Electroencephalographic Activity in Preterm Infants Younger Than 30 Weeks' Gestational Age

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ABSTRACT. *Objective.* **To prospectively investigate the development of amplitude-integrated electroencephalographic (aEEG) activity during the first 2 weeks of life in neurologically normal and clinically stable preterm infants <30 weeks' gestational age (GA).**

Patients and Methods. **Infants with a GA of <30 weeks admitted to the neonatal intensive care unit of the Vienna University Children's Hospital (Vienna, Austria) were studied prospectively by using aEEG and cranial ultrasound. Clinically stable infants without clinical or sonographic evidence of neurologic abnormalities were eligible for inclusion in the reference group. The distribution of 3 background aEEG activity patterns (discontinuous low-voltage, discontinuous high-voltage, and continuous), presence of sleep-wake cycles, and number of bursts per hour in the reference group were determined by visual analysis.**

Results. **Seventy-five infants (median GA: 27 weeks; range: 23–29 weeks) were eligible for inclusion in the reference group and had aEEG recordings during the first 2 weeks of life available. Analysis of aEEG background activity showed that with higher GA the relative amount of continuous activity increased while discontinuous patterns decreased. The number of bursts per hour decreased with increasing GA. Cyclical changes in aEEG background activity resembling early sleep-wake cycles were observed in all infants.**

Conclusions. **Normal values for aEEG background activity were determined in preterm infants <30 weeks' GA. Clinically stable and neurologically normal preterm infants exhibit at least 2 different patterns of aEEG activity. There is a correlation between the GA and the relative duration of continuous aEEG activity.** *Pediatrics* **2004;113:e61–e66. URL: http://www.pediatrics.org/cgi/content/full/113/1/e61;** ***amplitude-integrated EEG, aEEG, cerebral function monitor, preterm infant, reference values, sleep-wake cycles.***

ABBREVIATIONS. EEG, electroencephalography; aEEG, amplitude-integrated EEG; CFM, cerebral function monitor; IVH, intraventricular hemorrhage; GA, gestational age.

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Advances in neonatal intensive care during the last decades have led to an increased survival rate of extremely low birth weight infants. However, neurologic and developmental disability is still common among survivors.[1] Prevention of brain injury in these patients has become one of the main goals of modern neonatology. Continuous monitoring of neonatal brain function may aid in the identification of risk factors and patients at increased risk for neurologic morbidity. Early recognition and modification of potentially harmful environmental factors may prevent secondary brain injury.

Conventional electroencephalography (EEG) is one of the most useful tools for intermittent and continuous assessment of brain function and prediction of neurologic outcome in term infants and children.[2–4] However, conventional EEG has limitations in its application for extremely low birth weight infants. Registration and interpretation of conventional EEG in this age group are difficult because of the electrical interferences on the neonatal intensive care unit, the large volume of data generated during a longer recording, and the need for 24-hour availability of a skilled examiner experienced in EEG of preterm infants. Further, data on normal EEG patterns in extremely premature infants are still limited.[5,6]

Recently, amplitude-integrated EEG (aEEG) provided by the cerebral function monitor (CFM),[7] a single-channel, time-compressed aEEG monitor, has gained widespread popularity as an alternative to conventional EEG monitoring in neonates. aEEG circumvents most of the problems of conventional EEG in this age group by generation of a compressed curve allowing continuous point-of-care monitoring for hours and a relative ease of application and interpretation.

Two studies have shown a good agreement of aEEG findings with those of conventional EEG in term infants.[8,9] aEEG has further been shown to be of value in the assessment of infants with hypoxic-ischemic encephalopathy,[10–12] seizures,[13–15] and intraventricular hemorrhage (IVH).[16]

However, before embarking on larger trials using aEEG in extremely low birth weight infants, normal patterns for this age group need to be established. To date, normal values for aEEG activity in preterm and term infants have only been described for patients >30 weeks of gestation.[17,18] Information on aEEG

activity in extremely premature infants is still limited.[19]

Therefore, the objective of this study was to prospectively investigate the development of aEEG activity in preterm infants <30 weeks of gestation. We have already published preliminary results on the occurrence of sleep-wake cycles in 38 preterm infants from this cohort.[20] The present study expands the previous report, because large numbers of patients increased the power of the study, allowing for a more in-depth analysis of the development of aEEG activity in preterm infants. This article details the characteristics, occurrence, and frequency of aEEG patterns in neurologically normal and clinically stable preterm infants <30 weeks of gestation.

PATIENTS AND METHODS

Newborn infants with a gestational age (GA) of <30 weeks admitted to the neonatal intensive care unit at the Vienna University Children's Hospital (Vienna, Austria) were eligible for inclusion in the study. All infants were studied prospectively by using aEEG and cranial ultrasound.

aEEG

aEEG recordings were performed in each infant on a weekly basis until tracings showed a normal pattern according to the data published by Thornberg and Thiringer[18] or until the infant was discharged, transferred, or died. The aEEG was recorded as a single-channel EEG from biparietal surface disk electrodes by using a CFM (CFM 5330, Lectromed Devices Ltd, United Kingdom). The technique of the CFM has been described in detail elsewhere.[7] In brief, the obtained signal is filtered, rectified, smoothed, and amplitude-integrated before it is written out at slow speed (6 cm/hour) at the bedside. The quality of the recording is monitored by continuous impedance tracing. Duration of the recordings was at least 90 minutes. The CFM was calibrated before each recording. Handling or routine nursing care periods were marked on the tracing. The quality of recording was checked at close intervals by the nurse caring for the patient or by one of the investigators.

Cranial Ultrasound

Cranial ultrasound scans were performed on days 1, 3, 5, 7, and 10 of life and then once a week until discharge by using an Acuson (Mountainview, CA) 128XP with a 7.5-MHz transducer. IVH and periventricular leukomalacia were classified according to Volpe[21] and de Vries et al,[22] respectively.

Patients

Recording time and impedance of the aEEG tracing, birth weight, GA at birth, and postnatal age at the time of the recordings, medication, cranial ultrasound findings, and clinical condition were recorded in all patients. Based on clinical history and ultrasound findings, infants were classified as being clinically stable and eligible for inclusion in the reference group if they fulfilled the following conditions: no evidence of IVH or periventricular leukomalacia of any grade on cranial ultrasound; no evidence of asphyxia[12]; no sedation or analgesia <48 hours before aEEG recording; no clinical evidence of seizures; and no cerebral malformations, central nervous system infection, or metabolic disorders.

GA was determined from the date of the mother's last menstrual period and according to antenatal ultrasound scans.

Evaluation of aEEG Tracings

In the reference group, the first aEEG recording obtained during the first 2 weeks of life was evaluated. Tracings were evaluated visually and classified according to a modified version of the method adapted from Hellström-Westas et al[19] and Thornberg and Thiringer.[18] Descriptive analysis of aEEG tracings was done by dividing each trace in 10-minute epochs. These 10-minute epochs were classified into 3 pattern categories as follows (Fig 1):

- Discontinuous low-voltage pattern: tracing with irregular bandwidth and marked variations of amplitude and voltage, minimal amplitude <3 μV, and maximal amplitude between 15 and 30 μV.
- Discontinuous high-voltage pattern: tracing with irregular bandwidth and marked variations of amplitude and voltage, minimal amplitude between 3 and 5 μV, and maximal amplitude between 20 and 40 μV.
- Continuous pattern: tracing with regular bandwidth, without marked variations of amplitude and voltage, minimal amplitude >5 μV, and maximal amplitude between 20 and 40 μV.

This classification is based on visual perception, which can be confirmed by quantitative analysis of minimal and maximal amplitudes. Although there is an overlap concerning maximal amplitudes between the discontinuous low-voltage (15–30 μV) and the discontinuous high-voltage (20–40 μV) patterns, there is a clear distinction concerning minimal amplitudes (<3 μV for the discontinuous low-voltage pattern versus 3 to 5 μV for the discontinuous high-voltage pattern).

Sleep-wake cycles were defined as cyclical sinusoidal variations of both amplitude and continuity of aEEG activity with a minimum epoch duration of 20 minutes.[19,20] Bursts were defined as amplitudes >100 μV.

Statistical Analysis

Infants were divided into 3 groups based on their GA (24–25 weeks [corresponding to 24,0–25,84 weeks], 26–27 weeks [corre-

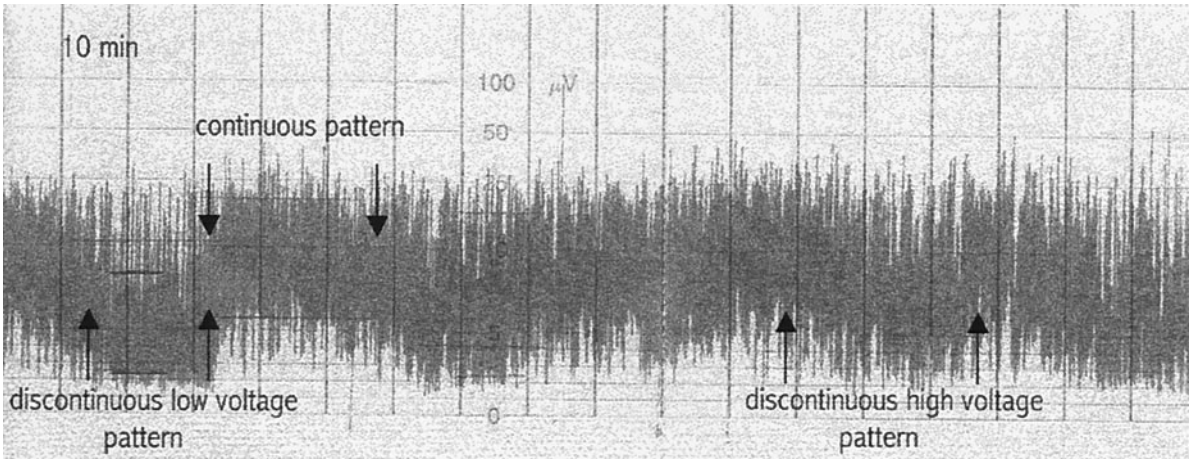

Fig 1. The 3 observed types of aEEG patterns in a patient of 28 + 2 weeks' GA (the period between 2 vertical bars corresponds to 10 minutes).

sponding to 26,0–27,84 weeks), and 28–29 weeks (corresponding to 28,0–29,84 weeks]) for further analysis. The frequency of the occurrence of each of the 3 aEEG patterns in percent was determined as the ratio between the duration of the pattern and the duration of the entire recording. Frequencies of the patterns are given as median, range, and 5th, 25th, 75th, and 95th percentiles.

Correlations between the GA and duration of aEEG patterns and number of bursts per hour, respectively, were examined by using Spearman's rank correlation analysis. *P* values were calculated 2-sided. $P < .05$ was considered significant. Statistical analysis was performed by using SPSS 10.0.1 (SPSS Inc, Chicago, IL).

The study was approved by the local ethics committee. Informed parental consent was obtained in all cases.

RESULTS

During the study period from January 1, 2000 to March 31, 2002, a total of 230 preterm infants <30 weeks of gestation were admitted to the neonatal intensive care unit of Vienna University Children's Hospital. Of the 230 infants, 86 fulfilled the inclusion criteria. In 11 of 86 infants no aEEG tracings during the first week of life were available. The remaining 75 (33%) infants were in the following groups: 24 to 25 weeks' GA (including [weeks + days] 24 + 0 to 25 + 6; $n = 11$); 26 to 27 weeks' GA (including 26 + 0 to 27 + 6; $n = 38$); and 28 to 29 weeks' GA (including 28 + 0 to 29 + 6; $n = 26$). One patient born in the 23rd week of gestation was included in the 24- to 25-week group.

Median GA was 27 weeks (range: 23–29 weeks), and median birth weight was 940 g (range: 491-1646 g). aEEG recordings were performed at a median postnatal age of 5 days (range: 1–14 days). Median duration of the recordings was 3.8 hours (range: 1.5–19.7 hours), and median impedance of the tracing was 3 kO (range: 2–20 kO).

The median duration of the discontinuous low-voltage pattern showed an inverse correlation to GA ($r = -.408$; $P < .001$), decreasing from 55.6% at 24 to 25 weeks to 34.0% at 26 to 27 weeks and 7.1% at 28 to 29 weeks.

The median duration of the continuous pattern increased with increasing GA ($r = .373$; $P < .001$), ranging from 0% at 24 to 25 weeks to 5.9% at 26 to 27 weeks and 16.9% at 28 to 29 weeks.

The duration of the discontinuous high-voltage pattern showed a nonsignificant trend to increase with higher GA.

The median number of bursts per hour showed an inverse correlation to GA ($r = -.364$; $P = .001$) decreasing from 20.4 per hour at 24 to 25 weeks to 14.9 per hour at 26 to 27 weeks and 4.4 per hour at 28 to 29 weeks.

The results are summarized in Table 1.

Cyclical variations of aEEG patterns were observed in all infants of the reference group. At lower GA, the patterns mostly varied between the discontinuous low-voltage and discontinuous high-voltage patterns (Fig 2), whereas at higher GA patterns mostly varied between the discontinuous high-voltage and continuous patterns (Fig 3).

DISCUSSION

The present study describes for the first time the characteristics and developmental changes in aEEG background activity during the first 2 weeks of life in neurologically normal and clinically stable preterm infants <30 weeks' GA. Analysis of aEEG background activity showed that with higher GA the relative amount of continuous activity increased while discontinuous activity decreased. The number of aEEG amplitudes >100 μV decreased with increasing GA. Cyclical changes in aEEG background activity resembling early sleep-wake cycles could be

TABLE 1. Median (Range) and 5th, 25th, 75th, and 95th Percentiles for the Relative Duration of the 3 aEEG Patterns Observed

	*n**	Percentiles						Minimum	Maximum
		50†	5	25	50†	75	95		
Duration of discontinuous low-voltage pattern (%)									
Gestational week 24 or 25	11	55.6	0.0	46.2	55.6	70.0	88.5	0.0	88.5
Gestational week 26 or 27	38	34.0	0.0	3.3	34.0	58.9	79.8	0.0	100.0
Gestational week 28 or 29	26	7.1	0.0	0.0	7.1	32.0	82.6	0.0	88.9
Duration of discontinuous high-voltage pattern (%)									
Gestational week 24 or 25	11	33.3	11.5	17.6	33.3	53.6	100.0	11.5	100.0
Gestational week 26 or 27	38	56.4	5.9	31.4	56.4	64.7	95.9	0.0	100.0
Gestational week 28 or 29	26	51.8	2.9	26.2	51.8	74.2	100.0	0.0	100.0
Duration of continuous pattern (%)									
Gestational week 24 or 25	11	0.0	0.0	0.0	0.0	8.7	14.8	0.0	14.8
Gestational week 26 or 27	38	5.9	0.0	0.0	5.9	21.3	58.6	0.0	64.3
Gestational week 28 or 29	26	16.9	0.0	0.0	16.9	66.9	76.9	0.0	76.9
Bursts/hour									
Gestational week 24 or 25	11	20.4	3.9	9.0	20.4	32.1	45.0	3.9	45.0
Gestational week 26 or 27	38	14.9	0.2	5.2	14.9	25.4	50.2	0.0	52.4
Gestational week 28 or 29	26	4.4	0.0	0.8	4.4	16.6	66.1	0.0	74.6
Impedance									
Gestational week 24 or 25	11	1.0	0.0	0.0	1.0	4.0	7.0	0.0	7.0
Gestational week 26 or 27	38	2.0	0.0	0.0	2.0	3.0	7.2	0.0	10.0
Gestational week 28 or 29	26	4.5	0.0	2.0	4.5	6.0	18.3	0.0	20.0

* Number of patients with first recording in first 2 weeks of life.
†Percentile 50 is equal to the median.

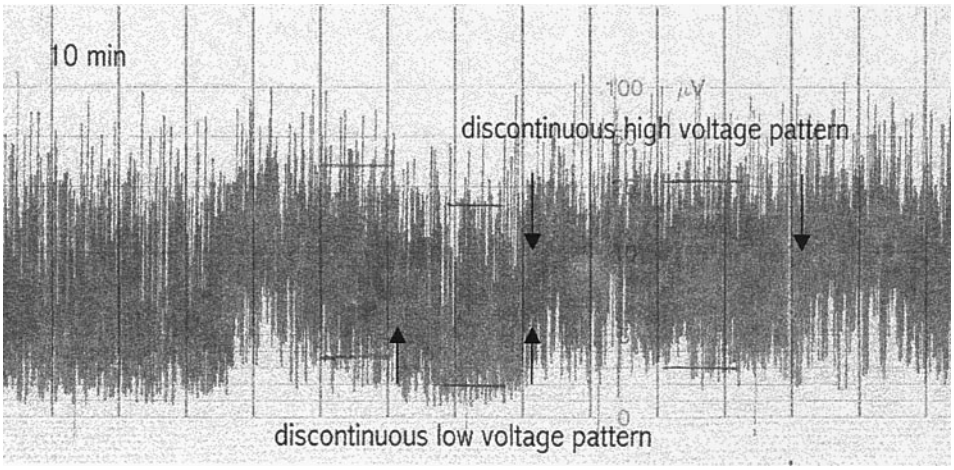

Fig 2. Cyclical rhythmical variations as a change between the discontinuous low-voltage and discontinuous high-voltage patterns in a patient of 26 + 0 weeks' GA (the period between 2 vertical bars corresponds to 10 minutes).

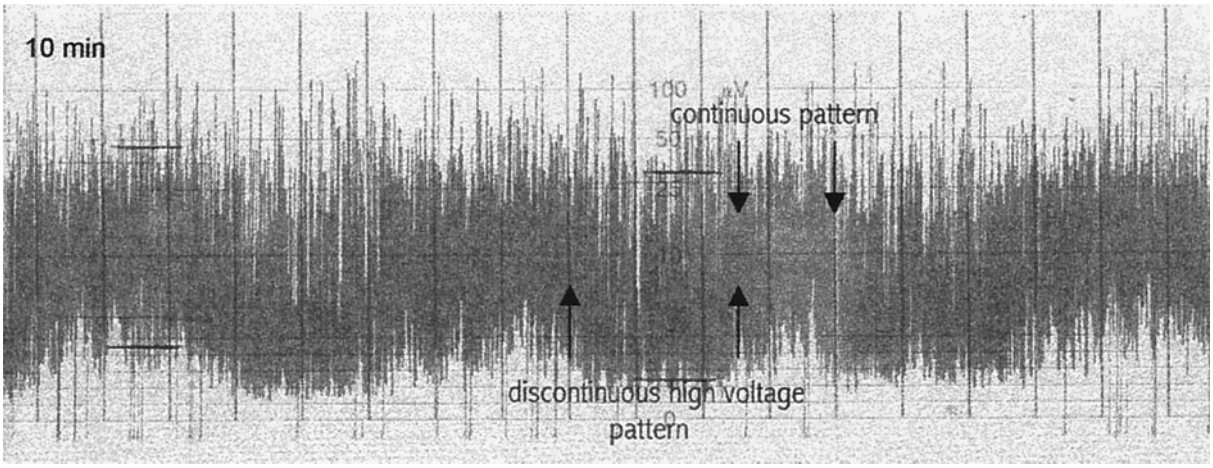

Fig 3. Cyclical rhythmic variations as a change between the discontinuous high-voltage and continuous patterns in a patient of 29 + 5 weeks' GA (the period between 2 vertical bars corresponds to 10 minutes).

observed in all preterm infants during the first 2 weeks of life.

To date, only 3 studies have investigated aEEG activity in preterm infants. Thornberg and Thiringer[18] studied healthy preterm infants between 30 and 36 weeks' GA. They described a broader, discontinuous pattern and a more narrow, continuous pattern of aEGG activity in 30- to 31-week-old infants. These patterns correspond well to the continuous and discontinuous high-voltage patterns found in the more mature infants in the present study (Fig 3). Hellstrom-Westas et al[19] studied aEEG activity in extremely low birth weight infants between 26 and 33 weeks' GA during the first week of life. A more recent study by the same group described the use of aEEG for prediction of outcome in preterm infants with large IVHs.[16] In contrast to findings in the current study, "burst suppression" was the prevailing pattern in the vast majority of infants. Only a small number of infants had brief episodes of intermixed continuous activity. However, most infants in these studies were severely ill, required ventilation at the time of the recording, and had received phenobarbitone, which may have caused increased aEEG discontinuity.[23] By contrast, the infants in the current study were neurologically normal and clinically stable at the time of the recording and had not received any sedative medication. Therefore, the results of the current study are most reliable.

aEEG background activity in preterm infants commonly is classified into continuous and discontinuous patterns.[16,19] However, based on our experience with aEEG in very preterm infants,[20] we determined that there are 2 discernible discontinuous aEEG patterns in most preterm infants: one pattern that resembles a more immature form of discontinuity (frequently labeled burst suppression) with lower minimum amplitudes (<3 μV) and higher maximum amplitudes; and one pattern that resembles a more mature form of discontinuity with higher minimum amplitudes (between 3 and 5 μV) and higher maximum amplitudes. In the current study, we therefore decided to divide the discontinuous pattern further into 2 called the "discontinuous low-voltage" (which shows a peak at 24–25 weeks' GA) and "discontinuous high-voltage" (which shows a peak at 26–27 weeks' GA) patterns (Figs 1 and 2).

In keeping with the results from the present study, other investigators using conventional EEG in preterm infants found that with increasing GA continu-

ous background activity increased while discontinuous activity decreased.[6,24,25] Similarly, the interburst interval, a surrogate measure of EEG discontinuity, was reported to decrease as GA increases.[5,6,24,25] Interestingly, in the present study, periods of continuous aEEG activity were found in preterm infants as early as 23 weeks of gestation. Hayakawa et al,[6] using 8-channel conventional EEG, also found brief episodes of continuous activity as early as 23 weeks' GA. Connell et al[25] found brief periods of continuous activity at 26 weeks' GA. Other authors did not find continuous activity at these early GAs.[5,26] However, this discrepancy may be explained by differences in the study population. Further, most of the infants in our study received caffeine citrate for treatment of apnea. Possibly, the central arousing effects of caffeine led to an increase of continuous activity in the infants.

Cyclical variations of aEEG background activity could be detected in even the most premature infants in our study. These variations may be interpreted as early sleep states.[19,20] Similar variations of aEEG activity were found in 2 other studies using aEEG and clinical observation. The authors referred to these patterns as "sleep-wake cycles."[19,27] The concept of sleep states in the very premature infant is controversial. Earlier studies suggested that organized sleep states do not appear before 32 weeks of gestation.[28,29] However, possibly because of improvements in neonatal intensive care in the last decades, more recent studies have described rudimentary sleep states in extremely premature infants.[5,30] Intact sleep organization is a prognostic factor in preterm infants.[31,32] Thus, the presence of cyclical variations of aEEG activity may be useful for prediction of outcome in preterm infants.[19] In that context, it is of interest that only a few of the infants with large IVH in the study by Hellstrom-Westas et al had sleep-wake cycles.[16]

The possibility exists that the cyclical variations of aEEG activity found in the present study were caused by changes in environmental factors during the recording and do not represent changes in state. However, because impedance remained unchanged during the recording, technical artifacts can largely be excluded. The fact that the aEEG changes were also observed between routine nursing care rounds when the infants were not disturbed makes reactivity to handling also unlikely.[19] We therefore hypothesize that the cyclical variations of aEEG activity found in our cohort of preterm infants are early, rudimentary sleep states that may represent switches between different, possibly thalamocortical and neocortical pattern generators.[33]

The number of burst (amplitudes >100 μV) per hour on aEEG background activity found in the preterm infants in the present study was relatively high compared with term infants. Although in term infants the presence of repeated bursts may indicate seizure activity,[8] our results show that in neurologically normal and clinically stable preterm infants <30 weeks' GA, the presence of bursts seems to be a physiologic phenomenon. This finding is in agreement with conventional EEG studies, in which amplitudes up to 500 μV may still be physiologic.[26]

The present study aimed to establish normal values and patterns for aEEG activity in healthy preterm infants <30 weeks of gestation. However, the criteria of what constitutes a healthy, normal preterm infant are not easy to define, because prematurity itself is a pathology. We defined "healthy" in our study population as the absence of neurologic abnormalities (including sedation and analgesia) at the time of the aEEG recording and a normal cranial ultrasound scan throughout the study period. Therefore, the data of the preterm infants in this study may be considered normal values.

CONCLUSIONS

The characteristics and development of aEEG activity during the first 2 weeks of life were described in this cohort of 75 neurologically normal and clinically stable preterm infants <30 weeks' GA. Percentiles for frequencies of discontinuous and continuous patterns have been established and may be used as reference values for patients at these very early GAs. Cyclical variations of aEEG background activity corresponding to early sleep-wake cycles can be found in preterm infants as early as 23 weeks' GA.

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