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Functional brain maturation assessed during early life correlates with anatomical brain maturation at term-equivalent age in preterm infants

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BACKGROUND: Amplitude-integrated electroencephalogram (aEEG) is a reliable monitoring tool for electrocortical activity with good predictive value in preterm infants. Magnetic resonance imaging (MRI) is a good neuroimaging tool to detect brain lesions and to evaluate brain maturation. We hypothesized that early aEEG measures, recorded over the first 3 d of life in very preterm infants, correlate with brain maturation and injury score assessed by conventional MRI at term-equivalent age.

METHODS: Thirty-nine infants born at a mean (range) gestational age (GA) of 29.5 (27.0–31.9) wk and birth weight 1,230 (680–2,020) g had continuous aEEG during the first postnatal 72–84 h. aEEG maturity scores and average maximum and minimum amplitudes were evaluated. Conventional brain MRI was performed at 41.2 (37.1–44.1) wk postmenstrual age (PMA) on a 3T GE system and scored qualitatively for injury and maturation.

RESULTS: The average aEEG total maturity score and its cycling subscore were positively and significantly associated with the total MRI maturation score after adjustment for GA, morphine sedation, and PMA at MRI examination. No association was found between the aEEG measures and the MRI injury scores.

CONCLUSION: Early aEEG maturity seems to relate to structural MRI brain maturation at term-equivalent age in preterm infants.

Despite improved survival of extremely preterm infants within the past two decades, long-term cognitive, motor, and behavioral impairments remain a significant burden for children born preterm (1), with the extremely preterm infants being most affected (2). Neuroprotective studies in preterm infants are being conducted to improve long-term outcome (3), and robust biomarkers would help to guide such interventional strategies and to help in parental counseling. Amplitude-integrated electroencephalogram (aEEG) is a valuable neurophysiologic diagnostic tool for early continuous bedside monitoring of brain function, and its background activity can predict short- and long-term outcomes in preterm infants (4). Some aEEG studies have shown that the background activity pattern changes as the brain matures (5–8). In addition, early signs of dysmaturity in brain activity have been associated with later neurodevelopmental impairments (9–11). Conventional magnetic resonance imaging (MRI) in recent years has helped to describe both brain maturation and brain lesions and to elucidate the nature of brain injuries in preterm infants. Brain maturation can be evaluated with a simple MRI scoring system (12). It was shown that preterm infants at term-equivalent age had delayed brain maturation scores as compared with term control infants, and this was associated with neurobehavioral outcome in preterm infants (12). However, the correlation between early maturational aEEG pattern and brain maturation on MRI has not been established to date. Hence, the aim of this study was to analyze the association between the findings of these two assessment methods performed at two different periods of early life in preterm infants. We hypothesized that the level of early aEEG tracing maturation could be predictive of later brain structural maturation and injury as measured with conventional MRI at term-equivalent age.

RESULTS

Study Subjects

Thirty-nine infants were included in this study with a mean (range) gestational age (GA) of 29.5 (27.0–31.9) wk and birth weight of 1,230 (680–2,020) g. Perinatal characteristics of the subjects are listed in **Table 1**. None of the infants suffered from sepsis or necrotizing enterocolitis. aEEG tracings of all infants were evaluated. The aEEG recording began at a median (interquartile range) age of 13.0 (11.5–19.0) h and was continuously performed until 88.5 (78.75–93.75) h after birth. MRI was performed at a mean postmenstrual age (PMA) of 41.2 (37.1–44.1) wk. Two infants had intraventricular hemorrhage on early ultrasound imaging, of which one required an Omaya reservoir to treat posthemorrhagic ventricular dilatation. No other major ultrasound lesions were seen.

Early aEEG Measurements

Average aEEG total maturity score and cycling subscore over the first 3–4 d of life of all 39 infants correlated positively with

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Table 1. Perinatal characteristics of the study infants

Perinatal variable	*n* = 39
Gestational age (wk) mean (SD; range)	29.5 (1.4; 27.0–31.9)
Birth weight (g) mean (SD; range)	1,230 (330; 680–2,020)
SGA, *n* (%)	6 (15)
Sex: male, *n* (%)	19 (49)
Preeclampsia, *n* (%)	9 (23)
Chorioamnionitis/funisitis, *n* (%)	9 (23)
Antenatal corticosteroids, *n* (%)[a]	34 (87)
Cesarean section, *n* (%)	39 (100)
Arterial cord pH, mean (SD)	7.32 (0.1)
5-min Apgar score, mean (SD)	7.1 (2.1)
Days on artificial ventilation, M (IQR)	0 (0–1)
CRIB score, M (IQR)	1 (1–4)
Respiratory distress, *n* (%)	39 (100)
Surfactant, *n* (%)	13 (33)
Sedation during aEEG, *n* (%)	7 (18)
Caffeine[b], *n* (%)	9 (23)
Indomethacine[c], *n* (%)	14 (36)

aEEG, amplitude-integrated electroencephalogram; CRIB, clinical risk index for babies; IQR, interquartile range; M, median; SGA, small for gestational age, defined as the birth weight <10 centile.

[a]Three infants (8%) did not receive any and two infants (5%) received incomplete antenatal steroids (i.e., one of two doses of 12-mg betamethasone given intramuscularly within 24 h before delivery). [b]First bolus of 20 mg/kg intravenous or arterial, from the median (range) 47th (27th–69th) hour of life and further daily administration of 5 mg/kg/d. [c]Six doses of 0.1 mg/kg/d (*n* = 8) or three doses of 0.2 mg/kg/12 h (*n* = 6) intravenous from the 63rd (54th–72nd) hour of life.

GA ($r = 0.70$ and 0.69, respectively; both $P < 0.001$) and negatively with morphine sedation ($r = -0.49$ and -0.43; $P = 0.001$ and 0.007, respectively). No other significant correlation was found between aEEG scores and perinatal data. Average aEEG maximum amplitude correlated positively with GA ($r = 0.35$; $P = 0.027$) and negatively with morphine sedation ($r = -0.35$; $P = 0.031$), whereas average minimum aEEG amplitude did not correlate with any perinatal data. Values of each aEEG measure tended to increase over the monitoring time. The median (interquartile range) slopes were 0.33 (0.03–0.73) for the total maturity score, 0.29 (0–0.78) for the cycling subscore, 0.39 (−0.27 to 0.80) for the maximum aEEG amplitude, and 0.70 (0.60–0.78) for the minimum aEEG amplitude (all $P < 0.001$).

Retrospective off-line analysis of the aEEG tracing showed that one infant with cranial ultrasound examination had two brief (2 and 3 min) periods of suspected electrical seizure activity in the left hemisphere during the 2nd and the 26th hours of life, respectively. No abnormal movement was noted, no standard EEG was performed, nor was any treatment given at those times.

Conventional MRI at Term-Equivalent Age

Seven infants (18%) had no white matter abnormalities (scores: 5–6), 22 (56%) had mild white matter abnormalities (scores: 7–9), and 10 (26%) had moderate white matter abnormalities (scores: 10–12). None had severe white matter abnormalities.

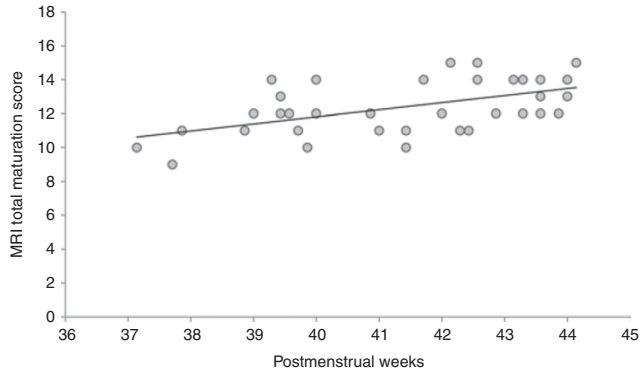

Figure 1. Spearman correlation between postmenstrual age at MRI examination and total maturation score in the study group ($r = 0.55$; $P < 0.01$). MRI, magnetic resonance imaging.

All infants had gray matter scores between 3 and 5, reflecting normal gray matter. No correlation was found between injury scores and GA at birth. Two infants had punctate hemorrhagic cerebellar lesions. Quality of gyral maturation (gray matter injury subscore) was negatively correlated with PMA ($r = -0.36$; $P = 0.02$). There were no other significant correlations between PMA and injury scores. Total maturation score (TMS) ranged between 9 and 15. TMS correlated significantly with PMA ($r = 0.55$; $P < 0.01$) (**Figure 1**) but not with GA at birth. **Figures 2** and **3** show two examples of qualitative low- and high-scored conventional MRI study, respectively.

Relation Between Early aEEG and MRI at Term Equivalent

Table 2 shows the Spearman rank's correlation coefficients between the aEEG and MRI scores. The average aEEG total maturity score, its cycling subscore, and the maximum aEEG amplitude over the first 3 d of life were positively and significantly correlated with the MRI TMS at term-equivalent age. Among all MRI maturation subscores, cortical folding correlated moderately with both the aEEG total maturity score and its cycling subscore; cortical folding correlated weakly with the minimum aEEG amplitude. The MRI subscores of germinal matrix and bands of migrating glial cells correlated positively with the aEEG TMS, the average minimum aEEG amplitude, and the average maximum aEEG amplitude. We found that no aEEG measure correlated with the MRI lesion scores in all study infants. The slopes of the different aEEG measurement series did not correlate with any of the MRI scores. In the multivariate linear regression analyses, the aEEG total maturity score and the cycling subscore were positively associated with the MRI total maturity score. For each unit increase of aEEG total maturity score and cycling subscore, there was an increase of 0.48 units of MRI total maturity score and 0.39 units of cycling score, respectively, explaining 48 and 45%, respectively, of the variance. These relationships were adjusted for GA, morphine sedation during aEEG monitoring, and PMA at MRI examination. In the subgroup of patients with no sedation ($n = 32$), the aEEG total maturity score was significantly associated ($\beta = 0.21$; $P < 0.04$) and the cycling subscore tended to be associated ($\beta = 0.52$; $P = 0.05$) with the MRI total

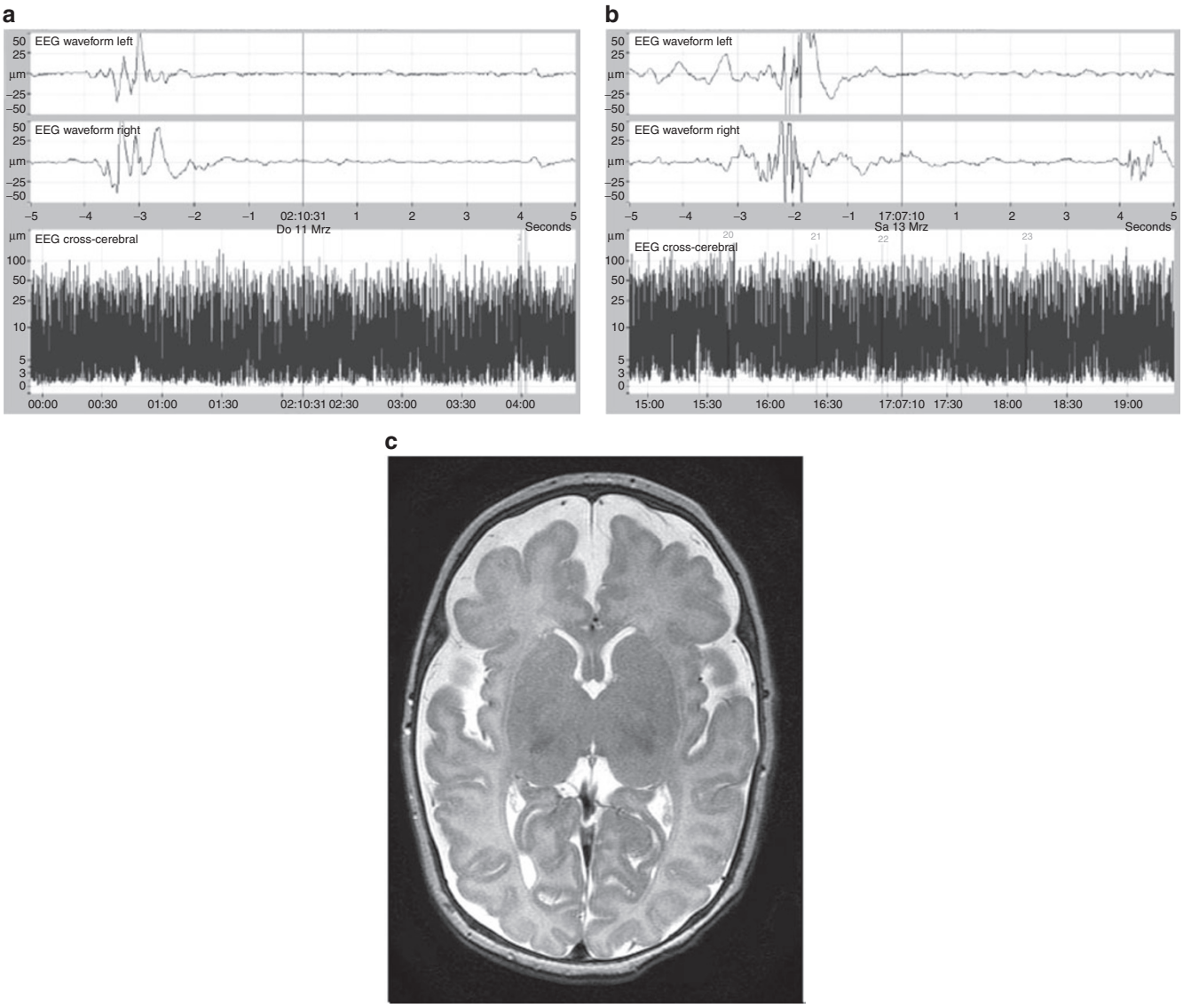

Figure 2. Development over time of the aEEG background between days 1 and 3 after birth in a preterm newborn of 27 5/7 wk of gestation. (**a**) Prevalently burst suppression aEEG background pattern at day 1 after birth with total maturity score 2. (**b**) Progressively discontinuous aEEG background pattern with variable minimum aEEG amplitude below 5 μV and total maturity score 2. (**c**) Axial T2-weighted MRI scanned at 38 0/7 wk PMA. Scores: germinal matrix: 3, cortical folding: 2, myelination: 2, bands of migration: 2, and total maturation score: 9. (**a**) Day 1; (**b**) day 3; and (**c**) at term-equivalent age. aEEG, amplitude-integrated electroencephalogram; MRI, magnetic resonance imaging; PMA, postmenstrual age.

Table 2. Spearman correlation coefficients between aEEG measurements and MRI maturation and injury scores

	MRI maturational score					MRI injury score		
	Total	Myelination	Cortical folding	Germinal matrix	Bands of migrating glial cells	WM injury	GM injury	PWML
Total maturity score after Burdjalov *et al.* (5)	0.44**	0.21	0.42**	0.34*	0.30	0.16	−0.05	0.06
Cycling subscore after Burdjalov *et al.* (5)	0.41**	0.20	0.45**	0.26	0.30	0.18	−0.05	0.05
Maximal aEEG amplitude	0.42**	0.27	0.13	0.29	0.34*	−0.22	−0.25	0.17
Minimum aEEG amplitude	0.26	0.23	0.34*	0.39*	−0.00	−0.22	0.04	−0.28

aEEG, amplitude-integrated electroencephalogram; GM, gray matter; MRI, magnetic resonance imaging; PWML, punctate white matter lesion; WM, white matter.

*$P < 0.05$. **$P < 0.01$.

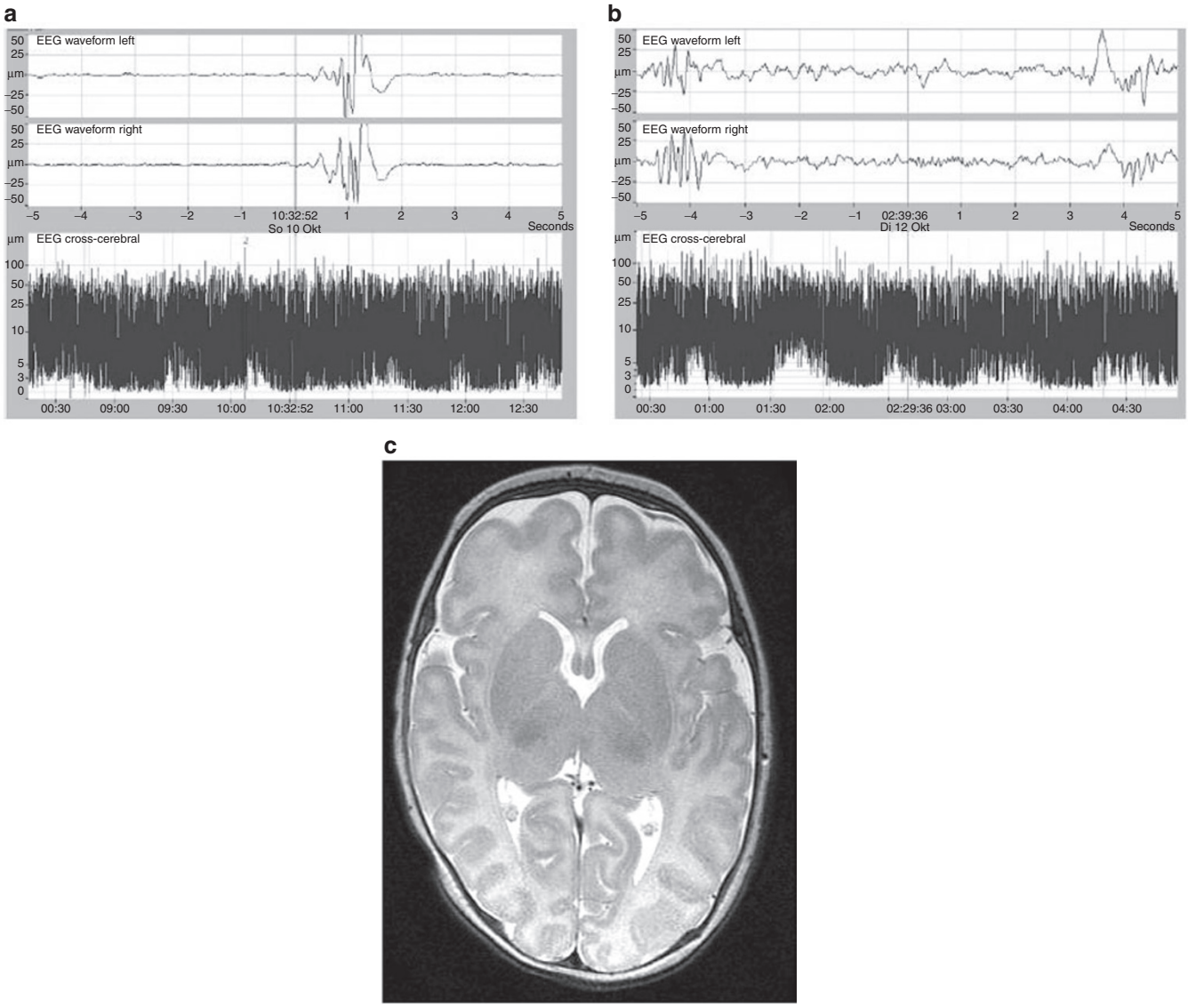

Figure 3. Development over time of the aEEG background between days 1 and 3 after birth in a preterm newborn of 27 4/7 wk of gestation. (**a**) Prevalently discontinuous aEEG background pattern at day 1 after birth with total maturity score 6. (**b**) Progressively continuous aEEG background with more mature cycling activity and total maturity score 8. (**c**) Axial T2-weighted MRI scanned at 41 0/7 wk PMA. Scores: germinal matrix: 4, cortical folding: 3, myelination: 2, bands of migration: 4, and total maturation score: 14. (**a**) Day 1; (**b**) day 3; and (**c**) at term-equivalent age. aEEG, amplitude-integrated electroencephalogram; MRI, magnetic resonance imaging; PMA, postmenstrual age.

maturity score. In both the ventilated ($n = 9$) and nonventilated infant ($n = 30$) subgroups, significant associations between the aEEG total maturity score ($\beta = 0.21$; $P < 0.04$ and $\beta = 1.15$; $P < 0.04$, respectively) or its cycling subscore ($\beta = 0.56$; $P < 0.05$ and $\beta = 5.82$; $P < 0.02$, respectively) and the MRI total maturity score were found. **Table 3** shows the results of the four models calculated for each aEEG measure, after correction for GA, morphine sedation during aEEG monitoring, and PMA at MRI examination.

DISCUSSION

The results of our study show that aEEG monitoring in preterm infants early after birth may be predictive for brain maturation on conventional MRI performed at term-equivalent age. That confirms our hypothesis of a correlation between neurophysiological maturity, measured early after birth, and structural brain maturity assessed at term-equivalent age. The early detection of brain dysmaturity provides the clinicians with an instrument to identify preterm infants at risk for abnormal cortical development and for unfavorable neurodevelopmental outcome (13). This would enable the implementation of targeted neuroprotective intervention to prevent subsequent impairment. However, the role of early aEEG as possible biomarker for structural brain maturation needs to be further evaluated in a study with a larger cohort in order to define cut-off points for aEEG measures and to assess the range of MRI TMS for specific GAs. Among all MRI parameters, the score for cortical folding, so gyrification and cortical maturation at

Table 3. Summary of multiple regression analyses for aEEG predictors of anatomical brain maturation assessed at term-equivalent age by conventional MRI in preterm infants

		Multivariate linear regression				
		MRI maturation total score adjusted for GA, morphine sedation,[a] and PMA				
Equation	aEEG measurements	β	SE	95% CI	% Variance explained	*P* value
1	Total maturity score after Burdjalov *et al.*	0.48	0.10	0.54–0.44	48	0.014
2	Cycling subscore after Burdjalov *et al.*	0.39	0.26	0.31–1.09	45	0.039
3	Maximal aEEG amplitude	0.27	0.05	−0.01 to 0.19	44	0.067
4	Minimal aEEG amplitude	0.16	0.10	−0.10 to 0.31	40	0.313

Equation 1: $F = 7.89$; $P < 0.001$; $R^2 = 0.48$; R^2 adjusted = 0.42. Equation 2: $F = 7.04$; $P < 0.001$; $R^2 = 0.45$; R^2 adjusted = 0.39. Equation 3: $F = 6.62$; $P < 0.001$; $R^2 = 0.44$; R^2 adjusted = 0.37. Equation 4: $F = 5.61$; $P = 0.001$; $R^2 = 0.40$; R^2 adjusted = 0.33.

aEEG, amplitude-integrated electroencephalogram; β, change in score or amplitude for 1-unit increase in MRI maturation score; CI, confidence interval; GA, gestational age; MRI, magnetic resonance imaging; PMA, postmenstrual age; SE, standard error of the regression coefficient.

[a]Morphine sedation during aEEG monitoring (maximum 12 mg/kg/h endovenous).

term-equivalent age correlated best with early aEEG measures. The findings of the current study are consistent with the work by Buchmann *et al.* (14) showing slow-wave EEG activity as a marker for cortical maturation in normal adolescents. In preterm infants (<30 wk of GA at birth without brain lesions on MRI), Biagioni *et al.* (15) showed a positive correlation between maturational EEG features and cortical folding and PMA. However, no independent correlate of global cortical maturity on EEG parameters was found because PMA had a strong influence on both anatomical and electrophysiological maturation. In contrast to their study in which both EEG and MRI were performed soon after birth, in the current study, early aEEG was correlated with late MRI at term-equivalent age, showing a correlation between early aEEG measures and cortical folding adjusted for PMA. A study using auditory event–related potentials showed that an earlier right neurophysiological maturation was paralleled by an ipsilateral structural development seen on MRI in preterm infants (16). Of note, in a study on early cortical folding, increased gyrification was associated with more mature behavioral function at term-equivalent age (17). To what extent early cortical electrical activity as measured by aEEG can induce structural cortical maturation cannot be determined by this study and would require serial MRI.

Many MRI studies at term-equivalent age have shown that cortical development is delayed in preterm infants (18–20). Of note, the total white matter and gray matter injury score on MRI at term-equivalent age did not correlate with any early aEEG measure. The total injury score was derived from composite white and gray matter scores. Even when the individual white or gray matter scores were correlated with early aEEG measures, no significant correlations were found. However, this might not be surprising because most of the infants in this cohort had mild-to-moderate white matter injury and none had abnormal gray matter injury scores. This narrow range of abnormalities could explain the lack of correlation between early aEEG measures and MRI injury score. Moreover, the MRI injury scores are mainly focused on white matter abnormalities and not on cortical abnormalities. Visual assessment of cortical abnormalities is difficult, and perhaps, a more objective quantitative volumetric assessment of the cortex would show additional correlation between early aEEG measures and cortical abnormalities. Several studies showed that aEEG background activity can indicate large intracerebral hemorrhage (10,11,21–24) or cystic periventricular leukomalacia in preterm infants (25). Although we had a narrow range of mild-to-moderate brain abnormalities defined by the Woodward score, one could expect a correlation between presence of injury on MRI and aEEG measures. However, this was not the case, probably because of localization and timing of the aEEG monitoring. In fact, in the current study a two-channel aEEG device was used, with electrodes being placed in the C3 and P3 as well as in the C4 and P4 locations; this setting obviously does not cover all cortical regions and therefore might miss regional cortical activity alterations. Alternatively, brain injury could have not been detected by electrophysiological monitoring because the insult or evolution of injury occurred after the first 3 d after birth, hence after the aEEG monitoring period. Indeed, it has been reported that events such as postnatal infection (26) or chronic lung disease (27) influence brain maturation. Hence, it is likely that if serial aEEG monitoring until term-equivalent age had been performed, a correlation with brain injury on MRI at term-equivalent age would have been seen.

Some limitations of this study have to be mentioned. Continuous aEEG measures cortical activity through two parieto-central channels only; therefore, a limited sector of cortex can be monitored. It may be that we missed regional brain dysfunction. However, this method enabled us to monitor the newborns continuously during many days after birth, which is impracticable with a multichannel EEG device. In addition, in our study the assessment of the electrocortical maturity and the outcome measure were based on the semiquantitative aEEG and MRI assessment, respectively, which could be subjected to bias. However, we used two validated assessment methods, and we reached good interobserver agreement levels. Another important limitation of the current work is the relatively small sample size, which limits the power of the statistical analysis.

The wide GA range and the lack of extremely immature preterms in the study group do not allow a generalization of our findings to preterm newborns with GA below 27 wk. Further research with larger numbers, including more immature preterms, serial MRI, and focus on the long-term neurodevelopment of these infants will be needed.

Conclusion

In conclusion, the results of this study indicate that early quantitative aEEG measures in preterm infants seem to correlate with brain maturation on MRI at term-equivalent age. This implies that early aEEG monitoring could play a role for the assessment of later cortical maturation. These results are important because they show a good correlation between functional and structural brain maturation.

MATERIALS AND METHODS

The institutional ethics boards of the University Children's Hospital Zurich and of the Canton of Zurich approved the study protocol. Informed consent was obtained from the parents of the subjects.

Subjects

This was a prospective observational study including inborn preterm infants born before 32 wk, who were admitted to the neonatal intensive care unit of Zurich University Hospital between January 2009 and May 2011. Infants who had both early aEEG monitoring and MRI at term-equivalent age were eligible for the study. Exclusion criteria were chromosomal and/or congenital anomalies, central nervous system infection, or metabolic disorders. GA was assigned on the basis of the best obstetrical estimate, based on the last menstrual cycle and prenatal ultrasonography scans. Small doses of intravenous morphine sedation (maximum 12 μg/kg/h) during aEEG monitoring were not considered as exclusion criteria for the analysis. aEEG sequences of infants with other sedative medication were excluded from the analysis. Each infant had serial cranial ultrasound examinations at days 1, 3, and 7 after birth and weekly or every 2 wk, as clinically indicated, until discharge.

Amplitude-Integrated Electroencephalography

Two-channel aEEG monitoring with a Brainz BRM3 monitor (Natus Medical, San Carlos, CA) was recorded from biparietal hydrogel electrodes, corresponding to C3 and P3 as well as C4 and P4, according to the international electroencephalogram classification 10–20 system, ground F_z (28). The reference electrode was placed on the right or left shoulder. The technique and the physiological basis of the aEEG have been outlined in detail elsewhere (29). The raw EEG signal is amplified and filtered, attenuating the activity <2 Hz and >15 Hz, and its amplitude is semilogarithmic integrated, rectified, and time compressed (1 h/6 cm of recording-display scale). Duration of the aEEG monitoring lasted from the first to the third day of life. For pattern analysis, aEEG tracings were divided into epochs of 3 h each. Only tracings with impedance below 12 kOhm were analyzed. Tracing epochs with either suspect seizure events or artifacts were excluded from the analysis. Cross-cerebral P3–P4 aEEG records were analyzed. One observer (G.N.) experienced in aEEG interpretation performed the visual assessments of aEEG offline on the basis of a previously published score (5), and these scores were used for statistical analysis. Visual analysis was performed blinded to quantitative analysis of the aEEG, neonatal outcome, and MRI findings. A second observer (C.H.) analyzed aEEG tracings of 10 infants only for interobserver agreement testing.

Visual aEEG Analysis

Visual semiquantitative aEEG analysis was performed according to the scoring system for the evaluation of brain maturity as suggested by Burdjalov *et al.* (5). The following four aEEG pattern components were included: continuity; cycling; amplitude of the lower border of the aEEG traces, which was visually estimated as the average lower microvolt level during the recording periods; and aEEG bandwidth, which refers to a combination of the voltage span (peak-to-trough) of the tracing and the amplitude of the lower aEEG border. For each 3-h artifact, free aEEG epoch components' subscores were summed to obtain a total maturity score, ranging from 0 to 13, the lower the score the more immature the brain activity. Subscores for cycling, ranging from 0 to 5, were analyzed separately. Cohen's kappa (95% confidence interval) for interrater agreement was 0.79 (0.75–0.82) for the total maturity score and 0.60 (0.52–0.66) for the cycling subscore, respectively.

Quantitative aEEG Analysis

Quantitative automated analysis of the aEEG tracings was performed using the BrainZ Analyze Research software (Chart analyser 1.71; Liggins Institute, Auckland, New Zealand). Raw aEEG data were exported and 1-min average values for the maximum and minimum amplitudes of each aEEG epoch were calculated (30). Maximum and minimum aEEG amplitude correspond to the upper and lower borders of the aEEG envelope, respectively.

MRI Data Acquisition and Analysis Procedure

The MRI protocol included the following imaging sequences: axial T2-weighted FSE images (TE: 102 ms; TR: 5640; ETL: 24; FOV: 18 × 14.4 cm; matrix: 512 × 320; slice thickness: 2.5 mm; gap: 0.5 mm, 2 NEX), 3D T1-weighted images (TE: 2.6 ms; TR: 5.7 ms; TI: 750 ms; flip angle: 12 degrees; FOV: 18 × 18 cm; matrix: 224 × 224; slice thickness: 1.4 mm; gap: 0 mm, 1 NEX), proton-density T2 FSE images (TE: 26, 128 ms; TR: 6,600 ms; ETL: 16; FOV: 18 × 13.5 cm; matrix: 256 × 192; slice thickness: 1.5 mm; gap: 0 mm, 2 NEX), and sagittal T2-weighted FSE images (TE: 102 ms; TR: 3,900 ms; ETL: 24; FOV: 18 × 18 cm; slice thickness: 3 mm; gap: 0 mm; matrix: 384 × 320, 1 NEX). Cerebral structural maturation was assessed (by C.H.) according to a previously published protocol (31). The degree and localization of myelination and cortical folding, the presence and distribution of the germinal matrix, and the bands of migrating glial cells were scored separately. The MRI TMS was calculated as the sum of the four separate scores ranging from 4 to 21, the higher the score the higher the brain maturation. T1- and T2-weighted images were assessed (by C.H.) for injury according to a previously published scoring system by Woodward *et al.* (32). A total injury score and subscores for gray and white matter injury were calculated. Scores of 5–6 reflect no white matter abnormality, 7–9 mild, 10–12 moderate, and 13–15 severe white matter abnormality. Gray matter scores of 3–5 reflect normal and scores of 6–9 reflect abnormal gray matter. Cohen's kappa for interrater agreement (data of 20 infants assessed by a second observer, R.H.-V.L.) was (95% confidence interval) 0.59 (0.37–0.81) for the TMS and 0.77 (0.61–0.92) for the injury score, respectively.

Statistics

Means (SD) of all epochs' values were calculated for each subject and all aEEG measures. The slope of the development of each aEEG measure over the monitoring time was computed by a linear regression model for all subjects and averaged. For testing the correlation between aEEG measurements and MRI scores, the Spearman's rank correlation coefficients were calculated. In a second step, the following perinatal variables were tested for their association with aEEG measurements: GA, PMA, morphine sedation, caffeine and indomethacin administration, arterial cord pH, 5-min Apgar score, clinical risk index for babies score, intraventricular hemorrhage greater than grade II after Papile (33), and cystic periventricular leukomalacia. In a third step, aiming at analyzing an adjusted association between aEEG measures and MRI scores, a multivariate linear regression analysis was performed, in which variables that were significantly associated with the aEEG and MRI scores were entered (GA, PMA, and sedation). Two-sided tests were used throughout, and a P value < 0.05 was considered statistically significant. SPSS 18.0 software (SPSS, Chicago, IL) was used.

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