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Brain maturation in the first 3 months of life, measured by electroencephalogram: A comparison between preterm and term-born infants

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HIGHLIGHTS

- Topographical analysis of sleep EEG shows qualitative differences in preterm infants in early life.
- A central activation at term age predicts being more mature at 3 months of age.
- In future, automated tools using topographical power distribution may identify infants at risk.

ABSTRACT

Objective: Preterm infants are at risk for altered brain maturation resulting in neurodevelopmental impairments. Topographical analysis of high-density electroencephalogram during sleep matches underlying brain maturation. Using such an EEG mapping approach could identify preterm infants at risk early in life.

Methods: 20 preterm (gestational age < 32 weeks) and 20 term-born infants (gestational age > 37 weeks) were recorded by 18-channel daytime sleep-EEG at term age (GA 40 weeks for preterm and 2–3 days after birth for term infants) and 3 months (corrected age for preterm infants).

Results: Preterm infant's power spectrum at term age is immature, leveling off with term infants at 3 months of age. Topographical distribution of maximal power density however, reveals qualitative differences between the groups until 3 months of age. Preterm infants exhibit more temporal than central activation at term age and more occipital than central activation at 3 months of age. Moreover, being less mature at term age predicts being less mature at 3 months of age.

Conclusion: Topographical analysis of sleep EEG reveals changes in brain maturation between term and preterm infants early in life.

Significance: In future, automated analysis tools using topographical power distribution could help identify preterm infants at risk early in life.

1. Introduction

Preterm-born infants are a major risk group for long-term neurodevelopmental impairments (Johnson et al., 2009) because they are exposed to extrauterine life in an early stage of developmental processes of the brain. Specific insults such as intraventricular haemorrhage lead to severe motor, cognitive, hearing, and visual impairments in 20–30% of very preterm infants (Saigal and Doyle, 2008). Even in the absence of these specific insults, exposure

Abbreviations: AS, active sleep; EEG, electroencephalogram; FDR, false discovery rate; GA, gestational age; GM, general movement; LMI, lateral maturation index; OS, optimality score; PMA, post menstrual age; SD, standard deviation; SMI, sagittal maturation index; TIMP, Test of infant motor performance; QS, quiet sleep.

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to harmful stimuli outside the womb may lead to metabolic injuries during migration, differentiation, and myelination of cortical neurons (Aylward, 2005). These structural alterations can be observed in MRI studies as smaller volumes of cortical grey matter, basal ganglia, corpus callosum, amygdala, and hippocampus and less white-matter volume in frontal areas (for reviews, see Aylward, 2005; Murray et al., 2014). Their impact on later life impairments such as learning difficulties, executive function deficits, short attention span, and emotional and behavioural problems is well known and may affect school performance and social well-being (Larroque et al., 2008; Saigal and Doyle, 2008).

In contrast to the difficulties of processing and collecting MRI images in infants, sleep EEG represents a validated bedside tool. Furthermore, brain maturation has been successfully linked to specific sleep EEG markers such as slow wave activity (EEG spectral power in the 0.75–4.5 Hz frequency band, SWA) (Campbell and Feinberg, 2009; Giedd, 2004; Huttenlocher and Dabholkar, 1997; Jenni and Carskadon, 2004). The topographical progression of SWA from occipital to frontal areas from childhood to adolescence parallels cortical maturation measured by MRI (Buchmann et al., 2011a; Gogtay et al., 2004; Kurth et al., 2010; Shaw et al., 2008; Sowell, 2004). In early childhood (first 4 years) also other frequency ranges show age related changes. For example, Novelli et al. (2016) revealed a posterior-anterior trajectory in theta and alpha activity with age, which statistically most robust results within the 11 Hz frequency range of so called "slow spindles". Studies addressing sleep homeostasis also highlighted theta activity as an early sign of brain maturation (Fattinger et al., 2014; Jenni, 2004). Topographical analysis of sleep EEG could therefore be used to identify infants at risk for deviant brain maturation at an early stage in life.

This study aims to quantify brain maturational changes in sleep EEG at birth and at 3 months of age in both preterm and term-born infants. Furthermore, sleep EEG measures are related to motor development measured by General movements and Test of infant motor performance. We examine whether markers of brain maturation assessed with sleep EEG is delayed or qualitatively different in preterm infants at corrected ages from those of term-born infants, as suggested by MRI studies (Bouyssi-Kobar et al., 2017; Hüppi et al., 1996). Knowledge of normal brain development and possible aberrant development in a risk group is important for both caregivers and timely interventions. We have chosen multi-density EEG recordings during daytime sleep nap because the EEG is a promising bedside tool and has been shown to represent brain maturational changes in later childhood and adolescence (Campbell and Feinberg, 2009; Jenni and Carskadon, 2004; Kurth et al., 2010). In contrast to amplitude-integrated electroencephalography (aEEG, single-channel EEG with integrated amplitude), which is a sensitive tool for early detection of brain injuries (Middel et al., 2018), multi-density EEG has the advantage of enabling topographical analysis of brain activity. Minor differences in brain maturation of preterm infants without overt brain injuries are more likely detected by topographical analysis. We included examination of (mostly) motor development to relate our EEG findings to clinical outcome variables. Both, General movement assessment (GM) and Test of infant motor performance (TIMP) are validated measurements with GM being highly predictive for later motor outcome (Bosanquet et al., 2013) and TIMP revealing numerous items on motor performance elicited by handling, visual or acoustic stimuli with high correlation to later motor performance as tested by the Alberta Infant Motor Scale and the Bayley Scales of Infant Development (Campbell et al., 2002; Campbell and Hedeker, 2001; Kim et al., 2011).

2. Methods

2.1. Population

In total, 20 very preterm infants (gestational age $\leq$ 32 weeks) and 20 term-born infants (gestational age > 37 6/7 weeks, control group) were recruited at the Clinic for Neonatology and Gynaecology of the University Hospital Zurich, Switzerland, between February 2014 and August 2015. Exclusion criteria were major cerebral injuries such as intraventricular haemorrhage grade III (according to Papile et al. (1978)), periventricular leukomalacia or venous infarction (according to Govaert and De Vries (1997)), congenital malformations, small for GA (birth weight less than the third percentile), genetic syndromes, intrauterine drug exposure, intrauterine infections, and parental language difficulties.

2.2. Study procedure and assessments

The Ethics Committee of the Canton of Zurich approved the study protocol. The study was performed according to the Declaration of Helsinki. Parents were personally informed about the study. After written informed consent was received from all parents, medical data relating to childbirth were retrieved from the patients' hospital records and socio-demographic data was collected by interview.

Recording took place at two time points: (1) at term age (40 weeks postmenstrual age (PMA) for preterm and 2–3 days after birth for term infants) and (2) at age 3 months (corrected age for preterm infants: 40 weeks PMA + 3 months). In cases of drop-out after first assessment (3 term infants moved abroad) infants were excluded from analysis and replaced by newly enrolled ones. Infants were recorded in a quiet room. For preterm infants the time points of recording matched their planned neurodevelopmental follow up appointments. All preterm infants had already been discharged and returned to the hospital for examination. Term infants were first recorded before discharge and came in for the appointment at three months.

A clinical and neurodevelopmental examination was performed, including the test of infant motor performance (TIMP) and the assessment of general movements (GMs). Afterwards, an 18-channel EEG cap was placed on the infant's head, and electrodes were filled with electrolyte gel (Electro-Cap International) while the caregiver fed the child. For the nap, the child was placed in a stroller or baby cot (term infants at first recording usually slept in the hospital baby cot), whenever possible a supine sleeping position was sought (prone: term age: 2; 3 months: 3) and the EEG was recorded during one daytime nap between 10:30 and 12:00 noon.

2.3. Socio-demographical data

Socioeconomic status (SES) was calculated as a sum score of 2 standardised 6-point scales of paternal occupation and maternal education ranging from 12 (lowest SES) to 2 (highest SES). This measure has been used in previous studies and is a reliable and valid indicator of SES (Largo et al., 1989; Seitz et al., 2006). Demographic variables were analysed using T-tests.

2.4. Neurodevelopmental tests

2.4.1. General movement (GM) assessment

Each infant was video-recorded from above, lying in a supine position, to assess spontaneous movements during active wakefulness. Two developmental pediatricians, both trained in Prechtl's

GM assessment (Einspieler et al., 2004) analysed the material; one was not familiar with the infant's clinical history or assessments. In cases of disagreement, the raters re-evaluated the recordings until a consensus for a final score was reached.

At term age, scoring included primarily global judgment (normal, normal non-optimal, poor-repertoire, cramped–synchronised, chaotic, hypokinetic) and sequence (variable and complex, broken, monotonous, synchronised, disorganised). Thereafter, a detailed analysis of the limbs followed, including such features as amplitude, speed, space, rotatory components, onset and offset of movements, and tremulous and cramped components. Finally, the optimality score (OS) for general movements was obtained (minimum 5, maximum 42) (Einspieler et al., 2016).

At 3 months of age, general movements were analysed according to the assessment of motor repertoire, containing five subcategories: (1) fidgety movements, (2) age-adequacy of motor repertoire, (3) quality of movement patterns other than fidgety movements, (4) posture, and (5) overall quality of the motor repertoire (Yuge et al., 2011).

Overall, 5 infants at term age had to be excluded from analysis because of failure of video recording (n = 2) or crying (n = 3), so at term age 18 preterm and 17 term infants were used for further analysis. No infants had to be excluded at 3 months of age.

Because GM measurement differed between the ages, Mann-Whitney U-tests for not-normally distributed data were used to detect differences between the groups and the age.

2.4.2. Test of infant motor performance (TIMP)

Infants underwent the TIMP at both ages. The examiner was a developmental pediatrician trained in TIMP and with broad experience in preterm follow-up assessments. Scoring took place during and right after the assessments and was double-checked by viewing video recordings. The TIMP consists of 13 observed items and 28 elicited items; motor reactions are elicited by specific input from the examiner (mostly motor, some visual and acoustic). A total TIMP score, z-score, and age standards (average range: +/− 1 SD, low average: −0.5 to −1 SD, below average: −1 to −2 SD, far below average: > −2 SD) can be calculated. A higher score indicates more mature motor reaction; therefore, maturational changes of the infant can be objectively measured.

At term age, many infants reacted with crying when handling started, making evaluation difficult or impossible. If more than 5 items could not be scored properly, the infant was excluded from further analysis, resulting in 16 preterm and 15 term infants available for TIMP analysis. No infants had to be excluded at 3 months of age.

For TIMP scores at term age and 3 months of life, repeated-measure ANOVAs were used with factor group and age. For age standards, the Chi-square test was applied.

2.5. Electroencephalography (EEG)

Sleep EEG (18-channel) was recorded using NicoletOne (Neuroswiss, VIASYS Healthcare Inc) with a sampling rate of 250 Hz and stored in European data format (EDF). Impedance was held below 10 $k\Omega$. The EEG was bandpass-filtered (0.5–40 Hz) offline and down-sampled to 128 Hz. Artefacts were rejected on a 4 s basis both after visual inspection and if power exceeded a threshold based on a mean power value in the 0.75–4.5 and 20–30 Hz bands (Huber et al., 2000). Poor-quality EEG channels were excluded. Sleep was scored visually according to Anders et al. (1971) and standard guidelines (Grigg-Damberger, 2016) as quiet sleep (QS) or active sleep (AS).

Spectral analysis was performed for all channels (fast Fourier transform routine, Hanning window, 4 s epochs, frequency resolution of 0.25 Hz, frequency range 0–25 Hz). As a first step, average EEG power density over all electrodes in each frequency bin (0.25 Hz) was compared using repeated-measures ANOVAs with factor age and group. Post hoc T-tests were performed, paired for testing between the ages and unpaired for testing between the groups. To correct for multiple comparison, false discovery rate (FDR) was used and p-levels were adjusted.

To assess topographical differences, EEG power for each electrode was normalised to the average power over all electrodes. This was first done over the common frequency bands (data not shown). But because of the immature aspect of power spectrum at term age, common frequency bands seemed to represent an arbitrary division at this early age. Therefore, analysis was redone over each 1 Hz frequency bin, with intent to visualize continuous changes.

To further investigate the topographical location of maximal power in the two groups, left and right electrodes were pooled (frontopolar = Fp1/Fp2, frontal = F3/F4, antero-temporal = T3/T4, central = C3/C4, parietal = P3/P4, postero-temporal = T5/T6, occipital = O1/O2), and the electrode pair of maximal power was identified for each child and each 1 Hz frequency bin. Differences of maximal power distribution between preterm and term infants were analysed using Chi-square tests for term age and 3 months separately.

Earlier studies introduced the occipital-frontal (or posterior-anterior) maturational index, which represents a maturational change of power density moving from occipital to frontal regions of the brain with increasing age (Kurth et al., 2010; Novelli et al., 2016). Accordingly, we aimed to quantify the distribution differences of maximal power density between the groups of preterm and term infants. Therefore, two maturational indices were formed:

1. Term age: lateral (central/temporal) maturation index (LMI), consisting of the mean of power over the (F3F4C3C4P3P4)/(T3T4T5T6) electrodes and
2. 3 months of age: sagittal (central/occipital) maturation index (SMI): C3C4/O1O2, in accordance to the occipital-frontal maturational index used in earlier studies to characterise the posterior-anterior gradient.

Within frequency ranges (low delta 0.75–1.75 Hz, high delta 2–4 Hz, theta 5–9 Hz, sigma 12–18 Hz and beta 20–25 Hz), group differences of preterm and term infants' maturational indices were analysed using Mann-Whitney U-tests. Next, correlation to clinical parameters (GMs and TIMP scores) were analysed using Spearman's rank test (non-normal distribution). Finally, correlation between the central/temporal maturation index and the central/occipital maturation index was calculated to assess whether the activity pattern at term-age is predictive for the activity pattern at 3-months of age.

3. Results

Apart from the parameters used to stratify the groups (i.e., gestational age and birth measures), preterm and term infants only differed in SES; parents of term-born infants were better educated than parents of preterm-born infants. Demographic variables of preterm and term-born infants are presented in Table 1.

GM assessment revealed group differences at term age in total OS, OS lower limb, and sequence; preterm infants scored lower than term infants. More detailed analysis (Supplementary Appendix: Table A1) indicated that the differences were driven by the lower subscores in upper and lower limbs regarding amplitude, space, proximal rotatory components, onset, offset, and more cramped components for lower limbs. Furthermore, differences

Table 1
Demographic variables.

	Preterm (n = 20)[a]	Term (n = 20)[a]	*p*-value[b]
At birth			
GA, weeks	28.9 (2.1)	40.0 (0.9)	<0.01
Birth weight, g	1197 (267)	3528 (409)	<0.01
Birth length, cm	37.8 (3.3)	50.0 (1.8)	<0.01
Head circum., cm	26.8 (2.2)	35.3 (1.4)	<0.01
Apgar, 1 min	4.9 (2.4)	8.1 (0.9)	<0.01
Apgar, 5 min	6.8 (1.9)	8.9 (0.6)	<0.01
Female gender, %	50	35	0.5
SES (total)	4.0 (2.1)	2.3 (0.7)	0.02
First recording			
Weight, g	3573 (386)	3528 (409)	0.72
Length, cm	49.8 (1.9)	50.0 (1.8)	0.77
Head circum., cm	35.9 (1.1)	35.3 (1.4)	0.1
age, GA	40.3 (0.4)	40.3 (0.9)	0.59
Second recording			
Weight, g	5704 (773)	6053 (773)	0.16
Length, cm	59.6 (2.1)	61 (2.5)	0.72
Head circum., cm	40.5 (1.3)	40.5 (1.3)	0.92
age, GA	12.3 (0.4)	12.2 (0.7)	0.79

[a] Mean (standard deviation).
[b] T-test, GA: gestational age.

Table 2a
General movement total scores term age.

	Preterm (n = 18)[a]	Term (n = 17)[a]	*p*-value[b]
OS upper limb	15.1 (3.6)	17.3 (0.8)	0.09
OS lower limb	12.4 (4.2)	16.9 (1.4)	<0.01
OS neck and trunk	3.1 (1.1)	3.8 (0.4)	0.09
OS sequence	1.5 (0.7)	2 (0.0)	0.01
OS total	32.2 (9.1)	40 (2.1)	<0.01

[a] Mean (standard deviation).
[b] Mann-Whitney U, OS: Optimality score.

Table 2b
General movement total scores 3 months.

	Preterm (n = 18)[a]	Term (n = 17)[a]	*p*-value[b]
Fidgety movements	12.0 (0.0)	12.0 (0.0)	1
Repertoire of coexistent mov	3.2 (1.0)	3.2 (1.0)	1
Quality of other mov	4.0 (0.0)	4.0 (0.0)	1
Posture	4.0 (0.0)	4.0 (0.0)	1
Movement character	3.5 (0.9)	3.8 (0.6)	0.22
Motor optimality score	26.7 (1.6)	27.0 (1.4)	0.60

[a] Mean (standard deviation).
[b] Mann-Whitney U.

were statistically more pronounced in the lower limb. No differences between preterm and term-born infants occurred at 3 months of age (Tables 2a and 2b).

For TIMP assessment, repeated-measures ANOVAs revealed a significant age effect representing the expected maturation in motor development, but no group effect or interaction was found (Table 2c). For both GM and TIMP, no correlations (Pearson correlation) were found between the clinical variables and the SES within the two groups.

In a first step we investigated the duration and structure (quantity) of sleep: Overall, the infants slept about 50 minutes at first assessment and about 40 minutes at second assessment. Total sleep duration did not differ between preterm and term infants at term age (50.2 ± 12.1 min, 45 ± SD 13.7 min, $p = 0.21$) or at 3 months of age (40 ± 12.7 min, 40.9 ± 10.2 min, $p = 0.80$). Similarly, AS did not differ between groups at term age (25.2 ± 10.9 and 22.6 ± 12.1 min, $p = 0.48$) or at 3 months (11.3 ± 9.9 and 13.7 ± 7.7 min, $p = .42$) and neither did QS at term age (25 ± 4.9 and 22.4 ± 5.2 min, $p = 0.11$) or at 3 months (29.3 ± 6.4 and 27.9 ± 5.6 min, $p = .49$). Total sleep time decreased with increasing age ($p < 0.001$), mostly due to a decrease in active sleep ($p < 0.001$). Infants at 3 months most often woke up after quiet sleep, skipping active sleep. QS length increased significantly with age ($p < 0.001$). Because of the large number of movement artefacts in active sleep, only quiet sleep was taken into account for further analysis.

In a next step we assessed sleep EEG changes (quality) by performing power spectral analysis: Fig. 1 shows power spectra plotted separately for term age and 3 months of age, illustrating (1) differences between the groups for the two age points (term age and 3 months) and (2) change over age for the two groups (preterm and term infants).

Repeated-measures ANOVAs revealed an age effect in frequency bins up to 15 Hz, no group effect, and a significant interaction of group with age for frequency bins > 5 Hz.

An immature power spectrum at term age developed into the mature form with spindle peak by 3 months of age in both groups. At term age, preterm infants showed lower total power above 5 Hz. Total power increased over almost all frequency bands until 3 months of age. In contrast, term infants' total power increased mainly within the delta and sigma range but decreased over the beta range from term to 3 months of age. Differences in power spectrum between term and preterm infants at term age disappeared by 3 months of age.

To look for frequency dependent topographical differences we visualised power density in each channel and within 1 Hz frequency bins for term age and 3 months and the two groups separately (see Fig. 2).

At term age, in both preterm and term infants, there is a shift from frontal to occipital areas with increasing frequency except for the first two frequency bins in which power maxima are localised over occipital areas. Striking differences in the topographical distribution can be seen between the two groups: preterm infants show a more temporal localisation of maximal power density while term infants show a more central one. Fig. 3 further quantifies these findings, showing the temporal localisation (T3T4 and T5T6) for preterm infants compared to the central localisation and wider range in term infants, with shift from frontal (Fp1Fp2/F3F4) to central (C3C4), parietal (P3P4) and finally occipital (O1O2) areas with increasing frequency.

Finally, the lateral maturation index (LMI) within common frequency ranges (Table 3) summarises these results.

Topographical analysis at 3 months of age shows maximal power over occipital areas for low frequencies while thereafter the maximum lies over central areas in both groups. The shift from occipital to central areas of power maxima starts in lower frequency ranges for term infants than for preterm infants, reaching statistical significance between 5–9 Hz, also quantified in Fig. 3. Moreover, the sagittal maturation index (SMI) in Table 3 reveals a trend for more central distribution in term infants within high delta range.

Combining both preterm and term infants, we looked at correlation between topographical differences measured by the maturational indices and clinical parameters: At term age, the LMI correlated significantly and positively with the clinical parameters of the GM optimality score, including the two subscores for lower limb cramped and optimality score lower limb. The more EEG power in central than in temporal areas, the better was the motor performance at term age (Table 4a). At 3 months, no significant correlations occurred with the SMI in any frequency band or clinical factors.

The LMI at term age correlated positively with the SMI at 3 months within the frequency range of high delta and theta band.

Table 2c
Test of infant motor performance (TIMP) scores term age and 3 months.

	Term age		3 months		Repeated measure ANOVA *p*-value		
	Preterm (n = 16)	Term (n = 15)	Preterm (n = 20)	Term (n = 20)	Age	Group	Age*group
Observed items total score	8.8 (1.2)	9.0 (1.1)	12.0 (0.9)	11.7 (0.9)	<0.01	0.93	0.54
TIMP total score	59.9 (6.6)	59.5 (6.5)	111.4 (7.7)	110.0 (8.9)	<0.01	0.65	0.70
TIMP Z-score	−0.3 (0.4)	−0.3 (0.5)	0.2 (0.4)	0.3 (0.5)	<0.01	0.87	0.87

Therefore, the more central than temporal the power was at term age, the more central than occipital the power was at 3 months of age (Table 4b).

4. Discussion

This study illustrates brain maturational changes from birth to 3 months of age measured by sleep EEG and differentiates between preterm infants and term-born infants by visualising possible qualitative alterations in preterm infants' brain development. Furthermore, topographical differences are correlated to clinical motor development using general movement assessment and test of infant motor performance.

The power spectrum at term age and the clinical features represent the relatively immature newborn brain, as first mentioned by Portmann (1944) and later set into evolutionary context by Prechtl

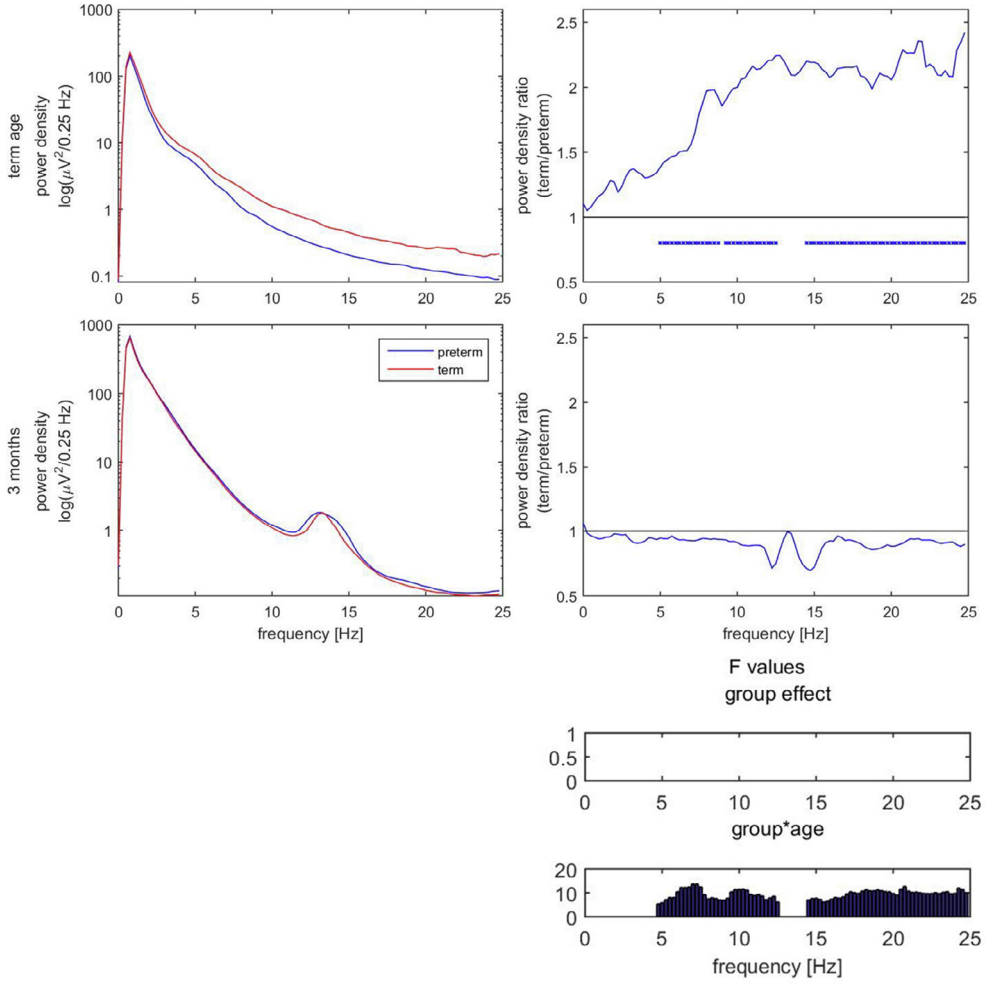

Fig. 1. Power spectrum over all electrodes. (a) Term age and 3 months separately; with differences between preterm and term-born infants: Legend: Average electroencephalogram (EEG) power spectra (18 channel) of the first quiet sleep daytime nap at term age and 3 months of age. Left column: absolute spectra for preterm infants (blue) and term infants (red). Right column: relative spectra (each frequency bin of term infants expressed relative to the corresponding bin in preterm infants). Blue stars (★) indicate frequency bins in which absolute power density in term and preterm infants differed significantly (post hoc T-test, adjusted (FDR) p value < 0.041, performed for bins for which a 2-way repeated measures ANOVA factor "group" or the interaction "group" x "age" was significant (bottom right). Only significant F-values (adjusted (FDR) p value "group" < 0.001 and "group" x "age" < 0.028) are depicted. (b) Preterm infants and term infants separately, with differences between term age and 3 months of age: *Legend:* Average electroencephalogram (EEG) power spectra (18 electrodes) of the first quiet sleep daytime nap for preterm infants and term infants. Left column: absolute spectra for the two ages "term age" (blue) and "3 months" (red). Right column: relative spectra (each frequency bin of the age "3 months" expressed relative to the corresponding bin in the age "term age"). Blue stars (★) indicate frequency bins in which absolute power density at "3 months" and "term age" differed significantly (post hoc T-test, adjusted (FDR) p value < 0.041, performed for bins for which a 2-way repeated measures ANOVA factor "age" or the interaction "group" x "age" was significant (bottom right). Only significant F-values (adjusted (FDR) p value "age" < 0.029 and "group" x "age" < 0.028) are depicted.

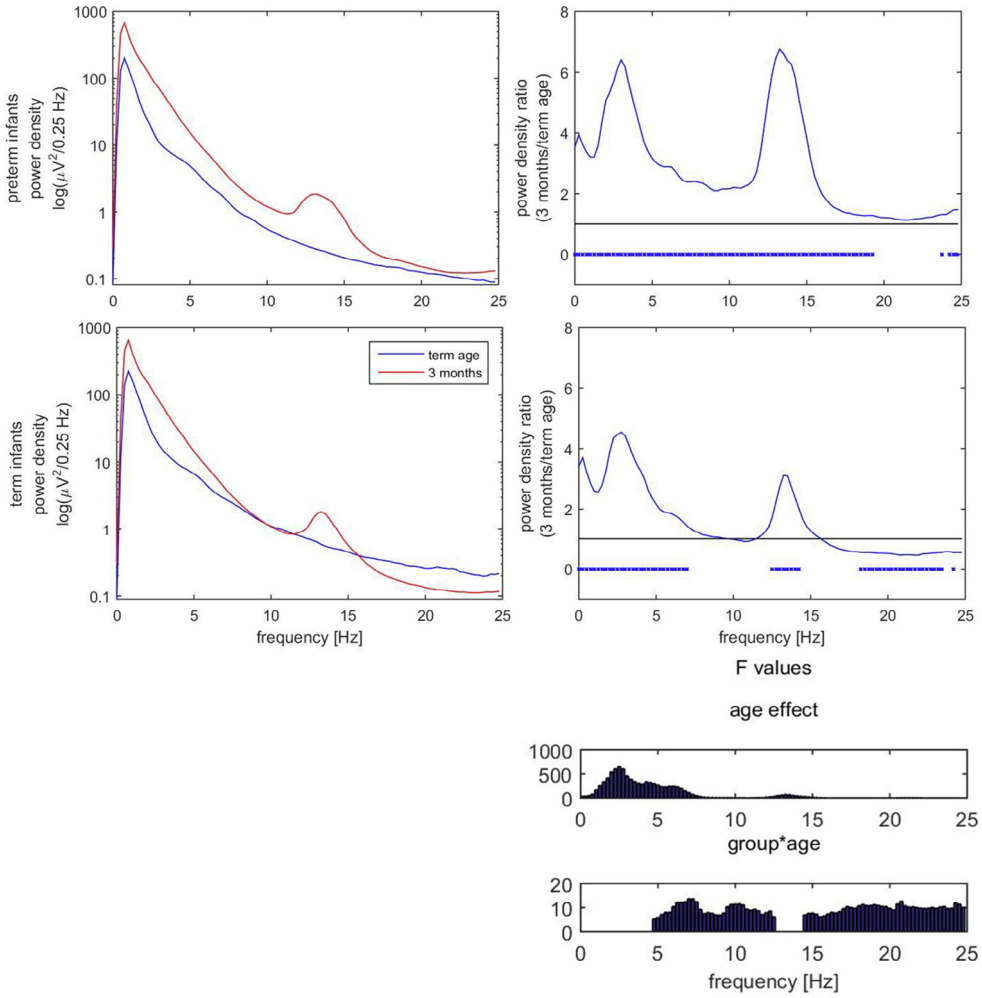

Fig. 1 (*continued*)

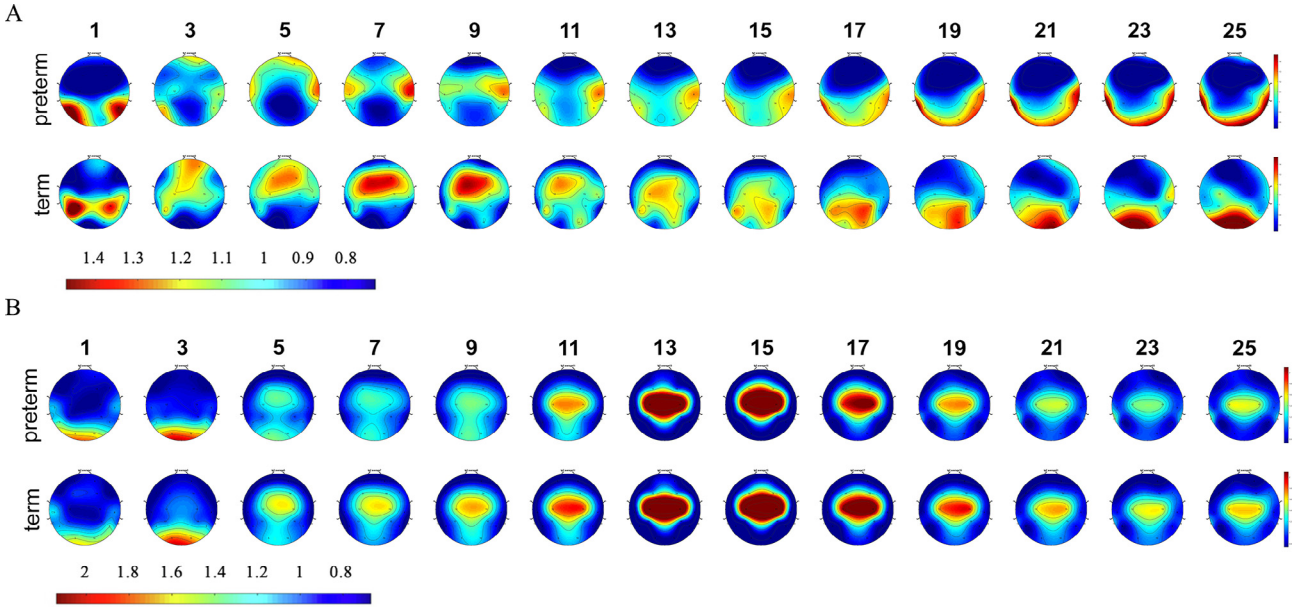

Fig. 2. Topographic map of normalised power density (pd): 2a: term age. 2b: 3 months. Legend: Topographical maps of 18 channel-EEG power during first quiet sleep daytime nap. Maps were normalised for each individual (absolute power density in each electrode divided by absolute power density in all electrodes), averaged for each group and analysed within 1-Hz frequency bin. Every second bin is plotted. Normalised power density is colour coded (maxima in red, minima in blue) and bars indicate values in square microvolts.

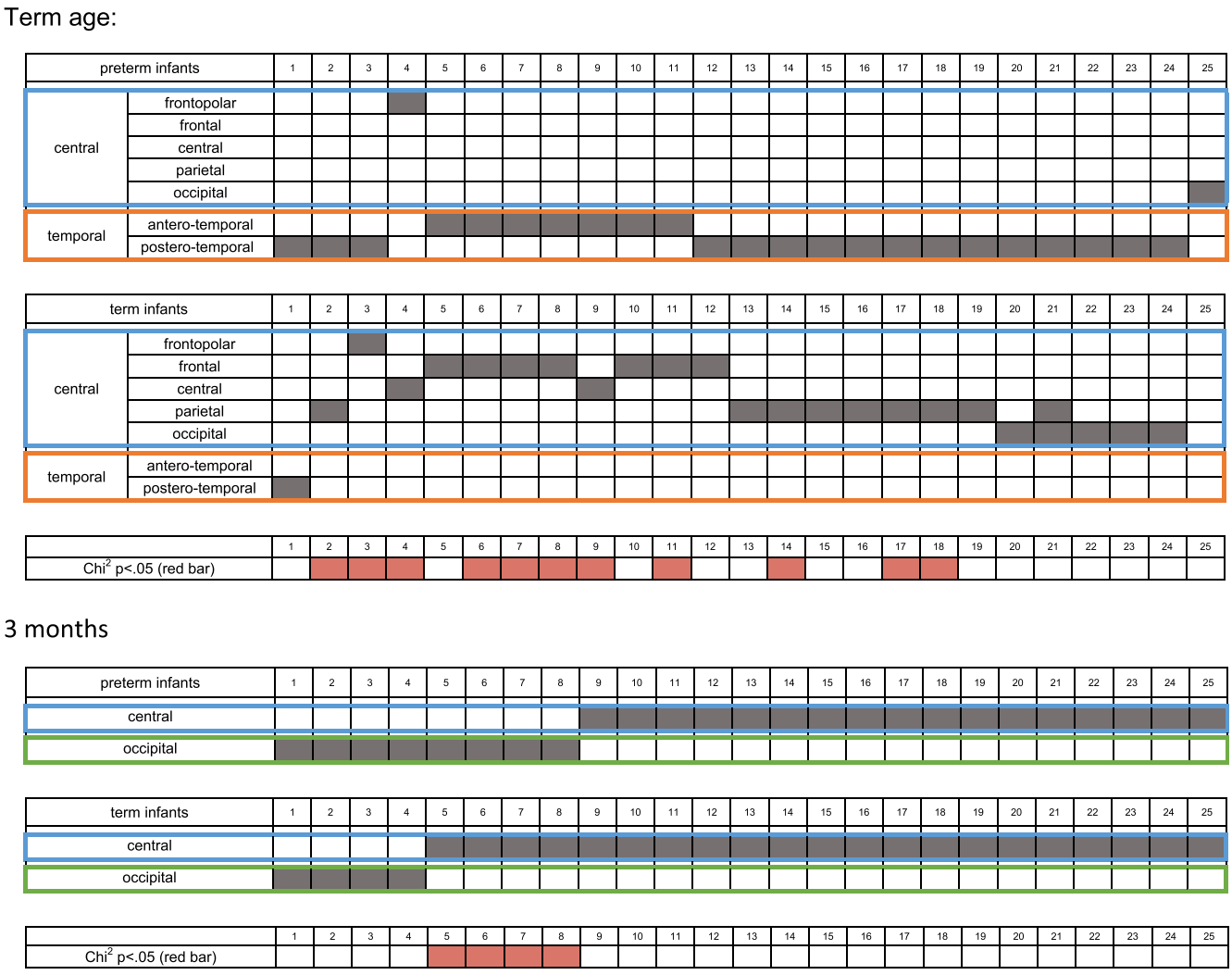

Fig. 3. Topographical distribution of maximal power density (grey bar) within 1 Hz frequency bins in preterm and term infants. Legend: Locations of maximal normalised power density in pooled left and right electrodes (frontopolar = Fp1/Fp2, frontal = F3/F4, antero-temporal = T3/T4, central = C3/C4, parietal = P3/P4, postero-temporal = T5/T6, occipital = O1/O2) are coded with black rectangles within each 1 Hz frequency bin for both groups (preterm and term infants) and both ages (term age and 3 months). Red rectangles indicate significant differences between the groups for both ages separately, using Chi-square tests ($p < 0.05$).

Table 3
Group differences (Mann-Whitney U) of maturational indices within different frequency bands.

	0.75–1.75 Hz	2–4 Hz	5–9 Hz	12–18 Hz	20–25 Hz
Maturation indices (MI):					
Term age: lateral MI	<0.001	<0.001	<0.001	<0.001	0.16
3 months: sagittal MI	0.30	0.11	<0.001	0.63	0.91

Table 4a
Correlation coefficients between maturational index (LMI at term age) and clinical scores (general movements at term age).

	Term age: lateral maturation index				
	0.75–1.75 Hz	2–4 Hz	5–9 Hz	12–18 Hz	20–25 Hz
General movements:					
Optimality score	0.33*	0.42**	0.37**	0.27	0.44***
Optimality score Lower limb	0.44***	0.49***	0.42**	0.36**	0.45***
Lower limb cramped	0.47***	0.56***	0.49***	0.42**	0.30*

*** $p < 0.01$.
** $p < 0.05$.
* $p < 0.1$.

Table 4b
Correlations between maturational index (LMI at term age) and maturational index (SMI at 3 months).

	Term age: lateral maturation index				
	0.75–1.75 Hz	2–4 Hz	5–9 Hz	12–18 Hz	20–25 Hz
3 months:					
Sagittal maturation index (5–9 Hz)	0.20	0.38**	0.36**	0.31*	0.14

*** $p < 0.01$.
** $p < 0.05$.
* $p < 0.1$.

(1986). The human brain is still immature when at around 40 weeks of gestation the mother-infant nutritional supply reaches a limit and birth is induced (Marschik et al., 2017; Prechtl, 1986). Brain development continues into the postnatal period (Prechtl, 1986), represented by the continuation of fetal movement patterns seen in the GM assessments after birth. These are replaced by the end of the second month by fidgety movements, increasing muscle power, postural changes, visual attention, binocular integration, social smiling, and cooing vocalisation (Marschik et al., 2017). Our clinical motor examinations using GM and TIMP strengthen these maturational steps and at the same time confirm our selection of relatively healthy preterm infants with slight conspicuous features regarding general movements at term equivalent age but reaching normal movements at 3 months corrected age. Also sleep measurements match the maturational steps of both term and preterm born infants between term age and (corrected) 3 months, with decrease of total sleep time resulting from replacement of active sleep by wakefulness and the maturation of sleep power spectrum due to the appearance of Non-REM sleep characteristics such as K-complexes, spindles, and sleep slow waves (Anders et al., 1995; Coons and Guilleminault, 1982; Fagioli and Salzarulo, 1982; Jenni, 2004).

Group differences in sleep EEG power spectrum at term age with lower power density above 5 Hz in preterm infants is in line with previous results. Preterm infants' power spectra mature after preterm birth, showing a total power decrease and a relative power increase within theta, alpha, and beta frequency ranges (Jennekens et al., 2012; Niemarkt et al., 2011; Scher et al., 1994a, 1994b), but they do not reach levels at term-equivalent age equal to those of term infants after birth (Scher et al., 1997, 1994a, 1994b). Our results illustrate a continuation of power spectrum maturation until 3 months of age, when preterm infants level out with term-born infants. It seems from a sleep electrophysiological point of view that the preterm infants catch up with term-born infants at the corrected age of 3 months. However, whether this catch up remains stable in the course of further maturation has to be investigated in future studies. Whether it translates to other modalities is unclear. Again, the leveling out could also reflect our inclusion criteria of relatively healthy preterm infants and could therefore not necessarily be extrapolated to all preterm born infants.

According to the topographical distribution of EEG power in previous studies (Kurth et al., 2010; Novelli et al., 2016), we aimed to compare term and preterm infants at the two ages.

At term age, maximal power shifts from frontal to central, parietal, and finally occipital areas with increasing frequency. Interestingly, although preterm infants follow the same frontal to occipital shift, maximal power moves through temporal instead of central areas, and preterm infants therefore present a lower LMI (LMI = lateral maturational index) than term infants. Until the age of 36 PMA, preterm infants' power density changes mainly over centro-temporal (Niemarkt et al., 2011) and fronto-temporal (Jennekens et al., 2012) areas. To our knowledge, the only study presenting topographical power differences between preterm infants at term-equivalent age and term infants reveals concordant results, with less power in theta, alpha, and beta frequency ranges over central areas (Scher et al., 1997). These group differences may be interpreted as indicating delayed brain maturation in preterm infants. This may imply that the topographical pattern measured a few weeks later would fit the central distribution of term infants at term age. However, it is more likely that preterm infants' brain maturation is not only delayed but takes a qualitatively different path outside the womb. Such a conclusion would be in line with Scher et al.'s results, which not only showed less power over central and sagittal areas but also higher correlations between channels in the same areas. Scher et al. concluded that fewer functional neuronal aggregates coincide with more cortical connectivity, indicating a functional alteration in preterm infants' brain development (Scher et al., 1994a). In fact, the exposure to harmful stimuli in infants after preterm birth coincides with a crucial time of migration, myelinisation, and gyration of brain tissue. Hypoxic-ischemic injury to preoligodendrocytes, axons, and subplate structures can lead to hypomyelination, interruption of thalamocortical/corticocortical connections, and a decrease in grey matter volumes (Ortinau and Neil, 2015). Indeed, neuroimaging studies confirm less grey and white matter differentiation and myelinisation in preterm infants that reach term-equivalent age (Hüppi et al., 1996) and reduced brain volumes and slower brain growth trajectories in cerebrum, cerebellum, brainstem, and intracranial cavity than in in utero healthy foetuses (Bouyssi-Kobar et al., 2017). We also found a positive correlation between the LMI and general movement assessment. A more central than temporal localisation of power maxima at term age correlates with a better GM OS and two subscores, lower limb cramped and OS lower limb, at term age. This further indicates, that topographical differences of sleep EEG power distribution correlates with clinical (motor) development.

Topographical analysis after 3 months of age shows the expected occipital localisation for lower and central localisation for higher frequency ranges (Fattinger et al., 2014; Kurth et al., 2010; Novelli et al., 2016). Group differences are more subtle, appearing within the frequency range of 5–9 Hz. Preterm infants have their power maxima over occipital areas, while those of term infants have already shifted to central areas. This is in line with previous studies concerning slow wave activity (SWA) and power density in the delta frequency range (Buchmann et al., 2011b). SWA is highest over active brain maturation areas (Campbell and Feinberg, 2009; Giedd, 2004; Huttenlocher and Dabholkar, 1997; Jenni and Carskadon, 2004) and shows a shift from occipital to frontal areas with increasing age (Kurth et al., 2010); this parallels the time course of brain maturation (Buchmann et al., 2011b; Gogtay et al., 2004; Kurth et al., 2012, 2010; Shaw et al., 2008; Sowell, 2004). Interestingly, our data show group differences not in the delta but in the theta frequency range. SWA is both a marker for brain maturation and reflects sleep homeostasis; it increases in proportion to time spent awake and decreases during sleep (Borbély and Achermann, 2005). However, it was proposed that sleep EEG spectral power in the theta frequency band reflects sleep homeostasis development during the first 6 months after birth

(Jenni, 2004). Also, in the first four years of life, Novelli et al. could show the main occipital-frontal shift within the theta and alpha frequency range (Novelli et al., 2016). Furthermore, the in-depth analysis of these dataset (D'Atri et al., 2018) distinguished between slow and fast spindles and found that the variation of the two spindles go in opposite direction across age. Power in our fastest frequency range (13–15 Hz) matches their specific peak of fast spindles at 4–12 months of age. Within these frequency range, however, we found no differences between the groups and only further analysis using individual spindle detection algorithm might be able to reveal additional differences.

These findings together with our results could indicate that, besides the occipital-to-frontal axis shift, maturation seems to start in higher frequency ranges during the first months of life, moving towards lower frequency ranges (delta) in older infants. Our data also exhibit a trend for group differences in SMI (SMI = sagittal maturational index) at 3 months within delta frequency range. This could mark the beginning of an occipital-to-frontal axis shift in term infants in the delta range that is not yet observable in preterm infants. Although not visible on the power spectrum, preterm infants at 3 months still show delayed or altered brain maturation as seen in topographical differences. Moreover, these topographical differences – in the absence of differences regarding power spectrum or clinical parameter – may again be specific for our relatively healthy preterm infants. These infants usually show no major impairments at 3 months of age, measured by motor performance tests, still slight qualitative differences in muscular tone can often be perceived by an experienced examiner.

A first limitation of this study is its relatively small sample size, though comparable to other studies (Scher et al., 1997, 1994a, 1994b). Sleep EEG measurements were heterogeneous, especially in the preterm sample, and assessment of clinical parameters was difficult at the first time point. A larger sample size would have addressed these difficulties. Second, recording time of the sleep episodes is very short, only one day-time quiet sleep episode could be analysed. Therefore, results are not representative of the whole sleep pattern. Thirdly, for the first recording, preterm infants had already experienced extrauterine life for an average of 3 months as opposed to 3 days in term born infants. This timepoint was chosen because the term infants were still in hospital with their mothers, while arranging their participation two weeks later would have been more difficult. Additionally, reliability of a sleep EEG recording as soon as 6 hours after birth is approved (Korotchikova et al., 2009). Lastly, SES differed between the groups, with term infants' parents exhibiting higher educational status than parents from preterm infants. SES is known to influence developmental outcome. Our results, however, did not show any correlations between SES and our clinical variables. Still, they cannot be extrapolated to the general population.

5. Summary and conclusion

Neonates at term age are still immature, reflecting their clinical status with foetal-like behaviour. Within 3 months, major steps in brain development occur, as confirmed in sleep EEG by the mature power spectrum and topographical power maxima distribution. Preterm infants' brain maturation is delayed and altered topographically, indicated by more temporal than central activation at term age and more occipital than central activation at 3 months. Finally, the topographical distribution quantified by the maturation indices show that being less mature at term age predicts being less mature at 3 months of age. Therefore, brain maturation indices – and in future maybe automated analysis tools - as presented in this study may help to better assess newborn and preterm infants' brain development in an early stage.

Declaration of Competing Interest

This is an unbiased study without conflicts of interest. All authors have made substantive contributions to this study in conception and design, acquisition of data, analysis and interpretation of data and in drafting and revising the article. All authors give their final approval of the submitted version. None of the authors have potential conflicts of interest to be disclosed. The Swiss Foundation for the Health of Children and Adolescents and the Forschungszentrum für das Kind had no influence on study idea or design, recruitment of patients, data analysis, interpretation of results, writing of the manuscript, or submission of the manuscript.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.06.230.

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